

## EXTENDED REPORT

## Lymphoma risk in systemic lupus: effects of disease activity versus treatment

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**ABSTRACT**

**Objective** To examine disease activity versus treatment as lymphoma risk factors in systemic lupus erythematosus (SLE).

**Methods** We performed case-cohort analyses within a multisite SLE cohort. Cancers were ascertained by regional registry linkages. Adjusted HRs for lymphoma were generated in regression models, for time-dependent exposures to immunomodulators (cyclophosphamide, azathioprine, methotrexate, mycophenolate, antimalarial drugs, glucocorticoids) demographics, calendar year, Sjogren's syndrome, SLE duration and disease activity. We used adjusted mean SLE Disease Activity Index scores (SLEDAI-2K) over time, and drugs were treated both categorically (ever/never) and as estimated cumulative doses.

**Results** We studied 75 patients with lymphoma (72 non-Hodgkin, three Hodgkin) and 4961 cancer-free controls. Most lymphomas were of B-cell origin. As is seen in the general population, lymphoma risk in SLE was higher in male than female patients and increased with age. Lymphomas occurred a mean of 12.4 years (median 10.9) after SLE diagnosis. Unadjusted and adjusted analyses failed to show a clear association of disease activity with lymphoma risk. There was a suggestion of greater exposure to cyclophosphamide and to higher cumulative steroids in lymphoma cases than the cancer-free controls.

**Conclusions** In this large SLE sample, there was a suggestion of higher lymphoma risk with exposure to cyclophosphamide and high cumulative steroids. Disease activity itself was not clearly associated with lymphoma risk. Further work will focus on genetic profiles that might interact with medication exposure to influence lymphoma risk in SLE.

in SLE was generated from our recently updated large, multicentre, international cohort study (16 409 patients at 30 centres), which confirmed a slight increased risk for all cancers combined and a striking threefold increased risk for haematological cancers, particularly lymphoma.<sup>1</sup> However, the relative importance of disease activity versus treatment in driving lymphoma risk is unknown. Our objective was to determine the relative importance of disease activity versus treatment in SLE.

**METHODS**

A case-cohort study was performed within the large multisite SLE cohort referred to in the introduction, with the participation of collaborating centres from two research networks, the Systemic Lupus International Collaborating Clinics and the Canadian Network for Improved Outcomes in Systemic Lupus, as well as other collaborators. These included centres from Calgary, Montreal, Toronto, Winnipeg, Baltimore, Boston, Chapel Hill, Chicago, New York City, Los Angeles, Pittsburgh, San Francisco Bay Area, South Carolina, Mexico City, Copenhagen (Denmark), Birmingham (UK), London (UK), Bizkaia (Spain), Hannover (Germany), Lund (Sweden) and Seoul (South Korea). Cancers were ascertained by regional registry linkages, except at Boston—where lymphomas were ascertained through validated hospital discharge summaries—and Mexico City—where lymphomas were ascertained through medical chart review.

We used the case-cohort study design for optimal flexibility and efficiency. In this design, exposure and covariate information is collected from all cases and a random representative sample of the cohort at each centre as the source for controls. To ensure the efficient use of available control data, we included within the control pool 100% of the cohort (cancer-free at cohort entry) when the necessary data were already available electronically, and, when centres had to perform chart review to

Lymphoma risk in systemic lupus erythematosus (SLE) is of considerable interest; patients and practitioners are both concerned about the potential increased risk from immunosuppressive SLE treatments. The most definitive data on lymphoma risk

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## Clinical and epidemiological research

provide data, we included a lower percentage of their cohort (cancer-free at baseline), ranging from 2.5% to 10% of control subjects. Observations within these subsets were then appropriately weighted using the Barlow method as previously described.<sup>2</sup>

All study subjects had definite SLE according to the revised American College of Rheumatology (ACR)<sup>3</sup> or clinical criteria. (Each investigator follows a cohort of clinically confirmed SLE patients in follow-up, the vast majority of whom fulfil ACR criteria.) We included only lymphomas that had occurred after entry into the lupus cohort at each centre; the index time for each risk (case-control) set was the date of the case's lymphoma occurrence expressed as time elapsed since SLE diagnosis. The analyses were thus adjusted for SLE disease duration. The controls for each risk set, for each lymphoma case, represented all the subcohort members who remained cancer-free up to that index time. Cancer registries generally require at least one calendar year period to have elapsed before they can confirm that their cancer data are adequately complete and accurate, so the end of the observation interval for each centre's SLE cohort was based on the earliest of that date, or the last date the patient was seen in clinic (or date of death, if relevant).

