Smoking Is the Most Significant Modifiable Lung Cancer Risk Factor in Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To assess lung cancer risk in systemic lupus erythematosus (SLE), relative to demographics, drug exposures, smoking, and disease activity.

Methods. We analyzed data from 14 SLE cohorts. We calculated adjusted HR estimates for lung cancer in SLE, relative to demographics, smoking, time-dependent medication exposures, and cumulative disease activity [mean adjusted SLE Disease Activity Index (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 toward 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. (First Release January 15 2018; J Rheumatol 2018;45:393–6; doi:10.3899/jrheum.170652)

Key Indexing Terms:
LUNG CANCER SYSTEMIC LUPUS ERYTHEMATOSUS

Data have highlighted the increase in cancer in systemic lupus erythematosus (SLE) overall; lung cancer specifically is 30%–50% more common in patients with SLE 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

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regarding demographics, drug exposures, and disease activity.

MATERIALS AND METHODS

Since about 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 centers that were able to provide detailed information on drug use, disease activity, and other factors. These centers were Canadian (Halifax, Calgary, Montreal, Toronto, Winnipeg), American (Baltimore, Chicago, 2 in New York, San Francisco), and abroad (Birmingham and London, UK; Sweden; and Seoul, Korea). At all these centers, 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 HR for lung cancer risk in SLE, relative to their exposure in 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, identified using mean adjusted SLE Disease Activity Index (SLEDAI) scores, which involved calculating the area under the curve between 2 SLEDAI scores as the average of the values at those 2 visits, multiplied by the length of time between the 2 visits. All the calculated areas were 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 time[2]. To aid in interpretation, the mean adjusted SLEDAI score was categorized within quartiles. At 1 center (University of California, San Francisco), disease activity was identified only with self-report items[3]. Thus, at this center the variable for cumulative SLE disease activity was similarly categorized within quartiles. The time-dependent disease activity in our model reflected whether 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/American College of Rheumatology Damage Index, using a dichotomous time-dependent variable. This was done because 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 bias[5]). SLE duration as the time axis was used because our earlier work suggested that cancer risk in SLE depended on SLE duration, in a nonlinear way[1]. However, we did perform a sensitivity analysis in which age was the time axis (and SLE duration was a model covariate).

We included lung cancers occurring after entry into the SLE 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 subanalysis was also performed for 6 centers where more precise, time-dependent data on smoking exposure had been collected (Lund, Sweden; San Francisco; Montreal; Halifax; Toronto; and Winnipeg) to measure the effect of smoking intensity (in dose-effect of pack-yrs). 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), SLE patients with lung cancer cases more likely to be white (84.8% vs 61.8% in SLE controls without lung cancer), older at cohort entry (mean 51.2 yrs, median 52.2 yrs vs mean 38.2 yrs, median 36.8 yrs in controls), and male (20.4% of lung, 95% CI 10.2–34.3 vs 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 patients with SLE who 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 patients with SLE 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% CI 42.1–74.4), in contrast to only 40.8% (95% CI 39.4–42.3) of patients with SLE who went on to remain free of lung cancer. The average SLE duration at the time of lung cancer diagnosis was 14.2 years.

Regarding the medication profiles in the patients with SLE who developed lung cancer versus those who did not, none of the patients had been exposed to cyclophosphamide (CYC) 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 subanalyses, 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) 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 patients with SLE[6]. 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 CYC 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 patients with SLE who 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 CI for both the unadjusted and adjusted HR estimates included the null value. In our sample, detailed smoking exposure was only available on 11 patients with lung cancer 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

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Table 1. Characteristics of lung cancer cases versus cancer-free SLE subjects.

Variable	Lung Cancer Cases, n = 49	Cancer-free, n = 4938
Mean age at cohort entry, yrs	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, yrs	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-yrs 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% CI, aside from pulmonary fibrosis, where since none of the cancer cases had pulmonary fibrosis at entry, we only have uncertainty on 1 side of the interval, hence we have a 1-sided 97.5% interval rather than a 95% CI. **A subanalysis was also performed for 6 centers where more precise, time-dependent data on smoking exposure had been collected: Lund, Sweden; San Francisco; Montreal; Halifax; Toronto; and Winnipeg. Those analyses included 11 cases of lung cancer and 724 cancer-free subjects. †Except in 1 center (University of California, San Francisco) 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. SLE: systemic lupus erythematosus; SLICC/ACR: Systemic Lupus International Collaborating Clinics/American College of Rheumatology.

Table 2. Unadjusted and adjusted HR estimates for lung cancer in SLE.

Variable	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Calendar yr	1.01 (0.97–1.05)	1.03 (0.97–1.09)
Age, yrs	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 g	1.01 (0.51–2.02)	1.92 (0.69–5.33)
Cumulative CYC ≥ 6 g	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 yr	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)
NSAID 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 yrs	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 1 center (University of California, San Francisco) where self-report items were used, SLE activity is assessed by the mean adjusted SLE Disease Activity Index, and categorized within quartiles over the full observation period. **Pulmonary fibrosis was assessed by the relevant item on the SLICC/ACR Damage Index. SLE: systemic lupus erythematosus; NSAID: nonsteroidal antiinflammatory drugs; SLICC/ACR: Systemic Lupus International Collaborating Clinics/American College of Rheumatology; CYC: cyclophosphamide.

the general population, and the 5-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 US Surveillance, Epidemiology, and End Results database, 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 men and

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women (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 men and women. Squamous cell carcinoma was also the second most common histology type, and made up 27% of the lung cancer histology in female patients with SLE, 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 the general population of female lung cancers (15%; the 95% CI for the difference between proportions is –0.02 to 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 smoking[10]. Squamous cell carcinoma rates have been declining in males but gradually increasing in females, possibly related to the increasing number of females who smoked after the 1950s[11]. A study published by the National Cancer Registry of Ireland calculated that from 1994 to 2009, the incidence of squamous cell lung carcinoma in women increased by 1.3% annually. However, at the same time, the annual incidence of adenocarcinoma in women increased by even more (6.5%)[12,13]. Thus, it is intriguing that there should be a higher-than-expected number of squamous cell cancers in female patients with SLE, while the percentage of adenocarcinoma in SLE seems to be what is expected.

We have reviewed the evidence to guide cancer screening in SLE[14]. There are no original research studies directly comparing cancer screening strategies in SLE, and most authors recommend that patients with SLE adhere to the 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.

Smoking appears to be the most significant modifiable risk factor for lung cancer in SLE. For obvious reasons, those who care for patients with SLE 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.

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