



Published in final edited form as:

Cancer Causes Control. 2008 October ; 19(8): 887–894. doi:10.1007/s10552-008-9151-8.

Cancer risk in a cohort of patients with systemic lupus erythematosus (SLE) in California

A. Parikh-Patel,

California Cancer Registry, Public Health Institute, 1825 Bell Street, Suite 102, Sacramento, CA 95825

M. Allen,

California Cancer Registry, Public Health Institute, 1825 Bell Street, Suite 102, Sacramento, CA 95825

R. Cress, and

California Cancer Registry, Public Health Institute, 1825 Bell Street, Suite 102, Sacramento, CA 95825. Department of Public Health Sciences, University of California, Davis, CA, USA

R. H. White

Department of Internal Medicine, University of California, Davis, CA, USA

Abstract

Objective—We conducted a retrospective cohort study to examine cancer risk in a large cohort of systemic lupus erythematosus (SLE) patients in California.

Methods—The cohort consisted of individuals with SLE derived from statewide patient discharge data during the period 1991–2002. SLE patients were followed using cancer registry data to examine patterns of cancer development. Standardized incidence ratios (SIRs) and 95% CI were calculated to compare the observed to expected numbers of cancers based on age-, race-, and sex-specific incidence rates in the California population.

Results—The 30,478 SLE patients were observed for 157,969 person-years. A total of 1,273 cancers occurred within the observation interval. Overall cancer risk was significantly elevated (SIR=1.14, 95% CI=1.07–1.20). SLE patients had higher risks of vagina/vulva (SIR=3.27, 95% CI=2.41–4.31) and liver cancers (SIR=2.70, 95% CI=1.54–4.24). Elevated risks of lung, kidney, and thyroid cancers and several hematopoietic malignancies were also observed. Individuals had significantly lower risks of several screenable cancers, including breast, cervix, and prostate.

Conclusions—These data suggest that risks of several cancer types are elevated among SLE patients. Detailed studies of endogenous and exogenous factors that drive these associations are needed.

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by chronic inflammation and the production of autoantibodies directed against numerous antigens [1]. Because SLE patients are now living longer due to recent advances in treatment, the incidence of chronic comorbid conditions has been rising [2–5]. Rates of several types of cancer, particularly hematopoietic malignancies, appear to be increasing in the SLE population [6–15]. One of the proposed biologic mechanisms for this association is a defect in the body's immunosurveillance process. In a healthy immune system, aberrant cells produced during cell replication are removed to prevent them from becoming malignant and progressing to clinical cancer [16]. Among individuals with SLE, this regulation process is likely impaired, contributing to increased cancer risk [16]. In addition to increased baseline cancer risk in SLE patients relative to the general population, other factors which are thought to play a role include exogenous exposures to medication [17, 18] and viral agents known to be associated with cancer [12].

Several epidemiologic studies have attempted to characterize cancer incidence among SLE patients. Existing literature on this subject includes results from small case series [19–22], population-based studies using administrative data sets [8–11], and studies using clinical cohorts of patients [6, 14, 15, 23–26]. Although older studies suffered from small sample sizes and limited generalizability, results of recent studies are based on larger population-based cohorts and multicenter clinical cohorts. Increased incidence of non-Hodgkin's lymphoma (NHL) and other hematologic malignancies appears to be a consistent finding [6, 8–11, 23, 24, 26], although there is considerable variation in the magnitude of excess risk and precision of the estimates across studies. The results for solid tumors, however, have not been as consistent. Some studies have reported excess risks of lung [6, 9, 15, 24], liver [6, 9], cervix [24], and vagina/vulva cancer [9] among SLE patients; in the case of the latter two cancers, the results were based on very small numbers of cases.

In this paper, we present the results of a retrospective cohort study designed to examine cancer incidence in a cohort of SLE patients in California who required hospitalization during the period 1991–2002. The cohort was defined and cancer outcomes were measured using a data set created via electronic linkage of cancer registry and patient discharge data. The aims of the project were to describe patterns of cancer development among patients with SLE in this large and racially diverse population, compare the observed cancer incidence in the cohort to the expected incidence in the general California population, and to examine cancer risk across age, sex, and race/ethnic strata. To the best of our knowledge, this is the largest cohort of SLE patients in which this question has been addressed.

Methods

Description of data sets

The cohort for this study was identified from California patient discharge data. The Patient Discharge Dataset is produced annually by the California Office of Statewide Health Planning and Development (OSHPD). This dataset contains a record for each inpatient discharged from all non-federal, licensed, acute care hospitals. Information on basic

demographic characteristics, diagnostic codes, and procedure codes related to the hospitalization are included in the data set. The diagnoses and procedures utilize codes specified by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9- CM) [27].