We performed descriptive analyses of our variables and used modified Cox proportional hazards regression to calculate the unadjusted and fully adjusted HR for lymphoma related to each covariate in our model, which included demographics (age, sex, race/ethnicity, geographic residence), calendar year, medication exposure and disease activity. Sjogren's syndrome, an autoimmune phenomenon characterised by dry eyes and mouth and anti-Ro/anti-La antibodies, can either occur as a primary syndrome or secondarily in a disease such as SLE. Because of the strong lymphoma risk seen in primary Sjogren's syndrome,<sup>4</sup> the presence of 'secondary Sjogren's syndrome' in our SLE subjects was also included as a potential risk factor.

Partially adjusted models were also performed (with the same modified Cox proportional hazards regression approach) using stepwise selection. Although the full model adjustment allows us in principle to distinguish between all independent effects, it does so at the cost of decreased precision. The partially adjusted model can minimise the variance that results from strong correlations between a larger number of predictors, thus providing more precise estimation. In the partial model, disease activity was forced in, as it was a primary exposure of interest in this study.

The data on clinical characteristics and all medications were prospectively recorded in the clinic database and/or medical records at each centre. Data from each centre were either exported as character-encoded files or abstracted from these sources using a standardised form, and compiled in Montreal. All time-varying variables were treated as time-dependent, assessed for each case-control risk set at the index time. Age was a continuous variable, geographic residence was included as a dichotomous variable indicating whether or not a given centre was outside North America, and presence or absence of Sjogren's syndrome was based on clinical judgment and documentation within each participating centre's records (as opposed to requiring patients to fulfil specific criteria for Sjogren's). Medications were included as time-dependent variables for ever/never use for all the medications listed in table 1. Since there is some concern about dose effects for cyclophosphamide and azathioprine (AZA), we also included a variable indicating cumulative dose category for these agents. To better control for corticosteroid use, which could be associated with disease activity and potentially with lymphoma risk,<sup>5</sup> we also included a

**Table 1** Characteristics of lymphoma SLE cases and the cancer-free SLE controls

Characteristic	Lymphoma cases (n=75)	Cancer-free (n=4961)
Age at entry (years), mean (SD)*	45.2 (14.5)	38.5 (13.8)
Female	60 (80.0)	4511 (90.9)
White	53 (70.0)	3049 (61.5)
Sjogren's syndrome	16 (21.3)	983 (19.8)
Disease duration at entry (years), mean (SD)†	6.2 (8.1)	6.2 (7.5)
Disease activity at entry, mean (SD)‡	5.2 (4.9)	6.3 (6.6)
Glucocorticosteroids ever used§	58 (77.3)	3959 (79.8)
Cyclophosphamide ever used	15 (20.0)	834 (16.8)
Azathioprine ever used	19 (25.3)	1717 (34.6)
Methotrexate ever used	9 (12.0)	960 (19.4)
Mycophenolate mofetil ever used	6 (8.0)	884 (17.8)
Antimalarial drugs ever used¶	55 (73.3)	4022 (81.1)

Unless otherwise indicated, values are number (%).

\*Median age was 47.3 in lymphoma cases and 37.1 in controls.

†Median disease duration at cohort entry was 3.1 for cases and 3.5 for controls.

‡SLE Disease Activity Index-2K (SLEDAI-2K); median value was 4 for both cases and controls.

§Only systemic steroid exposures were included.

¶Antimalarial drugs included hydroxychloroquine and chloroquine. SLE, systemic lupus erythematosus.

cumulative dose categorical variable. Sensitivity analyses were performed lagging cyclophosphamide by 5 years (based on literature suggesting that malignancies may arise many years after exposure).<sup>6</sup> Here, any lymphomas occurring within the 5-year period immediately after initiation of cyclophosphamide were not attributed to that exposure.

