



Published in final edited form as:

J Rheumatol. 2018 March ; 45(3): 393–396. doi:10.3899/jrheum.170652.

Smoking is the most significant modifiable lung cancer risk factor in SLE

Sasha Bernatsky¹, Rosalind Ramsey-Goldman², Michelle Petri³, Murray B Urowitz⁴, Dafna D Gladman⁴, Paul R. Fortin⁵, Edward Yelin⁶, Ellen Ginzler⁷, John G Hanly⁸, Christine Peschken⁹, Caroline Gordon¹⁰, Ola Nived¹¹, Cynthia Aranow¹², Sang-Cheol Bae¹³, David Isenberg¹⁴, Anisur Rahman¹⁴, James E Hansen¹⁵, Yvan St. Pierre¹, and Ann E Clarke¹⁶

¹The Research Institute of the McGill University Health Centre, 687 Pine Avenue, V Building, Montreal, Quebec H3A 1A1, Canada

²Northwestern University Feinberg School of Medicine, McGaw Pavilion, 240 E. Huron Street, Suite M-300, Chicago, IL 60611, USA

³Johns Hopkins University School of Medicine, 1830 E. Monument Street, Suite 7500, Baltimore, MD 21205, USA

⁴Toronto Western Hospital, 399 Bathurst Street, IE-410B, Toronto, Ontario M5T 2S8, Canada

⁵Université de Laval, Service de rhumatologie, 2705, boulevard Laurier, Local S-763, Quebec, Quebec G1V 4G2, Canada

⁶University of California, Department of Medicine, Suite 270, Laurel Heights Campus, San Francisco, California, 9413-0920 USA

⁷State University of New York–Downstate Medical Center, 450 Clarkson Avenue, Box 42, Brooklyn, NY 11203, USA

⁸Dalhousie University and Capital Health, Second Floor, 1341 Summer Street, Halifax, Nova Scotia, Canada B3H 4K4

⁹University of Manitoba, RR149 800 Sherbrook Street, Winnipeg, MB R3A 1M4 Canada

¹⁰University of Birmingham, College of Medical and Dental Sciences, Edgbaston, University of Birmingham, B15 2TT, UK

¹¹Lund University Hospital, S-22185 Lund, Sweden

¹²The Feinstein Institute for Medical Research, 350 Community Drive, Manhasset, NY 11030 USA

¹³The Hospital for Rheumatic Diseases, Hanyang University, Seoul, Korea

¹⁴University College, Faculty of Medicine, Department of Rheumatology, 5 University Street, London WC1E 6JF, UK

¹⁵Therapeutic Radiology, Yale University, Hunter Building, 15 York Street, Ste HRT 313B New Haven, CT 06510 USA

Conflict of interest

The authors declare no conflict of interest.

¹⁶Division of Rheumatology, Cumming School of Medicine 3330 Hospital Drive NW Calgary, AB T2N 4N1 Canada

Abstract

Objective—To assess lung cancer risk in SLE, relative to demographics, drug exposures, smoking, and disease activity.

Methods—We analyzed data from 14 SLE cohorts. We calculated adjusted hazard ratio (HR) estimates for lung cancer in SLE, relative to demographics, smoking, time-dependent medication exposures, and cumulative disease activity (mean adjusted SLE Disease Activity, SLEDAI, scores). This project was approved by the ethics boards of all participating institutions, including the institutional review board of the McGill University Health Centre. The ethics approval Number for the Cancer Risk study is GEN-06-031.

Results—Within these 14 SLE cohorts, 49 incident lung cancers occurred. Among lung cancer cases, 59.0% were in the highest SLEDAI quartile at baseline versus 40.8% of lung-cancer free SLE controls. The vast majority (84.2%) of SLE lung cancer cases were ever-smokers at baseline, versus 40.1% of those without lung cancer. In adjusted models, the principal factors associated with lung cancer were ever smoking (at cohort entry) and current age. Estimated adjusted effects of all drugs were relatively imprecise but did not point towards any drug exposures as strong lung cancer risk factors.

Conclusion—We saw no clear evidence for drugs as a trigger for lung cancer risk in SLE, although drug risk estimates were relatively imprecise. Smoking may be the most significant modifiable lung cancer risk factor in SLE.

Keywords

Lung cancer; systemic lupus; SLE

Introduction

Recent data have highlighted the increase in cancer in SLE over-all; lung cancer specifically is 30–50% more common in SLE patients than their sex and age-matched counterparts.¹ Our objective was to assess lung cancer risk in SLE, comparing SLE patients with and without lung cancer regarding demographics, drug exposures, and disease activity.

