Cancer Risk Factors in SLE: Multivariate Regression Analysis in 16,409 Patients

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Abstract: *Background*: We assessed factors associated with cancer risk in systemic lupus erythematosus (SLE), relative to the general population, using a large international multi-centre clinical cohort (30 centres, 16,409 patients).

Methods: Cancers were ascertained by registry linkage. We used Poisson hierarchical regression to assess for potential independent effects of sex, race/ethnicity, age group, SLE duration, and calendar-year period on the standardized incidence ratios (SIR; ratio of cancers observed to expected). The hierarchical model allowed for differences in effects across countries. The primary regression analyses were done using the overall cancer SIRs; in secondary analyses we focused on hematological cancer SIRs.

Results: In adjusted analyses, we demonstrated lower SIR estimates for overall cancer risk, in black versus white SLE patients, in SLE patients of older versus younger age, and for patients with SLE duration of 5 years or more (versus lower duration). Female sex and calendar year were not clearly associated. Regarding hematological cancers specifically, SLE duration of 5 years or more again appeared to be associated with lower SIR estimates.

Conclusion: Cancer risk in SLE is increased relative to the general population; this is particularly true for patients of white race/ethnicity, younger age, and of shorter SLE duration.

Keywords: Cancer, systemic lupus erythematosus.

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INTRODUCTION

In systemic lupus erythematosus (SLE), there appears to be specific differences in the cancer susceptibility, compared to the general population. To date, the evidence indicates an overall increase in cancer in SLE of about 15% [1], with prominent increases in hematologic cancers, particularly non-Hodgkin lymphoma [2], as well as lung, thyroid cancer, and vulvar cancer [3, 4]. Our study aimed to examine the independent effects of demographics (age, sex, and race/ethnicity), SLE duration, and calendar year, on cancer risk a very large cohort of clinically confirmed SLE patients. These types of analyses have not previously been done with our multi-centre cohort data.

MATERIALS AND METHODS

Our sample was a multisite international SLE cohort (30 centres, 16,409 patients). The patients, who all have clinically confirmed SLE, are enrolled in clinical cohort registries and followed by specialists from the time of presentation onward. Cancers were ascertained by registry linkage. Standardized incidence ratio (SIR; ratio of cancers observed to deaths expected) estimates have previously been calculated for all cancers and by cancer types[4].

We used hierarchical regression to determine independent effects of the factors examined (sex, age group, SLE duration, calendar-year period) on the SIRs among the patients in the SLE cohort. The hierarchical model allowed for differences in effects from one country to the next. Poisson regression methods were used, with the logarithm of the expected number of deaths serving as the offset variable. The model included an extra variance term to handle slight over-dispersion in the data.

Our primary analyses focussed on over-all cancer experience, but in exploratory analyses we also looked specifically at hematological cancers.

RESULTS

As has been published previously [4], across 30 centres, 16,409 patients were observed for 121,283 (average 7.4) person years. In total, 644 cancers occurred, versus 566.3 expected (SIR 1.14, 95% confidence interval, CI 1.05 1.23).

Table **1** presents the results for over-all cancer experience in SLE versus the general population. With concurrent adjustment for race, sex and calendar year, an effect could be demonstrated for lower SIR estimates in black versus white SLE patients, in SLE patients of older age, compared to younger age, and for patients with SLE duration of 5 years or more (compared to those with lower duration). Female sex and calendar year were not clearly associated with any differences in the SIR estimates for SLE patients.

Table 1: Results of Adjusted Multivariate Regression to Determine Independent Effect of Variables on SIR* Estimates for Cancer Over-All

	Incidence ratio†	95%	CI
Female sex	1	0.77	1.3
Race/ethnicity			
White	Reference group		
Black	0.75	0.58	0.97
Asian	1.18	0.85	1.62
Age			
<40	Reference group		
40-59	0.72	0.55	0.94
60+	0.55	0.42	0.73
SLE duration			
< 5 years	Reference group		
>=5 years	0.74	0.61	0.89
Calendar Year Period			
<2000	Reference group		
>=2000	0.95	0.79	1.15

*SIR = standardized Incidence ratio; 95% CI =95% confidence interval. SLE= systemic lupus erythematosus.
†Variables adjusted concomitantly for all others (sex, race/ethnicity, age, SLE duration, calendar-year period).

Table **2** presents the results for hematological cancer experience in SLE versus the general population. With concurrent adjustment for race, sex and calendar year, an effect could only be demonstrated for lower SIR estimates in patients with SLE duration of 5 years or more (compared to those with lower duration). No other factors were clearly associated with any differences in the SIR estimates for hematological cancer risk in SLE.