Information on cancer outcomes was obtained through electronic linkage of the patient discharge data set to the California Cancer Registry (CCR) data set for the period 1991–2002. The CCR is the largest, population-based cancer registry for a geographically contiguous area in the world, collecting incidence reports on over 140,000 new cases of cancer diagnosed annually in California. Standards for data abstracting, collection, and reporting are specified by the CCR [28–31]. The CCR has consistently met the highest standards for data quality and completeness [32], and participates in the National Cancer Institute’s Surveillance Epidemiology and End Results (SEER) program [33]. The CCR database contains information on basic demographic factors, tumor characteristics, and cancer directed surgeries and treatment. Follow-up for vital status on patients in the database is conducted through routine linkages with several administrative databases, the primary one being the California statewide mortality file. Based on our current definition of loss to follow-up (no identification of patient through passive follow-up methods for 22 months from data of dataset creation), we estimate that approximately 3–5% of our cases are lost to follow-up.

Linkage procedures

The two data sets were electronically linked using Integrity software [34] and a combination of deterministic and probabilistic linkage strategies. The primary variables used to link the two data sets were social security number, date of birth, sex, and residential zip code. Approximately 90% of matches were identified through the deterministic linkage method. A probabilistic linkage method was used to identify the remaining matches. A probabilistic linkage utilizes a set of identifiers contained in both data sets to calculate the probability that records from different data sets are matches, allowing for errors such as transpositions of digits and spelling. Matches with weights higher than a predetermined cutoff are accepted, whereas those that are much lower than the cutoff are rejected. Matches that fall in between these limits are manually reviewed. Approximately 5% of matches were visually confirmed. Based on prior linkages of these data sets, we estimate that our algorithm identified 95%-99% of the matches [35].

Definition of study cohort and measurement of variables

All individuals with an ICD-9-CM code of 710.0 in any of the 25 diagnostic fields (principal diagnosis and up to 24 other diagnoses) hospitalized during the period 1991–2002 were included in the study. Only information on the first relevant hospitalization was included for each individual. International Classification of Diseases for Oncology, 2nd edition (ICD-02) site and histology codes were used to identify specific cancer outcomes in the cohort [36].

Other demographic variables included in the analysis were classified as follows: age (<30, 30–54, 55–59, 60+), race/ethnic group (non-Hispanic white, non-Hispanic black, Hispanic, non-Hispanic Asian/Pacific Islander and Other/Unknown), and sex (male and female). The

race/ethnic categories were mutually exclusive. Individuals identified as Hispanic were included only in the Hispanic category, and could be of any race. Individuals classified as any of the following were lumped into the Other/Unknown category: non-Hispanic American Indian/Alaskan Native, other race, or unknown race.

Statistical analysis

Descriptive statistics were generated for the entire cohort as well as for members of the cohort diagnosed with cancer during the study period. Person-years of follow-up were calculated for each individual. Time from the first hospitalization with a diagnosis of SLE to one of the following three events (whichever occurred first) was calculated: date of cancer diagnosis, date of death, or the end of the calendar year 2002. The expected numbers of cancers were calculated by sex, race/ethnicity, and five-year age group using rates from the general California population for the same time period. Standardized incidence ratios (SIRs), or the ratio of observed to expected cancers, and their 95% CI were calculated for all cancers combined and for all major cancer types. Race-specific and age group-specific estimates for specific cancer types (those for which we had adequate power) were calculated. Estimates were generated assuming that the number of observed cancers follows a Poisson distribution [37]. All estimates were adjusted by sex, age, and race/ethnicity.

The first six months of follow-up were excluded from the analysis, to minimize the possibility that the presenting symptoms of cancer overlapped with those of the SLE. When this period was expanded to one year, we observed minimal differences in the results, and therefore we chose to exclude only the first six months of follow-up to increase statistical power.

We also chose to present SIRs for each cancer type for males and females combined. When we calculated sex-specific SIRs, we did not see large differences between the sexes with respect to the magnitude of the effect measures, only the confidence intervals. Again, to increase our power, we chose to combine males and females for the presentation of data by cancer type.

We also assessed the internal consistency of our SLE diagnoses across multiple hospitalizations by examining the number of hospitalizations for each individual that recorded a diagnosis of SLE after the initial hospitalization for SLE, relative to the total number of times an individual was hospitalized.

Results

The study cohort consisted of 30,478 individuals who contributed 157,969 person-years of follow-up. The average length of follow-up was 5.1 years. Over 99% of individuals in our cohort who were hospitalized more than once had an SLE diagnosis recorded for every hospitalization (data not shown). Approximately 70% of individuals in the cohort had SLE listed as the primary or secondary diagnosis for their hospitalization. A total of 1,273 patients (4.2%) were diagnosed with at least one cancer during the study period. The most common cancer types were breast, lung, colon/rectum, and NHL. Among the NHL cases, large B-cell lymphoma was the most common subtype. The vast majority of the cohort

(89%) consisted of female patients, although a higher proportion of males were diagnosed with cancer (17%), compared to the overall proportion of males in the cohort (11%) (Table I). Half of the SLE patients diagnosed with cancer were over the age of 60 at the time of hospitalization, compared to 27% of the whole cohort. Approximately 42% of the SLE cohort members were identified as races other than non-Hispanic white. A larger proportion of SLE patients with cancer were non-Hispanic white (69%), compared to the overall proportion in the entire cohort (58%).