Materials and Methods

Since approximately 2000, we have been working with investigators from the Systemic Lupus International Collaborating Clinics (SLICC) and other research networks, to further elucidate cancer risk in SLE. The current cohort analysis of lung cancer risk factors is based on 14 centres that were able to provide detailed information on drug use, disease activity, and other factors. These centres were Canadian (Halifax, Calgary, Montreal, Toronto, Winnipeg), American (Baltimore, Chicago, two in New York, San Francisco) centres abroad (Birmingham and London UK, Sweden, and Seoul Korea). At all these centres, cancer cases were determined on the basis of linkage of the patients to the appropriate tumor registries.

We used Cox proportional hazards regression to calculate the hazard ratio (HR) for lung cancer risk in SLE, relative to their exposure in terms of demographics (sex, race/ethnicity, and age, as a continuous time-dependent variable), smoking status, and time-dependent medication exposures.

We also adjusted for time-dependent cumulative disease activity, captured using mean adjusted SLE Disease Activity Index (SLEDAI) scores, which involve calculating the area under the curve between two SLEDAI scores as the average of the 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 has the same units as SLEDAI, and is interpreted in the same way. The adjusted mean SLEDAI has been shown to be a valid measure of cumulative SLE activity over time². To aid in interpretation, the mean adjusted SLEDAI score was categorized within quartiles. At one centre (University of California San Francisco), disease activity was captured only with self-report items.³ Thus at this centre the variable for cumulative SLE disease activity was similarly categorized within quartiles. The time-dependent disease activity in our model reflected whether or not a patient had reached the highest quartile of cumulative disease activity. We also controlled for any prior record of pulmonary fibrosis, based on the SLICC/ACR Damage Index, using a dichotomous time-dependent variable. This was done since it has been suggested that pulmonary fibrosis may predispose to lung cancer.⁴

Time zero for the observation interval was SLE diagnosis, so that our analyses adjusted for SLE duration (with left-censoring for the time from SLE diagnosis to cohort entry, when relevant, to avoid immortal time bias⁵). The use of SLE duration as the time axis was chosen because our earlier work suggested that cancer risk in SLE depends on SLE duration, in a non-linear way.¹ However, we did perform a sensitivity analysis where age was the time axis (and SLE duration was a model covariate).

We included lung cancers occurring after entry into the lupus cohort and up to the time of cohort exit (defined by death, cancer event, or date of last visit). Patients who developed a cancer other than lung cancer during the observation interval, were right-censored at that time.

Additionally, a sub-analysis was also performed for 6 centers where more precise, time-dependent data on smoking exposure had been collected (Sweden, San Francisco, Montreal, Halifax, Toronto and Winnipeg), in order to measure the effect of smoking intensity (in terms of a dose-effect of pack-years). Those analyses included 11 cases of lung cancer and 724 cancer-free subjects.

Results

Across all the SLE cohorts that participated in our study, 49 new lung cancer cases occurred and were included in our analyses. Compared to SLE controls without cancer (Table 1), persons with SLE with lung cancer cases were more likely to be white (84.8% versus 61.8% in non-lung cancer SLE controls), older at cohort entry (mean 51.2 and median 52.2 years; versus mean 38.2, median 36.8 years in controls) and male (20.4% of lung, 95% CI 10.2,

34.3 versus 9.2%, 95% CI 8.4, 10) of the remaining cohort). At cohort entry, the mean disease duration was similar, while the median disease duration in lung cancer cases was 1.1 years, versus 3.1 years in SLE patients that did not develop cancer. The vast majority (84.2%) of the lung cancer cases in SLE were ever-smokers at baseline, versus 40.1% of the SLE patients who did not develop lung cancer.

Among lung cancer cases, 59.0% had high disease activity (that is, a disease activity within the highest quartile) at baseline (95% confidence interval, CI 42.1,74.4%), in contrast to only 40.8% (95% CI 39.4, 42.3) of SLE patients that went on to remain free of lung cancer. The average SLE duration at time of lung cancer diagnosis was 14.2 years.

Regarding the medication profiles in the SLE patients who developed lung cancer versus those who did not, none of the patients had been exposed to cyclophosphamide prior to a lung cancer. In both univariate and adjusted models (Table 2), the principal factors associated with lung cancer risk were ever smoking (at cohort entry) and current age. There was no definitive evidence for greater cancer risk in SLE patients with higher cumulative disease activity over time. The estimated adjusted effects of all drugs were relatively imprecise. In a sensitivity analysis using age as the time axis, the results were similar.

