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**CUTANEOUS LUPUS
ERYTHEMATOSUS; EPIDEMIOLOGY,
ASSOCIATION WITH SLE AND
COMORBIDITY**

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Cover: A butterfly in Skåne, photograph taken by Gustaf Grönhagen. A “butterfly rash” is a typical manifestation of acute CLE and a butterfly is also the symbol of the European Society of cutaneous lupus erythematosus (EUSCLE).

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Science is the literature of truth

Josh Billings (Henry Wheeler Shaw) (1818-85)

To Mum and Dad and Gustaf

Abstract

Lupus erythematosus (LE) is a disease that includes a broad spectrum of symptoms, from localized cutaneous LE (CLE) to severe systemic LE (SLE). Based on histopathological changes, the skin manifestations of LE can be divided into LE-specific (=CLE) and LE-non-specific manifestations. CLE is a chronic, inflammatory skin disease with a wide range of manifestations that can be seen in patients with or without SLE. As defined by clinical symptoms, average duration of symptoms, histological and serological findings, CLE can be further divided into three main subsets (acute CLE [ACLE], subacute CLE [SCLE] and chronic CLE [CCLE]). All four studies in this thesis focused on CLE and different comorbidities: the classification of cutaneous manifestations in SLE patients, the risk for progression to SLE, risk for cancer among CLE patients and the association between drug exposure and the development of subacute CLE.

In study I we investigated the frequency of cutaneous manifestations in a cohort of 260 SLE patients. We compared clinical and serological manifestations in SLE patients with and without CLE. LE-non-specific skin manifestations (43 %) were almost twice as frequent as CLE (23 %). Raynaud's phenomenon was significantly more common but arthritis and serositis were less common in the CLE group than in the non-CLE group. Of the SLE patients, 42 % had symptoms consistent with polymorphic light eruption.

In study II a cohort study of 1,088 CLE patients from the National Patient Register was undertaken to calculate the incidence of CLE in Sweden. The incidence rate was estimated to 4.0/100,000 inhabitants. We also calculated age- and gender-specific incidence rates for different CLE subsets (i.e. discoid LE, SCLE and other local LE). We estimated the probability of also being diagnosed with SLE during the first 3 years after diagnosis of CLE. We found the cumulative probability of receiving an additional diagnosis of SLE to be 18 %, highest for women and the SCLE subset.

In study III we evaluated the overall and specific cancer risks in CLE patients. In a cohort of 3,663 CLE patients we found increased risks for cancer overall (hazard ratio 1.8 (95 % confidence interval 1.5-2.2) and about a fourfold increased risk for buccal cancer, lymphomas, respiratory cancer and non-melanoma skin cancer. The elevated risks remained when we excluded patients also diagnosed with SLE.

In study IV, we performed a case-control study to examine the association between previously dispensed drugs and a subsequent development of SCLE in a group of 234 incident SCLE patients. We found increased relative risks for exposure to terbinafine, TNF- α inhibitors, antiepileptics, proton pump inhibitors, thrombocyte inhibitors, ACE-inhibitors and NSAIDs 0-6 months before the diagnosis of SCLE. About one third of all SCLE cases could be attributed to previous drug exposure.

This thesis adds to previous knowledge about epidemiology, prognosis, disease progression to SLE, comorbidity and the association with certain drugs in CLE. Swedish population-based epidemiological data on CLE will potentially be useful in the planning of health care as well as clinical trials. For prospective studies, especially of the intermediate group between CLE and SLE, population-based quality registers will be needed to further improve the health care for CLE patients.

List of Publications

This thesis is based on the following studies, which will be referred to in the text by roman numbers.

- I:** Cutaneous manifestations and serological findings in 260 patients with systemic lupus erythematosus

C. M Grönhagen, I. Gunnarsson, E. Svenungsson, F. Nyberg

Lupus 2010 Sep; 19 (10):1187-94.

- II:** Cutaneous lupus erythematosus and the association with systemic lupus erythematosus: a population-based cohort of 1088 patients in Sweden

C. M Grönhagen, C. M. Fored, F. Granath, F. Nyberg

British Journal of Dermatology 2011 Jun; 164 (6):1335-1341.

- III:** Increased risk of cancer among 3,663 patients with cutaneous lupus erythematosus- a Swedish nationwide cohort study

C. M Grönhagen, C. M. Fored, F. Granath, F. Nyberg

Accepted for publication in British Journal of Dermatology, Epub ahead of print

- IV:** Subacute cutaneous lupus erythematosus and its association to drugs: a population-based matched case-control study of 234 patients in Sweden

C. M Grönhagen, C. M. Fored, M Linder, F. Granath, F. Nyberg

Submitted for publication

Permission to reprint the published articles has been granted from the publishers.

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List of Abbreviations

ACE	angiotensin-converting enzyme
aCL	anticardiolipin
ACLE	acute cutaneous lupus erythematosus
ACR	American College of Rheumatology
AD	anno domini, after Christ
ADCC	antibody-dependent cell mediated cytotoxicity
AF	attributable fraction
ANA	antinuclear antibody
aPL	antiphospholipid antibodies
APS	antiphospholipid syndrome
ATC	Anatomical Therapeutic Chemical
β2GP1	beta 2 glycoprotein 1
BLyS	B-lymphocyte stimulator
BMI	body mass index
C	complement component
CCLE	chronic cutaneous lupus erythematosus
CDR	cause of death register
CI	confidence interval
CLE	cutaneous lupus erythematosus
CNS	central nervous system
DIF	direct immunofluorescence
DI-SCLE	drug-induced subacute cutaneous lupus erythematosus
DI-SLE	drug-induced systemic lupus erythematosus
DLE	discoid lupus erythematosus
DNA	deoxyribonucleic acid
dsDNA	double stranded DNA
EBV	Epstein-Barr virus
EM	effect modification
EpC	Centre of Epidemiology

EUSCLE	European Society of Cutaneous Lupus Erythematosus
HHV	human herpes virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HMBG1	high mobility group box chromosomal protein 1
HPV	human papilloma virus
HR	hazard ratio
HSV	herpes simplex virus
HTLV	human T-lymphotropic virus
IARC	International Agency for Research on Cancer
ICAM	intercellular adhesion molecule
ICD	International Classification of Diseases
IF	immunofluorescence
IFN	interferon
Ig	immunoglobulin
IL	interleukin
ITGAM	integrin, alpha M
IQR	interquartile range
IU	international unit
kDa	kilo Dalton
LA	lupus anticoagulant
LE	lupus erythematosus
LEP	lupus erythematosus profundus
LET	lupus erythematosus tumidus
MCTD	mixed connective tissue disease
MHC	major histocompatibility complex
MPA	Medical Products Agency
NLE	neonatal lupus erythematosus
NMSC	non melanoma skin cancer
NPR	National Patient Register

NSAID	nonsteroidal anti-inflammatory drug
OR	odds ratio
PCR	polymerase chain reaction
PDR	prescribed drug register
PIN	personal identity number
PLE	polymorphic light eruption
POR	prevalence odds ratio
PPI	proton pump inhibitor
QoL	quality of life
RA	rheumatoid arthritis
REM	reticular erythematous mucinosis
RF	rheumatoid factor
RNA	ribonucleic acid
RNP	ribonucleoprotein
RR	relative risk
SCC	squamous cell carcinoma
SCLE	subacute cutaneous lupus erythematosus
SCR	Swedish Cancer Register
SLE	systemic lupus erythematosus
SLICC	Systemic Lupus International Collaborating Clinics
Sm ag	Smith antigen
SS	Sjögren's syndrome
ssDNA	single stranded DNA
TNF	tumor necrosis factor
UV	ultraviolet
VAS	visual analog scale
WHO	World Health Organization

1 Introduction

Cutaneous lupus erythematosus (CLE) is a disfiguring, chronic skin disease, with a significant impact on the patients' everyday life. Much research has been focused on the underlying pathogenesis with special emphasis on cellular mechanisms. Epidemiological research of CLE has been hampered by a shortage of case ascertainment and much of the knowledge is based on rather small and often retrospective studies. Because of the Swedish Health Care Registers, we have now been able to study larger groups of CLE patients based on information collected prospectively.

The word epidemiology comes from the Greek words; epi, meaning 'on or upon', demos meaning 'people' and logos meaning 'the study of'. One definition of epidemiology is "the study of the distribution and determinants of disease frequency" (1). A famous epidemiologist, Sir Richard Doll, explained epidemiology: "Epidemiology is the simplest and most direct method of studying the causes of diseases in humans and many contributions have been made by studies that have demanded nothing more than an ability to count, to think logically and to have an imaginative idea."

Aim of this thesis was to answer the specific questions: How large is the proportion of SLE patients that also have a diagnosis of CLE? How many patients in Sweden suffer from CLE and what proportion of them has an additional diagnosis of SLE? Do CLE patients have an increased risk for cancer? To what extent is SCLE triggered by exposure to certain suspected drugs? The results we achieved can be found in the second part of this thesis but the thesis begins with a summary of the CLE disease.

2 Background

2.1 Lupus erythematosus (LE)

LE is a chronic, autoimmune, multisystem disease that displays many diverse symptoms in which localized CLE is on one end of the spectrum and severe systemic LE (SLE) on the other end. LE is included among the connective tissue diseases (2). The underlying cause of LE is unknown but the etiology is thought to be multifactorial and polygenic.

Although CLE and SLE can occur both together and separately, they are thought to have the same underlying pathogenic mechanisms but different clinical pictures (3). The cutaneous manifestations in LE are very heterogeneous and therefore it has been difficult to develop a unifying concept of LE-terminology. A breakthrough came with the two American dermatologists, James Gilliam and Richard Sontheimer's, (4) classification (1979) which improved classification and therapy follow-up, although some controversies still remain. Several attempts have been made to improve this classification since then but none have gained wide acceptance (5-9).

According to Gilliam and Sontheimer, the cutaneous manifestations of LE can be divided into LE-specific or LE-non-specific skin manifestations based on histopathological findings. LE-specific skin changes can be further subdivided into acute CLE (ACLE), subacute CLE (SCLE) and chronic CLE (CCLE), where classic discoid LE (DLE) is the most common form (Figure 1) (10).

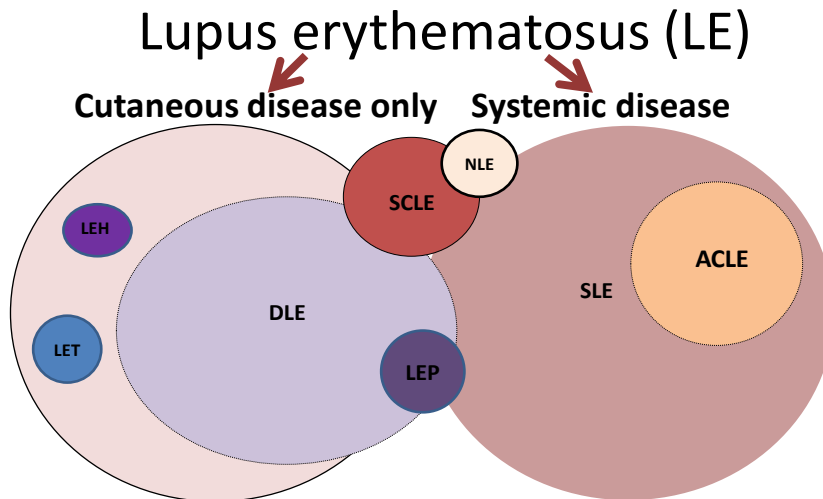


Figure 1. Schematic illustration of the CLE subsets and their relation to SLE. LEH –LE hypertrophicus, LET –LE tumidus, DLE-discoid LE, SCLE-subacute LE, LEP-LE profundus, NLE-neonatal LE, ACLE-acute cutaneous LE, SLE-systemic LE.

2.2 Historical background

Lupus is the Latin word for wolf and lupus has been used to name various diseases at least since the tenth century. Herbernus of Tours (916 AD) was probably the first to use the term lupus for a skin disease (11). In the mid-nineteenth century two skin diseases were named: Lupus erythematosus and Lupus vulgaris (= tuberculosis) (12), perhaps the skin lesions were thought to resemble wolf bites?

Robert Willan (1757-1812) who is considered “the father of British Dermatology” (13), classified skin diseases and used the term lupus for destructive and ulcerative diseases of the face (11). His disciple Laurent-Théodore Biétt gave a detailed description of DLE but used the name Erythema Centrifugum, his student Alphée Cazénave was the first to use the term *lupus érythémateaux* in 1851 when he described DLE and separated LE from cutaneous tuberculosis (13, 14). He also noticed that outdoor workers were predisposed to LE and thus was the first to make an association between LE and ultra violet (UV) light. Moritz Kaposi further subdivided LE in 1872 into the discoid and systemic form (11, 15); he also described the butterfly erythema (Figure 2) (16). The photosensitive nature of LE was first described by Jonathan Hutchinson (1888) and who may have been the first to describe SCLE using the name “lupus marginatus” (16).

The term “collagen vascular disease” was introduced for SLE and scleroderma in the 1940s. At that time, it was (wrongly) believed that the pathogenesis was due to defect collagen fibers (17). Knowledge about immunology was minimal when LE was first described (15), so several other etiologic factors were first suggested (e.g. infectious and socioeconomic factors). The detection of the antinuclear antibody (ANA) in 1957 by George Friou (17) led to the recognition of LE as an

immunological disease. Researchers have continued their attempts to subdivide LE into different forms. For instance, Dubois and Tuffanelli (1964) established the concept of a disease spectrum in LE (18) and Gilliam and Sontheimer (4) based their classification on this spectrum concept but developed it further to include SCLE as an own entity.

An old dermatological saying is that LE and syphilis are the “great imitators” among diseases.

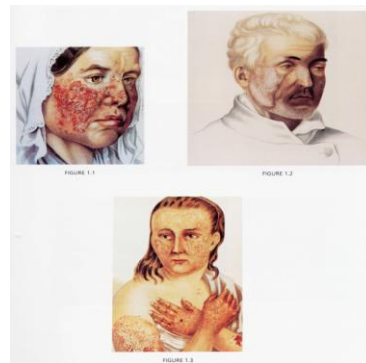


Figure 2. Historical drawings of cutaneous lupus erythematosus from Kaposi's Handatlas der Hautkrankheiten, 1898 (19).

2.3 Genetics

A strong genetic component seems to be involved in the LE pathogenesis and genetic susceptibility is probably one of the greatest risk factors for developing LE (20). Genome-wide scans in families with SLE and twin studies have identified more than 25 risk loci but probably many more remain to be discovered (21-24). No such searches has been performed in CLE patients (20).

Monozygotic twins have a concordance rate for SLE between 25 and 57 % compared with dizygotic twins that only have 2-9 % (23, 24). The risk for LE is also much higher for first-degree relatives and siblings of SLE patients(23).

Genome-wide scans have also confirmed different susceptibility loci in different ethnic groups of SLE patients (24). SLE is overrepresented in females but also in males with Klinefelter's syndrome (47, XXY), which suggests a gene-dose effect from the X-chromosome as a risk factor (25).

Several susceptibility genes encoding for the major histocompatibility (MHC) complex, which plays a very important role in the immune response for SLE, have been identified (20, 24). Deficiency of the complement pathway, especially C1q, is a strong risk factor for developing SLE and C2 and C4 deficiencies are associated with SCLE and DLE (23, 26-29). Genes coding for complement components are also situated on the MHC complex and deficiencies are thought to decrease the clearance of immune complexes and apoptotic cells (28). The integrin alpha M (ITGAM) gene has recently been found to be associated with both SLE and DLE (30).

Several autoimmune disorders (SLE and rheumatoid arthritis (RA)) are associated with certain human leukocyte antigen (HLA) subtypes (20). The predisposition to different subsets of CLE seems to be related to different haplotypes (23). SCLE has been most strongly associated with HLA-A1-B8, DR-3, a haplotype that is prevalent in about 25 % of white people in North America and associated with increased tumor necrosis factor alpha (TNF- α) expression (20, 29, 31-34).

LE is a complex genetic disease and multiple genes and different loci seem to be involved. This diversity reflects in the development of different LE phenotypes (23, 24). Genetic factors, however, must interact with environmental factors for the development of clinical disease.

2.4 LE-specific skin disease (synonymous CLE)

The LE-specific cutaneous manifestations are further divided into three main subsets: ACLE, SCLE and CCLE (Table 1). These subsets are defined by clinical symptoms, average duration of symptoms and histological and serological findings, although the three subtypes can have overlapping clinical features (10, 32, 35-37). One study showed that about two thirds had one type of LE-specific skin disease and one third had two types and only 3 % had three types (38).

CLE patients display well-defined skin lesions, often in sun-exposed areas. The disease often has a chronic and relapsing course that can be induced or aggravated by UV light. It is important to confirm a CLE diagnosis histopathologically by a biopsy in that there are several differential diagnoses and because CLE is a chronic disease in which regularly follow-up is important and systemic treatment is sometimes indicated.

Table 1: A modified version of Gilliam's classification of LE-specific skin manifestations (3, 10, 27, 32, 35, 39-41).

