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A Danish nationwide cohort study

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Increased cancer risk in patients with cutaneous lupus erythematosus and systemic lupus erythematosus compared with the general population: a Danish nationwide cohort study

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ABSTRACT

Objectives

To investigate if patients with cutaneous lupus erythematosus (CLE) or systemic lupus erythematosus (SLE) have an increased risk of cancer compared with the general population, and furthermore to identify specific cancer types associated with increased risk.

Methods

This is an observational cohort study of 5310 patients with CLE or SLE identified in the Danish National Patient Register from 1 January 1995 to 31 December 2014. The cohort was followed up for cancer by linkage to the Danish Cancer Registry. Based on the age, sex, and calendar specific cancer rates of the general population of Denmark, standardised incidence ratios (SIRs) were calculated.

Results

The patients with CLE or SLE were followed for 40.724 person-years, each group's average duration of follow-up being 6.9 and 8.1 years. The SIR for overall cancer (except non-melanoma skin cancer (NMSC)) was increased in patients with CLE 1.35 (95%CI 1.15 to 1.58) and patients with SLE 1.45 (95%CI 1.30 to 1.62). Both groups had high risks of hematological – including a 3-4-fold increased risk of non-Hodgkin lymphoma –, pancreatic, and lung cancers. Several cancers associated with oncogenic viruses as liver and tongue/mouth/pharynx were increased in the SLE group, while the risk of ovarian cancer was increased 2-4-fold only in the CLE group.

Conclusion

The overall risk of cancer was significantly increased in both patients with CLE and SLE. SIRs for hematological, pancreatic and lung cancers were elevated in both groups. Extra awareness of cancer in patients with SLE *and* patients with CLE should be considered.

Keywords

Cutaneous Lupus Erythematosus
Systemic Lupus Erythematosus
Cancer
Autoimmune Diseases
Epidemiology

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic systemic inflammatory disease with various manifestations including involvement of joints, skin, blood, brain, and kidneys.[1-4] Cutaneous lupus erythematosus (CLE) can occur independently of SLE, characterised by the presence of primarily skin symptoms, or as a manifestation of SLE.[5] Indeed, the acute type of CLE exists almost exclusively in combination with SLE. CLE may persist localised to the skin; however, it can also progress to SLE.

The link between SLE/CLE and cancer remains unclear. While studies indicating that SLE is associated with an overall elevated risk of cancer compared with the general population exist,[6-15] the size and magnitude of the risk varies – including both increased and decreased risks for different types of cancer. Potential factors mediating the increased risk include intrinsic autoimmune properties such as chronic inflammation, use of immunosuppressive drugs (ISDs), virus susceptibility, and external environmental factors such as smoking.[1, 6] In case the increased cancer risk mainly is driven by inflammatory load and immunosuppression, the cancer risk may be lower in patients with CLE, who experience more limited disease and less aggressive treatment compared with patients with SLE. Various cancers have been linked with an increased occurrence in SLE, e.g. non-Hodgkin lymphoma (NHL), lung, skin, and cancers associated with oncogenic viruses.[6-15] In contrast, SLE seem to play a "protective" role in hormone-sensitive cancers such as breast and prostate.[16-19] To our knowledge only two studies investigating the overall risk of cancer for patients with CLE exist, and the results are contradictory.[20, 21]

METHODS

Study design

The study is a register-based cohort study with a study period from 1 January 1995 to 31 December 2014. We examine the cancer risk in patients with CLE and patients with SLE.

Data sources

To conduct the study, nationwide Danish health registers were used. Accurate linkage between nationwide Danish health registers is possible on an individual-based level in Denmark by using the unique civil registration number (CPR-number) assigned at birth or upon immigration. From the Danish Civil Registration System (CRS), information on date of birth, sex, migration, and vital status was collected.[22] Diagnoses of SLE and CLE were acquired from the Danish

National Patient Register (DNPR).[23, 24] DNPR contains information on all inpatient (since 1977) and outpatient (since 1995) contacts at Danish hospitals. DNPR covers both administrative data such as CPR-numbers and clinical data comprising diagnoses codes. Since 1994 all diagnosis codes have been coded according to International Classification of Diseases-10 (ICD-10), with previous coding according to ICD-8. Information on cancer diagnoses in the cohort comes from linkage to the Danish Cancer Registry (DCR).[25-27] All cancers in Denmark have been registered in DCR since 1943. Based upon manual notification forms until 2003, the register underwent a modernisation and has since 2004 been automatised through linkage between various registers. In DCR all tumors back to 1978 are converted into ICD-10 codes by use of ICD-O morphology and topography codes. Completeness of the cancer registry has been reported to be high.[27-29]