In the sub-analyses, based on centers where pack-years had been measured, for smokers at cohort entry who went on to develop lung cancer, the median number of pack-years of smoking accumulated at baseline was 25 (mean 28.2, 95% CI 11.1, 45.2) pack-years, versus 8 (mean 11.9, 95% CI 10.9, 12.9) for smokers who remained cancer-free (n = 724). Adjusting for current age, there was an increase in the HR of lung cancer equal to 1.04 (95% CI 1.02, 1.05) for each additional pack-year.

Discussion

Cancer is an important outcome for SLE patients⁶. In our analyses, we saw no clear evidence for drugs as a trigger for lung cancer risk in SLE, although drug risk estimates were relatively imprecise. It is worth noting in particular that none of the lung cancer cases had a history of cyclophosphamide exposure. Smoking appeared to be the most significant modifiable lung cancer risk factor in SLE. Among lung cancer cases, 59.0% were in the highest SLEDAI quartile at baseline versus 40.8% of SLE patients that remained lung-cancer free. Adjusted analyses were consistent with a possible trend for greater cancer risk in subjects within the highest quartile of SLE activity but the confidence interval for both the unadjusted and adjusted HR estimates included the null value. In our sample, detailed smoking exposure was only available on 11 lung cancer patients and 724 controls. Fortunately, we were still able to show the expected dose-related effects, in this subgroup analysis.”

Lung cancer is one of the most common malignancies in the general population, and the five-year survival associated with advanced stages of this disease is poor. Lung cancer is in fact the second most common lung cancer to occur in SLE. Patients with SLE are at greater risk not only for developing lung cancer, but also for dying from it; previous analyses have suggested a standardized mortality ratio for lung cancer of 2.3 (95% CI 1.6–3.0) in SLE

versus the general population.⁷ It is thus very important to understand what drives lung cancer risk in systemic autoimmune rheumatic diseases such as SLE. According to data published by the SEER, adenocarcinoma is the most frequent histologic type of lung cancer in women and men (41% and 33%, respectively), followed by squamous cell carcinoma (15% and 24% in women and men respectively)^{8,9}. The remaining types (large cell, small cell and others) are roughly equal in males and in females (representing about 45% of the remaining cancer types). In the predominantly female SLE population, we have previously published that adenocarcinoma was indeed the most common carcinoma, making up half of the lung cancers in SLE, in males and in females. Squamous cell carcinoma was also the second most common histology type, and made up 27% of the lung cancer histology in female SLE patients, and 17% of the lung cancer histology in male patients. The percentage of squamous cell carcinomas in females with SLE is higher than the percent of this histologic type in general population of female lung cancers (15%; the 95% confidence interval for the difference between proportions is $-0.02, 0.27$ and thus just scarcely includes the null value). It is interesting that in our prior publication of lung cancer histology in SLE, there were no large cell lung cancers noted, while about 9% of lung cancers in the general population are large-cell carcinoma.

In the general population, small cell and squamous cell carcinomas are nearly always associated with smoking¹⁰. Squamous cell carcinoma rates have been declining in males but gradually increasing in females, possibly related to the increasing number of females that smoked after the 1950's¹¹. A recent study published by the National Cancer Registry of Ireland calculated that from 1994 to 2009 the incidence of squamous cell lung carcinoma in women has increased by 1.3% annually. However, at the same time, the incidence of adenocarcinoma in women has increased by even more (6.5%) annually^{12,13}. Thus, it is intriguing that there should be a higher than expected number of squamous cell cancers in female SLE patients, while the percentage of adenocarcinoma in SLE seems to be what is expected.

We have recently reviewed the evidence to guide cancer screening in SLE¹⁴. There are no original research studies directly comparing cancer screening strategies in SLE, and most authors recommend that SLE patients adhere to general population screening measures. Interestingly, the US Preventive Services Task Force recommended annual low-dose computed tomography of the chest for adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years (based on Grade B evidence)¹⁵. Admittedly, this has been contested by the American Academy of Family Physicians. Still, evidence suggests that women may be more susceptible to the carcinogenic effects of smoking versus men.¹⁶ It seems reasonable that SLE patients with the specified smoking history follow local recommendations for cancer screening; this decision could be made by the patients' primary care doctor, who is generally in charge of cancer screening. Regardless of screening, emphasizing the importance of smoking cessation in SLE is critical.