Acute CLE (15 %)	Localized ACLE (malar rash, butterfly rash) (90-95 %)
	Generalized ACLE (morbilliform) (5-10%)
	Toxic epidermal necrolysis-like ACLE (very rare)
Subacute CLE (8 %)	Annular SCLE (42 %)
	Papulosquamous/psoriasiform SCLE (39 %)*
	Vesiculobullous annular SCLE
	Toxic epidermal necrolysis-like SCLE (very rare)
Chronic cutaneous LE (73 %)	Discoid LE (80-85 %) -Localized DLE (70 %)
	-Generalized DLE (30%)
	Hypertrophic/verrucous LE
	LE profundus/panniculitis
	LE tumidus/papulomucinous LE
	Mucosal LE (Oral, nasal, conjunctival, genital)
	Chilblain LE
	Lichenoid DLE: LE-lichen planus overlap syndrome (lupus planus), probably represent the coexistence of two skin diseases.

*16 % is a combination of the annular and the papulosquamous form.

CLE subsets

2.4.1 Acute cutaneous lupus erythematosus (ACLE)

ACLE is strongly associated with the onset of systemic disease. The symptoms often start abrupt and show a predominance for young, fair-skinned females in their 30s with previous UV exposure (10). Women are affected up to six times more often than men (23, 42-45). These non-scarring lesions can be localized (head and neck) or generalized.

Most typical are the localized form, which presents as a classic “butterfly rash” (its distribution resembles the shape of a butterfly) or as a “malar rash”, which consists of a confluent, symmetrical erythema and/or edema centered over the malar eminence with a tendency to spare the nasolabial folds (because of its photo protected localization). The malar rash can have a fine surface scale and the patient may mistake this manifestation for sunburn at onset (46, 47). Some patients also develop severe facial swelling (24). Symptoms last hours to days (sometimes even a few weeks) then clear spontaneously or become more scaly (48); post inflammatory hyperpigmentation is common (10).

Differential diagnoses are rosacea, dermatomyositis (can have a facial erythema, “heliotropic erythema” but not sparing the nasolabial folds or knuckles, sparing instead the interphalangeal skin), erysipelas, contact dermatitis, atopic and seborrheic dermatitis, drug-induced phototoxic reactions, perioral dermatitis and viral rash (Parvo-B19 virus) (10, 48).

The more uncommon generalized form of ACLE (also known as photosensitive lupus rash) is seen as a widespread maculopapular or exanthematous eruption with a pruritic component, most commonly involving sun-exposed areas such as the face, scalp, neck and arms (preferred sites are above the waistline) (23, 47, 49). This generalized form is a phototoxic reaction that can simulate a drug reaction, viral exanthema, erythema multiforme or toxic epidermal necrolysis (50).

ACLE is associated with nail changes, including periungual erythema, erythema of the nail bed (red lunula), splinter hemorrhages and cuticle abnormalities (48), symptoms that can also be seen in other rheumatic diseases (e.g. dermatomyositis and antiphospholipid syndrome (APS)). Many patients also suffer from ulcers orally or in the nasal mucosa.

ANAs are usually present as well as anti-dsDNA antibodies in 40-90 % (10, 14, 51). The cutaneous findings can precede the systemic symptoms by weeks to months (sometimes even years) (5, 23, 43) but 100 % develop SLE (23, 48). About 30-70 % of SLE patients are thought to display ACLE sometime during their disease course (10, 35, 38, 43, 49, 52-54). A majority of these patients are taken care of by rheumatologists (dermatologists are seldom involved).

2.4.2 Subacute cutaneous lupus erythematosus (SCLE)

SCLE was first described as a subset of its own by Gilliam and Sontheimer in 1979 (4). The previous terminology (symmetrical erythema centrifugum of Brocq, lupus marginatus, LE gyrates repens, psoriasiform LE, pityriasiform LE or disseminated DLE) was unsatisfactory (3, 55). SCLE is characterized by distinctive clinical, serologic and genetic features.

Women are reported to be affected 3-4 times more than men (23, 56). About 85 % of the patients are very photosensitive and the distribution of lesions is mainly in sun-exposed areas that include the upper back, shoulders, dorsal part of the arms and hands, neck and chest (Figure 3) (32, 36, 40). Surprisingly, the face, scalp and lower legs are less involved (57). If the lower legs are involved, the lesions are often hemorrhagic, looking like a small vessel vasculitis (57).

The lesions are usually widespread, typically starting out as sharply demarcated, elevated, erythematous plaques or papules with fine scaling and then expanding into annular (ring-like), polycyclic lesions that clear centrally or papulosquamous (psoriasiform) lesions or a combination of these (10, 46, 55). The different forms do not imply any prognostic differences (48). The lesions last weeks to months and are often exacerbated by sun exposure (10). However, they can also be triggered by trauma (Koebner phenomenon) (40). The lesions tend to heal without scarring but long-lasting pigmentary changes are common (often looking like vitiligo) (23, 32).

Serological abnormalities are common among SCLE patients, where about 60-80 % display positive ANA (10, 28) and about 70 % display the anti-Ro/SSA antibody (ranging from 40 % to 100 % depending on what test is used for detection) (32, 58, 59). Anti-La/SSB antibodies are also often associated with SCLE (30-50 %) and are almost always seen together with anti-Ro/SSA antibodies (14). Between 30 and 80 % of SCLE patients have high titers of rheumatoid factor (RF). A negative correlation between SCLE and other autoantibodies often noted in SLE (such as anticardiolipin and anti-DNA) has been found (14, 58).



Figure 3. Subacute cutaneous lupus erythematosus on the back of a patient.

About 15-20 % of patients with SCLE display DLE lesions or ACLE at some point (23, 28, 32, 55, 60). SCLE is thought to occur in 10-15 % of patients with SLE (38, 54, 59). About 50 % of the patients with SCLE are thought to subsequently fulfill the American College of Rheumatology (ACR) criteria for SLE but they rarely develop serious systemic involvement (20, 23, 40, 57). Arthralgias (36 %) and arthritis (20 %) are the two most usual non-cutaneous manifestations in SCLE patients (33, 60).

Possible differential diagnoses for the papulosquamous variant are psoriasis vulgaris, lichen planus, pityriasis rosea, pityriasis rubra pilaris, mycosis fungoides and polymorphic light eruption; for the annular form, diagnoses include tinea corporis, nummular eczema, erythema marginatum (streptococcal infection-associated fever), erythema annulare centrifugum, granuloma annulare, Sneddon-Wilkinson disease, pemphigus erythematosus, drug rash and dermatomyositis (14, 24, 48, 54, 55, 61, 62).

2.4.2a Drug-induced SCLE (DI-SCLE)

This subset can be induced by a wide variety of drugs. It was first described by Reed and coworkers in 1985, a case-series of five patients was implicated to have triggered the development of SCLE after use of hydrochlorothiazide (57). DI-SCLE presents with the same clinical symptoms as the idiopathic form of SCLE and these two types cannot be separated serological or histopathological either (63-65). No formal diagnostic criteria for DI-SCLE have been developed but to be considered as a side effect of a drug, symptoms must be temporally related to drug exposure in a patient with no prior history of the disease. Withdrawal should lead to clearance and re-challenge should induce new symptoms (66). Most cases of DI-SCLE resolve clinically within 1-3 months after withdrawal of the triggering drug, although the serologic resolution takes longer (67-69).

Systemic symptoms are very seldomly seen but the patients often have ANA and anti-Ro/SSA antibodies (both around 80 %) (63, 70, 71). ANAs decrease but are still detectable and anti-Ro/SSA antibodies often seem to persist after symptom resolving (63). However, one small study showed that anti-Ro/SSA antibodies became negative again after remission but that could be due to longer follow-up in this study (72).

More than 40 commonly used drugs from various drug classes have been implicated in the development of SCLE (57, 63). Thiazides are the most frequently used drug associated with induction or in the aggravation of SCLE (33). Other associated drugs include terbinafine, calcium channel blockers, angiotensin-converting enzyme inhibitors (ACE -inhibitors) and the two most recently reported drugs are TNF- α antagonists and chemotherapeutic agents (47, 54, 58).

The latency between drug intake and development of clinical symptoms varies widely between drug classes, ranging from 3 days to 11 years with a median latency of 6 weeks (64, 72). Thiazide diuretics and calcium channel blockers display the longest latency periods, whereas anti-fungals and chemotherapeutic drugs show shorter periods (63).

The underlying mechanisms of DI-SCLE remain obscure but are probably multifactorial and complex (73, 74). Pharmacologically diverse drugs can form metabolites with similar characteristics, which can explain the diversity among suspected drugs to trigger SCLE (75). Several hypotheses for the underlying mechanism of DI-SCLE have been proposed. One hypothesis is that the drugs (or its metabolites) induce autoantibodies or trigger autoimmunity, such as through translocation of the Ro/SSA antibody from the nucleus to the surface of keratinocytes (in the same way as UV exposure induces translocation) (75, 76). Another hypothesis is that the drugs trigger the disease in predisposed individuals. Ro/SSA autoantibodies are known to be present long before clinical LE

disease, suggesting that certain suspected drugs are the last trigger needed for a subclinical disease to become evident in prone individuals (57, 63, 69, 77, 78). SCLÉ patients are also associated with genetic polymorphisms that appear to make them more susceptible to drug exposure (57, 64, 76, 79). Association with photo toxicity has also been proposed (57, 67) (e.g. PPIs have a photosensitizing potential) (80).

2.4.2b Neonatal LE (NLE)

The first references about NLE dates back to the 1950's describing LE-like eruptions in infants. Already at that time, some sort of placental transmission was suspected and preventive treatment of the mother with corticosteroids was suggested (81, 82). NLE develops in fetuses whose mothers have anti-La/SSB and/or anti-Ro/SSA antibodies (29, 32, 83); the main symptoms are congenital heart block and cutaneous manifestations. A transplacental transmission of maternal anti-Ro/SSA antibodies may lead to the development of NLE in a small percentage (about 2 %) of exposed fetuses (14, 20). About half of the mothers are asymptomatic. The incidence of NLE is thought to be 1 in 20,000 live births (24).

The skin lesions develop shortly after birth (0-2 months) and resolve spontaneously in the first 3 to 6 months of life when the titers of maternal antibodies degrade (48). The cutaneous manifestations include a SCLÉ-like rash, erythematosus, non-scarring, photosensitive annular plaques, most often localized on the head and particularly periorbital ("owl eye" or "raccoon eye"), which is in contrast to adult SCLÉ that very rarely involves the central part of the face (48). Avoiding breastfeeding does not seem to reduce the cutaneous manifestations (83). About one-half of the NLE patients are thought to have skin manifestations and the other half congenital heart block. In addition, about 10 % of the children have both manifestations (24). Histological changes are similar to SCLÉ (24). Possible differential diagnoses are seborrheic and atopic dermatitis.

2.4.3 Chronic cutaneous lupus erythematosus (CCLE)

2.4.3a Discoid LE (DLE)

DLE is the most common subtype of CLE (80-85 %). It is a disfiguring, photosensitive, chronic (lasts months to years) skin disease that heals with scar formation (14, 56, 61). Female to male ratio is about 2-3:1 (2, 40). Localized DLE (lesions limited above the neck) accounts for 60-80 % of the patients and the generalized (lesions are both above and below the neck) form accounts for 20-40 % (40, 46, 60).

About 70-90 % of DLE patients are reported to be photosensitive or suffer from summer exacerbations (24, 40). DLE can be induced or exacerbated by several other exogenous factors as well, such as mechanical trauma (Koebner phenomenon), cold, diathermy and chemical trauma and perhaps infections and drugs (24, 84).

Light-exposed sites such as the scalp, ears and cheeks are the most usual places for involvement followed by the dorsal part of the arms and V-area of the neck; however, it can appear in other areas normally not sun-exposed (e.g. trunk, palmoplantar and inguinal folds) (23, 40, 48). Involvement of the conchal bowl and external ear canal is not uncommon (10, 47). The scalp is involved in about 60 % of DLE patients and in 10 % this is the only involved area. The long-term result is permanent scarring alopecia and important differential diagnoses are lichen planus and folliculitis decalvans (47, 48).

The lesions present as well-defined round or oval, erythematous macula or papule (flat or slightly elevated) with a scaly surface that later spreads peripherally into larger discoid scarring plaques (size varying from a few millimeters up to 15 cm) with central atrophic scarring and hypopigmentation and active inflammatory peripheral growth with associated hyperpigmentation (10, 23, 24, 32, 39, 46). A prominent clinical feature is the adherent, thick keratotic scale with follicular involvement: keratin accumulates in follicles that become devoid of hair which leads to follicular plugging. Peeling back this thick adherent scale is painful but a follicle-sized keratotic spike can be seen protruding from the undersurface of the scale (carpet-tack sign) (23, 46). The extent of atrophy and scarring depends on the length of the active phase and the severity of the lesions (46). Old lesions have irregular borders, are depigmented, hairless and thin and if located in acral regions (tip of the nose and ears) there can also be mutilation with tissue loss (24). The presence of scar or atrophy distinguishes DLE from SCLE (61).

Nail involvement is common in DLE patients but it is seldom the only localization. Some investigators consider nail involvement as a sign of systemic spread of the LE disease. Symptoms are nail plate dystrophy, pitting, leukonychia striata, onycholysis, cuticle abnormalities and erythema of the nail bed (40, 47, 48, 55, 84).

The role of autoantibodies is less clear in DLE than in SCLE, but about 50 % of the patients have ANA in low titers while other autoantibodies are rarely seen (20, 61, 85, 86).

Based on rather small, retrospective studies, it has been estimated that about 5 % with the localized form and 20 % with the generalized form are thought to progress to SLE (10, 23, 85). About 15-30 % of SLE patients display DLE lesions (10, 38, 45, 54, 87) and DLE lesions are the first symptom of SLE in 5-10 % of the patients (3).

Possible clinical differential diagnoses to fresh DLE lesions are superficial basal cell carcinoma, actinic keratosis, Bowen's disease, lichen planus, psoriasis, superficial fungal infection, secondary syphilis, polymorphic light eruption (PLE), sarcoidosis, nummular eczema, seborrheic dermatitis. For older lesions, the diagnoses are cutaneous tuberculosis, hypertrophic lichen planus, leprosy, atrophic scar (especially after burns), vitiligo (48).

Less common forms of CCLE:

2.4.3b LE Hypertrophicus (verrucous LE, LE hypertrophicus et profundus)

This is a rare form of CCLE, about 2 % of CCLE patients show this form (24). The lesions often appear solitary. They appear raised, red, verrucous and hyperkeratotic. They can appear anywhere on the body but are most often seen on the extensor parts of the extremities, upper back, face, palms and soles (28). The patients often display more typical DLE lesions that help to facilitate diagnosis (61).

It can mimic hypertrophic lichen planus, verrucous psoriasis, common warts, prurigo nodularis, squamous cell carcinoma (SCC) and keratoacanthomas (17, 24, 46). These patients rarely develop systemic symptoms but the skin manifestations are often chronic and refractory to therapy.

2.4.3c LE profundus (lupus panniculitis)

LE profundus is an unusual clinical variant of CCLE, a rare panniculitis in which the pathological inflammatory changes primarily occur in the lower dermis and subcutaneous adipose tissue. LE profundus is most usual in middle-aged women (2-4:1) (88, 89). LE profundus is often chronic with relapses and UV light seems to be of minor importance in this subset (61). It has a predilection for areas with increased fat deposition, such as the trunk, buttocks, breasts and proximal extremities but can also develop in the face, neck and scalp (17, 24, 90).

The clinical lesions are asymptomatic or painful subcutaneous firm nodules or plaques in which the surface can be normal or inflammatory and red. Moreover, the lesions vary in size and are often multiple and symmetrically distributed (24). The surface skin then gradually becomes attached to the lesions that create indurated lesions. When the lesions heal, they leave deep atrophic scars, lipatrophy and calcifications in the skin. Ulcerations occur in less than 30 % of patients (89).

About 70 % of these patients also display DLE lesions and 10-50 % mild systemic involvement. Positive ANA is found in 70-75 % of the patients (10, 48, 55, 89, 91). Two to three percent of SLE patients display this panniculitis (89).

Possible differential diagnoses are other types of lobular panniculitis, erythema nodosum, subcutaneous panniculitis T-cell lymphoma, subcutaneous sarcoidosis and schwannomas. In all cases, a biopsy including the subcutaneous tissue is necessary to confirm the diagnosis (14, 24).

2.4.3d LE tumidus (LET), (papulomucinous LE)

Including LET in the CLE subset is controversial in that LET heals without scarring and atrophy and the characteristic interface dermatitis is lacking (39, 61). LET is by some considered as a rare form of CLE that presents clinically on sun-exposed areas with an urticaria-like morphology (92). Together with SCLE this is reported by some authors to be the most photosensitive CLE subset. LET is characterized by single or multiple lesions that occur in sun-exposed areas, most commonly the face (zygomatic area), V-area of the neck, upper back and arms are affected.

The lesions are edematous plaques with a smooth surface and sharp borders, are bright red or purple and resemble urticaria lesions. The lesions are smooth, non-scaly and they have no tendency for scarring or hypopigmentation (24). A skin biopsy is required to confirm the diagnosis and shows dermal mucin deposition, where both superficial and deep perivascular and periadnexal lymphocytic infiltrates characterize this subset, which shows no epidermal or subcutaneous tissue changes (17, 92, 93). The lack of changes in the dermal-epidermal junction and epidermis distinguishes this subset from the other forms of CLE (92).