Study population

Patients registered with a first-time hospital diagnosis code of CLE or SLE in the DNPR during the study period were eligible. The date of the first-time hospital diagnosis code served as the index date/baseline. Patients were excluded if they were < 18 years at the time of CLE/SLE diagnosis or had a history of cancer (except non-melanoma skin cancer (NMSC)) prior to their index date.

Follow-up for cancer started at the index date and ended at the date of cancer, emigration, death, or on 31 December 2014, whichever came first. In patients who had both a SLE and a CLE diagnosis recorded, the SLE diagnosis overruled the CLE diagnosis. If the CLE diagnosis was registered first, the patient contributed with person-years of follow-up to the CLE cohort until the date of the SLE diagnosis, from which on the individual contributed with person years of follow-up to the SLE cohort. (See *Figure 1 and Figure 2)*

Outcomes

The primary outcome was defined as any cancer diagnosis (except NMSC) registered in the DCR during follow-up. Secondary outcomes were defined as site-specific cancer diagnoses (including NMSC) registered in the DCR during the same span of follow-up.

Statistical methods

The observed number of cancers in the CLE and SLE groups were compared with the expected number of cancers in the general population, and standardised incidence ratios (SIRs) were calculated. We calculated the expected number of cancers by multiplying the number of person-years experienced by members of the respective groups by appropriate national cancer incidence rates among Danish men and women in 5-year age groups and 5-year calendar time periods of observation. Corresponding 95% confidence intervals (95%CI) were calculated assuming a Poisson distribution for the observed number of cancers. All calculations were performed using R version 3.6.1. 95%CIs not crossing unity were considered statistically significant.

Sensitivity analysis

The sensitivity analysis was performed by introducing two additional stepwise criteria before study eligibility. Firstly, we excluded all diagnosis codes of drug-induced SLE (M32.0, ICD-10). Drug-induced and idiopathic SLE cases share similar features, but the former often presents a milder and limited course of disease.[30] While cases of drug-induced CLE also exist, these are not registered by a specific ICD code, and thus cannot be identified in the DNPR. Secondly, to potentially increase the validity of both CLE and SLE definitions, a first-time diagnosis had to be followed by a subsequent diagnosis code, i.e. patients with CLE required two CLE diagnosis codes and patients with SLE required two SLE diagnosis codes for eligibility. The date of the latter registration then served as the index date.

Ethical concerns

This study complies with the Declaration of Helsinki. Approval from the ethics committee is not required for registry-based research in Denmark. The study was approved by the Danish Data Protection Agency *(J.nr. 2007-58-0015 / local j.nr. GEH-2014-018, I-Suite nr. 02736)*

RESULTS

Baseline characteristics

A total of 5310 patients were eligible for follow-up. The cohort consisted of 3424 patients with SLE (84.1% women) and 1886 patients with CLE (78.0% women). Of these, 356 patients had a first-time CLE followed by a subsequent first-

time SLE diagnosis, thus contributing person-years to both groups. Average age at the time of diagnosis was 47.8 years for SLE and 51.5 years for CLE. (*See Figure 2)*

Overall risk of cancer

The 3424 patients with SLE and 1886 patients with CLE were followed for 27,676 and 13,048 person-years with corresponding mean follow-up times of 8.1 and 6.9 years, respectively. Based on 308 (SLE) and 155 (CLE) cancers, SIRs for overall cancer (except NMSC) was 1.45 (95%CI 1.30 to 1.62) in the SLE group and 1.35 (95%CI 1.15 to 1.58) in the CLE group. (*see Tables 1 and 2*) When stratified by sex, follow-up time, and age groups, all SIRs remained increased. SIRs for the first year of follow-up were highly increased in both groups.

Site-specific cancer risk

Table 3 presents SIRs for selected cancer sites in patients with SLE. Hematological cancers, particularly NHL 4.40 (95%CI 2.87 to 6.44) and Hodgkin's lymphoma 8.14 (95%CI 2.64 to 19.00), were all significantly increased. Other virus-associated cancers such as liver and mouth/tongue/pharynx were also elevated. Additional sites with increased SIRs included lung, esophagus, pancreas, meninges, melanoma and NMSC.