In conclusion, smoking appears to be the most significant modifiable risk factor for lung cancer in SLE. For obvious reasons, those who care for SLE patients should continue to actively counsel tobacco cessation in patients who smoke. Additional studies may also help

determine the relative distribution of stages of lung cancer in SLE and understand the reason for the increased mortality risk from lung cancer in SLE.

Acknowledgments

This work has been funded by the CIHR and NIH. The Johns Hopkins SLE cohort research activities are funded by the NIH AR grant #43727. The Montreal SLE cohort research activities are funded by the Singer Family Fund for Lupus Research. Dr. Bernatsky is the recipient of a senior career award from Fonds de recherche du Québec-Santé. Dr. Fortin is the recipient of a Canada Research Chair. The Northwestern SLE cohort is supported by NIH AR grant # 066464. The Birmingham UK lupus cohort has been supported by Lupus UK and the Birmingham NIHR/ Wellcome Trust Clinical Research Facility. The Korea lupus cohort was supported in part by unrestricted grant Hanyang University 20160000001387.

References

- Bernatsky S, Ramsey-Goldman R, Labrecque J, Joseph L, Boivin JF, Petri M, et al. Cancer risk in SLE: an updated international multi-centre cohort study. *J Autoimmun.* 2013; 42:130–5. [PubMed: 23410586]
- Ibanez D, Gladman DD, Urowitz MB. Adjusted mean Systemic Lupus Erythematosus Disease Activity Index-2K is a predictor of outcome in SLE. *J Rheumatol.* 2005; 32:824–827. [PubMed: 15868616]
- Yazdany J, Yelin EH, Panopalis P, Trupin L, Julian L, Katz PP. Validation of the systemic lupus erythematosus activity questionnaire in a large observational cohort. *Arthritis Rheum.* 2008; 59:136–143. [PubMed: 18163398]
- Antoniou KM, Tomassetti S, Tsioura E, Vancheri C. Idiopathic pulmonary fibrosis and lung cancer: a clinical and pathogenesis update. *Curr Opin Pulm Med.* 2015; 21:626–33. [PubMed: 26390339]
- Hanley J, Foster BJ. Avoiding blunders involving ‘immortal time’. *Int J Epidemiol.* 2014; 43:949–961. [PubMed: 24760815]
- Azrielant S, Tiosano S, Watad A, et al. Correlation between systemic lupus erythematosus and malignancies: a cross-sectional population-based study. *Immunol Res.* 2017; 65:464. [PubMed: 28091805]
- Bernatsky S, Boivin JF, Joseph L, Manzi S, Ginzler E, Gladman DD. Mortality in SLE. *Arthritis Rheum.* 2006; 54:2550–7. [PubMed: 16868977]
- Ries, LAG., Young, JL., Keel, GE., Eisner, MP., Lin, YD., Horner, MJ. SEER survival monograph: Cancer survival among adults: U.S. SEER program, 1998–2001. Patient and tumor characteristics. National Cancer Institute; Bethesda, MD: 2007. SEER Program. NIH Pub No. 07-6215
- Leitzmann MF, Koenig C, Abnet CC, et al. Prospective Study of Physical Activity and Lung Cancer by Histologic Type in Current, Former, and Never Smokers. *Am J Epidemiol.* 2009; 169:542–553. [PubMed: 19126591]
- Tran HN, Li Y, Siu S, Baer D, Friedman GD, Udaltsova N, Klatsky AL. Predictors of lung cancer: noteworthy cell type differences. *Perm J.* 2013; 17:23–9.
- Health Canada. Tobacco Use Statistics Canadian Tobacco Use Monitoring Survey. 2011. <http://www.hc-sc.gc.ca/hc-ps/tobac-tabac/research-recherche/stat/index-eng.php> Accessed Dec. 2013
- National Cancer Registry Ireland. Recent trends in lung cancer. *Cancer Trends.* 2009; 1:1–2.
- Devesa SS, Bray F, Vizcaino AP, Parkin DM. International lung cancer trends by histologic type: male:female differences diminishing and adenocarcinoma rates rising. *Int J Cancer.* 2005; 117:294–9. [PubMed: 15900604]
- Tessier-Cloutier B, Clarke AE, Pineau CA, Keeling S, Bissonauth A, Ramsey-Goldman R, Lee J, Bernatsky S. What investigations are needed to optimally monitor for malignancies in SLE? *Lupus.* 2015; 24:781–7. [PubMed: 25742688]
- Moyer VA. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2014; 160:330–338. [PubMed: 24378917]
- Papadopoulos A, Guida F, Leffondre K, et al. Heavy smoking and lung cancer: Are women at higher risk? Result of the ICARE study. *Br J Cancer.* 2014; 110:1385–1391. [PubMed: 24423926]

