Lung Cancer in SLE: An Update

M. Kale[1], A.E. Clarke[2], R. Ramsey-Goldman[3], M. Urowitz[4], D. Gladman[4], P.R. Fortin[5], S. Manzi[6], M. Petri[7], E. Ginzler[8], S. Jacobsen[9], O. Nived[10], C. Gordon[11], J.-L. Senécal[12], D. Isenberg[13], S.-C. Bae[14], D.J. Wallace[15], E. Yelin[16], D. Kamen[17], A. Rahman[13], K. Steinsson[18], G.S. Alarcón[19], S. Edworthy[20], J.G. Hanly[21], M.A. Dooley[22], L. Criswell[23], S. Barr[20], A. Zoma[24], G. Sturfelt[10], L. Dreyer[25], J.L. Lee[1], J. Labrecque[1], J. Sibley[26] and S. Bernatsky[1,27,*]

[1]Division of Clinical Epidemiology, Research Institute of the McGill University Health Centre, 687 Pine Avenue, V Building, Montreal, Quebec, H3A 1A1, Canada; [2]Division of Rheumatology, University of Calgary, 3280 University Drive NW, Calgary, Alberta, T2N 4Z6, Canada; [3]Northwestern University Feinberg School of Medicine, McGaw Pavilion, 240 E. Huron Street, Suite M-300, Chicago, IL 60611, USA; [4]Toronto Western Hospital, 399 Bathurst Street, IE-410B, Toronto, Ontario M5T 2S8, Canada; [5]Service de Rheumatologie, Université de Laval, 2705, boulevard Laurier, Local S-763, Quebec G1V 4G2, Canada; [6]West Penn Allegheny Health System, Allegheny General Hospital, Suite 295, 2nd Floor, South Tower, 320 East North Avenue, Pittsburgh, PA 15212, USA; [7]Johns Hopkins University School of Medicine, 1830 E. Monument Street, Suite 7500, Baltimore, MD 21205, USA; [8]State University of New York, Downstate Medical Center, 450 Clarkson Avenue, Box 42, Brooklyn, NY 11203, USA; [9]Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen, Denmark; [10]Lund University Hospital, S-22185 Lund, Sweden; [11]College of Medical and Dental Sciences, University of Birmingham, Edgbaston B15 2TT, UK; [12]University of Montreal School of Medicine and Division of Rheumatology, Centre Hospitalier de l'Université de Montréal , 1560 East Sherbrooke Street, Montreal, Quebec H2L 4M1, Canada; [13]Department of Rheumatology, Faculty of Medicine, University College, 5 University Street, London WCIE 6JF, UK; [14]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul 133-792, South Korea; [15]Cedars-Sinai Medical Center, David Geffen School of Medicine at UCLA, 8737 Beverly Blvd, Suite 302, West Hollywood, CA 90048, USA; [16]Department of Medicine, University of California, Suite 270, Laurel Heights Campus, San Francisco, CA 9413-0920, USA; [17]Medical University of South Carolina, 36 Jonathan Lucas Street, Suite 912, Charleston, SC 29425, USA; [18]Department of Rheumatology and Center for Rheumatology Research, Landspitali, University Hospital, Fossvogur, 108 Reykjavik, Iceland; [19]The University of Alabama, Birmingham, 1520 3rd Avenue South, MT 512, AL 5294-3408, USA; [20]University of Calgary, 3330 Hospital Drive, NW, Calgary, Alberta T2N 1N4, Canada; [21]Division of Rheumatology, Dalhousie University and Capital Health, Second Floor, Nova Scotia Rehabilitation Center, 1341 Summer Street, Halifax, Nova Scotia B3H 4K4, Canada; [22]University of North Carolina at Chapel Hill, CB #7280 3330 Thurston Building, Chapel Hill, NC 27599-7280, USA; [23]Department of Medicine, University of California, Rosalind Russell Medical Research Center for Arthritis, San Francisco, 374 Parnassus Avenue, first floor, San Francisco, CA 94117, USA; [24]Hairmyres Hospital, East Kilbride, G75 8RG Scotland, UK; [25]Department of Rheumatology, Copenhagen University Hospital Gentofte, Niels Andersens Vej 65, DK-2900 Hellerup, Denmark; [26]Royal University Hospital, Saskatoon, Saskatchewan, Canada; [27]Division of Rheumatology, McGill University Health Centre, 1650 Cedar Ave, Montreal, QC, H3A 1A4, Canada

Abstract: Objective: An increased lung cancer risk in systemic lupus erythematosus (SLE) has been previously suggested. Our objective was to provide an updated analysis of the lung cancer cases from a multi-site international cohort study, including descriptive statistics of the demographics (age, sex, and race/ethnicity) of cases, as well as the histology.

