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Cancer risk in a large inception SLE cohort: Effects of demographics, smoking, and medications.

Sasha Bernatsky, MD PhD[1], **Rosalind Ramsey-Goldman, MD DrPH**[2], **Murray B. Urowitz, MD**[3], **John G. Hanly, MD**[4], **Caroline Gordon, MD**[5], **Michelle A. Petri, MD MPH**[6], **Ellen M Ginzler, MD MPH**[7], **Daniel J Wallace, MD**[8], **Sang-Cheol Bae, MD PhD MPH**[9], **Juanita Romero-Diaz, MD MSc**[10], **Mary Anne Dooley, MD MPH**[11], **Christine A. Peschken, MD MSc**[12], **David A Isenberg, MD**[13], **Anisur Rahman, MB.ChB PhD**[13], **Susan Manzi, MD MPH**[14], **Soren Jacobsen, MD DMSc**[15], **S. Sam Lim, MD MPH**[16], **Ronald van Vollenhoven, MD**[17], **Ola Nived, MD PhD**[18], **Diane L Kamen, MD**[19], **Cynthia Aranow, MD**[20], **Guillermo Ruiz-Irastorza, MD**[21], **Jorge Sanchez-Guerrero, MD MSc**[3], **Dafna D. Gladman, MD**[3], **Paul R. Fortin, MD MPH**[22], **Graciela S Alarcón, MD MPH**[23], **Joan T. Merrill, MD**[24], **Kenneth C Kalunian, MD**[25], **Manuel Ramos-Casals, MD PhD**[26], **Kristjan Steinsson, MD**[27], **Asad Zoma, MD**[28], **Anca Askanase, MD MPH**[29], **Munther A. Khamashta, MD PhD**[30], **Ian Bruce, MD**[31], **Murat Inanc, MD**[32], **Ann E Clarke, MD MSc**[33]

[1]Divisions of Rheumatology and Clinical Epidemiology, Department of Medicine, McGill, University, Montreal, Quebec, Canada

[2]Northwestern University and Feinberg School of Medicine, Chicago, IL, USA

[3]Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital and University of Toronto, ON, Canada

[4]Division of Rheumatology, Department of Medicine and Department of Pathology, Queen Elizabeth II Health Sciences Centre and Dalhousie University, Halifax, Nova Scotia, Canada

[5]Rheumatology Research Group, Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

[6]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[7]Department of Medicine, SUNY Downstate Medical Centre, Brooklyn, NY, USA

[8]Cedars-Sinai/David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

[9]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Korea

[10]Instituto Nacional de Ciencias Médicas y Nutrición, Mexico City, Mexico

[11]Thurston Arthritis Research Centre, University of North Carolina, Chapel Hill, NC, USA

Address Correspondence and Reprints to: Dr. Sasha Bernatsky, Division of Clinical Epidemiology, 5252 boul. de Maisonneuve Ouest, (3F.51), Montreal, QC H4A 3S5, Canada. Telephone: 514 934-1934 ext. 44710; Sasha.bernatsky@mcgill.ca.

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[12]University of Manitoba, Winnipeg, Manitoba, Canada

[13]Centre for Rheumatology, Department of Medicine, University College London, UK

[14]Lupus Centre of Excellence, Allegheny Health Network, Pittsburgh, PA, USA

[15]Copenhagen Lupus and Vasculitis Clinic, 4242, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

[16]Emory University, Department of Medicine, Division of Rheumatology, Atlanta, Georgia, USA

[17]Department of Rheumatology and Clinical Immunology, Amsterdam University Medical Centres, Amsterdam, Holland.

[18]Department of Clinical Sciences Lund, Rheumatology, Lund University, Lund, Sweden.