The overall cancer risk in the cohort was significantly elevated (SIR=1.14, 95% CI=1.07–1.20) (Table 2). Approximately threefold increases in both vagina/vulva cancer (SIR=3.27, 95% CI=2.41–4.31) and liver cancer (SIR=2.70, 95% CI=1.54–4.24) risk were observed in the cohort. In addition, cohort members had roughly double the risk of lung (SIR=1.66, 95% CI=1.45–1.90), kidney (SIR=2.15, 95% CI=1.52–2.94), and thyroid (SIR=1.83, 95% CI=1.24–2.62) cancers relative to the general California population. SLE patients also had elevated risks of several hematopoietic malignancies including NHL (both large-B cell and follicular types), Hodgkin's Disease (HD), and myeloid leukemia. Cohort members had significantly lower risks of breast, uterus, cervix, and prostate cancers. Given the small number of HD cases, we were not able to calculate subtype-specific SIRs. Since HD has been found to be at least three distinct diseases, which can be crudely classified by age, we calculated SIRs for individuals under 50 and those 50 years of age and older (data not shown). We did not find significant differences in the magnitude of the SIRs for these age groups and therefore chose to present the aggregate SIR for all HD cases.

Table 3 presents race-specific SIRs for selected cancer types. The risk of developing breast cancer was lower for non-Hispanic white (SIR=0.72, 95% CI=0.61–0.83), black, and Asian/Pacific Islander SLE patients compared to their counterparts in the general population, although the risk estimates for the latter two groups were not statistically significant. Lung cancer rates were significantly elevated among non-Hispanic whites and Hispanics, with the Hispanics having a twofold increase in lung cancer risk relative to the general population. Both black (SIR=4.29, 95% CI=1.93–8.04) and Hispanic patients (SIR=3.48, 95% CI=1.53–7.00) had higher risks of kidney cancer than the general population. The risks of NHL and vagina/vulva cancers were higher among all race/ethnic groups, with the highest risks among Hispanics and Asian/Pacific Islanders for both cancers.

Table 4 presents the risks of selected cancers by age group. SLE patients under 30 years of age had a fivefold increase in breast cancer risk compared to the general population. Those 60 years of age or older had a 40% decreased risk of breast cancer. Lung cancer risk in the study cohort was significantly elevated in the two older age groups. Risks of kidney cancer were significantly higher in all age groups except those 60 years of age or older, with the risk decreasing with increasing age. NHL risk was elevated in all age groups with the risk exhibiting an inverse relationship to age. Cohort members under 45 years of age were at significantly increased risk of vagina/vulva cancer, with individuals under 30 at highest risk.

Discussion

Our findings confirm the results of previous research indicating both an overall increased risk of cancer and increased risk of hematologic malignancies among individuals with SLE [6, 9, 10]. Both the magnitude and direction of these effect measures are comparable to results from a large multicenter international cohort reported by Bematsky et al. [6]. New findings include the increased risks of kidney and thyroid cancer among SLE patients, which highlight the power of the present study to detect differences in rarer cancers. The findings regarding significantly decreased risks of prostate and cervix cancers have not been previously reported.

This study also confirms the increased risks of lung and liver cancer among SLE patients reported previously [6, 9, 14]. We did not have information on tobacco use in our cohort, but other cohort studies of SLE patients reported current smoking prevalences similar to the general population [38–42], although one study reported heavier use of tobacco by smokers with SLE [38]. Another possible explanation for the observed increase in lung cancer in our cohort is that lung involvement and fibrosis in particular is common in SLE patients [9]. One hypothesis for the association between SLE and liver cancer postulated by other researchers is an increased prevalence of hepatitis C infection among SLE patients [9, 43].

The SIR for vagina/vulva cancer in our study was very high and is supported by the results of only one other study that was based on only three cases [9]. Increased prevalence of human papillomavirus (HPV) in women with SLE has been observed in previous work [44, 45] and may be a possible explanation; although, similar to the results of Mellemkjaer et al. [9], we did not observe an increase in cervical cancer risk, which would be expected if HPV rates were high in our cohort. Vulvar cancer has also been associated with an autoimmune condition called lichen sclerosus et atrophicus, and thus may share a common inflammatory mechanism with SLE, or may be a secondary condition as it has occasionally been reported to occur in SLE [46].

Although increased cancer rates among SLE patients (particularly with respect to lymphomas and leukemias) have been linked to treatment with immunosuppressive agents such as cyclophosphamide, azathioprine, and methotrexate [47–50], we were not able to examine this association, as we did not have treatment information on the patients. Several case series have supported the contention that there is an increased risk of bladder cancer among SLE patients because many of them are treated with cyclophosphamide [51–53]. Surprisingly, the SIR for bladder cancer in our cohort was not significantly increased.

