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Short communication

Cancer risk in systemic lupus: An updated international multi-centre cohort study

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ABSTRACT

Objective: To update estimates of cancer risk in SLE relative to the general population.
Methods: A multisite international SLE cohort was linked with regional tumor registries. Standardized incidence ratios (SIRs) were calculated as the ratio of observed to expected cancers.
Results: Across 30 centres, 16,409 patients were observed for 121,283 (average 7.4) person–years. In total, 644 cancers occurred. Some cancers, notably hematologic malignancies, were substantially *increased* (SIR 3.02, 95% confidence interval, CI, 2.48, 3.63), particularly non-Hodgkin's lymphoma, NHL (SIR 4.39, 95% CI 3.46, 5.49) and leukemia. In addition, increased risks of cancer of the vulva (SIR 3.78, 95% CI 1.52, 7.78), lung (SIR 1.30, 95% CI 1.04, 1.60), thyroid (SIR 1.76, 95% CI 1.13, 2.61) and possibly liver (SIR 1.87, 95% CI 0.97, 3.27) were suggested. However, a *decreased* risk was estimated for breast (SIR 0.73, 95% CI 0.61–0.88), endometrial (SIR 0.44, 95% CI 0.23–0.77), and possibly ovarian cancers (0.64, 95% CI 0.34–1.10). The variability of comparative rates across different cancers meant that only a small increased risk was estimated across all cancers (SIR 1.14, 95% CI 1.05, 1.23).
Conclusion: These data estimate only a small increased risk in SLE (versus the general population) for cancer over-all. However, there is clearly an increased risk of NHL, and cancers of the vulva, lung, thyroid, and possibly liver. It remains unclear to what extent the association with NHL is mediated by innate versus exogenous factors. Similarly, the etiology of the decreased breast, endometrial, and possibly ovarian cancer risk is uncertain, though investigations are ongoing.

1. Introduction

Systemic lupus erythematosus (SLE) is one of the most common systemic autoimmune rheumatic diseases, often affecting young and middle-aged people. Females are particularly affected (female:male ratio of 9:1). Although survival in SLE has improved, morbidity related to the disease and its treatment remains considerable. One important consideration is cancer risk.

The immune system's role in cancer risk is a topic of increasing interest, and accordingly, the association between autoimmunity and cancer has been under study for over a decade [1]. Suggested pathways linking SLE and cancer include possible links with medication exposures, or even interactions between medications and viral exposures. Also potentially pertinent are clinical characteristics, such as co-existing Sjogren's syndrome or other overlap syndromes that may occur in SLE [2]. Some have hypothesized that an increased prevalence of traditional "lifestyle" cancer risk factors may influence malignancy incidence in SLE [3]. Additionally, inherent immune system abnormalities have been suggested as mediators of a potentially increased cancer risk in SLE [4].

To date, varying estimates of cancer risk in SLE have been generated, most with fairly wide confidence intervals (CIs). The standardized incidence ratio (SIR) estimates for over-all cancer in these studies ranged from 1.1 (95% CI 0.7–1.6) [5] to 2.6 (95% CI 1.5–4.4) [6]. These studies do not represent optimal estimates of cancer risk in SLE, due to small sample sizes and possibly non-representative sampling. In 2005 we published a large multi-centre study (23 centres, 9547 SLE patients) that clarified cancer risk in SLE, particularly with respect to a nearly 4 fold increase of non-Hodgkin lymphoma (NHL) [7]. Our current goal was to conduct in-depth, updated analyses of cancer risk in SLE, compared to the general population.

[1] Equal contributions as senior authors.
[2] Deceased.

2. Materials and methods

We assembled a multisite (30 centers) international cohort of patients diagnosed with SLE. These consisted of clinically confirmed SLE patients in follow-up, the vast majority of who fulfill American College of Rheumatology (ACR) criteria (one cohort, in Scotland, was assembled using administrative data). Patients were linked to regional tumor registries to determine cancer occurrence. Information was available on birth-date, sex, lupus diagnosis and cohort entry dates, and date of death, if applicable. The person–years of follow-up were calculated from the date of SLE cohort entry to the last date seen in clinic, end of the cancer registry information, or death (whichever occurred earliest). All new-onset observed cancers during the person–years of follow-up were included.