Materials and Methods: Data were obtained from an SLE sample of 16,409 SLE patients across 30 centers. Cancer occurrence was ascertained through linkages with regional tumor registries.

Results: We analyzed 85 lung cancers that had occurred across eight countries. The average age of the SLE patients at lung cancer diagnosis was 60 years and the majority (83.5%) of these cases was female. The average SLE duration at the time of cancer diagnosis was 11 years. Histological type was specified in 32 cases with adenocarcinoma reported as the most common histological type (N=16), followed by squamous cell carcinoma (N=8)and small cell cancer (N=6) and adenosquamous cancers (2).

Conclusion: Our results suggest a similar histological distribution of lung cancers in SLE to that of lung cancer in the general population with a possibly increasing proportion of squamous cell carcinomas.

Keywords: Lung cancer, systemic lupus erythematosus, Malignancy.

*Address correspondence to this author at the Royal Victoria Hospital, 687 Pine Avenue West, V-Building, Montreal, Quebec, H3A 1A1, Canada; Tel: 514-934-8292; Fax: 514-934-8293; E-mail: Sasha.bernatsky@mcgill.ca

E-ISSN: 2310-9874/14

An association between systemic lupus erythematosus (SLE) and an increased risk of lung cancer has been suggested in several cohort studies over a number of years [1, 2]. When compared to the general population, there is evidence for an increased risk in SLE, not only of developing lung cancer, but of dying from it [3]. An updated multi-site international cohort analysis by Bernatsky *et al*. involving 16,409 patients across 30centres, further confirmed the increased risk of lung cancer with a standardized incidence ratio of 1.30 (95% CI 1.04, 1.60) [4]. An earlier assessment of lung cancer cases in SLE had suggested that the histology of these lesions resembled that of the general population [5]. Our current objective was to provide an updated analysis of the lung cancer cases from this updated multi-site international SLE cohort to determine the descriptive statistics of the demographics (age, sex, and race/ethnicity), as well as to profile the histological distribution of cases.

1. MATERIALS AND METHODS

The cohort was assembledin the context of the international cohort study of cancer in 16,409 SLE patients, observed for 121,283 (average 7.4) person-years across 30 centres. For initial enrolment into this cohort, patient eligibility was based on American College of Rheumatology (ACR) criteria or a clinical diagnosis of SLE; however, the cohort in Scotland was assembled using administrative data. The lung cancer cases were distributed across 20centres in 8 different countries (in Canada, the United States, England, Denmark, Sweden, Scotland, Korea and Iceland). Information on date of birth, sex and race/ethnicity was available, along with the date of SLE diagnosis. Cancer occurrence was ascertained through linkages with regional tumor registries, which provided information on cancer type and date of occurrence and, for 14 registries, histology codes. We assessed the demographic characteristics for all invasive lung cancer casesoccurringany time after SLE diagnosis, and information on histology types was analyzed from the 14 centres where this information was available. We also compared our results to the expected histological distribution of lung cancers in the general population. This work has been approved by the appropriate ethical committees related to the institutions in which it was performed, and subjects providing informed consent where applicable.

2. RESULTS

We studied 85 lung cancer cases that had occurred in the SLE patients after cohort entry, for a rate of 0.7 lung cancers per 1000 person-years.Since SLE is a disease primarily of females, the majority of these cases were female (N=71, 83.5%). The average age of the SLE patients at lung cancer diagnosis was 60 years (median 61, standard deviation, SD 11.3). The average SLE duration at the time of lung cancer diagnosis was 11 years (median 8, SD 11.8). Race/ethnicity was not provided by 2 centres, Scotlandand Alberta (21 cases). Of the remaining 64lung cancers, the majority were Caucasian (N=48) followed by 10 African-American, 1 Asian, 1 Hispanic and 4 of other racial/ethnic origin. Of the 14 male SLE cancer cases, data on race/ethnicity was known for 8, and all of these were Caucasian.

As mentioned, histology codes representing lung cancer type were provided by the cancer registries serving 14 centres (49 cases). Within those 49 cases, 15 were carcinomas not otherwise specified, with 2 others being documented as non-small cell cancer but of unknown subtype. Out of the remaining 32 cases, the most common histological type reported was adenocarcinoma (N=16, 50% of 32 cases) followed by squamous cell carcinoma (N=8, 25%) and small cell cancer (N=6, 18.7%). The remaining 2 cases were adenosquamous cancers (6.2%)These 32 lung cancer cases of known histology occurred in 26 women and 6 men; the relative proportion of lung cancer types in females versus female SLE patients is presented in Figure **1**. This indicates that in both male and female SLE patients, the most common cancer type was adenocarcinoma; additionally 7 of 26 (almost one-third) of the female lung cancers were squamous cell carcinoma, while only one of 6 male lung cancers was squamous cell carcinoma.