Patients in our study were at decreased risk of several screenable cancers including breast, prostate, and cervix. The results of studies that examined breast cancer risk among SLE patients are variable. Some studies reported increased risks [14] and other lower risks of breast cancer among people with SLE [6]. Since breast cancer is strongly associated with hormonal and reproductive factors, differences in these risk factors across cohorts may explain the variation in results. Decreased risks of prostate and cervix cancer have not been reported by previous studies.

Our analysis of specific cancer types by race/ethnicity resulted in several new findings, including significantly increased risks among Hispanics for four out of the five cancer types we examined. In addition, blacks had elevated risks of vagina/vulva cancer and Asian/Pacific Islanders were at increased risk of both NHL and vagina/vulva cancer. Only one other study has examined cancer risk by race in SLE patients and did not report increased overall cancer risk in any race/ethnic group other than non-Hispanic whites [54]. It should be noted that the proportion of non-white individuals in that cohort was relatively small, and that less than seven cancers total were observed among Hispanics and Asians in the cohort. More information on risk factors among these race/ethnic groups is needed to investigate the relationship between race/ethnicity and risk of various cancers among individuals with SLE.

The high relative risk for developing several cancer types in younger SLE patients compared to the general population was striking. The majority of severe cases of SLE occur in younger women, particularly women other than non-Hispanic whites [55]. If the severity of the immunological deficits associated with SLE are also associated with an increased risk of developing cancer, the finding of a higher relative risk of cancer in younger SLE patients appear plausible. In addition, younger patients with severe disease may be treated more aggressively with immunosuppressive agents, which might also lead to an increased risk of cancer.

There are several limitations that should be considered in the interpretation of results from the present study. First, our cohort consisted of hospitalized individuals, which raises the possibility that our results might not be generalizable to all SLE patients. It is possible that our study population represents a more severely diseased portion of the population. It is worth noting, however, that our estimates of overall cancer risk and the risk of several cancers such as hematologic malignancies, lung, and liver cancer fall within the range of other published reports with both hospitalized and non-hospitalized individuals.

The use of hospitalized individuals also introduces the possibility of detection bias, in which hospitalized individuals might be more likely to be screened for cancer than other people with SLE, thus leading to an overestimate of risk. If there were a strong detection bias in effect, we would expect the SIRs for screenable cancers to be high. Instead we observed decreased risks of breast, prostate, and cervix cancer in our patient population. Moreover, the only published study to examine screening rates among SLE patients concluded that appropriate cancer screening might actually be overlooked in patients with SLE [56]. In addition, many researchers have hypothesized that the use of hospitalized individuals in cohort studies may introduce surveillance bias, based on the notion that they may be more likely to be screened and tested for various diseases. Our results do not support this hypothesis.

Although we were not able to verify the SLE diagnoses in the hospital discharge data, the diagnosis codes had very high levels of internal consistency among repeat hospitalizations for the same individuals. Validation studies using Medicare physician claims data reported 85% sensitivity for SLE claims using the medical record as the gold standard [57, 58]. A recent study conducted in Sweden found that 23 of 42 cases identified by administrative data did not have SLE according to their criteria [58]. One major limitation of the Swedish study,

however, was that the researchers included patients who were diagnosed over a 30-year period, but used current, more rigorous ACR classification criteria as the gold standard diagnostic criteria [59].

Other limitations of this study include the fact that this was not a closed cohort, thus we may have had some loss to follow-up, and the fact that we cannot definitively establish temporality. Both cancer and SLE are diseases with long latency periods and since we do not have definitive dates of diagnosis for SLE, we cannot be sure how long after diagnosis with SLE the cancer occurred. We attempted to address this issue by excluding cases that developed cancer during the first six months of the follow-up period. Finally, we did not have any information regarding treatment and other risk factors, such as smoking history, which affect both SLE and cancer risk.

Despite these limitations, our study has several strengths. To the best of our knowledge, this is by far the largest study of cancer and SLE conducted to date, providing enough statistical power and precision to confirm previous findings and to detect previously unreported increased risks of rarer cancers such as kidney, thyroid, and vagina/vulva cancer. In addition, we were able to examine risks of selected cancers by race/ethnic group with sufficient power to detect increased risks among blacks, Hispanics and Asians, which is also a novel contribution to the literature. Another advantage is the use of high quality cancer registry data to assess cancer outcomes.

The results of this exploratory study point to several interesting directions for future research, many of which we are currently pursuing. More detailed studies of the endogenous and exogenous factors that affect cancer risk among SLE patients are needed. Future studies should be directed toward examining the effects of treatment with immunosuppressive agents as well as the contribution of lifestyle factors such as diet and smoking on cancer risk in this population. In addition, further analysis of both cancer and SLE risk factors among various race/ethnic groups is needed to investigate the mechanisms that may underlie the increased risks. Finally, closer examination of the factors that influence cancer risk in younger populations of SLE patients is needed, as this is a group in which early intervention can potentially lead to better outcomes.