Standardized incidence ratios, SIRs, were calculated as the ratio of observed to expected cancers. Cancers expected were determined by multiplying person–years in the cohort by the geographically matched age, sex, and calendar year – specific cancer rates, and summing over-all person–years. We calculated 95% CIs, assuming that the observed number of malignancies followed a Poisson distribution. As well, we present analyses evaluating stratified rates of over-all cancers, and hematological cancers specifically, for groups characterized by demographics and SLE duration.

3. Results

In total 16,409 patients were studied (Table 1); 7700 of these originated from the United States, 3689 from Canada, 4250 from Europe and 770 from Asia (Korea). Ninety percent were female. The patients provided a total of 121,283 person–years of follow-up (mean 7.4 years) spanning the calendar period 1958–2009, although most of the person–years came from the 1970's onward.

Within the observation interval, 644 cancers occurred (Table 2). The data confirmed an increased risk of cancer among patients with SLE, particularly for specific cancer subtypes. For all cancers

Table 1
Participating centers: international cohort study of malignancy in SLE.

Center	n[a]	Cohort assembly	Inclusion
North America			
Baltimore, MD, USA	1691	Followed from first clinic visit¶	ACR criteria[b]
Pittsburgh, PA, USA	1587	University of Pittsburgh/regional rheumatology	ACR criteria[b]
Toronto, ON, Canada	1316	Followed from first clinic visit†	ACR criteria[b]
Downstate University–Brooklyn, NY, USA	1124	Followed from first clinic visit†	ACR criteria[b]
San Francisco, CA, USA	721	Lupus Outcomes Study cohort	ACR criteria[b]
Los Angeles, CA, USA	655	Followed from first clinic visit¶	ACR criteria[b]
Chicago, IL, USA	598	Followed from first clinic visit¶	ACR criteria
Calgary, AB, Canada	522	Enrolled from regional physician network†	ACR criteria[b]
Montreal General Hospital, QC, Canada	499	Followed from first clinic visit†	ACR criteria
Winnipeg, MB, Canada	402	Followed from first clinic visit[d]	ACR criteria[b]
Chapel Hill, NC, USA	357	Followed from first clinic visit¶	ACR criteria[b]
South Carolina, USA	351	Followed from first clinic visit	ACR criteria
Saskatoon, SK, Canada	306	Followed from first clinic visit	ACR criteria[b]
Birmingham, AL, USA	298	Inception cohort (consenting to linkage)†	ACR criteria
Albert Einstein University, NYC, USA	240	Followed from first clinic visit[d]	ACR criteria[b]
Halifax, NS, Canada	232	Followed from first clinic visit†	ACR criteria
Notre-Dame Hospital, Montreal, QC, Canada	121	Followed from first clinic visit¶	ACR criteria
Hôpital Maisonneuve-Rosemont Montreal, QC	120	Hospital discharge and clinic records[d]	ACR criteria[b]
London, Ontario, Canada	90	Followed from first clinic visit[d]	ACR criteria[b]
Vancouver, BC, Canada	81	Followed from first clinic visit[d]	ACR criteria[b]
New York University, NYC, USA	78	Followed from first clinic visit	ACR criteria
United kingdom			
Lanarkshire, Scotland	1937	Hospital discharge registry[d]	Discharge[c]
Birmingham, England	439	Followed from first clinic visit†	ACR criteria
London, England	273	Followed from first clinic visit†	ACR criteria[b]
Other centers			
Seoul, Korea	770	Followed from first clinic visit†	ACR criteria[b]
Copenhagen, Denmark	560	Followed from first clinic visit†	ACR criteria[b]
Barakoldo, Spain	298	Followed from first clinic visit†	ACR criteria[b]
Lund, Sweden	282	Inception cohort, enroll at SLE diagnosis	ACR criteria
Hannover, Germany	240	Followed from first clinic visit†	ACR criteria[b]
Reykjavik, Iceland	221	Unselected patients from national registry¶	ACR criteria
Total	16,409		

†Prospective assembly.
¶Retrospective and prospective assembly.
[a] Number of subjects at each center corresponds to those present during the time in which cancer registry data were available.
[b] At least 95% of cohort members met 4 components of the American College of Rheumatology (ACR) diagnostic criteria for SLE (18, 19); patients with a clinical diagnosis of SLE but meeting <4 ACR criteria were not excluded.
[c] Any hospital discharge diagnosis of SLE, primary, or non-primary. Cohort entry was date of first discharge with SLE diagnosis.
[d] Retrospective assembly.