Differential diagnoses are PLE, Jessner's lymphocytic infiltrate (by some regarded as the same disease (48, 94)), sarcoidosis, reticular erythematous mucinosis (REM, by some regarded as a variant of LE), granuloma faciale, pseudolymphoma (borreliosis), insect bites, papular mucinosis and erythema annulare centrifugum (24, 46, 48, 92).

2.4.3e Mucosal DLE

About 25 % of patients with CLE have mucosal involvement but this may be an underestimation because many patients have asymptomatic lesions (46, 48). The buccal mucosa is most commonly involved (24, 95). These oral lesions often start as tender, erythematous patches that progress into a chronic plaque with sharply demarcated irregular borders and radiating white striae (47, 48). Most patients with mucosal involvement have widespread disease, whereas patients with isolated mucosal DLE are rarely seen (61).

The mucosal lesions that occur in LE patients can display LE-specific histological changes or be non-specific ulcerations and erosions (55, 61). Oral ulcers have been reported in 18-60 % of SLE patients (40). Mouth ulcers are frequent in the normal population (5 %) and diagnosis can be challenging. Important differential diagnoses include aphthous ulcers, herpes simplex infections, side effects of drugs, traumatic injury, SCC, Langerhans cell histiocytosis, Wegener's granulomatosis, Behçet's, lichen planus and syphilis (48).

2.4.3f Chilblain LE (Hutchinson lupus)

Chilblain lupus is a rare form of CLE that affects acral areas and consists of symmetrically distributed, red-purple patches and plaques on the fingers, toes, heels, knees, elbows, calves, ears and nose. These lesions can sometimes be painful or cause itching (28, 39). The lesions are induced or exacerbated during cold, damp weather conditions (17, 62). The subtype is named chilblain because it looks like frostbites (28). Chilblain lupus is also called perniosis and must be separated from *lupus pernio* (Besnier) of cutaneous sarcoidosis (96, 97).

Chilblain can evolve secondary to cold injury or be associated with an underlying disorder such as LE (48). The pathogenesis is unknown but it is thought to be the result of Koebnerization or microvascular injury after heat or cold trauma to the skin (46). Recently a mutation in the TREX1 gene has been shown to cause familial Chilblain lupus (98). Women are more affected than men (24). Chilblain LE patients often display DLE lesions on other parts of their body as well (84).

To be diagnosed with chilblains lupus both major criteria should be fulfilled and at least one minor criteria (24, 96); Major criteria are lesions in acral locations induced or aggravated by cold and histopathological signs of LE. Minor criteria are coexistence of SLE or other manifestations of CLE, positive response to LE treatment and negative results of cryoglobulin and cold agglutinin studies. Differential diagnoses include cutaneous sarcoidosis, frost bites (chilblain), acral vasculitis, cryoglobulinemia and leukemia (48).

2.4.3g Palmoplantar LE

This is a rare subset of CCLE that is often difficult to treat. About half of these patients have SLE without other cutaneous manifestations which makes the diagnosis difficult (61). It is often a diagnostic problem in that both the clinical lesions and the histopathology resemble lichen planus.

2.4.3h Drug-induced CCLE (DI-CCLE)

Drug-induced CCLE is very rarely reported and associated drugs are fluorouracil agents or nonsteroidal anti-inflammatory drugs (NSAIDs) and more recently TNF- α antagonists have been reported (57, 74, 99, 100). The incubation period is very long, almost 8 months with improvement within 5 weeks after drug discontinuation (64). Certain mouse strains treated with fluorouracil have been used as models of drug-induced CLE in that the trigger is known. This has contributed to the understanding of both the CLE pathogenesis as well as other autoimmune disorders (64, 101).

2.5 LE-non-specific skin disease

LE-non-specific skin manifestations include a number of different skin symptoms (Table 2). LE-non-specific skin lesions are related to the LE process but are not specific for LE disease and do not show the typical histopathological findings that can be seen in CLE. LE-non-specific skin manifestations are often seen in patients with active SLE and can be displayed in other autoimmune diseases. Because it can imply systemic involvement, it is important to note their presence (40).

Table 2: A modified version of Gilliam's classification of LE-non-specific skin disease(3, 27, 32, 35, 54).

Cutaneous vascular disease	Vasculitis 1)Leukocytoclastic 2)Periarteritis nodosa-like	Leukocytoclastic: -Palpable purpura -Urticarial vasculitis
	Vasculopathy 1)Degos disease-like lesions 2) Secondary atrophie blanche	Associated with the antophospholipid antibody syndrome
	Periungual telangiectasia	Seen in 10-15 % of SLE patients, associated with dermatomyositis and systemic sclerosis (47).
	Livedo reticularis	Associated with APS
	Trombophlebitis	
	Raynaud's phenomenon	
	Erythromelalgia	
Non-scarring alopecia	Lupus hair (a frontal hairline with broken hairs and diffuse thinning)	
	Telogen effluvium	
	Alopecia areata	
Sclerodactyly		More associated with RA and scleroderma (62)
Rheumatoid nodules		More associated with RA and scleroderma (62)
Calcinosis cutis	Most often seen in dermatomyositis and systemic scleroderma but also in SLE (102).	
LE-non-specific bullous lesions	Epidermolysis bullosa acquisita-like bullous LE /Dermatitis herpetiformis-like bullous LE /Bullous pemphigoid /Porphyria cutanea tarda	
Urticaria		
Papulonodular mucinosis		
Cutis laxa/ anetoderma/ mid-dermal elastolysis	Loss of elastic fibers lead to depression of subcutaneous tissue (102). Often associated with APS.	
Acanthosis nigricans		
Erythema multiforme (Rowell's syndrome)	The association between LE and erythema multiforme-like lesions was first described in the 1960's by Rowell et al (103). It is very rare and it has been questioned if it is a separate type of non-specific LE or just a coincidence of two diseases occurring at the same time in the same patient.	
Leg ulcers		
Lichen planus		
Photosensitivity		
Chilblain (perniosis)		

2.5.1 Vasculitis

Vasculitis is probably the most common non-specific cutaneous manifestation seen in LE patients, affecting 10-20 % of SLE patients (24, 48, 104). Vasculitis has highly varying prognosis and more than 20 forms of vasculitis are recognized by the classification schemes used today. The most important clinical distinction is the vessel size it affects: small, medium-sized or large vessel vasculitis and if it involves skin or internal organs (104). Small vessel vasculitis is the most common (86 %) in SLE patients (104). Biopsies of vasculitic lesions in SLE patients show a leukocytoclastic vasculitis in 64 % and a necrotizing vasculitis in 22 % (104). In SLE patients cutaneous vasculitis (82-90 %) is more frequent than internal (105).

2.5.2 Livedo reticularis/racemosa/ livedoid vasculopathy

Livedo reticularis can be seen clinically as a net-like, bluish pattern on the legs and buttocks (the arms and trunk can also be involved). It is caused by hypo-oxygenation that is due to reduced arterial blood flow; the pathogenesis is thrombotic microangiopathy and not true vasculitis (47, 48). Livedo reticularis has been reported in 4-17 % of SLE patients and in 11-22 % of patients with APS (40, 47). APS is a systemic autoimmune disorder defined by the occurrence of antiphospholipid antibodies (aPL) together with clinical manifestations of thrombosis or pregnancy morbidity (106). Thrombocytopenia, valvular heart disease and pulmonary hypertension are other symptoms associated with APS (24, 107). APS is associated with SLE in 30-40 % of APS patients (28, 108).

2.5.3 Raynaud's phenomenon

Raynaud's phenomenon ("White fingers") is quite common in otherwise healthy individuals and only 2-10 % of the patients also have SLE (24). Raynaud's phenomenon is associated with several other diseases; in particular with scleroderma, but also with RA, dermatomyositis, vasculitis, mixed connective tissue disease (MCTD), hematologic disorders, arterial diseases, drugs and vibrator injury (109).

First, there is a severe vasospasm in the digital arteries with whitening of the fingers and/or toes that is followed by a reperfusion erythema, often associated with pain. SLE patients with RNP antibodies seem to have Raynaud's phenomenon to a greater extent (24). Effective treatments are vasodilators such as nifedipine (a calcium channel blocker) and nitroglycerine paste.

From 3–60 % of SLE patients have been reported to have Raynaud's, which is considered a good prognostic sign (40, 47). Raynaud's is more frequent among people living in cold, damp climates (84).

2.5.4 Erythromelalgia (Mitchell's disease)

Erythromelalgia is a rare disease that is sometimes linked to SLE. It mainly involves the feet but can also affect the hands (unilateral or bilateral). It is triggered by warmth and leads to intense painful burning attacks with diffuse erythema and increased skin temperature (24, 48, 110).

2.5.5 Non-scarring alopecia

Non-scarring alopecia is a common manifestation in SLE patients (up to 80 %) and often indicates a severer disease (40, 54). Scarring alopecia can be seen in patients with DLE lesions affecting the scalp. Non-scarring alopecia is divided into telogen effluvium, lupus hair and alopecia areata.

Telogen effluvium (diffuse hair thinning all over the scalp) is associated with SLE flare and is probably a result of severe catabolic effects and increased contents of circulating proinflammatory cytokines (84). Regrowth occurs after different length of times.

Lupus hair: "woolly hair", are thin broken hairs most obvious at the periphery of the scalp, which occurs in about 30 % of SLE patients during flares or in chronically active SLE patients (40, 84). It may or may not be associated with alopecia.

Alopecia areata has been noted in SLE patients but most probably reflects two autoimmune diseases in the same patient.

2.5.6 LE-non-specific bullous lesions

These bullous lesions occur infrequently in active SLE patients in normal or erythematous skin. They can resemble bullous pemphigoid or dermatitis herpetiformis. The degree of blistering may or may not be related to the activity of SLE disease (46, 61). Subepidermal blisters with neutrophilic microabscesses in the dermal papillae can be seen histologically (46). Deposits of IgG, IgA, and/or IgM and complement can be seen in direct immunofluorescence (46).

2.5.7 Papulonodular mucinosis (nodular cutaneous lupus mucinosis)

Cutaneous mucinosis is characterized by profuse mucin (acid glycosaminoglycans) deposition in dermis (111) and can be primary (pretibial or generalized myxedema or the rarer forms: lichen myxedematosus and reticular erythematosis mucinosis) or secondary to connective tissue disorders; the rare manifestation papulonodular mucinosis is associated with SLE and sometimes also CLE (46).

About half of the patients have associated kidney disease. Sun exposure and male gender seem to be risk factors (111). Asymptomatic, skin-colored, centrally depressed papules and nodules on the neck, trunk and extremities can be seen clinically, although it can also present with large plaques or confluent dermal and subcutaneous nodules resembling scleroderma (92).

2.5.8 Chilblain (pernio, frostbite)

Idiopathic chilblains are most common in patients living in cold, damp climates. It is an inflammatory disease with erythematous papules located on the fingers, toes, nose or ears combined with itching, burning or a painful sensation (24). It usually resolves within 1 to 3 weeks and not all patients have LE or will develop LE (62). Histopathologically, a lymphocytic infiltrate presents but no interface dermatitis (61).

2.6 Systemic lupus erythematosus (SLE)

SLE is a complex systemic autoimmune disease characterized by multiorgan involvement and the production of multiple autoantibodies. Most organs in the body can be affected, including the joints, skin, kidneys, cardiovascular system, lungs, central nervous system (CNS) and hematological systems (24, 112, 113).

SLE disease can start at any age but most SLE patients starts to display symptoms during the reproductive age with a mean age at onset of about 30 years (45). SLE occurs mainly in women (9:1), which has been attributed to hormonal changes (23, 45, 114). The natural course of the disease is recognized by episodes of flares and remission (115). SLE can often be difficult to diagnose because the disease evolves over time. In the Euro-Lupus cohort mean time from onset of symptoms to clinical diagnosis was 2 years (107). The autoantibodies have been shown to be present years before clinical disease (77, 116, 117).

Diagnose setting in clinical trials and other research is usually based on the ACR criteria (41), which require the presence of at least four of the 11 ACR criteria, including both clinical and laboratory criteria.

Studies examining the prevalence of CLE and other cutaneous manifestations in SLE patients show diverse figures in different populations (40, 118, 119) but over 80% of SLE patients are reported to have cutaneous manifestations some time during the disease (47, 118). Cutaneous manifestations are the second most frequent clinical sign of SLE after arthritis (32, 38). Most often, systemic manifestations precede the cutaneous findings, but in 20-25% of the patients cutaneous manifestations are the presenting sign of SLE and precede the systemic symptoms with weeks to months (32, 38, 40, 48, 119-121).

Arthritis or arthralgia is present in 95 % of SLE patients, where the arthritis presents clinically with motion-related pain, tenderness and swelling (47). The proximal interphalangeal joints (82 %) and knees (76 %) are most commonly involved (47). Photosensitivity, nephropathy, serositis, neurologic symptoms and thrombocytopenia are other frequent symptoms (107). Other common symptoms, not included in the ACR criteria, are fatigue, fever, Raynaud's, sicca, thrombosis, livedo reticularis and lymphadenopathy (47, 107).

Genetic predisposition, complement deficiency, autoantibodies, drugs and environmental factors have been proposed as causative factors for SLE (115). Its pathogenesis is not completely understood but major known findings include autoantibody production and impaired clearance of apoptotic

material in different tissues (21). A shift from Th1 to Th2 immune response leads to the enhanced B-cell function that is characteristic for SLE and causes increased production of autoantibodies (102, 122). Increased production of interferon alpha (IFN- α), a cytokine, is also thought to play a major role in the development of SLE (123, 124).

The course of the disease is highly variable, ranging from life threatening to mild disease not requiring hospitalization (47). Survival in SLE patients has greatly improved in the past decades, mostly due to better treatment but is still shortened mainly because of cardiovascular complications, infections, malignancies and immunosuppressive treatment (125-127). Five-year survival in the European Lupus cohort was 95 % (107). Antimalarials and systemic glucocorticoids are the base for treatment of SLE. NSAIDs are used to reduce pain and stiffness. More severe cases are treated with azathioprin, mycophenolate mofetil or cyclophosphamide (47). Belimumab is a B-lymphocyte stimulator (BLyS) specific inhibitor that has been recently approved for use in SLE patients (128, 129).

2.6.1 Drug-induced SLE (DI-SLE)

DI-SLE is one of the most extensive documented drug-induced diseases. It was first reported in 1945 after exposure to sulfadiazine (72) and then 1952 in association with hydralazine exposure (63). There are no standardized diagnostic criteria for DI-SLE but there must be no pre-existing lupus disease and it must be a temporal relationship between the drug exposure and development of symptoms and the symptoms must resolve after drug discontinuation and reoccurrence of symptoms if the drug is re-introduced, otherwise the SLE diagnosis is made on the same basis as idiopathic SLE (24, 72).

Although the two forms of SLE cannot be differentiated from each other based on symptoms, the clinical picture often slightly differs. Patients with DI-SLE rarely have skin manifestations; instead, they have systemic manifestations such as arthralgia or arthritis (90%), serositis, fever and weight loss but these patients often present a milder disease, i.e. involvement of the CNS and kidneys are uncommon (24, 37, 57, 74, 130, 131). Up to 95 % of the patients display antihistone autoantibodies, which is quite specific for DI-SLE (63, 64, 130, 131). Anti-dsDNA antibodies are rarely seen (75).

In DI-SLE there is less female predominance than in idiopathic SLE and the affected individuals are generally older when acquiring DI-SLE than the idiopathic form (37, 64, 74). The pathogenic mechanism underlying DI-SLE is unknown though probably there is more than one underlying mechanism. Known risk factors are certain genetic phenotypes (e.g. DI-SLE is more common in patients that are slow acetylators) (37, 74).

Unlike most other drug reactions the symptoms often start more than a year after initiation of the responsible drug but resolve within weeks after drug discontinuation (24, 74). About 10-12 % of SLE are thought to be drug-induced (37, 68, 132) but the use of drugs that are known inducers of DI-SLE are now decreasing except for the biological agents. The most frequently reported drugs are hydralazine, procainamide, minocycline, isoniazid, ticlopidine, D-penicillamine, quinidine, carbamazepine and TNF- α antagonists (also associated with DI-SCLE) although many more have been reported (37, 63, 71, 132).

2.7 Risk factors for progression of CLE to SLE

It is difficult to predict prognosis for progression from cutaneous disease to systemic disease at the individual level. Generalized DLE lesions, high ANA titers ($\geq 1:320$), arthritis/arthralgias, nail changes and blood dyscrasias have all been shown to be risk factors for progression of CLE to SLE (37, 133). LE-non-specific skin disease is also recognized as a sign of more widespread systemic disease compared with those with only CLE (119).

2.8 Prevalence and incidence

A number of studies have examined the epidemiology of SLE with varying results depending on which population is studied (gender, race and genetic inheritance), the study design used and whether the studies have been rheumatology clinic-based or not.

The prevalence of SLE varies considerably; 14-124/100,000 persons in the USA (23, 32, 134, 135), 42-68/100,000 in Sweden (136), 33-51/100,000 in Canada (137) and 67/100,000 in Taiwan (115). SLE is more common in African Americans, Afro-Caribbeans and Asians than in Caucasian populations (23, 115, 138).