[19]Medical University of South Carolina, Charleston, South Carolina, USA

[20]Feinstein Institute for Medical Research, Manhasset, NY, USA

[21]Autoimmune Diseases Research Unit, Department of Internal Medicine, BioCruces Health Research Institute, Hospital Universitario Cruces, University of the Basque Country, Barakaldo, Spain

[22]Division of Rheumatology, Department of Medicine, CHU de Québec, Université Laval, Quebec City, Canada

[23]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA

[24]Department of Clinical Pharmacology, Oklahoma Medical Research Foundation, Oklahoma City, OK, USA

[25]UCSD School of Medicine, La Jolla, CA, USA;

[26]Josep Font Autoimmune Diseases Laboratory, IDIBAPS, Department of Autoimmune Diseases, Hospital Clínic, Barcelona, Spain

[27]Department of Rheumatology, Center for Rheumatology Research Fossvogur Landspitali University Hospital, Reykjavik, Iceland

[28]Lanarkshire Center for Rheumatology, Hairmyres Hospital, East Kilbride, Scotland, UK

[29]Department of Rheumatology, Columbia University College of Physicians and Surgeons, New York, New York, USA.

[30]Lupus Research Unit, The Rayne Institute, St. Thomas' Hospital, King's College London School of Medicine, London, UK

[31]Arthritis Research UK Epidemiology Unit, Faculty of Biology Medicine and Health, Manchester Academic Health Sciences Centre, The University of Manchester, and NIHR Manchester Musculoskeletal Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre Manchester, UK

[32]Division of Rheumatology, Department of Internal Medicine, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey

[33]Division of Rheumatology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

Abstract

Objective: To assess cancer risk factors in incident SLE.

Methods: Clinical variables and cancer outcomes were assessed annually among incident SLE patients. Multivariate hazard regression models (over-all risk, and most common cancers) included demographics and time-dependent medications (corticosteroids, antimalarial drugs, immunosuppressants), smoking, and adjusted mean SLE Disease Activity Index-2K.

Results: Among 1668 patients (average 9 years follow-up), 65 cancers occurred: 15 breast, 10 non-melanoma skin, seven lung, six hematological, six prostate, five melanoma, three cervical, three renal, two each gastric, head and neck, and thyroid, and one each rectal, sarcoma, thymoma, and uterine cancers. Half of cancers (including all lung cancers) occurred in past/current smokers, versus one-third of patients without cancer.

Multivariate analyses indicated over-all cancer risk was related primarily to male sex and older age at SLE diagnosis. In addition, smoking was associated with lung cancer. For breast cancer risk, age was positively and anti-malarial drugs were negatively associated. Anti-malarial drugs and higher disease activity were also negatively associated with non-melanoma skin cancer (NMSC) risk, whereas age and cyclophosphamide were positively associated. Disease activity was associated positively with hematologic and negatively with NMSC risk.

Conclusions: Smoking is a key modifiable risk factor, especially for lung cancer, in SLE. Immunosuppressive medications were not clearly associated with higher risk except for cyclophosphamide and NMSC. Antimalarials were negatively associated with breast cancer and NMSC risk. SLE activity was associated positively with hematologic cancer and negatively with NMSC. Since the absolute number of cancers was small, additional follow-up will help consolidate these findings.

Keywords

Systemic lupus erythematosus; SLE; cancer; malignancy

Introduction:

There has been increasing interest in cancer risk and systemic autoimmune rheumatic diseases including systemic lupus erythematosus (SLE).[1] On one hand, inflammation may promote cancer occurrence[2], while on the other, some of the medications used in SLE and other autoimmune diseases could be associated with cancer risk (e.g. cyclophosphamide, which is an alkylating agent[3]). Previous studies of cancer risk in SLE were often limited by sample size or reliance on administrative data sources instead of clinical data[4]. No studies to date have focused on incident SLE patients. This may have lead to incomplete data on immunosuppressive drug exposures and other clinical variables.

To overcome these limitations, we studied cancer occurrence in a very large multi-centre cohort of clinically confirmed incident SLE patients[5], at centres in North America, Europe,

and Asia, with specific attention to clinical features, medications, and the onset of co-morbidity including cancer.