In the CLE group, SIRs for some hematological cancers were also increased, including NHL 2.97 (95%CI 1.42 to 5.47), while SIRs for lung and pancreatic cancers were elevated as well. Notably, the risk of ovarian cancer was quite high 2.22 (0.89 to 4.58). *(see Table 4)*

Also, the mean age at diagnosis of NHL was a little higher in the SLE group than in CLE group, 66.2 years versus 63.4 years, respectively.

Sensitivity analysis

When excluding drug-induced SLE and requiring two SLE/CLE diagnosis codes, the SIRs for overall cancer were not markedly altered: 1.45 to 1.36 (95%CI 1.16 to 1.58) in SLE and from 1.35 to 1.49 (95%CI 1.17 to 1.86) in CLE. In both groups, sex, time since diagnosis, and age group stratifications maintained increased SIRs and with risk estimates bearing close resemblance to those of the primary analyses. The only exception was the 10+ years follow-up strata in the CLE group now showing a lower SIR.

Only small changes were elicited in site-specific SIRs in the SLE group, which still had increased SIRs for several cancer sites, once again particularly NHL 4.50 (95%CI 2.52 to 7.43). The CLE group maintained an increased risk of lung cancer, while SIRs for NHL and ovarian cancer were further increased compared with the primary analysis: 4.76 (95%CI 1.91 to 9.81) and 4.33 (95%CI 1.59 to 9.42), respectively.
(See Supplementary Tables S1-S4).

DISCUSSION

In this nationwide study investigating the cancer incidence in patients with SLE and CLE compared with the general population, we found a statistically significant increased overall risk of cancer in both groups, but with slightly higher estimates for SLE than for CLE. The elevated risk of cancer was present in all strata regardless of sex, time since diagnosis, and age group, but both SLE and CLE groups had a particularly increased risk during the first year of follow-up. Both also had increased risks of hematological, pancreatic and lung cancers. Virus-associated cancer sites as liver and tongue/mouth/pharynx showed increased SIRs in the SLE group, while the risk of ovarian cancer was increased only in the CLE group.

Our findings for overall cancer risk in patients with SLE are in accordance with results from previous studies of patients with SLE,[6-15] e.g. pooled overall risks of cancer in two meta-analyses were 1.28 (95%CI 1.17 to 1.41) and 1.44 (95%CI 1.23 to 1.69) compared with the general population.[12, 15] To our knowledge only two studies have previously described the overall risk of cancer for patients with CLE.[20, 21] Grönhagen et al. found a hazard ratio (HR) of 1.7 (95%CI 1.3 to 2.1) after excluding patients also diagnosed with SLE,[20] while Singh et al. found no significant increase: HR 1.07 (95%CI 0.61 to 1.87) when excluding NMSC,[21] – both compared with the general population. In the present study, patients with SLE and CLE had highly elevated SIRs in the first year of follow-up. With similar observations in other studies of SLE and CLE,[8, 20] an explanation for this could be increased medical scrutiny around the time of SLE/CLE diagnosis.

Hematological cancers all showed increased SIRs in the SLE group. These results corroborate current consensus regarding SLE and hematological cancers.[6-15] The CLE group also had increased SIRs for NHL and myeloid/lymphatic leukemias. Increased incidences of hematological cancers in CLE were similarly found by Grönhagen et al. (Lymphoma HR 4.3, 95%CI 1.3 to 15.0; hematopoietic cancers HR 2.6, 95%CI 1.2 to 5.8) and a study by Fallah et al. (NHL SIR 2.7, 95%CI 1.6 to 4.1).[20, 31]