The reported incidence of SLE has also varied between studies and countries, from 3/100,000 person-years in Canada to 8/100,000 in Taiwan, with USA and Sweden somewhere in the middle (about 5/100,000) (115, 136, 137, 139-141). An increasing incidence of SLE has been seen during the past decades. One reason for this is recognition of milder disease and an increased use of serological methods.

CLE is thought to occur 2-3 times more often than SLE but no population-based data have been available until now. A retrospective study from Minnesota recently showed the age- and sex-adjusted incidence rate of CLE to be 4.0/100,000 inhabitants (142).

2.9 CLE pathogenesis

The pathogenesis of LE is multifactorial (23, 29). It has been shown in experimental models that different genes lead to different disease manifestations (29). Using an oversimplified view the skin lesion in CLE is thought to be mainly caused by cell-mediated immune injury, displaying few autoantibodies and few elements of immune complex disease. The other part of the spectrum is severe SLE nephritis, which is mainly an immune-complex-mediated injury. SCLE is thought to have an intermediate position on this spectrum (35).

Swedish researchers have shown that risk factors associated with SLE include drug allergy, Fitzpatrick skin type I and II and a family history of SLE. They were not able to show significant associations between smoking or exogenous estrogens and SLE (143).

There are still many more areas to investigate to clarify the complex inflammatory cascade leading to CLE but so far known triggering factors for CLE are UV light, hormones, stress, drugs, viruses and skin trauma (29) (Figure 4).

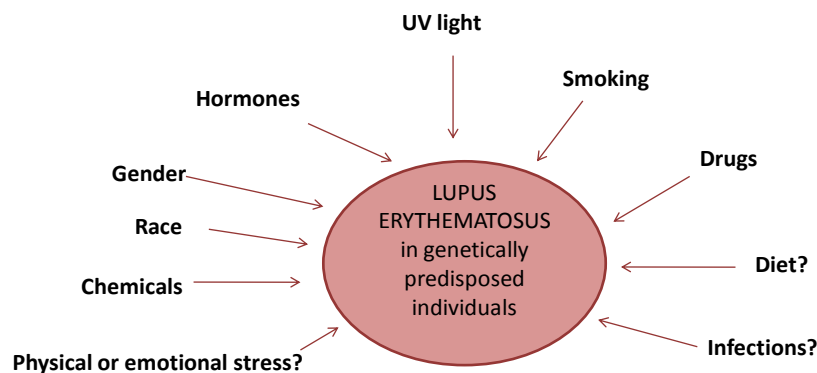


Figure 4. Factors associated with the development of LE, modified from Popovic (144).

2.9.1 Sex Hormones

An influence from sex hormones is reflected in the pathogenesis of autoimmune diseases in that a majority of these diseases displays a female predominance and there is a peak of onset during the reproductive ages.

Sex hormones are thought to play an important role in the development of autoimmune diseases. It has been shown experimentally that estrogens may up regulate the presence of Ro/SSA antibodies on the surface of keratinocytes (33, 145). Oral contraceptives containing estrogen have been associated with flaring in SLE. Premenstrual flares have been observed in 20 % of SLE patients and flaring both during and after pregnancy have also been noted (33, 37, 144).

2.9.2 Environmental factors

There are several known environmental triggering factors for CLE, including skin trauma, viruses, cold, heat, mechanical and physical stress and drugs but UV irradiation is by far the most studied one (29, 146).

2.9.2a Ultraviolet (UV) light

Table 3: Different UV wavelengths with different biologic effects (17, 32).

UV (ultraviolet)	Wavelength, nanometers (nm)	Remark
		Visible light 400-800 nm. The depth of penetration of UV light into the skin is directly proportional to its wavelength. Wavelengths from 200-400 nm are called UV.
UVA	320-400 nm	Long-wave UV light or black light UV. Penetrates the dermis, skin ageing, DNA damage. Constitutes 90-95 % of the UV radiation on earth's surface. Production of oxygen radicals.
UVAI	340-400 nm	UVAI and UVAIL have different biological effects. UVAI can penetrate the skin more deeply than UVAIL. Immunomodulatory? Treatment of SLE?
UVAIL	320-340 nm	Biological effects similar to UVB?
UVB	290-320 nm	Sunburn light, primarily absorbed in the epidermis, DNA damage in keratinocytes.
UVC	200-290	Blocked by the earth's ozone layer. Mutagenic, germicidal.

UV light greatly affects the immune system having both beneficial and adverse effects in humans. Each individual has different susceptibility or thresholds for the different responses (147-149). It is well-known that both natural and artificial UV irradiation induces or exacerbates CLE lesions; they often develop in sun-exposed skin often with a time delay of weeks to months (24, 51, 150). SCLE and LE tumidus are the most photosensitive LE subsets.

It is also believed that UV light can induce SLE and many SLE patients notice a flare of symptoms after sun exposure, often with a time delay of weeks to months. This delay means that many patients are unaware of the association between UV exposure and clinical symptoms (61, 150). Regular use of sunscreens is associated with better clinical outcomes in SLE patients (2, 23, 32, 151).

A model for the pathogenesis of photosensitive CLE lesions was suggested by Norris (152) in 1993 and has been further developed since then (29). Here it is described in a simplified version: UV irradiation induces DNA damage in the keratinocytes, which causes apoptosis of the keratinocytes that leads to translocation of normally intracellular nuclear antigens (Ro/SSA, La/SSB, RNP and Sm) in to apoptotic blebs located on the keratinocyte surface (24, 32, 151). These antigens may then be

recognized by circulating autoantibodies and T lymphocytes as foreign components that stimulate autoimmune responses such as the activation of the antibody-dependent cell-mediated cytotoxicity (ADCC) (153) with a subsequent destruction of the basal keratinocytes (20, 32). Apoptotic keratinocytes ("sunburn cells") can be seen at earliest 8 hours after UV irradiation with a peak after 24-48 hours (112).

The increase of apoptotic keratinocytes gathering in the epidermis after UV irradiation causes an overload of the clearance mechanisms and the resulting accumulation of apoptotic debris usually undergoes necrosis that may trigger the immune system (24, 26, 151, 154-156). Proinflammatory substances (e.g. TNF- α , IL-1, IL-6, ICAM and HMGB1) are released and the result is inflammatory skin lesions (32, 51, 144, 148). Cutaneous microdialysis (157) will hopefully provide real-time information of what is happening to the skin during UV irradiation to give more answers on this process.

Polymorphic light eruption (PLE)

PLE is characterized clinically by tiny itchy papules and/or vesicles arising one or a few days after sun-exposure on sun-exposed body areas and disappearing within a week if sun-exposure is prevented (17, 151, 158).

PLE is the most common photodermatosis (148). It is an idiopathic (immunological) photosensitivity disorder mainly induced by UVA (148). The disorder is more common in northern latitudes and in temperate climates and prevalence figures in Sweden are about 20 % with a majority being women (90 %) (17, 159). About half of LE patients also have PLE and PLE often precedes LE diagnosis (17, 24, 160, 161).

Photosensitivity in LE

Most of what is known about UV and CLE is derived from experimental photo provocation, developed in the current form by Lehmann (24). About 72 % of LE-patients reported worsening of their LE lesions by sunlight (160). Virtually all patients with lupus tumidus have a history of photosensitivity according to the ACR definition, 50-90 % of SCLE patients are considered photosensitive followed by 57-73 % of SLE patients and about half of DLE patients by this definition. This photosensitivity was a major impairment of their daily function (162). Photo provocation studies have confirmed induction of LE lesions by UVA and UVB in up to 72 % of the patients with LET, 63 % of SCLE patients, 45 % of DLE patients and 25-60 % of SLE patients (32, 151, 163).

Photosensitivity seems to be related to different ethnicity; for instance, Japanese CLE patients have reported lower incidence than Caucasian CLE patients (164).

It has been reported that about 70 % of CLE patients actively avoid sun exposure (165).

2.9.2b Smoking

Smoking has been associated with many dermatological disorders (e.g. hand eczema, pustulosis palmoplantaris and hidroadenitis) and many other inflammatory, autoimmune diseases (e.g. Grave's disease and RA) (166-168).

Smoking has been reported to be more usual in CLE patients than in controls and smokers also seem to have a more widespread disease (147, 169, 170).

2.9.2c Diet

Because of active sun avoidance, lower vitamin D levels have been found in CLE patients. Thus, some encourage that CLE patients that avoid the sun should complement their diet with at least 400 IU/day of vitamin D3 (cholecalciferol) (151, 165, 171). Vitamin D deficiency is known to cause osteoporosis and in recent years it has been proposed and frequently debated to have a role in the development of certain cancers and several autoimmune diseases (172).

2.9.2d Alcohol

Increased alcohol consumption has not been associated with CLE (169) though it has been negatively associated with SLE (143).

2.9.2e Chemicals

Aromatic amines and hydrazine containing drugs have been associated with SLE. Hydrazines are also ingredients in tobacco and pesticides and are used in plastic production (17, 143). Pesticide exposure has been associated with development of autoantibodies and other immunological changes (173).

2.9.3 Infections

Both virus and bacterial infections have been suspected as triggers of LE. In this respect, Parvovirus B19 has been most recently studied but no real evidence exists that show that LE can be induced by viruses (154, 173). Herpes zoster is known to be more prevalent in SLE patients (174).

2.10 To diagnose CLE

A CLE diagnosis must be based on the clinical appearance, histopathological findings, serology and sometimes also immunopathology and phototesting.

2.10.1 Histopathology

Typical histopathological findings in LE-specific skin manifestations are a lichenoid tissue reaction (interface dermatitis) in which the basal keratinocytes are the primary focus of injury. A lichenoid tissue reaction includes the following characteristics: hyperkeratosis; epidermal atrophy and flattening; hydropic degeneration (liquefaction degeneration) in the epidermal basal-cell layer and as a consequence melanin pigment incontinence, thickening of the basal membrane, a mononuclear cell

(T lymphocytes, both helper and suppressor) infiltrate focused at the dermal-epidermal junction, perivascular areas and perifollicular areas (10, 23, 32, 33, 48).

The interface dermatitis seen histopathologically is considered characteristic of CLE lesions (23, 32, 48, 94), the interface being the junction zone between epidermis and dermis (51). This interface dermatitis is absent in LET and LE panniculitis but can be observed in a few other diseases apart from CLE: lichen planus, lichen sclerosis et atrophicus, erythema multiforme, graft-versus-host disease and dermatomyositis (48, 153).

A histopathological diagnosis of CLE consists of the same type but different degree of features as noted above. It is often difficult to make a distinction between CLE subsets based on the histopathological picture only because the difference between subsets is gradual (48). The histopathological picture is also very dependent on the lesions stage of development ("early, fully developed, late") (153).

2.10.2 Direct Immunofluorescence (DIF)

The lupus band test was first described by Burnham et al. in 1963 (175). A "lupus band test" is the deposits of immunoglobulins (IgG, IgA and IgM) and complement components (C1q, C3 and C4) that can be found at the dermal-epidermal junction in DIF on skin biopsies from lesional or unaffected skin. Their function is still unclear as they can also be found in clinically normal skin in SLE patients (32).

The biopsy should be snap-frozen for the most reliable results (24). The skin lesions should preferably be older than 4-6 weeks and untreated before biopsy, fresh lesions can show a false-negative result (24, 176). Punch biopsy from non-lesional skin is by preference taken from the buttocks.

The interpretation of DIF is difficult and is not used so much nowadays because of the increasing serological tests available but can still have a part in the diagnosing puzzle sometimes (48, 61). It is most useful in patients in which the histopathology is not typical, especially in lesions in the palms or soles (61). The lupus band test has only little value for the distinction between the LE subsets. False positive lupus band tests can be seen in sun-damaged skin (facial lesions) and in other skin diseases such as rosacea, lichen ruber planus and PLE (24, 48). It can also be seen in dermatomyositis, systemic scleroderma, RA, Sjögren's syndrome (SS), porphyria cutanea tarda and leprosy (47).

2.10.3 Serology

Autoantibodies associated with LE

LE is an autoimmune disease in which the B cells are hyperactive and produce many different autoantibodies. When the autoantibodies bind to autoantigens, immune complexes are formed at the dermal-epidermal junction or in peripheral blood that activate the complement system (177). In LE clearance of these immune complexes seems to be defective and its prolonged circulation leads to inflammation, tissue injury and organ damage (102, 148).

Autoantibodies are characteristic for SLE and can precede the clinical symptoms by many years (22). More than 3 years before clinical onset of disease ANA, Ro/SSA, La/SSB and aPL antibodies can be detected and anti-dsDNA about 2 years before and anti-Sm and anti-RNP about 1 year before or at the same time as the clinical onset of the disease (77).

2.10.3a Antinuclear antibodies (ANA)

ANA are circulating autoantibodies that react with the cell nucleus and can be verified through different immunochemical techniques (62, 102). ANA is sensitive for SLE disease and is found in up to 96 % of SLE patients and in 4-63 % of CLE patients (24, 121) but it is not specific for SLE. Low ANA titers (1:10-1:40) can be seen in up to 6.5-10 % of the normal population. The incidence increases with age, autoimmune diseases, infections and medications (32, 55).

2.10.3b Anti-Ro/SSA antibodies

The Ro/SSA antigen is a complex of ribonucleoproteins (RNP) containing a major component of 60-kDa peptide (Ro60) and two smaller components, namely 52-kDa and 46-kDa. It has been named after the index patient from whom the antibody was characterized in the 1960s (first two letters of the surname, Ro). It is also identical to an antigen found in patients with SS, which was named SSA (Sjögren's syndrome-associated antigen A) (10, 32).

Ro/SSA autoantibodies are genetically associated with HLA-DRB1*03 (178) and clinically associated with photosensitivity, SS, SCLE, NLE, SLE and autoimmune hepatitis (102, 179). Anti-Ro/SSA antibodies have been found in 40-100 % of SCLE patients (the rate differs between populations and is dependent on technique), in about 15-30 % of SLE patients and in 0.1 % of healthy people (24, 28, 32, 107). The individual antibody titers can fluctuate over time but no correlation to disease activity has been noted (180, 181).

The function of the Ro/SSA antigen is still unknown but UV irradiation can induce translocation of Ro/SSA antigens to the keratinocytes surface; in SCLE patients circulating anti-Ro/SSA antibodies bind to the keratinocytes that express surface Ro/SSA antigen which lead to cell destruction of the basal keratinocytes (2, 24, 29, 182, 183). Oestradiol has also been shown to change the translocation of Ro/SSA and La/SSB antigens (184).

2.10.3c Anti-La/SSB antibodies

Anti-La/SSB antibodies are almost never found in the absence of anti-Ro/SSA antibodies (17, 185). La/SSB antigen is a 48-kd protein involved in the control of RNA polymerase III transcription and in a protein that inhibits apoptosis in cells during physical stress (32).

2.10.3d Anti-DNA antibodies

Anti-DNA antibodies include anti-single stranded DNA (ssDNA) antibodies and anti-double stranded DNA antibodies (dsDNA) (186). Anti-ssDNA antibodies are non-specific (102) but anti-dsDNA antibodies are the most specific marker of disease activity in SLE (107), present in about 60-80 % of SLE patients but not so frequent in CLE patients (28, 107, 178). It correlates with disease activity (especially LE nephritis) and can disappear during remissions (47). With the new techniques these autoantibodies can also be found in healthy individuals and in those with RA, SS and APS (186).

2.10.3e Histones

Anti-histone antibodies are associated with DI-SLE (102).

2.10.3f Anti-ribonucleoprotein (RNP) antibodies: rRNP and U1RNP

rRNP is highly specific for SLE but only prevalent in about 7 % of SLE patients (62). It is more associated with neuropsychiatric LE and fluctuates with disease activity (62, 107, 186). U1RNP is prevalent in about 20-25 % of SLE patients but are even more prevalent in mixed connective tissue disease, especially systemic sclerosis (28, 47, 102).

2.10.3g Anti-Smith (Sm) antibodies

This autoantibody attacks the Smith antigen, a soluble RNA-associated nuclear component. It is very specific for SLE disease, especially renal disease though only found in about 10-30 % of SLE patients (28, 62, 102, 107). Anti-Sm antibodies do not correlate with disease activity (47).

2.10.3h Rheumatoid factor (RF)

RF is antibodies against the Fc portion of IgG. Present in about 20 % of SLE patients, it is also associated with RA, SS and increased in otherwise healthy individuals during infections (28, 107). RF titer does not correlate with disease activity.

2.10.3i Antiphospholipid (aPL) antibodies

These antibodies form the serological part of the classification criteria for APS and consist of the lupus anticoagulant (LA) and anticardiolipin antibodies (aCL) of the IgG and IgM class (106, 108). They were originally thought to be directed against phospholipids or cardiolipin (hence the name) (186) but are now instead recognized to attach to β 2 glycoprotein 1 (β 2GP1), a serum protein that attaches to cardiolipin. Anti- β 2GP1, which is associated with thrombosis, is prevalent in about 25 % of SLE patients (62).