Methods:

Patients meeting American College of Rheumatology (ACR) classification criteria for new-onset SLE (within 15 months of diagnosis) were enrolled into the Systemic Lupus International Collaborating Clinics (SLICC) Inception Cohort, across 33 centres (from 1999 to 2011). From the first visit (time zero), patients were followed at yearly intervals according to a standardized protocol, with information on disease activity, medications, and new cancer diagnoses (recorded by the study physician and confirmed by reviewing medical files including pathology reports, where available).

Multivariate proportional hazard regression was performed, using baseline demographics (age at SLE diagnosis, sex, race/ethnicity) and time-dependent variables for drugs (corticosteroids, antimalarial drugs, immunosuppressive drugs), smoking, and SLE Disease Activity Index-2000 (SLEDAI-2K) scores (recorded yearly then averaged over time using the 'adjusted mean SLEDAI' approach, where the result has the same units as the original SLEDAI-2K[6]). The values for adjusted mean SLEDAI-2K scores over time were divided into quartiles for the risk set related to each event that occurred within the cohort (between first visit to end of the study; thus the time axis was time since cohort entry). Our primary time-dependent variable for disease activity was then categorized as ever having scored in the highest quartile of SLE activity, up to the time of each risk set (cancer event). Sensitivity analyses also assessed cancer risk according to whether or not subjects had been in a persistently low disease state (lowest quartile of disease activity as defined above), for each risk set.

We performed univariate and multivariate models; the primary multivariate models adjusted for baseline demographics (age at SLE diagnosis, sex, race/ethnicity), a time-dependent variable for ever smoking, a time-dependent variable indicating if the patient had ever had a mean adjusted SLEDAI-2K value in the highest disease activity quartile, and time-varying SLE medication exposures (ever-never use of corticosteroids, antimalarial drugs, immunosuppressive agents). The variable for race/ethnicity was dichotomous (white versus all other categories). Given the relatively low number of outcome events, we also ran more parsimonious multivariable models for each exposure of interest, adjusting only for demographics (age, sex, race/ethnicity) but these results are not shown as they were not significantly changed from the full model results.

As well as evaluating potential risk factors for over-all cancer risk, we also considered the most common cancer types, individually. In some of those analyses, we had zero events in certain ever-never exposure categories, which required altering the exposure definition to allow evaluation of the covariate. For example, if all cases of a certain cancer type had ever been antimalarial-exposed, we instead used antimalarial use as cumulative exposure for 5 years or more in our model. For some malignancy types, there were no exposures to certain drugs (e.g. biologics) so in such a case, that covariate could not be included in that specific regression model.

Analyses were performed using *R* software, with verification of underlying proportional hazards assumptions using Schoenfeld residuals. This study was approved by local ethics boards, and patients provided signed informed consent to participate in the cohort study.

Results:

Of 1,848 newly diagnosed SLE patients enrolled, 1,668 had at least one follow-up visit and formed the cohort analyzed in this study. These patients were followed until death, last visit, or end of study interval for this analysis (March 2019). Table 1 shows the baseline characteristics of the individuals, divided into those that ultimately had a cancer or remained cancer free.

Over a follow-up of 15,014 (mean and median 9) person-years, 65 cancers occurred (4.3 events per 1,000 patient-years). These included 15 breast cancers, 10 non-melanoma skin, seven lung, six hematological, six prostate, five melanoma, three cervical, three renal, two gastric, two head and neck, two thyroid, and one each rectal, sarcoma, thymoma, and uterine cancer. No patient had more than one type of cancer. The hematologic cancers included three non-Hodgkin's lymphoma, one acute myeloid leukemia, one chronic myeloid leukemia, and one myeloma.