Perhaps the chronic immune dysregulation central to SLE and CLE,[1, 32] a series of complex immune system mechanisms including aberrant T- and B-lymphocyte function, can cause uncontrolled activation and proliferation of lymphocytes to such an extent that it increases the likelihood of malignant transformation of lymphocytes as seen in Hodgkin's lymphoma, NHL, multiple myeloma and lymphatic leukemias.[33] Also, a study by Bernatsky et al. investigated the association between ISDs and development of lymphomas in patients with SLE. They found that cyclophosphamide and a high cumulative dose of systemic steroid use was associated with a higher risk, while disease activity itself was not clearly associated with lymphoma risk.[34] In CLE, topical steroids and behavior of restrictive sun exposure are the main treatment modalities. While cyclophosphamide is not used for CLE, treatment with systemic steroids are sometimes used in refractory or widespread CLE cases.[32] However, patients with CLE exposed to high cumulative doses of systemic steroid are a rarity. Therefore, even if extrapolating the results by Bernatsky et al. regarding the association between certain ISDs and increased risk of lymphomas from patients with SLE to patients with CLE, ISD use still presents an unlikely explanation for the increased occurrence of some hematological cancers in the CLE group.[34] Alternatively, the high risk of NHL could be influenced by Sjögren's syndrome (SS) - particularly among patients with SLE. SS is divided into primary Sjögren's syndrome (pSS) when occurring on its own, and secondary Sjögren's syndrome when in combination with other systemic inflammatory disease. pSS is associated with a 15-20 fold increased risk of lymphomas, of which most are NHL, relative to the general population. Meanwhile, pSS and SLE have many clinical and paraclinical similarities, and so diagnosis of pSS previous to SLE could confound the NHL SIR-estimates.[35, 36] To investigate such potential confounding by pSS, we cross-linked the patients that had NHL with the DNPR, hereby collecting information on all diagnoses of Sjögren's (M35.0, ICD-10). In summary, among patients with SLE diagnosed with NHL, 5 out of 26 patients had a SS diagnosis registered. However, all 5 qualified as secondary Sjogren's, i.e. 1st diagnosis was registered after SLE diagnosis. Among patients with CLE diagnosed with NHL, 0 out of 10 patients had a SS diagnosis registered. Thus, pSS does not appear to be a reasonable explanation for the increased incidences of NHL in either group.

Several cancer sites associated with oncogenic viruses such as liver (Hepatitis B and C virus), tongue/mouth/pharynx (Human Papilloma Virus; HPV), hematological (Epstein-Barr virus and Hepatitis C virus) and potentially also NMSC despite more limited evidence (Merkel cell polyomavirus and HPV types 5 and 8) had increased SIRs in the SLE group.[37, 38] Meanwhile, the CLE group only showed an increase in hematological cancers.

It has been demonstrated that HIV patients with low CD4 cell counts are prone to experience virus-associated malignancies,[39] and some patients with SLE similarly suffer from suppressed lymphocytes.[2, 10] Also, heavy ISD exposure could inhibit the immune system's ability to clear oncogenic viruses. In accordance with this, tongue/mouth/pharynx cancer, sites strongly associated with HPV-16,[40] was found highly increased in our SLE group. Additionally, women with SLE may experience defective clearance of cervical HPV.[41] This is supported by two Danish and Swedish studies, which found increased occurrences of pre-malignant cervical lesions in patients with SLE.[10, 42] We did not find an increased risk of cervical cancer in SLE, yet this could be attributed to the extensive cervical cancer screening program in Denmark.

Various studies have reported increased incidences of NMSC in patients with SLE and CLE compared with the general population.[10, 12, 20] While the SIR for NMSC in our SLE group supports this consensus, that was not the case in the CLE group: 0.84 (95%CI 0.60 to 1.19). This is in direct contrast to what was previously reported by Grönhagen et al., who found an elevated risk of NMSC (HR 2.8, 95%CI 1.2 to 6.2). NMSC is a well-known complication to some ISDs, which is a possible explanation for the increased risk in the more ISD exposed SLE group compared with both the CLE group and the general population. However, one would still think that the thorough skin examinations experienced by CLE patients would lead to more NMSCs being diagnosed compared with the general population. On the other hand, the behavior of restricted sun exposure could explain the lower risk of developing NMSC.