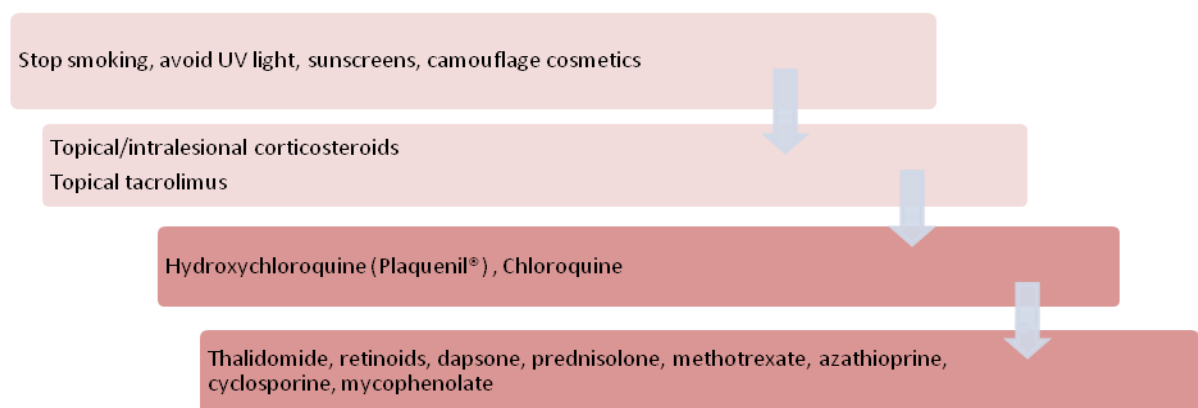
2.11 Treatment

CLE is a chronic disease that can be managed but not cured. If limited skin areas are involved local therapy and avoidance of triggering factors might be sufficient to control the disease. Treatment is generally the same for the different CLE subsets (Figure 5).

First-line of treatment is topical therapy and anti-malarials. As second-line therapy for refractory cases, a number of other systemic therapies can be tried. About 75 % of CLE patients respond with topical therapy and anti-malarials (27).

A small number of patients have a refractory disease that is hard to treat. It seems that widespread DLE more often is refractory and it has been proposed that a higher number of refractory patients are smokers (187, 188).

Figure 5: Brief summary of treatment in CLE patients.



2.12 Living with CLE

CLE is a chronic disease in which case patients often have to take medication for long periods. In addition, patients with photosensitivity are limited in their daily activity by the strict sun avoidance and the disfiguring symptoms of the disease are often in an easily visible area (facial lesions being common). An American study investigated quality of life (QoL) in patients with CLE and concluded that CLE patients have very limited QoL. The emotional part is most affected, a fact often missed by the treating physician (189). CLE patients' QoL is worse than the QoL in other dermatologic diseases, such as acne and alopecia, and even worse than in patients with recent myocardial infarction and congestive heart failure (189). The patients expressed annoyance and frustration and were most worried about their skin getting worse and that their condition might be serious (189).

2.13 ACR criteria

In 1971, the American Rheumatism Association (ARA, nowadays referred to as the American College of Rheumatology, ACR) established the well-known criteria for the classification of SLE. These criteria were then revised in 1982 and again in 1997 (41, 190). The ACR criteria were originally based on 14 criteria but are now limited to 11 clinical and laboratory criteria for SLE diagnosis: any four or more criteria should be fulfilled to obtain a diagnosis of SLE. The ACR criteria, which have become very influential, were established for classifying SLE patients for scientific studies. These criteria, however, were not developed in collaboration with dermatologists and it has been debated that they put too much weight to the skin in this multiorgan disease (32, 54, 117).

Mucocutaneous lesions account for four of the ACR criteria and include malar rash, discoid lupus, photosensitivity and oral ulcers (Table 4) (41). Thus, a group of patients can have mild systemic disease and still fulfil criteria for SLE while their disease is mainly located in the skin.

Malar rash has many dermatological differential diagnoses (e.g. rosacea, eczema and dermatomyositis). Malar rash and photosensitivity are not independent and can therefore be difficult to distinguish from each other. Oral ulcers are a very unspecific criterion and even a biopsy is uncertain because oral ulcers in SLE patients may not always have LE-specific histology (54). Other skin manifestations (such as alopecia and SCLE) are not included in the ACR criteria but have been suggested as potential criteria (54).

ACR criteria are currently undergoing revision that is undertaken by the Systemic Lupus International Collaborating Clinics (SLICC). Dermatologists are involved in this latest revision (117).

Table 4: Classification of SLE with the revised ACR criteria from 1982, abbreviated and modified from Tan *et al.* (117) and include the update by Hochberg (190). Colored cells represent mucocutaneous symptoms.

Criterion	Definition	Differential diagnoses
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds	Rosacea, facial eczema, contact dermatitis, dermatomyositis, seborrheic dermatitis, steroid erythema
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions	SCLE, psoriasis, eczema
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patients history or physician observation	Phototoxic drug eruption, photo-induced eczema, PLE, dermatomyositis, acne rosacea
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician	DLE, aphthous disease, intraoral herpes, Behcet's disease

Arthritis	Non-erosive arthritis involving ≥ 2 peripheral joints, characterized by tenderness, swelling or effusion
Serositis	a) Pleuritis: convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion <i>or</i> b) Pericarditis: documented by ECG or rub or evidence of pericardial effusion
Renal disorder	a) Persistent proteinuria > 0.5 g/d or $>3+$ if quantization not performed <i>or</i> b) Cellular casts
Neurologic disorder	a) Seizures <i>or</i> b) Psychosis: both in the absence of offending drugs or known metabolic derangements (e.g. uremia, ketoacidosis or electrolyte imbalance)
Hematologic disorder	a) Hemolytic anemia: with reticulocytosis <i>or</i> b) Leukopenia <i>or</i> c) Lymphopenia <i>or</i> d) Thrombocytopenia
Immunologic disorder	a) Anti-DNA: antibody to native DNA in abnormal titer <i>or</i> b) Anti-Sm: presence of antibody to Sm nuclear antigen <i>or</i> c) Positive finding of antiphospholipid antibodies based on 1) an abnormal serum level of IgG or IgM anticardiolipin antibodies 2) a positive test result for lupus anticoagulant using a standard method <i>or</i> 3) a false positive serologic test for syphilis known to be positive for at least 6 months and confirmed by Treponema pallidum immobilization or fluorescent treponema antibody absorption test
Antinuclear antibody	An abnormal titer of antinuclear antibodies by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

2.14 Autoimmunity

Autoimmunity occurs from an overactive immune response of the body against its own cells and tissues that may result in a pathological process known as autoimmune disease (16). The skin provides a first line of defense against microbial pathogens, as well as physical and chemical injury. If an immune response is inadequate, then overwhelming infections and tumors are the result. However, if an immune response is excessive, chronic inflammation and autoimmunity may develop (191).

About 5-10 % of the world population suffers from an autoimmune disease (68). Most autoimmune diseases are more common in females and onset of disease is most usual during the reproductive age, which suggest both a genetic role of the X chromosome and influence by estrogen hormones (16, 24). There are more than 40 autoimmune diseases that affect different organs or tissues in the body. In systemic autoimmune diseases (e.g. SLE and RA) the immune system attacks many organs and tissues but there are also organ- or tissue-specific diseases that affect only one organ or tissue (e.g. diabetes mellitus type 1, myasthenia gravis and hemolytic anemia).

Autoimmune diseases have been classified in many ways, but one of the latest classifications is based on their association with class I or class II MHC markers in which LE is associated with MHC class II (24). Genes of MHC class II encode for certain subtypes of the HLA (20).

2.14.1 Cancer and autoimmunity

Malignancies occur with higher frequencies in autoimmune disorders and in patients with malignancies autoimmune diseases can develop as a part of the paraneoplastic syndrome (192).

One explanation for this tumor proneness in autoimmunity diseases is Reines' "antitumor hypothesis". He suggests that patients with autoimmune diseases have inherited foci of prematurely aging cells that are prone to transform into cancer cells, but as long as they have not transformed completely they will signal "danger" to the immune system and create an autoimmune reaction (193).

In recent years epidemiologic studies have shown that patients with SLE and other autoimmune diseases (such as RA) have an increased morbidity and mortality in cancer (137, 141, 194-196). SLE patients have an increased risk for certain cancers, especially lymphomas and respiratory cancers and RA is associated with lymphomas (196).

Other autoimmune disorders are also associated with an increased risk of cancer. For instance, dermatomyositis is strongly associated with cancer, with about one fourth of the patients diagnosed with malignancy (197). Patients with systemic sclerosis also have an elevated risk for cancer, especially of the lungs and breasts (197). Primary SS is also associated with lymphomas (198) and Wegener's granulomatosis is associated with bladder cancer and SCC (196).

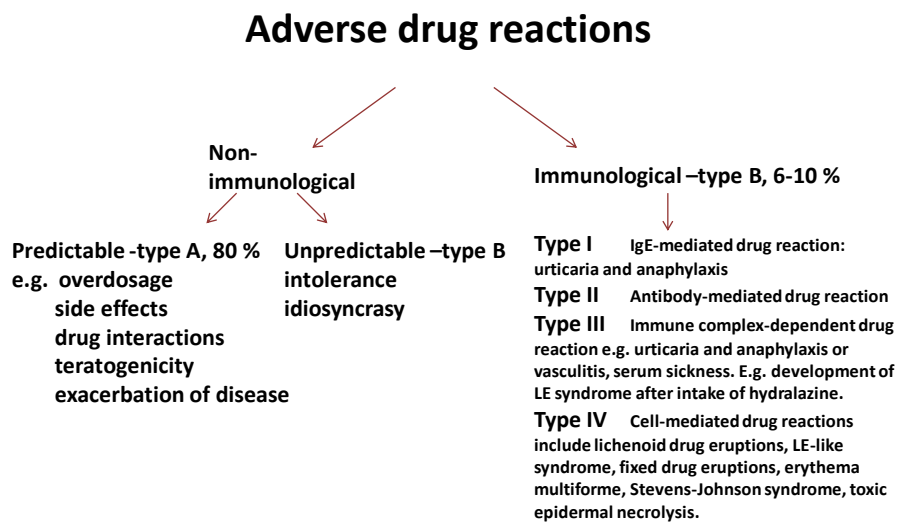
Hypothesis for these associations are genetic predisposition, immune system defects, chronic antigen stimulus, provoking factors (UV light), viral infections, greater prevalence of traditional cancer risk factors (smoking, alcohol abuse and obesity), hormonal factors and immunosuppressive therapy.

Patients with severe chronic disease tend to participate in screening programs (cervical cancer and breast cancer) to a lesser extent than the general population (196). It is very important to encourage screening in these potential high-risk-groups.

The first reports about the development of SCCs in CLE lesions were in the late 1950s and in the early 1960s (199-201). Since then, over 100 case reports have been published about SCC developing from DLE lesions (24, 202, 203). There have also been case reports about SCL and different internal cancers. Moreover, SCL has also been considered a paraneoplastic dermatitis (182, 204-207).

2.14.2 Drug-induced autoimmunity

Figure 6. Different types of immunological drug reactions (2, 68, 208).



Drug-induced autoimmunity has been implicated in many diseases in addition to LE (e.g. RA, dermatomyositis, pemphigus, pemphigoid and SS) (68). A majority of drug reactions are predictable and dose-dependent but there are unpredictable adverse drug reactions, i.e. type B reactions that are dose-independent, not related to the drug's pharmacological action, often immune-mediated and skin, liver and bone marrow are most often affected (73, 153). Many factors are involved, including genetic susceptibility, interaction with other drugs, food, physical activity, the patient's overall health status and environmental causes (e.g. UV light). Allergic reactions are included in type B reactions but differ from DI-LE in that DI-LE shows no drug-specific T cells or antibodies and there does not seem to be an immune sensitization to the drugs because provocation generally takes 1-2 days before symptoms reoccur (68, 74).

3 Aims of the studies

The overall aim of this thesis was to gain greater knowledge of CLE, its impact on society and associated comorbidities from an epidemiological point of view by studying population-based register data.

The specific aims were to:

- Describe the frequency of cutaneous manifestations according to dermatological classification in a well-characterized cohort of SLE patients and compare clinical and immunological features in SLE patients with and without CLE **(Study I)**.
- Estimate the age- and gender-specific incidence of CLE and its subsets and examine the short-term cumulative probability of receiving an additional diagnosis of SLE **(Study II)**.
- Estimate the overall and specific cancer risks in patients diagnosed with CLE **(Study III)**.
- Evaluate the associations between exposure to previously reported suspect drugs and a subsequent diagnosis of SCLE **(Study IV)**.

4 Material and Methods

4.1 Swedish health care registers

The Swedish health care registers are recognized world-wide for their high quality and completeness. The Swedish health care registers are among the oldest in the world; already in 1749 there was a nationwide register introduced in Sweden that registered cause of death (209). The Swedish National Board of Health and Welfare is now maintaining five national health care registers, three of which are described in more detail below. The health care registers include the whole Swedish population and enable medical research for a wide range of diseases. The research can include millions of people at a relative low cost and the information can quickly and efficiently be obtained.

Sweden offers exceptional possibilities for performing register-based epidemiological studies because of the structure of the health care system, reliable health care registers and the unique personal identifier assigned to all Swedish residents. Contrary to other autoimmune disorders such as SLE and RA in which register studies have contributed significantly to the understanding of the disorder, such studies have been more difficult to perform in CLE patients because a majority of these patients are diagnosed in outpatient care.

Much information from the registers is public but information on individual level for research purposes requires an application to the register holders as well as ethical approval. Register data are collected from the Centre of Epidemiology (EpC) (a part of the National Board of Health and Welfare) and are nearly always unidentifiable before leaving the EpC.

Control subjects for study III and IV were derived from the general Swedish population by means of the Swedish Population Register, which has been maintained by Statistics Sweden (the national statistical office in Sweden) since 1968. The Swedish Population Register comprises the entire Swedish population (the data included in the register come from the Tax authorities and are continuously updated).

4.1.1 National Patient Register (NPR), (Study II, III and IV)

The Swedish National Patient Register was launched by the National Board of Health and Welfare in 1964 and includes virtually complete coverage of all inpatient care (both public and private) in Sweden since 1987. The reporting is mandatory and from 2001 data from specialized out-patient care are also included (both public and private caregivers) but primary care is not included (210). Reporting from public caregivers to the outpatient register is almost 100 % complete (except for psychiatric care), but reporting from private caregivers is lower. It is estimated that the outpatient register has 80 % coverage (211). Private practices sustain less than 10 % of all health care in Sweden. More than 98 % of all diagnoses have been shown to be technically correctly coded in 2007 based on the Swedish National Board of Health and Welfare's own validation (1-2 % dropouts and 1 % missing

personal identity number(PIN)) (210). Validations with medical records of the inpatient care registered by NPR have shown different positive predictive values for different diagnoses but varying between 85-95 % (126, 211, 212). Patients diagnosed with RA in the inpatient register are correctly coded in 87-94 % of the cases (211) and patients with dermatomyositis have shown an accurate diagnosis in 72 % of the patients and a probable in 20 % (213). Several studies with diverse diagnoses have used data from the outpatient register (214-217). One of them validated the diagnosis of spondyloarthritis for 347 patients in both in- and outpatient care in a rheumatology clinic, the study found that 98 % of the codes were valid when compared with medical charts (216). No validation of the specific diagnosis of CLE has been performed and we are not aware of any published studies on data from the outpatient register for a dermatological disease.

From 1997 and onwards, diagnoses are coded according to the International Classification of Diseases (ICD), 10th revision (ICD-10). The register includes information about patient characteristics (PIN, sex, age and county of residence), administrative data, hospital identification and medical data (major interventions and discharge diagnoses (a main and up to seven secondary discharge diagnoses) and dates of diagnosis).

4.1.2 Cancer Register (Study III)

The Swedish Cancer Register (SCR), founded in 1958, was the first health care register. The register includes data on all malignant cancers in Swedish residents. It contains information about PIN, gender, domicile, reporting hospital and department, reporting pathology/cytology department, tumor characteristics (site of tumor, ICD-7, histological type and date of diagnosis) and follow-up data (date and cause of death and date of migration) (218).

It is compulsory for all physicians in Sweden to report all malignant tumors. The completeness of the register has been reported to be over 96 % (219, 220). More than 98 % of all tumors are notified twice: first by the clinical physician and then the pathologists or cytologists separately report all tumors diagnosed from “surgically removed tissues, biopsies, cytological specimens, bone marrow aspirates and autopsies” (218). Information of tumors based on death certificates only is not used because it is not considered sufficiently reliable. The reporting is first recorded at six regional cancer centers where all data are carefully controlled and, if needed, corrected. The information is further reported to the SCR. Less than 2 % of all cancer cases contains incomplete information (218). Information from the Cause of Death Register is cross-linked with the SCR to attain information about date and cause of death.