Acknowledgments

This work was funded by grant IR2ICAI00759-01A2 (A. Parikh-Patel) from the National Cancer Institute. The collection of cancer incidence data used in this study was supported by the California Department of Health Services as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology, and End Results Program under contract N01-PC-35136 awarded to the Northern California Cancer Center, contract N01-PC-35139 awarded to the University of Southern California, and contract N02-PC-15105 awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement #U55/CCR921930-02 awarded to the Public Health Institute. The ideas and opinions expressed herein are those of the author(s) and endorsement by the State of California, Department of Health Services, the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors is not intended nor should be inferred.

References

1. Abu-Shakra, M.; Buskila, D.; Shoenfeld, Y. SLE and cancer. In: Shoenfeld, Y.; Gershwin, ME., editors. *Cancer and autoimmunity*. Elsevier Science; 2000. p. 31-40.
2. Abu-Shakra M, Gladman DD, Urowitz MB. Mortality studies in SLE: how far can we improve survival of patients with SLE. *Autoimmun Rev*. 2004; 3:418–420. [PubMed: 15351308]
3. Stahl-Hallengren C, Jonsen A, Nived O, Sturfelt G. Incidence studies of systemic lupus erythematosus in Southern Sweden: increasing age, decreasing frequency of renal manifestations and good prognosis. *J Rheumatol*. 2000; 27:685–691. [PubMed: 10743809]
4. Urowitz MB, Gladman DD. How to improve morbidity and mortality in systemic lupus erythematosus. *Rheumatology (Oxford)*. 2000; 39:238–244. [PubMed: 10788530]
5. Urowitz MB, Gladman DD, Abu-Shakra M, Farewell VT. Mortality studies in systemic lupus erythematosus. Results from a single center. III. Improved survival over 24 years. *J Rheumatol*. 1997; 24:1061–1065. [PubMed: 9195509]
6. Bematsky S, Boivin JF, Joseph L, et al. An international cohort study of cancer in systemic lupus erythematosus. *Arthritis Rheum*. 2005; 52:1481–1490. [PubMed: 15880596]
7. Bernatsky S, Ramsey-Goldman R, Rajan R, et al. Non-Hodgkin's lymphoma in systemic lupus erythematosus. *Ann Rheum Dis*. 2005; 64:1507–1509. [PubMed: 16162903]
8. Bjornadal L, Lofstrom B, Yin L, Lundberg IE, Ekbom A. Increased cancer incidence in a Swedish cohort of patients with systemic lupus erythematosus. *Scand J Rheumatol*. 2002; 31:66–71. [PubMed: 12109649]
9. Mellemkjaer L, Andersen V, Linet MS, Gridley G, Hoover R, Olsen JH. Non-Hodgkin's lymphoma and other cancers among a cohort of patients with systemic lupus erythematosus. *Arthritis Rheum*. 1997; 40:761–768. [PubMed: 9125261]
10. Pettersson T, Pukkala E, Teppo L, Friman C. Increased risk of cancer in patients with systemic lupus erythematosus. *Ann Rheum Dis*. 1992; 51:437–439. [PubMed: 1586239]
11. Ragnarsson O, Grondal G, Steinsson K. Risk of malignancy in an unselected cohort of Icelandic patients with systemic lupus erythematosus. *Lupus*. 2003; 12:687–691. [PubMed: 14514131]
12. Xu Y, Wiemik PH. Systemic lupus erythematosus and B-cell hematologic neoplasm. *Lupus*. 2001; 10:841–850. [PubMed: 11787873]
13. Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. *Arch Intern Med*. 2005; 165:2337–2344. [PubMed: 16287762]
14. Ramsey-Goldman R, Mattai SA, Schilling E, et al. Increased risk of malignancy in patients with systemic lupus erythematosus. *J Investig Med*. 1998; 46:217–222.
15. Sweeney DM, Manzi S, Janosky J, et al. Risk of malignancy in women with systemic lupus erythematosus. *J Rheumatol*. 1995; 22:1478–1482. [PubMed: 7473469]
16. Kinlen LJ. Malignancy in autoimmune diseases. *J Autoimmun*. 1992; 5(Suppl A):363–371. [PubMed: 1503633]
17. Bernatsky S, Clarke A, Ramsey-Goldman R. Malignancy and systemic lupus erythematosus. *Curr Rheumatol Rep*. 2002; 4:351–358. [PubMed: 12126588]
18. Oertel SH, Riess H. Immunosurveillance, immunodeficiency and lymphoproliferations. *Recent Results Cancer Res*. 2002; 159:1–8. [PubMed: 11785833]
19. Bhalla R, Ajmani HS, Kim WW, Swedler WI, Lazarevic MB, Skosey JL. Systemic lupus erythematosus and Hodgkin's lymphoma. *J Rheumatol*. 1993; 20:1316–1320. [PubMed: 8230011]
20. Black KA, Zilko PJ, Dawkins RL, Armstrong BK, Mastaglia GL. Cancer in connective tissue disease. *Arthritis Rheum*. 1982; 25:1130–1133. [PubMed: 7126297]
21. Canoso JJ, Cohen AS. Malignancy in a series of 70 patients with systemic lupus erythematosus. *Arthritis Rheum*. 1974; 17:383–390. [PubMed: 4604718]
22. Green JA, Dawson AA, Walker W. Systemic lupus erythematosus and lymphoma. *Lancet*. 1978; 2:753–756. [PubMed: 80683]
23. Abu-Shakra M, Gladman DD, Urowitz MB. Malignancy in systemic lupus erythematosus. *Arthritis Rheum*. 1996; 39:1050–1054.