Almost half of cancer cases (including all of the lung cancers) occurred in past/current smokers, while only one-third of patients without cancers smoked prior to the onset of the event. As suggested in Table 1 and further verified by the univariate hazard ratios in Table 2, older age at SLE diagnosis, male sex, white race/ethnicity, and smoking were associated with greater cancer risk over-all. However, the multivariate regressions indicated that among SLE patients, over-all cancer risk was related primarily to older age at SLE diagnosis and male sex. There was no evidence of violation of the proportional hazards assumption in any of our models.

In the multivariate analyses specifically for breast cancer (Table 2), older age at SLE diagnosis remained a risk factor, while antimalarial use was associated with a lower risk of breast cancer. This effect of antimalarial drugs was also seen for non-melanoma skin cancer (Table 2), where both age at SLE diagnosis and cyclophosphamide use were also strongly associated with risk. Interestingly, patients who scored at least once in the highest quartile of SLE disease activity were at lower risk for non-melanoma skin cancer.

As mentioned, all lung cancer patients were smokers, so we could not calculate effects for ever/never smoking, but we were able to calculate a hazard ratio of about seven for heavier smoking and lung cancer (15 cigarettes a day or more). Lung cancer was also more common in SLE patients of male sex and older age at SLE diagnosis (Table 3). Interestingly, none of the lung cancer cases had been exposed to cyclophosphamide or methotrexate, and all had been exposed to antimalarial agents for at least 5 years; this precluded us being able to calculate specific estimates of risk for lung cancer for these agents.

Multivariate analyses of hematologic cancers produced relatively imprecise estimates of the effects of all exposures of interest (Table 3), aside from the effect of older age at SLE onset, which remained a risk factor across all analyses. All patients with hematologic malignancies

were white and smokers, and none had received cyclophosphamide, precluding study of these variables as hematologic cancer risk factors in SLE. There was no clear link with any other drug and hematologic cancer. The unadjusted hematologic cancer HR for ever having smoked 20 cigarettes per day or more (prior to index date of cancer) was 5.96 (95% CI 1.09, 32.5), but in the models in Table 3 where smoking was dichotomized at 15 cigarettes per day, as it was in lung cancer, the 95% CIs for smoking and hematologic cancer included the null value. There was a positive association between hematologic cancer and SLE activity (ever scoring in the highest quartile of adjusted mean SLEDAI-2K scores over time –univariate and adjusted analyses, Table 3) but no other clear associations between hematologic cancer risk and clinical factors were found.

Discussion:

We present novel data from a large, multicentre inception SLE cohort, suggesting how different cancer types in SLE may be associated with specific risk factors, including smoking, drug exposures, and disease activity.

The first message that these data highlight is that cancers, especially lung cancer, are more likely to occur in patients who report past/current smoking. Our previous work with prevalent SLE patients also found that the most important risk factors associated with lung cancer risk were older age, male sex, and positive smoking history[7]. In the current analyses, all of our lung cancer cases were ever smokers, thus precluding any estimate of the effect of this binary variable. However, we were able to illustrate that smoking 15 or more cigarettes a day was associated with about a seven-fold increased risk of lung cancer in SLE. This effect estimate is similar to a recent meta-analysis of the effects of smoking on lung cancer in the general population, in both men and women. [8]

Previous assessment of cancer risk in SLE had also highlighted white race/ethnicity as a risk factor[9], which may reflect a decreased risk of certain cancer types (particularly, breast) in women of non-white race/ethnicity.[10] Among 824 white patients, 44 cancers occurred (5.3%, 95% CI 4.0–7.1); this proportion was numerically higher than the percentage in blacks or Asians, but the confidence intervals overlapped (six cancers in 276 black patients, 2.2%, 95% CI 1.0, 4.7, versus 6 cancers in 255 Asian patients, 2.4%, 95%CI 1.1, 5.0). The trend for higher over-all cancer risk in white SLE patients did not quite reach statistical significance in our adjusted models. All of the lung and hematologic cancer cases in our analyses occurred in white patients, making it impossible to determine the effects of race/ethnicity in those specific analyses. Our analyses in prevalent SLE also suggested that white SLE subjects appeared to have a higher overall cancer risk than those of other race/ethnicity, though the heightened risk of lymphoma in SLE seemed fairly consistent across race/ethnicity.[11]

Male sex and older age of SLE onset were risk factors for cancer risk across most cancer types. This may be, at least in part, because these demographic groups are at greater cancer risk in the general population. However, further study of cancer risk in these potentially vulnerable SLE populations would be of interest, to determine if longer windows of observation result in the same findings and/or identify any additional risk factors.