Disease activity was characterised on the basis of SLE Disease Activity Index (SLEDAI, V2K) scores; for each risk set, we created an Adjusted Mean SLEDAI-2K score.<sup>7</sup> This involves calculating the area under the curve of SLEDAI-2K scores over time. Here, the area under the curve between each two visits is the average of the SLEDAI-2K values at those two visits multiplied by the length of time between the two visits. All the calculated areas are then summed and divided by the total length of the time period. The adjusted mean SLEDAI-2K has the same units as SLEDAI-2K and is interpreted in the same way. The adjusted mean SLEDAI-2K has been shown to be a valid measure of SLE activity. To aid interpretation of our results, the variable for high disease activity was dichotomised, where high activity was represented by an adjusted mean SLEDAI-2K value of 6 or more.

The SLEDAI-2K is normally completed by a physician, but, at two centres (Calgary and San Francisco), disease activity elements were self-reported by patients.<sup>8</sup> At the Birmingham UK centre, cumulative disease activity was measured with the British Isles Lupus Assessment Group index. For these three centres (Calgary, San Francisco and Birmingham UK), high activity was defined as the highest quartile of the adjusted mean activity scores. Although the disease activity measures from these centres were initially included when we dichotomised adjusted mean disease activity scores for the case-control sets, since this measure is not completely interchangeable with the formal SLEDAI-2K, we performed sensitivity analyses excluding these centres.

Since lymphomas constitute a heterogeneous group of diseases, as a sensitivity analysis, we repeated our analyses focusing

on lymphomas that were only of B-lymphocyte (as opposed to T-lymphocyte) origin.

For all analyses, Stata V.9 was used, including the 'stscocoh' routine for setting up the case-cohort data, and 'stcox' for the regression analysis, with Barlow weights and robust SE.

## RESULTS

In total, we studied 75 lymphoma cases (in 75 individuals), and the total set of cancer-free controls equalled 4961. The characteristics of these subjects are described in table 1. Lymphoma occurred a mean of 12.4 years (SD 9.6, median 10.9) after SLE diagnosis. Most (72) of the lymphomas were non-Hodgkin lymphoma, and the other three were Hodgkin lymphoma, with most (54) of the lymphomas arising from a B-cell line (nine were from a T-cell line, and in the remainder the histology was unavailable). In just over 20% of the lymphoma cases in the analysis (16 of the 75), secondary Sjogren's syndrome was diagnosed before the malignancy. Table 2 portrays the results of our unadjusted and adjusted analyses. As is consistent with the risk profile in the general population, lymphoma risk in SLE was higher in male than female patients and increased with age.

Of the 75 lymphoma cases, only 15 had prior exposure to cyclophosphamide, 19 to AZA, nine to methotrexate, and six to mycophenolate mofetil. In a slight majority (42/75=56%) of the lymphoma cases, there was no prior exposure to any of these immunosuppressants (vs 48% of cancer-free controls being unexposed). Cyclophosphamide was the only immunosuppressive drug exposure that tended to be higher in frequency in the lymphoma cases (20.0%) than in the controls (16.8%), although the CI for the difference between these two proportions includes the null value (of zero difference).

In univariate analyses and in our partially adjusted model (where covariates included age, sex, Sjogren's, cyclophosphamide, cumulative steroid and disease activity), a twofold increased risk of lymphoma was seen with both cyclophosphamide exposure and cumulative steroid of at least 3.5 g. However, in the fully adjusted model, the CI included the null value for both. In absolute terms, patients with SLE exposed to

cyclophosphamide still had a relatively low rate of lymphoma occurrence, with fewer than one new case of lymphoma per 1000 person-years of observation time (after cyclophosphamide exposure).

Regarding diseases activity, as can be seen in table 2, there was no clear independent association of disease activity and lymphoma risk in SLE, in either univariate or adjusted analyses.

Excluding the two centres where disease activity measures were based on patient self-report items only, sensitivity analyses showed similar results (data not shown). In addition, when we lagged exposures, or restricted our analyses to B-cell lymphomas only, the results were essentially unchanged.

## DISCUSSION

Our findings do not clearly substantiate that medication exposures drive most of the lymphoma risk in SLE. In fact, many of the lymphoma cases were not exposed to any immunosuppressant medications before the onset of the malignancy. On the other hand, there was a trend for a higher proportion of lymphoma cases being exposed to cyclophosphamide versus the cancer-free controls.