4.1.3 Prescribed Drug Register (PDR) (Study IV)

The Prescribed Drug Register was started in 1999 and since July 1, 2005 the PIN was included, making linkage with the other registries possible. The register includes complete coverage of all dispensed drugs in Sweden on an individual-level (about 90 million prescriptions dispensed annually) and is updated monthly. The register is pharmacy based so only dispensed drugs are captured. Thus, drugs used during inpatient care or sold over the counter are not included. Each pharmacy records the PIN,

date of prescription and dispensing and type of drug. Pharmacy dispensing is often seen as the gold standard in drug exposure information (221). The pharmaceuticals are classified according to the Anatomical Therapeutic Chemical (ATC) classification system, which is recommended by the WHO. According to the ATC classification system, all pharmaceuticals are divided into 14 main groups and thereafter further divided into subgroups based on pharmacological characteristics, therapeutic use and chemical structure (222).

4.1.4 Cause of Death Register (CDR) (Study II, III)

The register, updated annually, contains information about all deceased Swedish residents (223). Deaths that occur abroad are also included. The register started in its present form in 1961 and from 1994 is the register produced by the Swedish National Board of Health and Welfare (209). Death causes are coded according to the ICD codes, ICD-9 during 1987-1996 and ICD-10 was implemented in 1997.

4.2 Personal Identity Number (PIN)

A unique personal identity number (PIN) is assigned to all Swedish residents by the National Tax Board since 1947 (224). The PIN consists of a twelve-digit number with information about date of birth and sex (before the 1980s it was also linked to the county of birth). These personal identifiers are very important in health care research because they enable systematic collection of medical data among all national registries resulting in almost 100 % complete follow-up and also allow individual tracking over time (224).

4.3 ICD codes

International Classification of Diseases is an international collaboration with the purpose to gather information about diseases for statistical purposes in epidemiological, health management and clinical settings. The codes enable an overview over the general health situation and allow the observance of incidence and prevalence trends over time. ICD has existed in different setups from the 1850s and since 1948 has been withheld by the WHO.

L93, the ICD code for Cutaneous Lupus Erythematosus, can be further subdivided into L930; DLE, L931; SCLE and L932; other local LE, including LET, lupus panniculitis and other more rare subsets.

Table 5: Short summary of study I-IV

	Aim	Year	Number of study subjects	LE subset	Study design	Register used	Statistical analysis
I	Skin manifestations in SLE patients	2004-2007	260 SLE patients	SLE and CLE	Descriptive	-	Descriptive statistics
II	Incidence of CLE and association with SLE	2005-2007	1,088 CLE patients	CLE	Cohort	NPR, CDR	Incidence rate, Kaplan-Meier estimates, Cox regression model
III	CLE and cancer risk	1997-2007	3,663 CLE patients and 10,989 controls	CLE	Cohort	NPR, SCR, CDR	Cox regression model, logistic regression model
IV	SCLE and association with triggering drugs	2006-2009	234 SCLE patients and 2,311 controls	SCLE	Matched case-control	NPR, PDR	Conditional logistic regression model

Study I

Cutaneous manifestations are very common in SLE patients (over 80 % display skin symptoms some time during the course of the disease and in 20-25 % of patients cutaneous manifestations are the first symptom of SLE disease) (38, 47, 118-120). Four of the eleven ACR criteria are mucocutaneous (malar rash, discoid lupus, photosensitivity and oral ulcers). Not all of these criteria are well-defined and they are often hard to distinguish from other common skin diseases, this has been debated (54).

The aim of our study was to assess the frequency of cutaneous manifestations according to Gilliam and Sontheimer's classification (10) in a cohort of SLE patients compared to other previous studies. Our aim was also to compare clinical and serological characteristics in SLE patients with and without CLE. We also aimed to investigate the agreement between dermatologists and rheumatologists concerning the ACR criterion malar rash and study the frequency of PLE in SLE patients compared to the photosensitivity criterion.

A total number of 260 SLE patients (female/male ratio 9:1) were included, all of which fulfilled at least four of the revised ACR classification criteria for SLE (41, 190). All patients were enrolled at the Department of Rheumatology, Karolinska University Hospital. All patients went through medical interviews, a general physical examination including blood samples for routine laboratory tests and serological profiles. All included patients also completed an extensive questionnaire that consisted of several questions about photosensitivity and PLE. All participants were asked for skin symptoms. Patients who reported skin symptoms were referred to a dermatologist and went through a thorough skin examination (n=164), and if needed, a skin biopsy. Dermatology medical records and pathology records were evaluated for all 260 patients.

The definitions made by the ACR were used to diagnose malar rash, photosensitivity, DLE and oral ulcers at inclusion by the rheumatologists. According to ACR criteria, a history of malar rash or photosensitivity is sufficient to get the criteria. Oral ulcers have to be recurrent, with or without pain. PLE was defined as a history of itchy papules and/or vesicles occurring one or a few days after sun-exposure on sun-exposed body areas and disappearing within a week if sun is avoided (158).

Study II

There are no large, population-based studies reporting the incidence of CLE and its different subsets as well as the association between CLE and SLE. In this population-based cohort study we aimed to calculate overall incidence rate of CLE as well as the age- and gender-specific incidence of CLE and its subsets in Sweden. Finally, we aimed to assess the short-term probability of receiving an additional diagnosis of SLE.

We conducted a population-based open cohort study of CLE patients using the NPR. All patients (n=1,088) who received a diagnosis of CLE for the first time during the period, January 1, 2005 to December 31, 2007 were enrolled. To ascertain that only incident CLE cases were enrolled we included all patients diagnosed with CLE for the first time between 2001 and 2007. During the first years after the outpatient register was included in the NPR, there was a pool of prevalent cases (2001-2004) that successively stabilized on a lower number, which represents new incident cases. This is termed waiting time distribution and is a graphical approach often used when estimating drug use in epidemiological studies (225, 226).

To obtain the overall incidence rate we assumed that the entire Swedish population was at risk (n= 9 086 233); as the numerator, we used the average number of CLE cases for 2005-2007. Age- and gender-specific incidence rates were calculated by dividing the number of incident CLE patients in each age and gender group by the corresponding figures for the total Swedish population during the same period. The age-, gender- and calendar year-specific population-based figures were obtained from Statistics Sweden.

Each CLE patient was tracked backwards in the NPR to identify prevalent SLE cases. In order to identify incident SLE cases all CLE patients were then followed onwards until the end of observation period or death, whichever occurred first. We calculated Kaplan-Meier survival estimates for different subsets of CLE and the cumulative probability of receiving an additional SLE diagnose.

Study III

The aim of study III was to estimate the overall and specific cancer risks in a nationwide population-based cohort of patients diagnosed with CLE and compare those with a matched control cohort derived from the general population without a diagnosis of CLE. We also wanted to investigate the history of cancer for CLE patients before they were diagnosed with CLE and also what influence comorbidity with SLE had on cancer risk.

A cohort of 3,663 individuals was diagnosed with CLE in the NPR (1997-2007). As a comparison group, we identified a matched control cohort of 10,989 individuals (3 controls for each CLE case) from the general population that was not diagnosed with CLE. The health status in the control cohort represented that of the general population in Sweden. The control cohort was individually matched for possible confounders (age, gender and geographic region). Both the CLE cohort and the control cohort were then linked with the Cancer register and the Cause of Death Register to identify all cancers diagnosed from 1958-2007 and obtain information on death.

Study IV

Over 125 case reports of drug-induced SCLE have been published and more than 40 drugs with diverse latencies have been involved but large observational studies are lacking. The aim of this study was therefore to examine the association between exposure to certain suspected drugs (previously reported as possible triggers) and the subsequent development of SCLE in a large group of incident SCLE cases.

To decide which drugs to analyze a literature review was conducted. All published case reports of DI-SCLE 1985-2011 were identified through the Medline database and more case-reports were identified through the reference sections of the included reports.

To study the association between exposures of certain suspected drugs and a subsequent diagnosis of SCLE we performed a population-based matched case-control study that included all individuals registered with a SCLE diagnosis for the first time during 2006-2009 in the NPR.

For all incident SCLE cases, 10 controls from the general population were matched individually for age, gender and county of residence. A total of 234 SCLE patients were enrolled together with 2311 matched controls (most cases had 10 controls, except for 19 cases that had 9 controls and 5 cases that had 8 controls). By means of the PIN, case and control subjects were then linked to the PDR in order to determine information on drug exposure of the *a priori* suspected drugs 0-6 months before SCLE diagnosis.

5 Statistical analyses:

Study I-IV: Means and standard deviations were used to describe normally distributed continuous data; ordinal or continuous non-symmetrically distributed data were reported as medians and interquartile ranges (IQR).

Student's *t*-test was used for comparison of means between two unmatched groups with continuous data and normal distributions. The chi-square (χ^2) test or Fisher's exact test was used when comparing nominal and ordinal data between groups. Wilcoxon's rank-sum test or the Mann-Whitney U-test was used for non-parametric data. A two-sided *p*-value of less than 0.05 was considered statistically significant.

Study II: Incidence rate is defined as the number of new subjects developing disease in the population at risk divided by the sum of all the individuals risk time in the population during a certain period (227, 228). To calculate 95 % CIs for the estimated incidences a Poisson distribution was assumed for the number of newly diagnosed patients. A Poisson distribution is applicable for discrete distributions with a number of events occurring during a given period.

The Kaplan-Meier estimate was calculated to describe the cumulative probability of also being diagnosed with SLE during 3 years of follow-up. The Kaplan-Meier method is a non-parametric graphic method to estimate survival probability over time. A statistical hypothesis test (the log rank test) was performed to compare the different Kaplan-Meier curves. One limitation of the Kaplan-Meier method is that it is not adjusted for potential confounders in baseline data. However, we performed a Cox regression analysis of crude and adjusted HRs (adjusted for age, sex and subset). Because crude and adjusted HRs did not differ no substantial confounding was present.

Study III: A Cox proportional hazards regression model was used in this survival analysis. This model is a "semiparametric" model and is based on time to event and the effect measure is HR presented together with 95 % confidence intervals (CIs). HR is the hazard in the exposed group divided by the hazard in the non-exposed group: the event rate of being diagnosed with cancer in the CLE cohort compared with the control cohort. The hazard function can be interpreted as the probability of an event at a specific time point given that the individual is free of the event at the beginning of that time point. Risk estimates was stratified according to follow-up time, comorbidity with SLE, gender, CLE subset and different age categories (<50 years, 50-64 years and >65 years). The HRs were calculated for cancer overall and for all major cancer types. Patients diagnosed with any type of cancer before or simultaneously with CLE diagnoses were excluded in the overall analysis; for specific cancers, earlier cancers of that particular subtype were excluded in each subgroup analysis.

To examine the prevalence of cancer before CLE diagnosis logistic regression was used and relative risks were generated as prevalence odds ratios (PORs) with 95 % CIs.

Study IV: In this individual matched case-control study we used a conditional logistic regression model and ORs (representing the relative risk of being prescribed a suspected drug among the SCLE cases compared with the controls) with corresponding 95 % CIs were calculated. In cases where zero events were observed a median unbiased estimate is reported (229). Conditional logistic regression was used since the controls were individually matched (for age, gender and county of residence) for

each case and conditional analysis means that comparisons are undertaken within each risk set (the index cases was only compared with its own matched controls within the same strata). Odds ratio (OR) is the proportion of odds for a certain outcome divided by the odds of not having the outcome.

The attributable fraction (AF) was calculated by the formula of Coughlin et al. for matched case-control studies (230): $AF = P\left(\frac{E}{D}\right) \left(\frac{OR-1}{OR}\right)$, where $P\left(\frac{E}{D}\right)$ represents the proportion of exposed cases.

AF is the proportion of SCLE cases in the population that can be attributed to a previous drug exposure.

A multivariate analysis was also performed to adjust for the other drugs that gave increased ORs but no large differences were seen. Stratum-specific ORs for exposure to any drug 0-6 months before SCLE diagnosis were performed in order to assess possible effect modification by age and gender.

All statistical analyses were performed using the Statistica® software, version 8.0 (study I), JMP® software, version 7-9 (SAS Institute Inc., Cary NC, USA), (study I-IV) or SAS® software, version 9.2 (SAS Institute Inc., Cary NC, USA), (study III-IV).

6 Ethics approval

All studies in this thesis were approved by the Regional Ethical Review Board in Stockholm, Sweden and all participating patients gave informed consent to take part (study I), reference number 01-354, 03-339, 03-340, 03-556, and supplementary 2009/1020-32, 2011/351-32.

7 Results

Study I

A total of 260 SLE patients were included, skin involvement and arthritis were the most frequent clinical manifestations, present in 87 % respectively 86 % of the SLE patients. Photosensitivity and oral ulcers were diagnosed by rheumatologists in 69 % and 35 % respectively, malar rash occurred in 53 % and DLE in 18 % of the SLE patients.

Patients that only received the criteria photosensitivity and/or oral ulcers by a rheumatologist at inclusion were not always referred to a dermatologist that is why more patients have mucocutaneous ACR criteria than the number of patients examined by a dermatologist.

Examination by a dermatologist showed that 23 % (n=60) of the SLE patients had CLE; DLE (11 %) was most common followed by SCLE (8 %) and ACLE (4 %). LE-non-specific cutaneous manifestations were present in 43 % (n=111) of the SLE patients; Raynaud's phenomenon being the most common (25 %), followed by non-scarring alopecia (9 %), vasculitis (8 %) and urticaria (7 %). Both Raynaud's phenomenon and vasculitis were significantly more common in SLE patients that also had a diagnosis of CLE.

We found agreement between dermatologists and rheumatologists in the diagnosis of malar rash in just 60 %; corresponding to a kappa-coefficient (K) of 0.35. In our study 69 % of the SLE patients reported photosensitivity according to the ACR criteria and 42 % had a history of PLE according to the detailed questionnaire.

Table 6. Distribution of the ACR criteria between SLE patients with CLE compared with those without CLE.

	SLE patients with CLE (n=60)	SLE patients without CLE (n=200)	p-value
Arthritis	45 (75 %)	179 (90 %)	0.004
Serositis	17 (28 %)	88 (44 %)	0.03
Renal disorder	28 (47 %)	75 (38 %)	0.2
Neurologic disorder	8 (13 %)	22 (11 %)	0.6
Hematologic disorder	41 (68 %)	148 (74 %)	0.4
Immunologic disorder	41 (68 %)	126 (63 %)	0.5

A majority of the SLE patients had positive ANAs (96 %) and anti-dsDNA antibodies (62 %). The main serological findings were that Ro/SSA, La/SSB autoantibodies and RF were all significantly more frequent in SLE patients with CLE than those without. β 2GP1 on the other hand was significantly more common in SLE patients without CLE. Anti-dsDNA antibodies were less present in SCLE patients compared with the other CLE subsets but no difference was found between patients with CLE compared with those without.

Study II

In the present study, we estimated incidence rates for CLE overall as well as gender- and age-adjusted incidence rates for each CLE subset. A total of 1,088 patients were registered with CLE 2005-2007, the majority were diagnosed in outpatient care (88 %). DLE was the most common subset (80 %, n=868), followed by SCLE (16 %, n=171) and other local LE (<5 %, n= 49). The gender distribution was the same between the subsets with a female to male ratio of 3:1. Patients diagnosed with SCLE were significantly older than the other subsets; mean age 59 years compared with 53 years for DLE patients and 46 years for other local LE (p=0.008).

The average annual incidence of CLE in Sweden 2005-2007 was 4.0/100, 000 (95 % CI 3.9-4.2), for DLE was the incidence rate 3.2/ 100, 000 (95 % CI 3.0-3.4) and for SCLE 0.6/ 100, 000 (95 % CI 0.5-0.7). We found an incidence of CLE of 0.6/100,000 in children aged between 0-14 years.

CLE and DLE have similar age- and gender adjusted incidence rates with a steadily increasing curve peaking in age group 65-74 years for women and 55-64 years for men and decreasing after that. SCLE

on the other hand show a more stable curve after 45 years of age for women and for men the curve is continually increasing with a peak at 75-84 years of age where men and women suddenly display almost the same incidences.

Of the newly diagnosed CLE patients almost a quarter (24 %) had a previous known SLE diagnosis, the CLE subset distribution was the same in these patients as for the whole study group. During the study period an additional 107 patients (of whom 20 from inpatient care) were registered with a SLE diagnosis.

The Kaplan-Meier estimates show that the probability of receiving an additional diagnosis of SLE was 18.1 % (95 % CI 14.1-22.1 %) during the first three years after being diagnosed with CLE. The probability was highest in the SCLE subset; 24.7 % (95 % CI 16.7-32.7 %) compared with 16.7 % (95 % CI 12.1-21.3 %) in the DLE subset ($p < 0.001$). This difference in probability for receiving a SLE diagnosis between the DLE and SCLE subset corresponds to an age- and sex adjusted HR of 0.44 (95 % CI 0.3-0.7). The probability for being diagnosed with SLE was higher for women (20.7 %, 95 % CI 15.9-25.5 %) during the first three years after CLE diagnosis compared with men (10.4 %, 95 % CI 3.7-17.1 %) ($p = 0.003$), this difference corresponds to an age- and subset adjusted HR of 2.2 (95 % CI 1.3-4.0).

Study III

In all, 3663 patients (female to male ratio of 3.3:1) with CLE were included in the study with a median follow-up of 4.1 years. A majority displayed the DLE subset (85 %, $n = 3117$). Dermatologists or rheumatologists/internists (in several smaller hospitals in Sweden the rheumatology and internal medicine clinics are combined) registered 84 % ($n = 3077$) of the CLE diagnosis and 81 % ($n = 2953$) were registered in outpatient care. Almost a quarter (23 %, $n = 839$) of the CLE patients had a previous SLE diagnosis and 12 % ($n = 453$) were registered with an additional SLE diagnose during follow-up.