Table 2
Cancers observed and expected, with standardized incidence ratios (SIRs) and 95% confidence intervals (95% CIs).

	Observed	Expected	SIR	95% CI	
All	644	566.3	1.14	1.05	1.23
Hematologic*	111	36.8	3.02	2.48	3.63
Non-Hodgkin lymphoma	76	17.3	4.39	3.46	5.49
Hodgkin's lymphoma	7	3.1	2.28	0.92	4.70
Multiple myeloma	10	5.3	1.88	0.90	3.46
Leukemia	18	10.3	1.75	1.04	2.76
Breast	114	155.2	0.73	0.61	0.88
Ovary	13	20.2	0.64	0.34	1.10
Cervix	21	16.6	1.27	0.78	1.93
Vagina	2	0.5	3.80	0.46	13.74
Vulva	7	1.9	3.78	1.52	7.78
Endometrial	12	27.2	0.44	0.23	0.77
Lung	85	65.5	1.30	1.04	1.60
Hepatic	12	6.4	1.87	0.97	3.27
Pancreas	10	11.2	0.90	0.43	1.65
Gastric	14	11.8	1.19	0.65	2.00
Colorectal	51	58.2	0.88	0.65	1.15
Thyroid	24	13.7	1.76	1.13	2.61
Bladder	18	14.4	1.25	0.74	1.97
Prostate	11	16.9	0.65	0.32	1.16
Melanoma	11	16.3	0.67	0.34	1.20

*Hematologic = all lymphomas, leukemias, and multiple myeloma.

combined, the SIR estimate was 1.14 (95% CI 1.05–1.23). For all hematologic malignancies, it was 3.02 (95% CI 2.48–3.63). Regarding specific types of hematological malignancies, increased risk was demonstrated for all lymphomas (SIR 4.07, 95% CI 3.24–5.04) as well as for non-Hodgkin lymphoma (NHL) specifically, and leukemia. We also demonstrated an increased risk of cancers of the vulva, lung, and thyroid, and a suggestion of possible increased risk for hepatic cancer. Meanwhile, a substantial decreased risk was seen for breast and endometrial cancer, and possibly ovarian cancer.

When 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 over-all cancer risk, compared to the sex and age-matched general population, was not apparent for SLE patients aged ≥60 years (although the increased risk of hematological malignancies remained). Regarding trends over SLE duration, our stratified results previously suggested that an increased risk of cancer detection early in SLE, was followed by trends for somewhat lower SIRs, although the confidence intervals for some of the SLE duration-specific estimates overlapped.

4. Discussion

Our study results more precisely define cancer risk in SLE versus the general population, highlighting a dichotomy. On one hand,

there is an increased risk of NHL, leukemia and cancers of the vulva, lung, thyroid, and possibly liver. Conversely, there is a decreased risk of breast, endometrial, and possibly ovarian cancer. Hence, the over-all cancer risk in SLE is only slightly increased, compared to the general population.

This is in fact quite similar to the profile seen in another autoimmune rheumatic disease, rheumatoid arthritis (RA). A meta-analysis has demonstrated that in RA, the SIR for over-all malignancy is 1.05 (95% CI 1.01, 1.09), with an increase in lymphoma risk (SIR 2.08, 95% CI 1.80, 2.39) and lung cancer (SIR 1.63, 95% CI 1.43, 1.87) but a decreased risk of breast cancer (SIR 0.84, 95% CI 0.79, 0.90) [8].

There are various possible explanations for a link between lymphoma and SLE. It is known that translocations involving the juxtaposition of an oncogene beside a gene important for immune cell function [9] may favor the emergence of a lymphoma. Since the chances of a translocation are proportional to the rate of lymphocyte proliferation, possibly upregulated lymphocyte proliferation (related to autoimmunity) might explain some of the excess lymphoma risk in autoimmune diseases like SLE. Certainly in a related condition, primary Sjogren's syndrome, authors have implicated chronic antigenic stimulation of lymphocytes [10]. However, immunosurveillance is also a normal part of cancer defense, so a very active immune system might also be able to delete abnormal (precancerous) cells more efficiently. Detailed case-cohort analyses are currently underway, assessing both drugs and cumulative disease activity as potential mediators of lymphoma risk in SLE.

It has been shown that the most common NHL subtype among cases that arise in SLE is diffuse large B cell (DLBC) lymphoma [11]. In our multi-centre international cohort data, DLBC was the most common NHL histological subtype [12,13]. This NHL subtype arises from activated lymphocytes, again suggesting that chronic inflammation might heighten lymphoma risk in autoimmune diseases like SLE [11].