Our study did not find statistically significant risk reductions for hormone-sensitive cancers among patients with SLE. However, the decreased SIRs for breast and prostate cancer in the primary and even more in the sensitivity analysis, do indeed indicate a "protective" role of SLE as reported in other studies.[16-19] The incidences of breast and prostate cancer were not similarly lowered in the CLE group. Instead the patients with CLE somewhat surprisingly had an increased risk of ovarian cancer – a risk that was particularly high in the sensitivity analysis. To our knowledge, this is a novel finding. An explanation could be that paraneoplastic skin manifestations of ovarian cancer were wrongly classified as CLE.[43] However, paraneoplastic skin manifestations of ovarian cancer are quite rare, and even if it was the cause, it would be suspected that the cancer diagnoses were registered within the first year of follow-up due to medical scrutiny. Looking at our data (not shown), zero cases of ovarian cancer were registered during the first year of follow-up. Thus, the most likely explanation is probably finding an increased risk by chance, which is a well-known phenomenon in subgroup analysis. That being said, elevated SIRs in both the primary and the sensitivity analysis are

concerning, and we encourage that the association between CLE and ovarian cancer is further investigated in future studies.

There are limitations in this study that needs mentioning. In Denmark, all patients with SLE are followed and treated in hospital care and are therefore expected to be registered in the DNPR. This is not the case for all patients with CLE, who are also treated in the primary sector. Hence, the CLE patients identified in this study could reflect a selected group of patients with severe manifestations of CLE. If so, the results cannot necessarily be generalised to milder cases. Detection bias is also a concern; patients with SLE and CLE are subjected to more medical scrutiny compared with the general population, potentially increasing the chance of finding any type of cancer. Also, the DNPR do not register specific disease manifestations, neither clinical nor paraclinical, e.g. information on autoantibodies, and so it is not possible to identify specific clusters of patients that could have a particular cancer pattern. Additionally, manifestations of some cancers might mimic either SLE or CLE. This would lead to "false" SLE/CLE diagnoses, shortly after which the cancer is identified – hereby leading to an overestimation of cancer risk in our cohort. Indeed, stratification by follow-up time revealed that both patients with SLE and CLE showed particularly elevated SIRs in the first year of follow-up. Nonetheless, all follow-up time strata showed increased risk. Furthermore, we were not able to collect information on and adjust for smoking, a potential confounder.[3, 5, 21, 37, 44] It has been shown that smoking is the single most modifiable risk for lung cancer in patients with SLE.[45] Similarly, smoking could elevate the risk of lung cancer and potentially other smoking related cancer sites in our cohort.[37, 38, 40, 46, 47]

The strengths of the study lie in the use of national health registries. Cross-linking by CPR number provides an array of information and nullifies loss to follow-up. With mean follow-up durations of 8.1 (SLE) and 6.9 (CLE) years, and up to nearly 20 years of follow-up for many patients, our study provides time for the development of cancer. Additionally, a total of 27,676 (SLE) and 13,048 (CLE) person-years supplies the study with a large amount of power. Although our study is unable to provide an exact validation of the diagnosis codes, Hermansen et al. used a SLE-identification algorithm very similar to that of our primary analysis and found a positive predictive value of 73%.[48] While some degree of undifferentiated misclassification is therefore likely and we might have underestimated the true cancer risk, our sensitivity analysis, in which we tried to increase the validity of both SLE and CLE diagnoses, showed small SIR-alterations compared with the primary analysis. Moreover, completeness of the DCR has previously been reported to

be high.[27-29] Using SIR calculations we were able to standardise for important confounders such as sex, age, and calendar year, with the expected number of cancers based upon the entire Danish population. Together this makes the SIR calculations a powerful tool for estimating the risk of cancer. This study does not provide evidence regarding the causal relationship between SLE/CLE and cancer, but it calls for extra awareness of cancer in both patients with SLE and CLE.

CONCLUSION

Our study supports existing evidence that patients with SLE experience an increased incidence of cancer compared with the general population. We also found an increased risk of overall cancer for patients with CLE. Both groups showed increased risks of hematological, pancreatic and lung cancers. Patients with SLE experienced elevated risks for several cancer sites, while our study also showed a potential novel finding of an increased risk of ovarian cancer in patients with CLE. Generally, risk estimates for cancer were higher for SLE than for CLE, but our study underlines the importance of increased attentiveness to cancer in both patients with SLE *and* patients with CLE.

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Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

Data Availability Statement

The data underlying this article cannot be shared publicly due to compliance with the European General Data Protection Regulation (GDPR) and the privacy of individuals. In accordance with GDRP, the Danish health registers and Statistics Denmark prohibit extraction of data making individuals identifiable. Some additional data can be shared upon reasonable request to the corresponding author.