3. DISCUSSION

In the general population, the median age at lung cancer diagnosis is 71 years (interquartile range 64–78 years) in the United Kingdom [6] and 70 years in the United States, according to the Surveillance, Epidemiology and End Results (SEER) program from the National Cancer Institute [7]. The median age of our SLE patients at lung cancer diagnosis was 61 years, which likely reflects the relatively young age distribution of our SLE cohort (since SLE often affects individuals of workforce age). In the general population, the highest lung cancer incidence rates in females are found primarily in the Caucasian population [8]; which

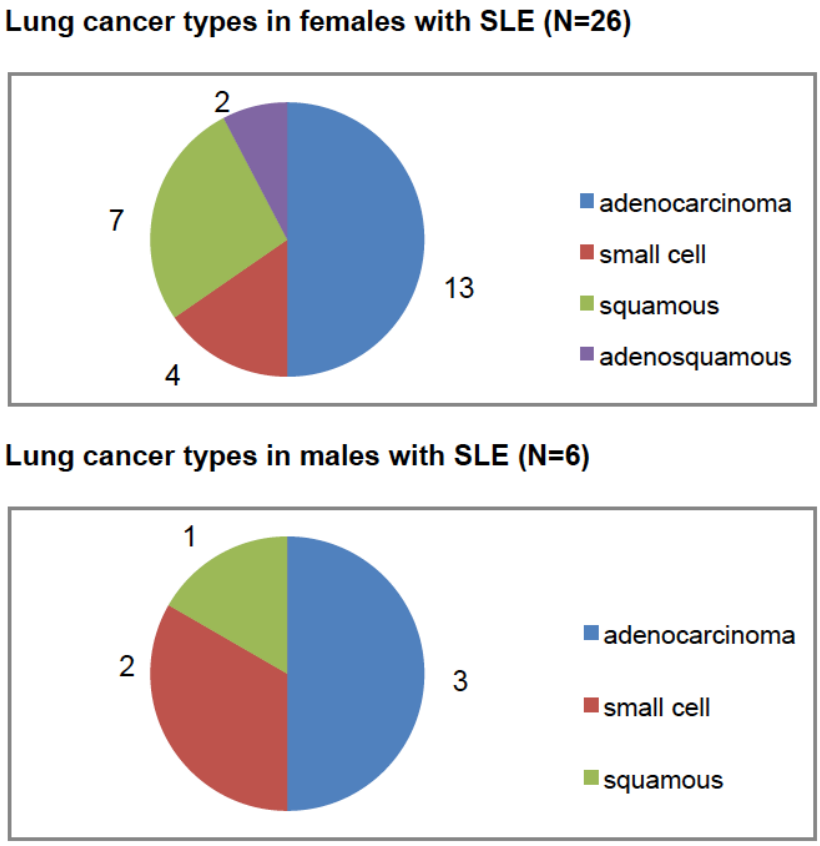

Figure 1: Lung cancer types in female versus male patients with systemic lupus (SLE).

is consistent with the fact that the majority of female lung cancer cases in our SLE cohort occurred in Caucasians (though admittedly, like the populations they are drawn from, the majority of the cohort subjects were Caucasian).

According to data published by the SEER program assessing a total of 201,067 lung cancer cases from 1998 to 2001, adenocarcinoma is the most frequent histologic type in women and men (41% and 33%, respectively), followed by squamous cell carcinoma (15% and 24%, respectively) [9, 10]. 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) [12]. In our SLE study population, which is composed mostly of females, adenocarcinoma was indeed the most common carcinoma; this histology made up half of the lung cancer histology in womenand in mean with SLE. Squamous cell carcinomas was also the second most common histology type in our SLE patients, and made up 27% of the lung cancer histology in female SLE patients, and 17% of the lung cancer histology in male patients. The slightly higher percentage of squamous cell carcinomas in females with SLE (27%) versus the general population of females (15%) is a strong trend (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 there were no large cell lung cancers noted in the SLE patients, since about 9% of lung cancers in the general population are large-cell carcinoma.

In the general population, small cell and squamous cell carcinomasare nearly always associated with smoking [11]. 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's,which now results in a more similar proportion of male and female smokers in much of the developed world (as opposed to fifty years ago, when the vast majority of males were smokers) [12]. 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 [13, 14]. Thus, it is intriguing that there should be such a higher than expected number of squamous cell cancers in our female SLE patients.

Smoking is likely an important factor for lung cancers in SLE. Our previous analyses (in a case-cohort sample from the large international multi-centre SLE cohort) demonstrated an increased risk of lung cancer among SLE smokers versus SLE non-smokers [15]. In our current study sample, we do not have information on smoking and immunosuppressive medication for all subjects with lung cancer. In our earlier assessment of lung cancers in SLE, we noted that most (71%) of the lung cancer cases in SLE patients were smokers, while exposure to immunosuppressants occurred in only 20% of these subjects

In summary, the histological distribution of our population of SLE patients with lung cancer was similar to the general population, although the possibility of a greater proportion ofsquamous cell carcinomas in the SLE population cannot be ruled out.