In addition, we found no clear relationship between SLE disease activity and lymphoma risk. This is in contrast with rheumatoid arthritis (RA), where Baecklund *et al*<sup>9</sup> suggested a strong association between disease activity and lymphoma risk. A priori, one might suspect that high disease activity in SLE, which is associated with heightened lymphocyte proliferation, might also heighten lymphoma risk. However, it is also known that the immune system has important roles in deleting abnormal cells.<sup>10</sup> Interestingly, in a recent study performed in a mouse model, inflammation driven by tumour-specific Th1 cells protected against B-cell lymphomas.<sup>11</sup> Moreover, some novel evidence suggests that anti-DNA antibodies may have antitumour effects (in vitro and in animal models) against certain cancer cell lines (including breast, ovarian and prostate);<sup>12</sup> in the current dataset, we saw no association between the presence of anti-DNA antibodies and lymphoma risk (data not shown).

**Table 2** Results of the unadjusted, partially adjusted and fully adjusted models to assess the HR of exposures in lymphoma development in patients with systemic lupus erythematosus (SLE)

Variable	Unadjusted HR (95% CI)	Partially adjusted model (95% CI)	Fully adjusted HR (95% CI)
Outside North America	0.81 (0.46 to 1.45)	–	0.91 (0.44 to 1.90)
Calendar year	1.02 (0.99 to 1.04)	–	0.99 (0.96 to 1.02)
Male	2.74 (1.45 to 5.19)	2.64 (1.39 to 5.02)	2.70 (1.38 to 5.28)
Age	1.04 (1.03 to 1.06)	1.04 (1.02 to 1.06)	1.04 (1.02 to 1.06)
White race/ethnicity	1.11 (0.67 to 1.84)	–	0.91 (0.53 to 1.56)
Sjogren's syndrome	2.08 (1.13 to 3.8)	1.94 (1.04 to 3.61)	1.79 (0.88 to 3.62)
Glucocorticosteroids ever used	1.69 (0.95 to 3.03)	–	0.79 (0.25 to 2.45)
Cumulative glucocorticosteroids >3.5 g*	1.82 (1.06 to 3.14)	1.94 (1.11 to 3.39)	2.57 (0.94 to 7.04)
Cyclophosphamide ever used	2.07 (1.13 to 3.81)	1.90 (1.02 to 3.53)	2.80 (0.87 to 8.98)
Cumulative cyclophosphamide >6 g	1.68 (0.80 to 3.55)	–	0.68 (0.18 to 2.59)
Azathioprine (AZA) ever used	0.72 (0.41 to 1.27)	–	0.84 (0.32 to 2.25)
Cumulative AZA >36.5 g	0.55 (0.27 to 1.11)	–	0.59 (0.18 to 1.92)
Methotrexate ever used	1.06 (0.50 to 2.26)	–	0.74 (0.31 to 1.78)
Mycophenolate ever used	1.47 (0.61 to 3.54)	–	1.47 (0.58 to 3.71)
Antimalarial drugs ever used	1.63 (0.94 to 2.84)	–	1.55 (0.81 to 2.96)
High disease activity†	0.62 (0.34 to 1.13)	0.65 (0.35 to 1.22)	0.68 (0.36 to 1.29)

\*Systemic glucocorticosteroids, considered in prednisone equivalent doses.

†Defined as Mean Adjusted SLE Disease Activity Index-2K (SLEDAI-2K) value of 6 or more. For centres using alternative disease activity measures, high activity was defined as the highest quartile of the mean adjusted activity scores.

Our study has important strengths. The case-cohort design represents flexible and efficient methodology.<sup>13</sup> The cancer registries we used are an excellent tool for cancer ascertainment. Each registry is patient-based and records the kind and number (incidence) of primary cancers diagnosed for each resident of the region, as long as they remain alive and residing there. In addition to information on cancer incidence, data are available about the characteristics of patients (age, sex, etc), as well as about the nature and type of these tumours. The registries also use specialised internal record linkage software for detecting duplicate records and for identifying death records.

Our work builds on previous efforts to determine what factors may predispose to malignancy in SLE, and is reassuring in that we did not see a marked increased risk in lymphoma related to most immunosuppressants. However, one great difficulty has always been differentiating the effects of medications from disease activity. That we were able to examine the independent effects of medication and disease activity is a strength of our work. On the other hand, perhaps some elements of disease severity may not be well-captured in our approach. In considering the association between cumulative glucocorticosteroids and lymphoma risk, it may be that this variable is a marker for residual differences in disease activity, not captured by our measures. Furthermore, it is possible that any effect of medications (eg, cyclophosphamide or steroids) may be due to the emergence of oncogenic viruses (eg, Epstein-Barr virus). Evaluation of this hypothesis is beyond the scope of this paper.