SUMMARY

Introduction

- Previous studies have linked systemic lupus erythematosus (SLE) to an increased risk of cancer, with risk estimates ranging widely, while cutaneous lupus erythematosus' (CLE) association to overall cancer as well as specific cancer sites remains almost unstudied.

Results

- In this cohort study spanning three decades, patients with CLE and SLE experienced 35% and 45% more cancers compared with the general population, certain sites such as lung, pancreatic, and hematological cancers showing several fold increased risks. The risks of several cancers associated with oncogenic viruses were high in SLE, while patients with CLE had a high risk of ovarian cancer.

Interpretation

- Our study calls for extra awareness of cancer in both patients with SLE and patients with CLE, particularly of symptoms from sites associated with high incidence rates compared with the general population.
- Worldwide, this is one of the first studies to investigate the overall cancer incidence in patients with CLE.

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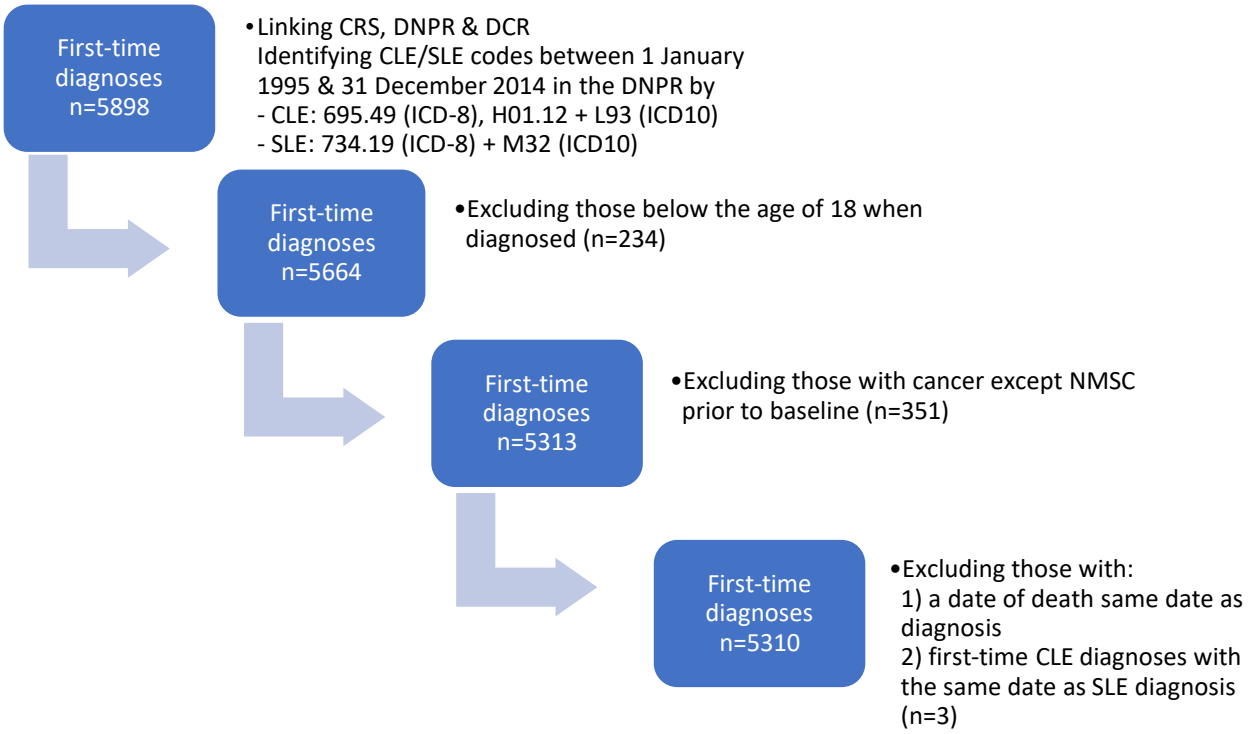
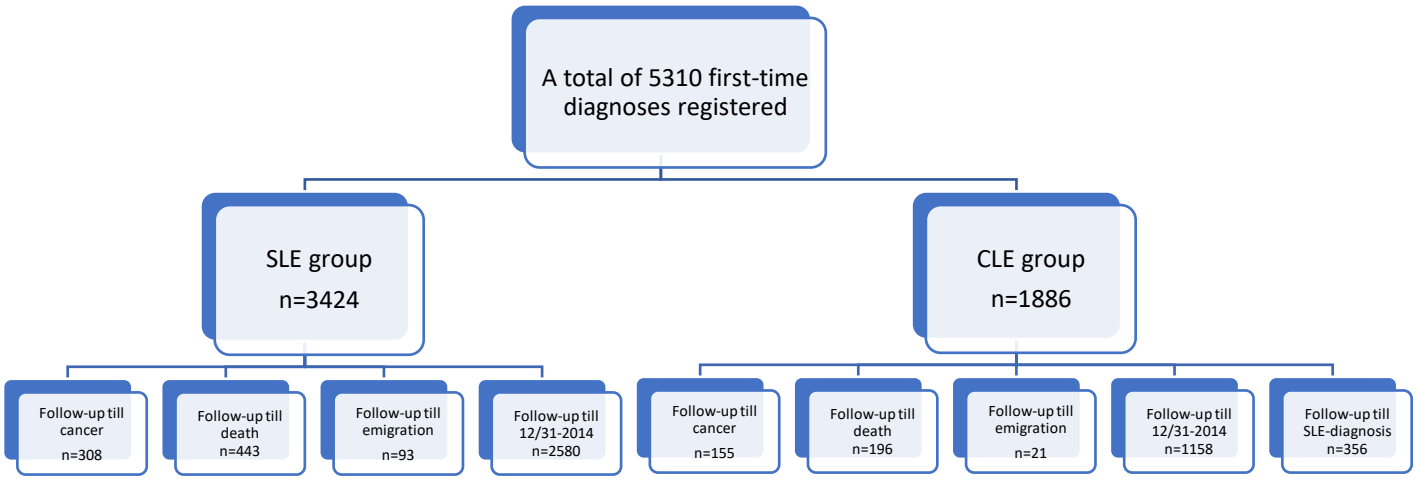
FIGURES AND TABLES