A comparison of cancer rates in SLE to the general population was not the purpose of our study, but our 2013 publication showed that the standardized incidence ratio for cancer in male lupus patients (that is, cancer risk compared to the age-matched male general population) was 1.08 (95 % CI 0.87, 1.24); the point estimate is consistent with a relatively small increased cancer risk in male SLE versus the male general population, but the 95% CI includes the null value. Since SLE patients are predominantly female, we were able to, in that study, show that the SIR in female lupus patients (cancer risk relative to general population females) was 1.15 (95% CI 1.05, 1.24)[12].

Longer follow-up would also allow more precise estimation of the effect of multiple sequential or combined immunosuppressive drug exposures and new drug exposures, including biologic therapies (for example belimumab, which was only approved for use in Europe, Canada and the United States in 2011).

In our study, the only cancer type for which cyclophosphamide appeared to be a risk factor was non-melanoma skin cancer. It is well known that non-melanoma skin cancers may be triggered by immunosuppressive drugs, for example in organ transplant populations.[13] Cyclophosphamide specifically has been implicated as a risk factor for non-melanoma skin cancer in vasculitis patients.[14] The adverse effects of cyclophosphamide suggest that additional efforts are needed to understand how best to use this drug (e.g. with lower doses and shorter courses) and to develop alternative drugs for serious SLE manifestations. On the other hand, only 3 of 164 (1.8%) of patients exposed to cyclophosphamide developed cancer over the current interval, which is a relatively small number. Interestingly, we did not observe any bladder cancers in our cohort, given concerns of cyclophosphamide-induced bladder cancer in vasculitis patients;[15] however, bladder is a rare malignancy type, thus completely ruling out associations with cyclophosphamide and rarer cancer types in SLE may require much longer follow-up. Putative associations between oncogenic viruses and non-melanoma skin cancer[16] might be augmented in patients treated with immunosuppressants including cyclophosphamide; some suggest this as a mechanism for the higher risk in SLE of other cancers (e.g. hepatobiliary, vulvovaginal).[17]

In SLE there is potential for further complex interactions between drugs and clinical variables like photosensitivity, which in the general population may put persons at risk for non-melanoma skin cancer. [18] For example, though SLE patients may be more sensitive than the general population to sun exposure (and hence theoretically to skin cancer), use of sunscreen by SLE patients might limit their ultraviolet ray exposure. In addition, chronic skin inflammation is itself a nidus for the development of non-melanoma skin cancer[19]; the apparently lower risk for non-melanoma skin cancer in SLE patients receiving antimalarial agents might be related to its effects on controlling many forms of cutaneous lupus manifestations. The negative association between higher SLE activity and non-melanoma skin cancer could hypothetically be because severe disease causes patients to be more compliant with antimalarials and/or photoprotection. Alternatively some have suggested that the immune system's activity in deleting abnormal cells may be protective against cancer in SLE[20]. These hypotheses remain to be tested.

Negative associations between antimalarial use and cancer (as was seen in our study, concerning breast and non-melanoma skin) were suggested in an earlier study of SLE patients[21], though this has not necessarily been found in other conditions (such as rheumatoid arthritis where antimalarial use is less common than in SLE).[22] There is a significant literature on the effects of antimalarial drugs on cancer in non-rheumatic disease, including one study which showed that chloroquine inhibited proliferation and autophagy in estrogen-receptor positive breast cancer cells (from non-SLE patients)[23,24]. Since all of the lung cancer cases in our study had been exposed to antimalarial agents, we were unable to calculate specific estimates of lung cancer risk, but a recent study suggested that hydroxychloroquine may suppress lung cancer cell growth (and make them more sensitive to chemotherapy)[25]. Hydroxychloroquine has even been employed as an adjunct in phase 1 studies of lung cancer therapy[26], although its usefulness remains unclear.