DISCUSSION

Our previously published data from this very large multicenter international cohort highlighted a slight increase in cancer rates overall, in SLE patients compared with the general population. However, as we show in the current analyses, the relative increase in cancer incidence for SLE patients, versus their age and

Table 2: Results of Adjusted Multivariate Regression to Determine Independent Effect of Variables on SIR* Estimates for Hematological Cancer

	Incidence ratio†	95%	CI
Female sex	0.86	0.48	1.54
Race/ethnicity			
White	Reference group		
Black	0.57	0.28	1.15
Asian	1.74	0.84	3.58
Age			
<40	Reference group		
40-59	0.84	0.46	1.53
60+	0.56	0.3	1.04
SLE duration			
< 5 years	Reference group		
>=5 years	0.5	0.32	0.79
Calendar Year Period			
<2000	Reference group		
>=2000	1.33	0.84	2.09

*SIR = standardized Incidence ratio; 95% CI =95% confidence interval. SLE= systemic lupus erythematosus.
†Variables adjusted concomitantly for all others (sex, race/ethnicity, age, SLE duration, calendar-year period).

sex-matched general population counterparts, seems to be most heightened for SLE patients of younger, not older, age. These new analyses also demonstrate similar independent effects for race/ethnicity, where there were lower SIR estimates in black versus white SLE patients, and for SLE duration, where patients with SLE duration of 5 years or more had lower SIRs (compared to those with lower duration). We dichotomized SLE duration at 5 years in order to provide an easily interpretable estimate of the potential effects of this variable on cancer risk, with adequate precision. Female sex and calendar year were not clearly associated with any differences in the SIR estimates for SLE patients.

Our previously published analyses [4] had suggested, in univariate analyses, that when cancer SIR estimates were stratified by age, SLE patients in the youngest age group (<40 years) appeared to have a particularly high relative cancer risk (compared to sex and age-appropriate general population rates). In contrast, an increase in overall cancer risk, compared to the sex and age-matched general population, was not clearly apparent for SLE patients aged >60 years (although the increased risk of hematological malignancies remained).

Similarly, regarding trends over SLE duration, our previous univariate, stratified results suggested that an increased risk of cancer detection early in SLE, was followed by trends for somewhat lower SIRs. In those earlier univariate analyses, in later periods of SLE duration, the cancer risk estimate suggested little or no difference for patients of more than 5 years SLE duration, compared to the general population; however, the confidence intervals for some of the SLE duration-specific estimates overlapped. This finding (increased risk of cancer detection early in SLE, was followed by trends for somewhat lower SIRs later on) is not, we believe, due to over-screening for cancer in SLE patients; in fact, we only included invasive (thus clinically significant) cancers in all of our analyses. Moreover, we have previously demonstrated that women with SLE are actually less likely to undergo cancer screening, compared to the age-matched general population[5].

The effects seen with SLE duration (for both over-all cancers, and for hematological cancers) in this cohort of primarily adult-onset SLE cases demonstrated in our analyses may suggest a 'depletion of susceptibles' effect. That is, in a cohort observed over time for a first-time event, there is a specific portion of subjects who are most likely (for genetic or other reasons) to succumb to that event. This "susceptible' group is depleted over time, so that as the group is followed out long-term, the increased risk of that event (compared, for example, to general population rates) which was initially seen early, is not clearly demonstrated as time goes on. This is not an artifact per se, but rather a demonstration that in real life, the relative risks that we calculate in a study cohort often do vary greatly over the course of time. Although it remains possible that some of the lymphomas that arose early after SLE diagnoses represented cases of 'paraneoplastic' lupus-like manifestations, in our earlier work with this cohort, when excluded all observed cancers in patients with an SLE duration of one year or less, the excess risk was still evident, with an SIR estimate of 1.1 (95% CI 1.0–1.2) for all cancers and 2.5 (95% CI 1.9–3.3) for hematologic cancers [6].

The association of cancer risk with younger age may suggest the importance of genetic risk factors that trigger SLE onset and also alter cancer risk. In recent analyses of 1,020 patients from pediatric SLE cohorts, observed for a total of 7,986 (average 7.8) patient-years, 14 invasive cancers occurred, compared to 3 expected, for an SIR of 4.7, 95% CI 2.6, 7.8). Three hematologic cancers were found (two non-Hodgkin's

lymphoma, one leukemia) [7]. Interestingly, in the pediatric group there was a trend suggesting highest cancer occurrence 10-19 years after SLE diagnosis. This suggests that cancer experience in pediatric-onset SLE may be quite different from adult-onset SLE. (Though we did not exclude pediatric onset SLE cases from our combined cohort of over 16,000 patients, the vast majority of patients in the current study are adult-onset SLE).

In summary, cancer risk in SLE is increased relative to the general population; this is particularly true for patients of white race/ethnicity, younger age, and of shorter SLE duration. Of course, when considering absolute rates, given that general population cancer rates are always higher in older individuals, SLE patients of older age are still at risk for cancer, and all SLE patients, regardless of age, race/ethnicity or sex, should follow cancer screening practices as per the general population guidelines.

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DISCLOSURES

The authors have no conflicts of interest.

CONTRIBUTIONS

All authors contributed to the study design and/or data collection and/or analysis; all authors contributed to the manuscript preparation and approved the final version for submission.

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