Figure 1: Identification of study population



CLE = Cutaneous lupus erythematosus, SLE = Systemic lupus erythematosus, CRS = the Civil Registration System, DNPR = The Danish National Patient Register, DCR = the Danish Cancer Registry, ICD = International Classification of Diseases, NMSC = non-melanoma skin cancer, n = number of diagnoses.

Figure 2: CLE/SLE distribution of follow-up



CLE = Cutaneous lupus erythematosus, SLE = Systemic lupus erythematosus, n = number of patients.

Table 1: Standardised incidence ratios (SIRs) for cancer in 3424 systemic lupus erythematosus (SLE) patients according to sex, time since diagnosis, and age.

Cancer (except NMSC)	Observed cancers	Expected cancers	PYRS	SIR (95%CI)
All	308	212.0	27,676	1.45 (1.30 to 1.62)
Female	246	170.0	23,925	1.45 (1.27 to 1.64)
Male	62	42.0	3,751	1.48 (1.13 to 1.89)
Time since SLE diagnosis				
< 1 year	52	20.3	3,213	2.56 (1.91 to 3.36)
1-4 years	103	70.3	10,270	1.47 (1.20 to 1.78)
4-9 years	83	64.4	8,163	1.29 (1.03 to 1.60)
10+ years	70	57.0	6,030	1.23 (0.96 to 1.55)
Age				
< 40 years	11	9.0	7,201	1.23 (0.61 to 2.20)
40-60 years	94	67.0	12,309	1.41 (1.14 to 1.73)
60+ years	203	137.0	8,166	1.49 (1.29 to 1.71)

NMSC = non-melanoma skin cancer, PYRS = Person-years of follow-up, CI = Confidence Interval.

Table 2: Standardised incidence ratios (SIRs) for cancer in 1886 cutaneous lupus erythematosus (CLE) patients according to sex, time since diagnosis, and age.

Cancer (except NMSC)	Observed cancers	Expected cancers	PYRS	SIR (95%CI)
All	155	114.7	13,048	1.35 (1.15 to 1.58)
Female	119	87.5	10,092	1.36 (1.13 to 1.63)
Male	36	27.2	2,956	1.32 (0.93 to 1.83)
Time since CLE diagnosis				
< 1 year	29	12.8	1,681	2.26 (1.51 to 3.24)
1-4 years	53	40.2	4,955	1.32 (0.99 to 1.72)
4-9 years	41	34.2	3,797	1.20 (0.86 to 1.63)
10+ years	32	27.4	2,615	1.17 (0.80 to 1.65)
Age				
< 40 years	6	2.9	2,369	2.04 (0.75 to 4.43)
40-60 years	49	31.4	5,962	1.56 (1.15 to 2.06)
60+ years	100	80.3	4,717	1.24 (1.01 to 1.51)

NMSC = non-melanoma skin cancer, PYRS = Person-years of follow-up, CI = Confidence Interval.