A significantly increased cancer risk was found in the CLE cohort (HR 1.8; 95 % CI 1.5-2.2) with 183 incident, individual cancers occurring during follow-up. The most increased risk estimates were found for buccal cancer (HR 5.4; 95 % CI 1.8-16.1), accompanied by an approximately four times increased risk for lymphomas (HR 4.4; 95 % CI 1.8-10.7), respiratory cancer (HR 3.8; 95 % CI 2.2-6.4) and non melanoma skin cancer (NMSC) (HR 3.6; 95 % CI 1.8-7.2).

The highest risk estimate was found in the first year after CLE diagnosis (HR 2.7; 95 % CI 1.9-3.8) but remained high more than 1 year after CLE diagnosis (HR 1.5; 95 % CI 1.2-1.9) (Table 7). The risk increase was highest for patients diagnosed in inpatient care and for incident CLE cases (2005-2007) during the first year after diagnosis (Table 7).

Table 7: Hazard ratios (HRs) for cancer overall in different subgroups of CLE patients over time. Patients diagnosed with any type of cancer before or simultaneously with CLE diagnoses were excluded in the overall analyse (n=300). Bold type, 95 % confidence interval (CI) does not include 1.00.

Cancer overall	CLE cohort (n=3363)	Excluding patients also diagnosed with SLE (n=2566)	Patients from outpatient care (n=2744)	Patients from inpatient care (n=619)	Only incident CLE cases, 2005-2007 (n=1612)
Observed no. cases (controls)	183 (347)	121 (347)	122 (243)	61 (104)	56 (80)
HR overall (95 % CI)	1.8 (1.5-2.2)	1.7* (1.3-2.1)	1.6** (1.2-2.0)	2.5 (1.7-3.6)	2.2 (1.5-3.1)
Observed no. cases (controls), during year 1	66 (79)	42 (79)	40 (61)	26 (18)	23 (29)
HR during year 1 (95 % CI)	2.7 (1.9-3.8)	2.5 (1.7-3.9)	2.0 (1.3-3.1)	5.2 (2.7-10.2)	2.5 (1.4-4.5)
Observed no. cases (controls), > 1 year of follow-up	117 (268)	79 (268)	82 (182)	35 (86)	33 (51)
HR > 1 year of follow-up (95 % CI)	1.5 (1.2-1.9)	1.4 (1.1-1.8)	1.4 (1.1-1.8)	1.8 (1.1-2.8)	2.0 (1.2-3.2)

*Men **2.0** (1.4-2.9), female **1.5** (1.1-2.0). **Men **2.0** (1.4-3.0), female **1.3** (1.0-1.8). SLE, systemic lupus erythematosus

The risk estimates remained elevated when we repeated the analysis after excluding cases that were also diagnosed with SLE (excluding all patients diagnosed with SLE before CLE diagnosis and censoring patients when being diagnosed with SLE after CLE diagnosis). A four-time higher risk was observed for buccal cancer and lymphomas and almost a threefold higher risk for NMSC.

A subset analysis showed a more elevated risk estimate for the SCLE subset the first year after CLE diagnosis than for the DLE subset (HR 3.1 (95 % CI 1.2-7.6) versus HR 2.5 (95 % CI 1.7-3.6)). One year before CLE diagnosis and one year after- 27 % (16 out of 59) of the cancers in the SCLE subset occurred. The equivalent number in the DLE subset was 26 % (107 out of 410).

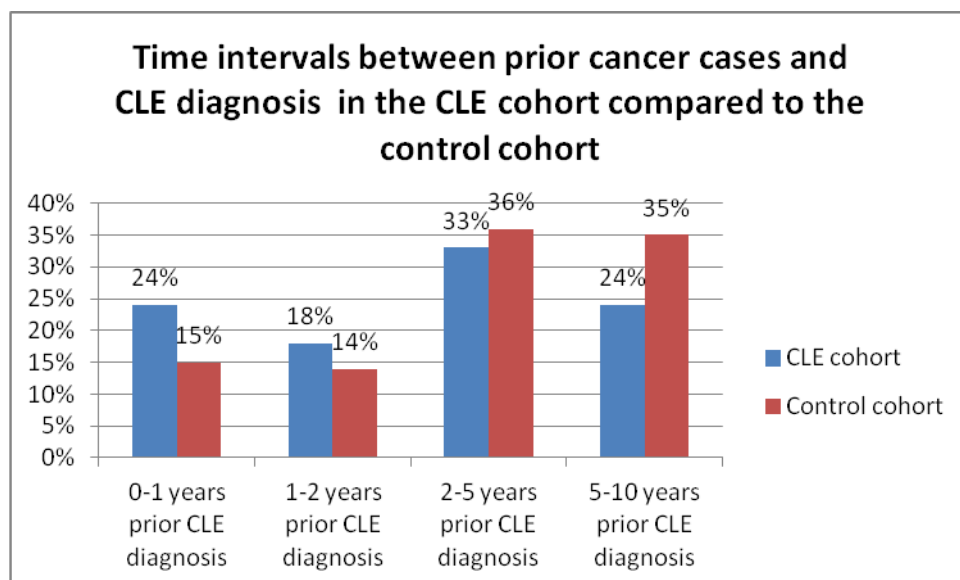
A slightly elevated risk for cancer was found for men with CLE (Table 8). The actual numbers of cancers are increasing with age for both the CLE cohort and the control cohort and a significantly increased cancer risk can be seen after age 50 but after that the cancer risk remained the same (Table 8).

Table 8: HRs for cancer overall and specific cancer types in a cohort of 3,663 CLE patients stratified on gender and age groups. Patients diagnosed with any type of cancer before or simultaneously with CLE diagnoses were excluded in the overall analysis (n=300). For specific cancers, earlier cancers of that particular subtype were excluded in each analysis. Bold type, 95 % confidence interval (CI) does not include 1.00.

Type of cancer (ICD-7* codes)	CLE cohort	Female	Male	<50 y	50-64 y	>65 y
All cancers Observed no. cases (controls)	183 (347)	120 (239)	63 (108)	9 (30)	76 (127)	98 (190)
HR (95 % CI)	1.8 (1.5-2.2)	1.7 (1.3-2.1)	2.0 (1.4-2.8)	0.9 (0.4-1.8)	2.0 (1.5-2.7)	1.8 (1.4-2.3)
Buccal cancer (140-148) Observed no. cases (controls)	9 (7)	6 (4)	3 (3)	2 (0)	2 (3)	5 (4)
HR (95 % CI)	5.4 (1.8-16.1)	6.0 (1.5-24.0)	4.5 (0.8-26.9)	- (-)	3.0 (0.4-21.3)	5.0 (1.2-20.9)
Digestive cancer (150-159) Observed no. cases (controls)	50 (72)	34 (48)	16 (24)	2 (4)	17 (19)	31 (49)
HR (95 % CI)	2.4 (1.7-3.5)	2.4 (1.5-3.7)	2.5 (1.3-5.0)	1.5 (0.3-8.2)	3.0 (1.5-5.9)	2.3 (1.4-3.6)
Respiratory cancer (160-164) Observed no. cases (controls)	32 (32)	24 (21)	8 (11)	0 (0)	19 (15)	13 (17)
HR (95 % CI)	3.8 (2.2-6.4)	4.2 (2.2-7.7)	2.9 (1.1-7.8)	- (-)	4.7 (2.3-9.7)	2.9 (1.4-6.3)
Non-melanoma skin cancer (191) Observed no. cases (controls)	21 (19)	14 (14)	7 (5)	3 (1)	1 (2)	17 (16)
HR (95 % CI)	3.6 (1.8-7.2)	3.2 (1.4-7.3)	4.9 (1.2-19.4)	9.0 (0.9-86.5)	1.5 (0.1-16.5)	3.5 (1.6-7.7)
All hematopoietic cancer (200-209) Observed no. cases (controls)	20 (25)	15 (13)	5 (12)	2 (2)	6 (6)	12 (17)
HR (95 % CI)	2.5 (1.4-4.7)	3.4 (1.6-7.2)	1.4 (0.5-4.2)	3.0 (0.4-21.3)	2.8 (0.9-8.7)	2.3 (1.0-5.1)
Lymphomas (200, 201, 202,204.1) Observed no. cases (controls)	13 (11)	10 (8)	3 (3)	1 (0)	5 (3)	7 (8)
HR (95 % CI)	4.4 (1.8-10.7)	4.0 (1.5-10.5)	7.2 (0.7-72.0)	- (-)	4.8 (1.1-20.0)	3.6 (1.1-11.6)

We also wanted to study the prevalence of cancers occurring before CLE diagnosis to determine whether CLE patients had a higher risk of cancer already before being diagnosed with CLE. In 298 of the CLE patients we found a history of cancer before they were diagnosed with CLE, which resulted in a POR of 1.3 (95 % CI 1.1-1.5). Buccal cancer and NMSC showed the highest PORs and they remained elevated when excluding patients diagnosed with SLE before CLE diagnosis. The median time was 2.5 years (IQR 0.9-4.8) between a previous cancer diagnosis and a subsequent CLE diagnosis. Figure 7 shows the time intervals between prior cancer cases in the CLE cohort compared with the control cohort.

Figure 7. Cancers prior to CLE diagnosis.



Study IV

In total, 234 incident SCLE patients were identified from the NPR and matched with 2311 control subjects from Statistics Sweden. Median age was 65 years and a majority of the SCLE patients were women (77 %). Of the SCLE cases, 18 % (n=41) had a SLE diagnosis before being diagnosed with SCLE and an additional 16 % (n=38) were diagnosed with SLE after SCLE diagnosis.

Exposure to terbinafine and TNF- α inhibitors 0-6 months before SCLE diagnosis showed the greatest increase in risk (OR 52.9, 95 % CI 6.6- ∞ and OR 8.0, 95 % CI 1.6-37.2, respectively) for a subsequent diagnosis of SCLE. No increased risks were found when other systemic antimycotics were investigated. Exposure to antiepileptic and proton pump inhibitors (PPIs) 0-6 months before SCLE diagnosis showed about threefold elevated risk estimates (3.4 (95 % CI 1.9-5.8) and 2.9 (95 % CI 2.0-4.0), respectively) and twofold elevated risks were seen for thrombocyte inhibitors (OR 2.2, 95 % CI 1.5-3.2), ACE-inhibitors (OR 1.7, 95 % CI 1.1-2.7) and NSAIDs (OR 1.6, 95 % CI 1.1-2.2).

The analysis was repeated after excluding SCLE cases previously diagnosed with SLE. However, no significant changes in the estimates were found (Table 9).

Table 9: Estimated odds ratios (ORs) and 95 % confidence intervals (CIs) for the association between exposures to certain suspected drugs 0-6 months before SCLE diagnosis when excluding SCLE cases previously diagnosed with SLE. Red type, 95 % confidence interval (CI) does not include 1.0.

Drug class	Generic name (ATC-code)	Excluding cases also being diagnosed with SLE before SCLE diagnosis, n= 193, (controls, n=1905) drug exposure 0-6 months before SCLE diagnosis	OR cases: controls when excluding cases also being diagnosed with SLE before SCLE diagnosis (95 % CI), drug exposure 0-6 months before SCLE diagnosis
Antihypertensives	Thiazides (C03A)	12 (86)	1.4 (0.7-2.7)
	Beta Blockers (C07)	42 (401)	1.0 (0.7-1.5)
	Calcium channel blockers (C08)	28 (211)	1.4 (0.9-2.2)
	ACE-inhibitors (C09A)	24 (175)	1.4 (0.9-2.3)
	ACE-inhibitors+ diuretics (C09BA)	4 (18)	2.2 (0.5-6.7)
	Angiotensin II antagonists (C09C+C09D)	25 (169)	1.5 (0.9-2.5)
Statins	HMG-CoA reductase inhibitors (C10AA)	34 (274)	1.3 (0.8-2.0)
Antithrombotic	Thromobocyte inhibitors (B01AC)	58 (357)	2.2 (1.4-3.2)
Proton Pump Inhibitors	Proton Pump Inhibitors (A02BC)	48 (255)	2.2 (1.5-3.2)
NSAIDs	NSAIDs (M01A)	40 (292)	1.5 (1.0-2.1)
Antifungals	Antifungals (D01B)	4 (0*)	52.9 (6.6-∞)
Antiepileptics	Antiepileptics (N03)	19 (45)	4.3 (2.4-7.6)
Biologics	TNF-α inhibitors (L04AB)	3 (4)	7.5 (1.1-44.3)
Immunomodulating agents	Pyrimidines analogues (L01BC)	1 (1)	10.0 (0.1-785)
	Interferon (L03AB)	0* (1)	10.0 (0.0-390)
Hormone Altering Drugs	Antihormones (L02B)	1 (19)	0.5 (0.0-3.3)
	Gonadotropin releasing hormone analogues (L02AE)	1 (10)	1.0 (0.0-7.5)
Antihistamines	H2 receptor antagonists (A02BA)	3 (24)	1.3 (0.2-4.2)
	Adrenergica (R01BA)	3 (36)	0.8 (0.2-2.7)
Antidepressants	Antidepressants (N06AX)	6 (57)	1.0 (0.4-2.4)
Antigout	Allopurinol (M04AA)	4 (25)	1.6 (0.4-4.6)

* In cases where zero events were observed a median unbiased estimate is reported (229).

We also analyzed shorter periods of exposure, 0-3 months and 3-6 months (with a wash out period of 0-3 months) before SCLE diagnosis but the risk estimates remained the same as for the longer exposure period of 0-6 months (Table 10). A continuous drug exposure both 0-3 months and 3-6 months before SCLE diagnosis also gave the same risk estimates (Table 10).

Table 10: Estimated odds ratios (ORs) and 95 % confidence intervals (CIs) for the association between exposure to certain suspected drugs and a subsequent diagnosis of SCLE for different periods. The three periods are mutually exclusive (0-3 months or 3-6 months or both 0-3 and 3-6). Red type, 95 % confidence interval (CI) does not include 1.0. Only drugs that showed significant increased ORs are shown.

<u>Drug class</u>	<u>Generic name</u> (ATC-code)	Cases, n= 234 (controls n=2311) OR SCLE: controls (95 % CI), drug exposure 0-3 months before SCLE diagnosis	Cases (controls) OR SCLE: controls (95 % CI), drug exposure 3-6 months before SCLE diagnosis	Cases (controls) OR SCLE: controls (95 % CI), drug exposure 0-3 and 3-6 months before SCLE diagnosis
Antihypertensives:	ACE -inhibitors (C09A)	12 (47) 1.7 (1.1-2.6)	3 (17) 1.3 (0.8-2.2)	17 (135) 1.3 (0.7-2.2)
Antithrombotic	Thromobocyte inhibitors (B01AC)	13 (85) 2.0 (1.3-2.9)	8 (36) 2.0 (1.4-3.0)	45 (285) 1.8 (1.2-2.7)
Proton Pump Inhibitors	Proton Pump Inhibitors (A02BC)	18 (82) 2.9 (2.0-4.1)	9 (50) 2.7 (1.8-3.9)	38 (154) 2.8 (1.8-4.2)
NSAIDs	NSAIDs (M01A)	18 (138) 1.9 (1.3-2.7)	10 (109) 1.7 (1.1-2.5)	23 (97) 2.5 (1.5-4.1)
Antifungals	Terbinafine (D01B)	2 (0*) 39 (4.1-∞)	1 (0*) 24 (1.9-∞)	1 (0*) 10 (0.3-∞)
Antiepileptics	Antiepileptics (N03A)	5 (11) 3.7 (2.0-6.6)	2 (11) 3.1 (1.6-5.7)	13 (39) 3.4 (1.6-6.7)
Biologics	TNF-α inhibitors (L04AB)	0* (4) 8.0 (1.6-37.2)	- (-) - -	4 (1) 40.0 (4.0-1970)

* In cases where zero events were observed a median unbiased estimate is reported (229).

Among the 234 cases, 166 (71 %) had a prior prescription of any of the suspected drugs as compared with 53 % of the controls 0-6 months before SCLE diagnosis, which is equivalent to an OR of 2.14 (95 % CI 1.6-2.9) and an attributable fraction of 38 %, i.e. about 38 % of all SCLE cases can be attributed to previous drug exposure.

	Exposed	Non-exposed	Total number
SCLE cases	166	68	234
Controls	1231	1080	2311
Total number	1397	1148	2545

Attributable fraction in a matched case-control study: (proportion of exposed cases) $((OR-1)/OR)$
 $\rightarrow (166/234) \times ((2.14-1)/2.14) = 0.378 \rightarrow 38\%$ of SCLE cases can be explained by exposure to suspected drugs.

Of the cases, 27 % were cared for in hospital during the 6 months preceding the SCLE diagnosis, which can be compared with 9 % of the controls.

We performed stratum-specific ORs for exposure to any of the suspected drugs 0-6 months before SCLE diagnosis to assess possible effect modification by age and gender (Table 11). When we estimated stratum-specific ORs we found effect modification by age, individuals under 50 years of age showed a higher relative risk of developing SCLE after drug intake than older individuals. The distribution of “high-risk drugs” (terbinafine, TNF- α inhibitors, antiepileptic, PPIs, thrombocyte inhibitors, ACE -inhibitors and NSAIDs) were the same between the age groups. No stratum-specific differences for gender were found.