24. Cibere J, Sibley J, Haga M. Systemic lupus erythematosus and the risk of malignancy. *Lupus*. 2001; 10:3900.
25. Nived O, Bengtsson A, Jonsen A, Sturfelt G, Olsson H. Malignancies during follow-up in an epidemiologically defined systemic lupus erythematosus inception cohort in southern Sweden. *Lupus*. 2001; 10:500–504. [PubMed: 11480849]
26. Sultan SM, Ioannou Y, Isenberg DA. Is there an association of malignancy with systemic lupus erythematosus? An analysis of 276 patients under long-term review. *Rheumatology (Oxford)*. 2000; 39:1147–1152. [PubMed: 11035137]
27. Services USDoHaH. ICD-9-CM: international classification of diseases, 9th Revision, Clinical modification. 6. Washington OC: 2000.
28. Cancer Reporting in California. Standards for automated reporting. California cancer reporting system standards, vol 11. California Department of Health Services, Cancer Surveillance Section; Sacramento, CA: Dec. 1997
29. Cancer Reporting in California. Data standards for regional registries and California Cancer Registry. California cancer reporting system standards. Vol. III. California Department of Health Services, Cancer Surveillance Section; Sacramento, CA: Dec. 1997
30. Cancer Reporting in California. Reporting procedures for physicians. California cancer reporting system standards. Vol. IV. California Department of Health Services, Cancer Surveillance Section; Sacramento, CA: Jan. 1998
31. Cancer Reporting in California. Abstracting and coding procedures for hospitals. California cancer reporting system standards. Vol. I. California Department of Health Services. Cancer Surveillance Section; Sacramento, CA: Jun. 1997
32. Chen, VW.; Howe, HL.; Wu, XC. Cancer in North America. 1993–1997. Volume I: incidence. North American Association of Central Cancer Registries; Springfield: 2000.
33. Seiffert JE, Price WT, Gordon B. The California tumor registry: a state-of-the-art model for a regionalized, automated, population-based registry. *Top Health Rec Manage*. 1990; 11:59–73. [PubMed: 10108499]
34. Integrity Program. Data reengineering environment soft- ware. Vality Technology Inc; Boston: 1999.
35. Allen, M. Validation of OSHPD and CCR insurance status. California Association of Central Cancer Registries Technical Conference; Riverside, CA. 2001.
36. Fritz, A.; Percy, C.; Jack, A., et al. International classification of diseases for oncology. 3. World Health Organization; Geneva: 2000.
37. Breslow, NE.; Day, NE. Statistical methods in cancer research, Volume II: the design and analysis of cohort studies. International Agency for Research on Cancer; Lyon: 1987.
38. Bematsky S, Boivin JF, Joseph L, et al. }Prevalence of factors influencing cancer risk in women with lupus: social habits, reproductive issues, and obesity. *J Rheumatol*. 2002; 29:2551–2554. [PubMed: 12465150]
39. Bruce IN, Gladman DD, Urowitz MB. Detection and modification of risk factors for coronary artery disease in patients with systemic lupus erythematosus: a quality improvement study. *Clin Exp Rheumatol*. 1998; 16:43540.
40. McAlindon T, Giannotta L, Taub N, D’Cruz D, Hughes G. Environmental factors predicting nephritis in systemic lupus erythematosus. *Ann Rheum Dis*. 1993; 52:720–724. [PubMed: 8257208]
41. Petri M, Perez-Gutthann S, Spence D, Hochberg MC. Risk factors for coronary artery disease in patients with systemic lupus erythematosus. *Am J Med*. 1992; 93:513–519. [PubMed: 1442853]
42. Rahman P, Urowitz MB, Gladman DD, Bruce IN, Genest J Jr. Contribution of traditional risk factors to coronary artery disease in patients with systemic lupus erythematosus. *J Rheumatol*. 1999; 26:2363–2368. [PubMed: 10555892]
43. Ahmed MM, Berney SM, Wolf RE, et al. Prevalence of active hepatitis C virus infection in patients with systemic lupus erythematosus. *Am J Med Sci*. 2006; 331:252–256. [PubMed: 16702794]
44. Berthier S, Mouglin C, Vercherin P, et al. Does a particular risk associated with papillomavirus infections exist in women with lupus? *Rev Med Interne*. 1999; 20:128–132.