Although we collected exposure information on immunosuppressive drugs other than cyclophosphamide and AZA (eg, mycophenolate), these exposures were not of sufficient frequency to warrant calculation of cumulative doses. The numbers of patients receiving mycophenolate were relatively small, reflecting in part the fact that this agent was not in general use for SLE for the earliest years of observation, although there certainly has been a general increase over time in the use of this agent. Future analyses could be useful for monitoring its long-term effects on the development of malignancies. Finally, the variable for secondary Sjogren's syndrome was based on clinical judgment and thus we remain very cautious regarding the influence of this variable on lymphoma risk in SLE.

Previous publications are consistent with our findings, including a review of patients with SLE (N=15) and RA (N=11) with lymphoproliferative neoplasms.<sup>14</sup> In that series, previous exposure to immunosuppressants (cyclophosphamide, AZA, methotrexate) was relatively low (fewer than half of the cases had been exposed to any of these drugs). A similar review of lymphomas in 12 RA and two SLE patients found that none were exposed to AZA or cyclophosphamide (five of the RA patients were exposed to methotrexate).<sup>15</sup> In addition, in logistic regression analyses (controlling for disease activity), in 1992, Pettersson *et al*<sup>16</sup> did not find immunosuppressants to be a cancer risk factor in a small SLE sample (N=205).

On the other hand, in our study, cyclophosphamide did tend to be a more common exposure in lymphoma cases than controls, and, in both unadjusted and adjusted analyses, the HR point estimate for cyclophosphamide was >1, which is consistent with a potentially increased risk. The partially adjusted analyses based on stepwise selection may be potentially misleading in terms of bias and artificially narrow CIs.<sup>17</sup> Fortunately, the findings in the fully adjusted model support the findings in the partially adjusted model, which is reassuring.

Our work suggests a potential role for cyclophosphamide in some of the lymphomas that arise in SLE. However, the number of patients with lymphoma receiving cyclophosphamide is small

(15; table 1). Regarding the route of administration, we were not provided with complete data for cyclophosphamide, but, in centres that did provide this information, the vast majority of cyclophosphamide exposures were intravenous. Exclusion of the few patients known to have received oral cyclophosphamide did not alter our results. Regarding cumulative cyclophosphamide, we used the cut-off of 6 g to reflect the fairly standard modern approach to cyclophosphamide use over the past decade at least, where clinicians tend to decrease exposure, wherever possible, to no more than 3–6 months of monthly intravenous pulses (which tend to be about 1000 mg per pulse).

Certainly the literature has consistently highlighted cyclophosphamide as a potential mediator of risk in rheumatic diseases, including RA and vasculitis,<sup>18</sup> for haematological, skin and bladder cancers. However, confounding by disease activity is a potential concern.<sup>19–21</sup> It is known that many adverse drug events are driven by genetic profiles related to drug metabolism,<sup>22</sup> such as cytochrome P450 genotypes. This could be the focus of future studies of cancer risk in SLE. Although it is beyond the scope of this paper, there is great clinical interest in what treatments patients with SLE receive for their lymphomas, and how this might have affected later outcomes. Our earlier study of survival in SLE after lymphoma suggested that the patients with SLE who developed non-Hodgkin lymphoma do not fare as well as most general population patients with non-Hodgkin lymphoma.<sup>23</sup> In those analyses, lymphoma cases in SLE were often aggressive and at a fairly advanced stage at presentation. If more aggressive tumour types or late stage of presentation are more common in SLE, this might lead to a lower than expected survival, regardless of treatment. Finally, although in our own experience, the cases of non-Hodgkin lymphoma that develop in patients with SLE who receive agents such as rituximab may initially do well, some of them will still eventually succumb to the lymphoma.<sup>24</sup>

In conclusion, we did not see evidence of disease activity as an independent risk factor for lymphoma in SLE. We found a suggestion of an increase after cyclophosphamide exposure, as well as after higher cumulative steroid use. The absolute number of lymphomas among subjects exposed to cyclophosphamide was relatively small, and the drug remains currently important for very severe SLE manifestations. However, this work supports an approach to SLE treatment that weighs both the pros (in terms of prevention of organ damage) and cons (in terms of long-term adverse events) for these exposures.

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