No observational study can ever prove causality. In fact, no single study is likely, on its own, to prove causality. However, randomized controlled trials are often considered the best way to examine cause-effect relationships between an intervention and outcome. If in the future, if we are able to perform long-term pragmatic trials assigning SLE patients to different regimens (e.g. low dose or short-term HQN use as opposed to long-term use) that might be the best way to provide evidence of a presumptive causal relationship. Given how useful HQN is to SLE patients, that kind of study would be difficult to conduct.For many years, hematologic cancer risk in SLE has been of particular interest, given previous hypotheses that both disease activity and drugs could potentially contribute to risk of these events. In two prior very large, multi-centre studies of prevalent SLE patients, we found signals for an increased risk of hematological cancers related to SLICC/ACR Damage Index scores [27], (which have been shown to correlate with cumulative lupus disease activity[28]), and also with cyclophosphamide[29]. Although no drug was clearly associated with hematologic cancers in our current multivariate analyses, the relatively few events produced rather imprecise estimates of cancer risk related to most of the drug exposures of interest. Although none of the hematologic cancers occurred in cyclophosphamide-exposed patients, we did see an association between high disease activity and hematologic cancer risk in the fully adjusted analyses. Not unexpectedly (given that risk of most hematologic cancers is higher in older individuals), older age at SLE onset was also a predictor of hematologic malignancies in our sample. Additional follow-up of our inception cohort would be essential to further delineate effects of medications and disease activity for hematologic cancers over-all, and potentially for specific types, such as non-Hodgkin's lymphoma, the most common hematologic cancer in SLE.

In our analyses, we did not calculate standard incidence ratios of cancer risk in SLE compared to the general population, since general population cancer rates are generated from cancer registry data, and our means of cancer incidence ascertainment was by physicians recording events at annual visits, confirmed by review of charts including pathology reports where available. In some jurisdictions, certain cancers (e.g. non-melanoma skin, cervix) are often incompletely recorded by cancer registries. It is possible that our ascertainment methods were more likely to pick up such cancers than cancer registry data. This should not raise a problem for the analyses of cancer risk factors in SLE (the focus of the current paper). However, attempts to compare physician-reported cancer events (in SLE)

to cancer registry data (i.e. general population cancer rates) would potentially be problematic due to differential misclassification error (of the outcome). In previous analyses of SLE cohorts (including a mix of prevalent and incident patients), there have been consistent, clear increased risks of hematologic cancer and lung cancer. Considering the age and sex distribution of our patients, and their countries of origin, the number of hematologic cancer cases observed in the current cohort are each about 3-fold higher than might be expected, which is compatible with our own earlier estimates.

In summary, in this large inception SLE cohort, we were able to see potential associations between cancer and smoking, demographic, and clinical factors. As expected, older age was associated with cancer overall, as well as with the most common cancer subtypes. As in the general population, females with SLE have fewer events than males (for cancer risk overall, as well as lung cancer specifically). Smoking is a key modifiable risk factor for lung cancer in SLE. For breast and non-melanoma skin cancer, antimalarial drugs were associated with lower risk. No other drug effects were clearly seen, but confidence intervals around many estimates were relatively imprecise. SLE activity was associated with increased hematologic cancer risk and decreased non-melanoma skin cancer risk. Further study of cancer risk in this inception cohort would be of interest, to determine if longer windows of observation result in different findings, particularly in relation to drug exposures and disease activity.