45. Tam LS, Chan AY, Chan PK, Chang AR, Li EK. Increased prevalence of squamous intraepithelial lesions in systemic lupus erythematosus: association with human papillomavirus infection. *Arthritis Rheum.* 2004; 50:3619–3625. [PubMed: 15529372]
46. Thomas RH, Ridley CM, Black MM. Lichen sclerosus et atrophicus associated with systemic lupus erythematosus. *J Am Acad Dermatol.* 1985; 13:832–833. [PubMed: 4078083]
47. Gibbons RB, Westerman E. Acute nonlymphocytic leukemia following short-term, intermittent, intravenous cyclophosphamide treatment of lupus nephritis. *Arthritis Rheum.* 1988; 31:1552–1554. [PubMed: 3196367]
48. Lishner M, Hawker G, Amato D. Chronic lymphocytic leukemia in a patient with systemic lupus erythematosus. *Acta Haematol.* 1990; 84:38–39.
49. Rosenthal NS, Farhi DC. Myelodysplastic syndromes and acute myeloid leukemia in connective tissue disease after single-agent chemotherapy. *Am J Clin Pathol.* 1996; 106:676–679. [PubMed: 8929481]
50. Vasquez S, Kavanaugh AF, Schneider NR, Wacholtz MC, Lipsky PE. Acute nonlymphocytic leukemia after treatment of systemic lupus erythematosus with immunosuppressive agents. *J Rheumatol.* 1992; 19:1625–1627. [PubMed: 1464880]
51. Elliott RW, Essenhigh DM, Morley AR. Cyclophosphamide treatment of systemic lupus erythematosus: risk of bladder cancer exceeds benefit. *Br Med J (Clin Res Ed).* 1982; 284:1160–1161.
52. Ortiz A, Gonzalez-Parra E, Alvarez-Costa G, Egado J. Bladder cancer after cyclophosphamide therapy for lupus nephritis. *Nephron.* 1992; 60:378–379. [PubMed: 1565199]
53. Thrasher JB, Miller GJ, Wettlaufer JN. Bladder leiomyosarcoma following cyclophosphamide therapy for lupus nephritis. *J Urol.* 1990; 143:119–121. [PubMed: 2294239]
54. Bematsky S, Boivin JF, Joseph L, et al. Race/ethnicity and cancer occurrence in systemic lupus erythematosus. *Arthritis Rheum.* 2005; 53:781–784. [PubMed: 16208671]
55. Alarcon GS, Calvo-Alen I, McGwin G, et al. Systemic lupus erythematosus in a multiethnic cohort: LUMINA XXXV. Predictive factors of high disease activity over time. *Ann Rheum Dis.* 2006; 65(9):1168–1174. [PubMed: 16905579]
56. Bernatsky SR, Cooper GS, Mill C, Ramsey-Goldman R, Clarke AE, Pineau CA. Cancer screening in patients with systemic lupus erythematosus. *J Rheumatol.* 2006; 33:459.
57. Katz JN, Barrett J, Liang MH, et al. Sensitivity and positive predictive value of Medicare Part B physician claims for rheumatologic diagnoses and procedures. *Arthritis Rheum.* 1997; 40:1594–1600. [PubMed: 9324013]
58. Lofstrom B, Backlin C, Sundstrom C, Ekblom A, Lundberg IE. A closer look at non-Hodgkin's lymphoma cases in a national Swedish systemic lupus erythematosus cohort: a nested case-control study. *Ann Rheum Dis.* 2007; 66(12):1627–1632. [PubMed: 17517757]
59. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 1997; 40:1725. [PubMed: 9324032]

Table 1

Demographic characteristics of a cohort of patients with systemic lupus erythematosus (SLE), California, 1991–2002 ($n = 30,478$)

Variable	Whole cohort ($n = 30,478$) n (%)	SLE patients diagnosed with cancer ($n = 1,273$) n (%)
<i>Sex</i>		
Female	27,133 (89.0)	1,053 (82.7)
Male	3,345 (11.0)	220 (17.3)
<i>Age -at hospitalization</i>		
<40	10,801 (35.4)	177 (13.9)
40–59	11,293 (37.1)	447 (35.1)
60+	8,384 (27.5)	649 (51.0)
<i>Race</i>		
Non-Hispanic White	17,593 (57.7)	872 (68.5)
Non -Hispanic Black	4,504 (14.8)	143 (11.2)
Hispanic	5,661 (18.6)	182 (14.3)
Non-Hispanic Asian/Pacific Islander	2,052 (6.7)	61 (4.8)
Other/Unknown	668 (2.2)	15 (1.2)
<i>Period of hospitalization</i>		
1991–1994	11,252 (36.9)	731 (57.4)
1995–1998	10,857 (35.6)	419 (32.9)
1999–2001	8,369 (27.5)	123 (9.7)
<i>Period diagnosed with cancer</i>		
1991–1994	-	808 (14.6)
1995–1998	-	1,919 (34.7)
1999–2002	-	2,806 (50.7)

Table 2

Age and race adjusted standardized incidence ratios (SIRs) for selected cancers among a cohort of patients with systemic lupus erythematosus (SLE), California, 1991–2002 ($n = 30,478$)^a