A PRoliferating-Inducing Ligand (APRIL) is a cytokine highly expressed in DLBC lymphomas in the general population. High concentrations of APRIL have been implicated as possible risk factors related to RA and SLE disease onset. Intriguingly, one study of APRIL expression in the SLE DLBC lymphoma tissues reported a strong association in SLE, but not in the RA [4]. The authors noted that the high expression of APRIL in DLBC lymphomas in some patients might indicate APRIL mediates lymphoma development in these disease subsets. However, the conclusions are by no means definitive. We are currently conducting a similar histology review on the DLBC lymphoma cases in our sample, to determine if the findings confirm high expression of APRIL and/or a role for other agents, such as Epstein Barr virus.

With respect to lung cancer risk, we have previously demonstrated that most SLE patients who develop this are smokers [14], emphasizing yet another reason to counsel SLE patients in smoking cessation. Interestingly, only the minority of the SLE patients with lung cancer had been previously exposed to immunosuppressive drugs [15].

Regarding the higher risk of vulvar cancers in SLE, one important factor is the possibility of altered clearance of viruses, particularly human papillomavirus, HPV, which is linked to this malignancy, as well as to cervical cancer. In young patients prior to initiation of sexual activity, vaccination against HPV may be useful [16,17]. Altered viral clearance can also predispose to hepatic cancer, and our group has noted at least one case of a hepatitis-positive SLE patient developing a hepatic malignancy (unpublished communication).

The higher risk of thyroid cancer in SLE has been suggested by some authors but few concerted efforts have attempted to determine why this might be so. Associations between SLE and thyroid autoimmunity have been well-documented [18] and thyroid autoimmunity itself increases thyroid cancer risk [19]. One case–control study noted an increased risk of papillary thyroid cancer in SLE, particularly for patients with thyroid autoimmunity [20].

SLE patients appear to have considerable decreased risk for certain hormone-sensitive cancers, as has been shown in this paper as well as in a recent meta-analysis, where decreased risk was seen in SLE for breast cancer (SIR 0.74, 95% CI 0.61–0.89), endometrial cancer (SIR 0.44, 95% CI 0.23–0.77) and ovarian cancer (SIR 0.64, 95% CI 0.49–0.90) [21]. The fact that women with SLE have decreased risk of several hormone-sensitive cancers suggests the possibility of alterations in estrogen metabolism and/or other hormones. Interestingly, results stratifying our female subjects according to age ($<$50 years, mainly premenopausal, and $\geq$50 years, mainly postmenopausal) showed decreased breast cancer risk in SLE (relative to the general population) for both age groups (data not shown).

It remains a possibility that medications may influence cancer risk in SLE, such as aspirin and non-steroidal anti-inflammatory drugs [22–24] and corticosteroids [25], and anti-malarial drugs [26]. Oncologists have proposed that antimalarials have potential applications in cancer treatment [27] possibly through a cell death process called autophagy [28]. These drugs will be further evaluated in ongoing analyses by our group.

It is an interesting potential hypothesis that the lower risk for certain cancers in SLE may be related to specific genetic factors that place individuals at risk for SLE, but protect against breast cancer. Though this hypothesis remains to be fully tested, our initial work thus far has failed to explain breast cancer risk in SLE on the basis of genetic factors [29].

We must acknowledge potential limitations of ours study. It is possible that, in some of the cancer cases that occurred within the first year of SLE diagnosis, the SLE-like manifestations were in fact paraneoplastic phenomena. To explore this, in sensitivity analyses, we calculated the SIRs excluding cancers diagnosed in the first year of SLE. The over-all estimates changed little. Thus, it seems unlikely that the elevated over-all cancer risk in SLE reflects a paraneoplastic process alone. Additionally, the majority of the cancers occurred more than 1 year after SLE had been diagnosed.

The persistence of an elevated cancer risk beyond the first year of SLE diagnosis also rules against the possibility that the observed number of cancers was inflated, due to subclinical malignancies being picked up in SLE patients, who tend to have close medical follow-up.