Table 3: Standardised incidence ratios (SIRs) for specific cancer sites in 3424 systemic lupus erythematosus (SLE) patients during 27,676 person-years of follow-up.

Cancer sites	Observed cancers	Expected cancers	SIR (95%CI)
Hodgkin's lymphoma	5	0.6	8.14 (2.64 to 19.00)
NHL	26	5.9	4.40 (2.87 to 6.44)
Multiple myeloma	7	2.1	3.29 (1.32 to 6.79)
Myeloid/Lymphatic leukemias	9	4.0	2.23 (1.16 to 4.29)
Tongue/Mouth/ Pharynx	13	3.5	3.68 (2.14 to 6.34)
Esophagus	7	1.9	3.60 (1.45 to 7.42)
Colon/Rectum	21	24.5	0.86 (0.56 to 1.32)
Liver	4	1.6	2.47 (0.67 to 6.33)
Pancreas	12	5.4	2.22 (1.15 to 3.88)
Lung	66	25.8	2.56 (1.98 to 3.25)
Melanoma	16	12.2	1.31 (0.75 to 2.13)
NMSC	91	71.2	1.28 (1.04 to 1.57)
Breast	43	53.3	0.81 (0.58 to 1.09)
Cervix	4	4.6	0.88 (0.24 to 2.25)
Uterus	8	8.1	0.99 (0.43 to 1.94)
Ovary	7	6.2	1.14 (0.46 to 2.34)
Prostate	8	10.7	0.75 (0.32 to 1.48)
Bladder	6	7.8	0.77 (0.28 to 1.67)
Meninges	11	3.3	3.36 (1.68 to 6.01)
Brain	4	4.6	0.86 (0.23 to 2.20)
Other sites [a]	31	25.8	1.20 (0.84 to 1.71)

NMSC = non-melanoma skin cancer, NHL = non-Hodgkin lymphoma, CI = Confidence Interval.

[a] Other sites: All cancer sites not shown in the table combined, none of which had 4 or more observations per site.

Table 4: Standardised incidence ratios (SIRs) for specific cancer sites in 1886 cutaneous lupus erythematosus (CLE) patients during 13,048 person-years of follow-up.

Cancer sites	Observed cancers	Expected cancers	SIR (95%CI)
Hodgkin's lymphoma	<4	0.3	- [b]
NHL	10	3.4	2.97 (1.43 to 5.47)
Multiple myeloma	<4	1.2	-
Myeloid/Lymphatic leukemias	5	2.3	2.17 (0.90 to 5.20)
Tongue/Mouth/ Pharynx	<4	2.1	-
Esophagus	<4	1.2	-
Colon/Rectum	10	14.3	0.70 (0.38 to 1.30)
Liver	<4	1.0	-
Pancreas	7	3.2	2.21 (0.89 to 4.56)
Lung	40	14.5	2.76 (1.97 to 3.76)
Melanoma	<4	6.0	-
NMSC	33	39.1	0.84 (0.60 to 1.19)
Breast	27	26.1	1.03 (0.68 to 1.50)
Cervix	<4	1.9	-
Uterus	7	4.2	1.65 (0.67 to 3.41)
Ovary	7	3.2	2.22 (0.89 to 4.58)
Prostate	6	6.7	0.90 (0.33 to 1.96)
Bladder	4	4.6	0.87 (0.24 to 2.23)
Meninges	<4	1.7	-
Brain	<4	2.4	-
Other sites [a]	16	14.6	1.09 (0.67 to 1.79)
All sites <4 combined	16	17.7	0.90 (0.55 to 1.48)

NMSC = non-melanoma skin cancer, NHL = non-Hodgkin lymphoma, CI = Confidence Interval.

[a] Other sites: All cancer sites not shown in the table combined, none of which had 4 or more observations per site.

[b] Calculations not available for display when the observed number of cancers per site were below 4 (<4).