Cancer type	Observed	Expected	SIR	95% CI
All cancers	1,273	1,120.8	1.14	1.07–1.20
Breast	237	311.9	0.76	0.67–0.86
Ovary	27	32.8	0.82	0.54–1.20
Uterus	29	48.1	0.60	0.40–0.87
Vagina/vulva	49	15.0	3.27	2.41–4.31
Cervix	38	69.7	0.55	0.39–0.75
Prostate	43	62.2	0.69	0.50–0.93
Lung	218	131.2	1.66	1.45–1.90
Esophagus	12	6.5	1.85	0.95–3.22
Stomach	18	14.6	1.23	0.73–1.95
Colon/rectum	99	108.2	0.91	0.74–1.11
Liver	17	6.4	2.70	1.54–4.24
Pancreas	25	22.1	1.13	0.73–1.67
Bladder	31	28.0	1.11	0.75–1.57
Kidney	38	17.7	2.15	1.52–2.94
Thyroid	30	16.4	1.83	1.24–2.62
Br. l.in/CNS	18	11.2	1.61	0.95–2.54
Non-Hodgkin's lymphoma	96	35.1	2.74	2.22–3.34
Large B-cell	42	12.9	3.26	2.33–4.39
Follicular	26	9.0	2.89	1.88–4.22
Hodgkin's disease	13	4.3	3.02	1.60–5.13
Leukemia	43	20.2	2.13	1.49–2.77
Lymphoid	9	8.7	1.03	0.47–1.96
Myeloid	29	9.8	2.96	1.99–4.26
Monocytic	2	0.4	5.00	0.68–20.17
Myeloma	15	11.1	1.35	0.76–2.23
Melanoma	37	54.9	0.67	0.47–0.93

^aSIR = standardized incidence ratio; CI = confidence interval

Table 3

Race-specific standardized incidence ratios for selected cancers among a cohort of patients with systemic lupus erythematosus (SLE), California, 1991–2002 ($n = 30,478$)^a

Race	Observed	Expected	SIR	95% CI
Breast				
Non-Hispanic white	165	230.6	0.72	0.61–0.83
Non-Hispanic black	31	35.8	0.87	0.58–1.23
Hispanic	31	27.1	1.15	0.79–1.63
Non-Hispanic Asian/Pacific Islander Lung	8	9.7	0.83	0.36–1.63
Non-Hispanic white	176	105.4	1.67	1.43–1.94
Non-Hispanic black	22	15.0	1.47	0.92–2.23
Hispanic	14	6.7	2.09	1.17–3.58
Non-Hispanic Asian/Pacific Islander	5	2.9	1.72	0.56–4.02
Kidney				
Non-Hispanic white	19	12.7	1.50	0.90–2.34
Non-Hispanic black	9	2.1	4.29	1.93–8.04
Hispanic	8	2.3	3.48	1.53–7.00
Non-Hispanic Asian/Pacific Islander		0.4	2.50	0.62–14.02
NHL				
Non-Hispanic white	59	25.5	2.31	1.76–2.98
Non-Hispanic black	7	3.0	2.33	0.93–4.75
Hispanic	22	3.6	6.11	3.80–9.18
Non-Hispanic Asian/Pacific Islander	8	1.1	7.27	3.08–14.07
Vagina/Vulva				
Non-Hispanic white	19	9.7	1.96	1.19–3.07
Non-Hispanic black	6	1.7	3.53	1.33–7.87
Hispanic	19	1.3	14.62	8.93–23.15
Non-Hispanic Asian/Pacific Islander	4	.02	20.00	4.83–45.35

^aSIR = standardized incidence ratio; CI = confidence interval

Table 4

Age-specific standardized incidence ratios for selected cancers among a hospitalized cohort of patients with systemic lupus erythematosus (SLE), California, 1991–2002 ($n = 30,478$)^a

Age at hospitalization	Observed	Expected	SIR	95% CI
Breast				
<30	6	1.2	5.00	1.91–11.3
30–44	45	38.0	1.18	0.86–1.58
45–59	84	106.3	0.79	0.63–0.98
60	102	166.8	0.61	0.50–0.74
Lung				
<30	6	1.2	5.00	1.91–11.3
30–44	45	38.0	1.18	0.86–1.58
45–59	84	106.3	0.79	0.63–0.98
60	102	166.8	0.61	0.50–0.74
Kidney				
<30	6	1.2	5.00	1.91–11.3
30–44	45	38.0	1.18	0.86–1.58
45–59	84	106.3	0.79	0.63–0.98
60	102	166.8	0.61	0.50–0.74
NHL				
<30	6	1.2	5.00	1.91–11.3
30–44	45	38.0	1.18	0.86–1.58
45–59	84	106.3	0.79	0.63–0.98
60	102	166.8	0.61	0.50–0.74
Vagina/Vulva				
<30	6	1.2	5.00	1.91–11.3
30–44	45	38.0	1.18	0.86–1.58
45–59	84	106.3	0.79	0.63–0.98
60	102	166.8	0.61	0.50–0.74

^aSIR = standardized incidence ratio; CI = confidence interval