Table 1

Characteristics of lung cancer cases versus cancer-free SLE subjects

Variables	Lung Cancer Cases (n = 49)	Cancer-free (n = 4,938)
Mean age (in years) at cohort entry	51.2 (47.3, 55.1)*	38.2 (37.8, 38.6)
Percent male	20.4 (10.2, 34.3)	9.2 (8.4, 10)
Percent white	84.8 (71.1, 93.7)	61.8 (60.4, 63.1)
Mean disease duration at entry, in years	5.4 (3.0, 7.7)	6 (5.7, 6.2)
Percent ever smoking at cohort entry	84.2 (68.7, 94)	40.1 (38.7, 41.5)
Mean pack-years at entry (in smokers)**	28.2 (11.1, 45.2)	11.6 (10.6, 12.6)
Percent positive for dsDNA at cohort entry	16.7 (7, 31.4)	27.1 (25.9, 28.4)
Percent with high disease activity at cohort entry***	59 (42.1, 74.4)	40.8 (39.4, 42.3)
Percent with pulmonary fibrosis at entry****	0 (0, 9.7)*	1.7 (1.4, 2.2)

* Brackets indicate 95% confidence intervals (CIs) aside from pulmonary fibrosis, where since none of the cancer cases had pulmonary fibrosis at entry, we only have uncertainty on one side of the interval, hence we have a one-sided 97.5% interval, rather than a 95% CI.

** A sub-analysis was also performed for 6 centers where more precise, time-dependent data on smoking exposure had been collected: Sweden, San Francisco, Montreal, Halifax, Toronto and Winnipeg. Those analyses included 11 cases of lung cancer and 724 cancer-free subjects.

*** Except in one center (UCSF) where self-report items were used, SLE activity was assessed by the mean adjusted SLE disease activity index (SLEDAI-2K), and categorized within quartiles over the full observation period.

**** Pulmonary fibrosis was assessed by the relevant item on the SLICC/ACR Damage Index.

Table 2

Unadjusted and adjusted hazard ratio estimates for lung cancer in systemic lupus

Variable	Unadjusted Hazard Ratios(95% CI)	Adjusted Hazard Ratios(95% CI)
Calendar year	1.01 (0.97, 1.05)	1.03 (0.97, 1.09)
Age (years)	1.09 (1.07, 1.12)	1.09 (1.06, 1.12)
Male	2.59 (1.20, 5.56)	1.13 (0.46, 2.74)
White	1.97 (0.85, 4.55)	2.10 (0.56, 7.93)
Smoking ever	6.92 (2.87, 16.7)	6.35 (2.43, 16.6)
dsDNA antibody positivity (weighted average)	0.21 (0.06, 0.72)	0.42 (0.11, 1.57)
Steroids ever	0.86 (0.41, 1.82)	0.60 (0.17, 2.15)
Cumulative steroid 3.5 grams	1.01 (0.51, 2.02)	1.92 (0.69, 5.33)
Cumulative cyclophosphamide 6 grams	0.28 (0.03, 2.49)	0.17 (0.03, 1.00)
Azathioprine ever	0.71 (0.29, 1.74)	0.68 (0.08, 5.63)
Azathioprine use 1 year	0.76 (0.28, 2.04)	1.81 (0.16, 21.0)
Methotrexate ever	0.67 (0.20, 2.20)	1.14 (0.32, 4.02)
Mycophenolate ever	0.73 (0.14, 3.74)	1.43 (0.39, 5.20)
NSAIDS ever	0.57 (0.28, 1.16)	0.57 (0.25, 1.26)
Antimalarial use ever	0.91 (0.43, 1.90)	1.65 (0.66, 4.15)
Cumulative antimalarial use 5 years	0.73 (0.32, 1.69)	0.55 (0.20, 1.51)
SLE activity top quartile*	0.93 (0.42, 2.04)	1.29 (0.64, 2.58)
Pulmonary fibrosis**	3.29 (0.86, 12.6)	2.41 (0.63, 9.22)

* Except in one center (UCSF) where self-report items were used, SLE activity is assessed by the mean adjusted SLE disease activity index (SLEDAI), and categorized within quartiles over the full observation period.

** Pulmonary fibrosis was assessed by the relevant item on the SLICC/ACR Damage Index.