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Significance and Innovation:

- Age at SLE diagnosis was associated with higher breast cancer, while anti-malarial drugs were associated with lower risk.
- Anti-malarial drugs were also associated lower non-melanoma skin cancer (NMSC) risk, whereas age and cyclophosphamide were positively associated with NMSC risk.
- Disease activity was associated positively with hematologic and negatively with NMSC risk.
- These findings not only help us better understand cancer risk in SLE, but also suggest potential approaches to improve the cancer risk profile in SLE, and provides future directions for research.

Table 1:

Descriptive analyses for the baseline characteristics of SLE patients, specifically for those who ultimately developed a cancer versus those that remained cancer free

Categories	Baseline characteristics	
	No Cancer (N=1603)	Cancer (N=65)
Female sex, N (%)	1432 (89.3)	48 (73.8)
White race/ethnicity, N (%)	780 (48.7)	44 (67.7)
Mean age at SLE diagnosis (SD*)	34.2 (13.1)	45.6 (14.5)
Mean SLE duration, months (SD*)	5.60 (4.20)	5.50 (3.7)
Top quartile SLEDAI-2K, N (%)	539 (33.6)	16 (24.6)
Current or past smoker, N (%)	534 (33.3)	31 (47.7)
Steroids, N (%)	1201 (74.9)	45 (69.2)
Cyclophosphamide, N (%)	139 (8.7)	3 (4.6)
Azathioprine, N (%)	457 (28.5)	16 (24.6)
Methotrexate, N (%)	187 (11.7)	9 (13.8)
Mycophenolate, N (%)	244 (15.2)	7 (10.8)
Antimalarial, N (%)	1263 (78.8)	50 (76.9)
Biologic, N (%)	39 (2.4)	0 (0.0)

*SD=standard deviation

Table 2.

Hazard ratio, HR estimates and 95% confidence intervals, CIs, for overall cancer risk in SLE

All type of cancers (65 events)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]
Age at SLE diagnosis (years)	**1.06 (1.04, 1.07)**	**1.05 (1.03, 1.06)**
Female Sex	**0.35 (0.20, 0.60)**	**0.47 (0.26, 0.85)**
White race/ethnicity	**2.24 (1.33, 3.78)**	1.34 (0.76, 2.37)
Top quartile SLE activity ever	0.59 (0.35, 1.02)	0.84 (0.47, 1.52)
Smoking ever	**1.72 (1.06, 2.80)**	1.21 (0.73, 2.01)
Steroids ever	0.61 (0.35, 1.07)	0.78 (0.42, 1.47)
Cyclophosphamide ever	0.72 (0.33, 1.58)	1.10 (0.46, 2.61)
Azathioprine ever	0.68 (0.40, 1.15)	0.92 (0.52, 1.65)
Methotrexate ever	1.39 (0.78, 2.49)	1.63 (0.89, 2.99)
Mycophenolate ever	0.81 (0.45, 1.45)	1.18 (0.62, 2.26)
Antimalarial use ever	0.64 (0.34, 1.20)	0.64 (0.33, 1.24)
Biologic ever	0.62 (0.23, 1.73)	0.70 (0.24, 2.05)

[a]Adjusted for all variables shown; disease activity, smoking, and all drug variables were time dependent.

Table 3:

Hazard ratios, HRs for breast, non-melanoma skin, lung and hematologic cancers

Breast cancer (15 events)	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI)** [a]
Age at SLE diagnosis (years)	**1.06 (1.03, 1.10)**	**1.06 (1.02, 1.10)**
White race/ethnicity	0.93 (0.34, 2.56)	0.49 (0.16, 1.55)
Top quartile SLE activity ever	0.53 (0.17, 1.66)	0.73 (0.20, 2.70)
Smoking ever	0.98 (0.34, 2.87)	0.88 (0.29, 2.65)
Steroids ever	0.45 (0.15, 1.31)	0.48 (0.13, 1.75)
Cyclophosphamide ever	1.08 (0.24, 4.78)	2.51 (0.42, 14.9)
Azathioprine ever	0.39 (0.11, 1.38)	0.49 (0.12, 1.97)
Methotrexate ever	2.13 (0.73, 6.23)	2.78 (0.90, 8.59)
Mycophenolate ever	0.64 (0.18, 2.28)	0.85 (0.19, 3.78)
Antimalarial ever	0.33 (0.10, 1.06)	0.28 (0.09, 0.90)
Non-melanoma skin (10 events)	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI)** [a]
Age at SLE diagnosis (years)	**1.08 (1.04, 1.13)**	**1.06 (1.02, 1.11)**
Female Sex	0.29 (0.07, 1.12)	0.65 (0.14, 3.02)
White race/ethnicity	**9.55 (1.21, 75.6)**	5.79 (0.64, 52.1)
Top quartile SLE activity ever	0.15 (0.02, 1.22)	0.10 (0.01, 0.92)
Smoking ever	2.68 (0.75, 9.49)	1.72 (0.44, 6.67)
Steroids ever	0.90 (0.19, 4.27)	0.66 (0.11, 4.15)
Cyclophosphamide ever	**4.01 (1.13, 14.3)**	**15.3 (3.03, 77.5)**
Azathioprine ever	0.68 (0.18, 2.64)	0.80 (0.16, 3.86)
Methotrexate ever	2.05 (0.53, 7.98)	3.58 (0.78, 16.4)
Mycophenolate ever	2.04 (0.55, 7.56)	2.63 (0.58, 12.0)
Antimalarial ever	0.22 (0.06, 0.84)	0.23 (0.05, 0.95)
Biologic ever	1.24 (0.15, 10.2)	1.06 (0.10, 11.1)
Lung cancer (7 events)	**Unadjusted HR (95%CI)**	**Adjusted HR (95% CI)** [a]
Female sex	**0.09 (0.02, 0.42)**	**0.18 (0.04, 0.86)**
Top quartile activity ever	0.24 (0.03, 1.98)	0.31 (0.02, 4.06)
Cigarettes 15+/day	**11.7 (2.61, 52.2)**	**6.64 (1.43, 30.9)**
Steroids ever	0.50 (0.10, 2.61)	0.66 (0.10, 4.52)
Azathioprine ever	1.08 (0.24, 4.82)	2.16 (0.36, 13.0)
Mycophenolate ever	0.39 (0.05, 3.31)	0.46 (0.04, 5.84)
Biologic ever	1.32 (0.16, 11.2)	2.89 (0.20, 42.3)
Hematologic cancer (6 events)	**Unadjusted HR (95%CI)**	**Adjusted HR (95% CI)** [a]
Age at SLE Diagnosis	**1.06 (1.01 , 1.11)**	**1.06 (1.00 , 1.13)**
Female Sex	0.59 (0.07 , 5.01)	0.84 (0.09 , 7.70)
Top quartile SLE activity ever	2.97 (0.54 , 16.2)	**7.14 (1.13 , 45.3)**
Cigarettes 15+/day	4.39 (0.80 , 24.0)	2.83 (0.49 , 16.4)

Steroids ever	0.44 (0.08 , 2.41)	0.52 (0.08 , 3.42)
Azathioprine ever	0.30 (0.04 , 2.60)	0.29 (0.03 , 2.81)
Methotrexate ever	0.91 (0.11 , 7.77)	0.67 (0.07 , 6.34)
Mycophenolate ever	0.54 (0.06 , 4.67)	0.50 (0.05 , 5.18)
Biologic ever	1.32 (0.16, 11.2)	2.89 (0.20, 42.3)

[a]CI=confidence intervals. Adjusted for all variables shown; disease activity, smoking, and all drug variables were time dependent. . All hematologic and lung cancer cases were smokers, all were white, and none were exposed to cyclophosphamide, so race/ethnicity and cyclophosphamide were not evaluated in those models. All lung cancers had been exposed to antimalarials.