ACKNOWLEDGEMENTS

We acknowledge the assistance of Elizabeth Turnbull and Autumn Neville. This research was made possible through the endorsement and support of the Systemic Lupus International Collaborating Clinics (SLICC) research network.

GRANT SUPPORT

This research was funded by Canadian Institutes of Health Research/Arthritis Society (CIHR/TAS) grant RG06/092 and National Institutes of Health (NIH) grant 1R03CA128052-01. We also acknowledge the grant that supports the Chicago Lupus Database, NIH/NIAMS P60 2 AR30692 and the grants that support the UCSF Lupus Outcomes Study, NIH/NIAMS P60 AR053308 and NIH/NIAMS R01 5R01AR56476-9, the grant that support the Hopkins Lupus Cohort NIH R01 AR43727, and the grant by the Department of Education, Universities and Research of the Basque Government supporting the Lupus-Cruces research project. Support for McGill University Health Centre cohort comes from Singer Family Fund for Lupus Research. Dr. Criswell would like to acknowledge support from the Alliance for Lupus Research and from a Kirkland Scholar Award. Dr. Bae's work is supported by the Korea Healthcare technology R&D Project, Ministry for Health and Welfare, Republic of Korea (A120404).

CONFLICT OF INTEREST STATEMENT

None of the authors have a conflict of interest.

REFERENCES

[1] Gayed M, Bernatsky S, Ramsey-Goldman R, Clarke AE, Gordon C. Lupus and cancer. Lupus 2009; 18: 479-85. http://dx.doi.org/10.1177/0961203309102556

[2] Bernatsky S, Ramsey-Goldman R, Clarke A. Exploring the links between systemic lupus erythematosus and cancer. Rheum Dis Clin North Am 2005; 31: 387-402. http://dx.doi.org/10.1016/j.rdc.2005.01.002

[3] Bernatsky S, Boivin JF, Joseph L, *et al*. Mortality in systemic lupus erythematosus. Arthritis Rheum 2006; 54: 2550-7. http://dx.doi.org/10.1002/art.21955

[4] Bernatsky S, Ramsey-Goldman R, Labrecque J. Cancer risk in systemic lupus: an updated international multi-centre cohort study. J Autoimmun 2013; 42: 130-5. http://dx.doi.org/10.1016/j.jaut.2012.12.009

[5] Bin J, Bernatsky S, Gordon C, *et al*. Lung cancer in systemic lupus erythematosus. Lung Cancer 2007; 56: 303-6. http://dx.doi.org/10.1016/j.lungcan.2007.01.007

[6] Rich AL, Tata LJ, Stanley RA, *et al*. Hubbard, lung cancer in England: Information from the National Lung Cancer Audit (LUCADA). Lung Cancer 2011; 72: 16-22. http://dx.doi.org/10.1016/j.lungcan.2010.07.002

[7] Howlader N, Noone AM, Krapcho M, *et al.* (eds). SEER Cancer Statistics Review, 1975-2009, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2009_pops09 Accessed Dec. 2013

[8] Jemal A. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90. http://dx.doi.org/10.3322/caac.20107

[9] Ries LAG, Young JL, Keel GE, Eisner MP, Lin YD, Horner M-J. SEER survival monograph: Cancer survival among adults: U.S. SEER program, 1998-2001, Patient and tumor characteristics. National Cancer Institute, SEER Program, NIH Pub No. 07-6215, Bethesda, MD, 2007.

[10] Leitzmann MF, Koebnick C, Abnet CC. Prospective study of physical activity and lung cancer by histologic type in current, former, and never smokers. Am J Epidemiol 2009; 169: 542-53. http://dx.doi.org/10.1093/aje/kwn371

[11] Tran HN, Li Y, Siu S, *et al*. Predictors of lung cancer: noteworthy cell type differences. Perm J 2013; 17: 23-9. http://dx.doi.org/10.7812/TPP/12-104

[12] 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

[13] National Cancer Registry Ireland. Recent trends in lung cancer. Cancer Trends 2009; 1: 1-2.

[14] 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. http://dx.doi.org/10.1002/ijc.21183

[15] Bernatsky S, Joseph L, Boivin J-F. The relationship between cancer and medication exposures in systemic lupus erythaematosus: a case-cohort study. Ann Rheum Dis 2008; 67: 74-9. http://dx.doi.org/10.1136/ard.2006.069039

Received on 28-04-2014 Accepted on 09-06-2014 Published on 07-07-2014

DOI: http://dx.doi.org/10.12970/2310-9874.2014.02.02.1