There are additional reasons why we believe that this potential bias does not entirely explain our findings of increased cancer risk in SLE. First, breast cancer is one of cancer type where routine screening is available, yet breast cancer was not increased in SLE, in contrast to the striking increase in lymphoma (where no formal screening strategy exists). Furthermore, we have previously demonstrated that in women with SLE do not necessarily present in earlier stages of cancer, compared to the general population [30]. Moreover, evidence suggests that patients with SLE may undergo cancer screening much less frequently than recommended [31]. Last but not least, it has been shown that cancer mortality (not just incidence) is increased in SLE [32], which is convincing evidence of a true increased cancer risk in SLE.

We did not analyze risk according to race in the current analyses, since we did not have data on race for all subjects. This could be important because, in the general population, breast cancer is less common in blacks than whites. However, an earlier paper from our group suggested that the decreased risk of breast cancer was fairly homogenous across white and non-white SLE patients [33]. That earlier paper also suggested that lymphoma risk was fairly homogeneous across different race/ethnicity groups in SLE.

Table 3
Cancers observed and expected, with standardized incidence ratios (SIRs) and 95% confidence intervals (95% CIs), according to sex and age.

	Observed	Expected	SIR	95% CI	
Total cancers					
Sex					
Female	559	487.8	1.15	1.05	1.24
Male	85	78.4	1.08	0.87	1.24
Age (years)					
<40	80	51.2	1.56	1.24	1.94
40–59	294	243.1	1.21	1.08	1.36
60+	270	271.9	0.99	0.88	1.12
Hematological cancers					
Sex					
Female	90	30.9	2.91	2.34	3.58
Male	21	5.9	3.56	2.21	5.45
Age					
<40	21	4.9	4.29	2.65	6.55
40–59	48	13.7	3.51	2.59	4.65
60+	42	18.2	2.31	1.66	3.12

Although cancers in general are more common with increasing age, younger SLE patients have a particularly high relative cancer risk (compared to the general population). However, it must be kept in mind that the absolute rate, even in those aged <40 years, is about 1.56 cases per 1000 person–years for SLE, versus about 1 per 1000 per person–year in the general population. Patients need to be aware that their risk for other adverse events, such as cardiac disease, may actually be equally (or more) important. For example, the Mayo clinic calculator demonstrates that for a smoker aged <40 years, the risk of a heart attack or death from heart disease is 3 per 1000 person–years [34]. Smoking cessation, optimizing exercise and optimal weight control are lifestyle factors that most people, including SLE patients, can focus on to improve cancer risk (as well as risk for even more common adverse outcomes) [35].

Regarding trends over SLE duration, an increased risk of cancer detection was apparent initially, followed by trends for somewhat lower SIRs. This suggests perhaps that not all of the excess cancer risk in SLE is caused by drug exposures. Though there was a trend of highest SIRs earliest in the course of SLE, followed by a trend towards lower cancer risk later on, for hematological cancer, the elevated risk in SLE compared to the general population persists in both terms of increased age and SLE duration (Tables 3 and 4).

An additional limitation of the current analyses is that we were unable to assess clinical effects such as types of organ involvement or drug use across the cohort, since we did not have this information for all the cohort members. However, we are currently analyzing, in a case-cohort subset of patients, the effects of these variables on lymphoma risk in SLE.

Table 4
Cancers observed and expected, with standardized incidence ratios (SIRs) and 95% confidence intervals (95% CIs), according to duration of systemic lupus erythematosus (SLE).

SLE duration (years)	Observed	Expected	SIR	95% CI	
Total cancers					
<1	59	26.9	2.20	1.67	2.83
1–4	148	117.4	1.26	1.07	1.48
5–10	151	141.8	1.06	0.90	1.25
10–19	189	179.9	1.05	0.91	1.21
>20	97	97.8	0.99	0.80	1.21
Hematological cancers					
<1	10	1.7	5.82	2.79	10.70
1–4	32	7.5	4.24	2.90	5.99
5–10	21	9.2	2.27	1.41	3.48
10–19	36	11.7	3.09	2.16	4.28
>20	12	6.4	1.88	0.97	3.29

5. Conclusion

To summarize, our data support an association between SLE and cancer, highlighting the risk for NHL and leukemia, but also demonstrating an increased risk of vulvar, lung, thyroid, and possibly liver cancers. It remains unclear to what extent the association with NHL is mediated by innate versus exogenous factors. On the other hand, women with SLE appear to have a decreased risk of breast, endometrial, and possibly ovarian cancer. The etiology of this phenomenon is also uncertain, though investigations are ongoing.

Potential conflicts of interest

None.

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