Table 11: Stratum-specific odds ratios (ORs) and 95 % confidence intervals (CIs) for age and gender. Exposure to any suspected drug 0-6 months before SCLE diagnosis.

	<50 years		50-65 years		>65 years		p-value for interaction
Drug	SCLE (cases) n= 62 (Controls n=613)	OR SCLE: controls (95 % CI)	SCLE (cases) n= 56 (Controls n=570)	OR SCLE: controls (95 % CI)	SCLE (cases) n= 116 (Controls n=1128)	OR SCLE: controls (95 % CI)	
Exposure to any suspected drug	31 (122)	4.0 (2.4-6.9)	36 (260)	2.1 (1.2-3.8)	99 (849)	1.9 (1.1-3.3)	0.005

	Women		Men		p-value for interaction
Drug	SCLE (cases) n= 180 (Controls n=1779)	OR SCLE: controls (95 % CI)	SCLE (cases) n= 54 (Controls n=532)	OR SCLE: controls (95 % CI)	
Exposure to any suspected drug	126 (927)	2.1 (1.5-3.0)	40 (304)	2.1 (1.1-4.0)	0.84

The Medical Products Agency (MPA) is the Swedish national authority responsible for regulation and surveillance of drugs. During 2006-2009, the MPA received 15 reports (8 women, 7 men) about drugs suspected of inducing LE; 12 of those were connected to SLE and 2 to skin reactions. In addition, there was one case of lichenoid tissue reaction and one case of vitiligo. Nine of these reports were associated with the use of TNF- α inhibitors.

8 Discussion

8.1 Overall methodological considerations

Both cohort studies and case-control studies are analytical, observational studies and both methods have their strengths and weaknesses. The particular aim of the study determines which method that is most appropriate and the decision is based on achieving high internal and external validity as well as high efficiency.

8.1.1 Cohort studies (Study II,III)

In a cohort study a number of individuals with a certain exposure or characteristic in common are defined. They are then followed over a specified period and the occurrence of different outcomes are studied and compared with an unexposed cohort. Cohort studies are efficient for unusual exposures but usually not for rare outcomes (227, 228). An advantage with cohort studies is that it is possible to study multiple endpoints. Incidence rates, relative risks and attributable risks can be calculated as well as cumulative risks (227, 231). A disadvantage with cohort studies is that they can be very costly and time consuming but this does not apply to our retrospective cohort studies using register data for follow-up. The risk for selection and information bias is generally less in cohort studies than in case-control studies. A disadvantage is that the validity of the results is often influenced by losses to follow-up and differential losses to follow-up bias the results, this is not applicable in our studies since we achieved complete follow-up.

Advantages with **study II** and **III** are that individual information from an entire population is included with no losses to follow-up that could bias the results. All data come from nationwide databases guaranteeing a high quality of information with high completeness. In **study III** the same sources of information were used for both the cohort and the control cohort as a means to avoid information bias. Exposure in **study III** was a registered diagnosis of CLE and the outcome was cancer. In **study III** the unexposed control cohort was individually matched for age, gender and county of residence (three individuals in the unexposed control cohort for every individual in the exposed CLE cohort). The goal of the unexposed control cohort is that it should be as similar as possible to the exposed cohort except for the exposure itself. Our control cohort was derived from the general population and was matched for important possible confounders. The matching procedure increased statistical efficiency in the study by limiting the needed number of individuals in the control cohort.

8.1.2 Case-control studies (Study IV)

Case-control studies originate from the cases that are defined by a certain outcome of interest. They are compared with the controls that do not have the outcome and the proportion of different exposures or characteristics are then compared between the two groups (228). Case-controls studies are time efficient and cost-effective for rare outcomes or for outcomes that have a long latency time but are not suitable for rare exposures (227). An advantage with case-control studies is that they enable simultaneous study of multiple exposures, although limited to one outcome.

It is crucial in case-control studies to select controls in an appropriate way so that they are representative of the source population in every important way except for not having the outcome studied. It is also important to use the same information sources for both cases and controls in order to avoid bias. In particular, recall bias is often a major problem in case-control studies (228). ORs are used to measure associations in case-control studies and for diseases as CLE (with a incidence of <5 % in the population) OR and relative risk are equivalent (227).

Matching in case-control studies control for confounding for the matching variables and improves accuracy and efficiency in the study. Matching should just be performed for possible confounders in order to avoid decreased accuracy or bias. The effect of matched variables cannot be analyzed. Age and gender are typical confounders. In **study IV** we also matched for county of residence because geographic location within Sweden is a possible source of bias, i.e. people living in metropolitan areas often have better access to and use more health care than people living in rural areas.

The number of controls affect the accuracy of the results and improves the study's power, i.e. the more controls the -> higher the accuracy, narrower CI (232). This relationship, however, is not linear and consideration for cost and time related to each control must be taken into account when deciding how many controls should be studied for each case. The number of SCLE cases in **study IV** was limited (because it is a rare disease and because the PDR is only available since July 1, 2005). To improve efficiency and have a sufficient number of subjects exposed to each suspected drug we decided to have 10 controls for each case.

A limitation with case-control studies is that they often use retrospective collected data for information on exposure but in our study we were able to use exposure data collected before SCLE onset, which is an advantage for minimizing bias.

8.1.3 Internal validity- do we measure what we set out to measure?

8.1.3a Bias

Bias is a systematic error in the study design introduced by the researcher. Systematic errors can be divided into confounding and bias. Bias can be further divided into information and selection bias.

Information bias (Syn. Observation/Classification/ Measurement)

Information bias is caused by systematic differences or insufficient methods for collecting and measuring data and can contribute to over- or underestimation of the study results. It cannot be controlled for afterwards by statistical methods (228). Information bias is common in most studies and can cause differential or non-differential misclassification of the study subjects. Common types of information bias are recall bias, surveillance (=detection) bias and interviewer bias (228). Both cohort and case-control studies suffer from information bias but recall bias is more common in case-control studies.

Differential (non-random) misclassification can occur if the outcome is measured differently for exposed and non-exposed subjects or if exposure is measured differently depending on whether the study subjects have the outcome or not. The result is either over- or underestimation of associations.

Non-differential (random) misclassification can occur if the exposure or outcome is misclassified but the probability for this is the same in all studied groups. This kind of misclassification tends to underestimate real differences (228).

Because not all 260 SLE patients in **study I** were examined by a dermatologist there is a risk of missing cutaneous manifestations in the non-examined group which would lead to differential misclassification. We consider this risk as small for all major cutaneous manifestations (e.g. CLE, skin malignancies, vasculitis) because all patients were asked in a structured way about skin manifestations and both pathology and dermatology records were reviewed for all 260 patients. However, an underreporting of non-scarring alopecia is likely because neither patients nor rheumatologists may have considered this as a skin disease and thus these patients were not included in the dermatological investigation.

The risk for information bias was minimized in **study II-IV** because both exposure and outcome data came from health care registries with high quality and no losses to follow-up. In the Swedish health care registries data are prospectively collected. Thus, even if our studies were retrospective in design, information on both outcome and exposure was collected in a prospective manner and recorded independently of each other, which results in no risk for recall bias.

A possible misclassification of the CLE diagnosis cannot be excluded. To avoid misclassification it is important to have strict diagnostic criteria for the disease to be studied so the correct cases are chosen. CLE is not always an easy diagnosis but most often specific clinical, pathological and immunological features are seen so the diagnosis is not set arbitrarily. According to Swedish guidelines and clinical practice, a histopathological examination, together with clinical findings and a serological profile, is the ground for a CLE diagnosis (233). Over 80 % (84 %-98 %) of the CLE diagnosis in **study II-IV** were diagnosed by dermatologists or rheumatologists/internists, which supports a

correct diagnosis. If a misclassification were present, it would most probably be non-differential in **study II** between patients receiving an additional diagnosis of SLE and those that do not and in **study IV** between patients being exposed to certain suspected drugs and those that are non-exposed. In these cases the estimated results would actually be diluted. Earlier validations of the NPR have shown very reliable figures for diverse diseases, which also decreases the risk for misclassification.

Differential misclassification is often an important source of error, especially in cohort studies. We tried to minimize the risk for differential misclassification in **study II-IV** by including everyone that was diagnosed with CLE instead of selecting subgroups diagnosed in different ways (e.g. only those that were diagnosed by a dermatologist).

Our findings could be influenced by detection bias because of more screening among individuals with a chronic disease who are continually followed by a physician. This could lead to an overestimate of the cancer risk in **study III**. In this case NMSC would be especially influenced by detection bias because the patients are regularly checked by a dermatologist. The increased risk for NMSC seen already during the first year after CLE diagnosis could partly be due to detection bias although the risk estimate was increased already before CLE diagnosis and remained elevated afterwards.

The risk for bias was reduced in **study IV** because all information on drug exposure for both cases and controls came from the PDR and the data was complete with no losses to follow-up. However, because we were only able to evaluate dispensed drugs, patient non-compliance may have overestimated the exposure, which would bias the result towards null.

Selection bias

Selection bias is introduced when the sampling of individuals included in the study is not representative of the source population to be studied. The concluding results can be both over- or underestimated and this cannot be adjusted for afterwards (228). Selection bias is usual, especially in case-control and retrospective cohort studies, and identification of the controls is often insufficient. Self-selection bias, loss to follow-up and “healthy worker effect” are examples of selection bias.

The risk of selection bias was minimized in **study II-IV** in that all individuals obtaining a diagnostic code for CLE were included. In **study III** and **IV** the risk for selection bias was minimized because both the CLE groups and the comparator groups without CLE came from the same source population, i.e. the whole Swedish population.

Berkson’s bias or *admission-rate bias* is one type of selection bias in which the cases and controls differ in rates of hospitalization, either because of the presence of another disease or that exposure of interest might lead to a higher degree of hospitalization (234, 235). In **study III** we found higher risks for patients diagnosed in inpatient care versus outpatient care. We suspect that patients identified in inpatient care may suffer from severer CLE disease which could increase the risk of cancer or suffer from another disease that could also increase the risk for cancer compared with patients identified from outpatient care. Study III is a mixture of incident and prevalent CLE cases which can also influence the results because of different follow-up time.

In **study IV** there is a risk for *protopathic bias* if “early symptoms of a disease influence the likelihood of being exposed to a certain drug” (132). We believe this risk is small because first-line therapy for

SCLE is topical corticosteroids which are not suspected of triggering the disease. However, terbinafine is an exception because SCLE can be misdiagnosed as tinea corporis and treated with terbinafine.

8.1.3b *Confounding*

Definition: a factor associated with both the exposure and the outcome but not an intermediate link in the causal pathway (228), “a mixing or blurring of effects” (235). Controlling for a confounder should change the relative risk for that association. A confounder can have positive or negative influence over the association. Known confounders can be adjusted for by restriction, matching, stratification and regression analysis but randomization is the only method to handle both known and unknown confounders.

A limitation of **study II-IV** is that we were not able to control for possible confounding factors such as smoking, UV exposure, serological findings and specific genotypes. On the other hand, we were able to control for some important confounders such as age and gender.

8.1.3c *Random error or chance*

The third thing to consider when evaluating the internal validity is the random error or the role of chance that can always affect the results. To decrease the findings that are due to chance two of the most important things are to have valid sample size and enough power in the study, both of which will lower the variability within the study population and make the inference more reliable (236). To quantify the degree of chance variability p-values are often used. The definition of p-value is “the probability that an effect at least as extreme as that observed in a particular study could have occurred by chance alone, given that there is truly no relationship between the exposure and disease” (236). In medical research a finding is considered statistically significant if the p-value is less or equal to 0.05. In such a case the null hypothesis (i.e. no difference) is rejected.

Another way to measure the role of chance is the confidence interval that can be defined as “the range within which the true magnitude of effect lies with a certain degree of assurance” (236). A CI provides the same information as the p-value but provides more information regarding precision of the study (“the strength, direction, and a plausible range of an effect”) (227)(236). A 95 % CI provides a range of values that include the unknown mean with 95 % confidence.

8.1.4 *External validity*

External validity is whether the results from one study can be extrapolated to other populations (236). To satisfy the external validity, a high internal validity must first be fulfilled (228).

Asian and Black ethnic groups are known to have a higher CLE incidence. The population in our studies was mainly Caucasians and the results could therefore be generalized primarily to other Caucasian populations. Racial differences and cancer risk could influence the external validity in

study III but stratification on race and cancer risk in SLE patients has shown no racial differences (237). However, NMSC are known to be more prevalent in fair skinned individuals (238). Racial differences for drug-induced skin reactions could possibly affect the external validity in study IV.

The population-based setting, the large number of study subjects included in the studies, patients recruited from both inpatient and outpatient care, multiple, matched population-based controls recruited in an unbiased way, no losses to follow-up and a plausible biological explanation underlying the results all affect the external validity in a positive way. We believe that the external validity is high in these studies given that the CLE diagnosis is given for the same criteria as in Sweden and that the general health care is quite similar to that in Sweden regarding drug intake, smoking habits, etc.

8.2 Further discussion points for each study

Study I

This study describes the frequency of cutaneous manifestations in a large cohort of SLE patients and the main clinical and immunological differences in SLE patients with and without CLE are assessed. LE-non-specific cutaneous manifestations were almost twice as usual as LE-specific manifestations among SLE patients in this study. Raynaud's phenomenon and vasculitis were significantly more common in the CLE group.

Malar rash was the most common skin manifestation among SLE patients in this study but the present definition of malar rash showed just fair agreement between rheumatologists and dermatologists and the definition does not exclude several common skin diseases. Malar rash is also associated with photosensitivity, which was diagnosed in about 70 % of the SLE patients in this study. However, 42 % had a history of PLE. A history of photosensitivity can be present in several other dermatological diseases, including photo induced drug eruption, photo induced eczema, dermatomyositis and PLE. A detailed history of photosensitivity should include questions clarifying whether the patient has PLE and /or newly induced or worsened LE skin lesions to make the diagnose more accurate.

ANA and anti-ds-DNA antibodies were the most common serologic findings, being equally present in the CLE patients and the non-CLE patients. In comparison with the other CLE subsets, anti-ds-DNA was less present in the SCLE patients. This finding may reflect the milder disease in SCLE patients with less nephritis. As expected, Ro/SSA and La/SSB autoantibodies were more common in the CLE patients than those without. These antibodies are mostly associated with the SCLE subset, in our study 70 % of SCLE patients had Ro/SSA compared with 45 % in the other CLE group ($p=0.067$).

The SLE patients with CLE more often displayed Raynaud's phenomenon, vasculitis and anti-Ro/SSA, anti-La/SSB antibodies and RF but had less arthritis, serositis and β 2GP1 than the patients without CLE, suggesting that the SLE patients with CLE sustain a separate phenotype.

To our knowledge this is the largest study that has been published of cutaneous manifestations in SLE patients. In conclusion, we found the Gilliam criteria for cutaneous manifestations in SLE to be useful for this type of study, except concerning the use of ACLE and malar rash. Based on our findings, we suggest that a more specific definition of malar rash and photosensitivity is needed to avoid misclassification and that the criteria for CLE diagnosis should only include histopathologically confirmed CLE. Collaboration between rheumatologists and dermatologists would improve the care of this patients group and regular examination of the skin is important in SLE patients.

Study II

For the first time population-based data on a large cohort of CLE patients are presented, describing the incidence of CLE and the short time probability of receiving an additional diagnosis of SLE. An annual incidence of CLE of 4/100,000 was found. About 25 % of the CLE patients had a SLE diagnosis already when they were diagnosed with CLE and the probability was about 20 % of being diagnosed with an additional SLE diagnosis during the first 3 years of follow-up.

Durosaro et al. found an age- and sex-adjusted incidence rate of CLE to be 4.3 (3.6/ 100,000 in DLE patients and 0.6 /100,000 in SCLE patients) (142). Although Durosaro et al. have similar results to ours, the data are not directly comparable in that their data were collected over a longer observation period during which time the CLE classification have changed and several immunological markers developed. Moreover, they did not include patients with SLE before CLE diagnosis.

No figures of the isolated incidence of CLE in childhood have been previously reported. In the present study the incidence of CLE during childhood was the same among boys and girls (0.6/100.000) but during adolescents the girls outnumbered the boys, which supports the idea that sex hormones may play a role in initiating CLE. The incidence of SLE in childhood has earlier been reported to also be 0.6/100,000 (24). We found a reduction in gender differences in CLE patients with higher age. Minorities of SLE patients (6-18 %) are diagnosed after 50 years of age and there is a characteristic reduction in female dominance from 9:1 in early-onset disease to 6-7:1 in late-onset SLE (239, 240).

On the other hand, this study showed that CLE patients were considerably older (mean age 54 years) at onset than SLE patients (mean age 30 years) (45), suggesting other underlying pathomechanisms, in which there is perhaps less influence from hormones and greater influence from cumulative UV exposure, smoking and other unknown risk factors?

Most of the CLE cases that received an additional diagnosis of SLE were given it within the first 6 months after CLE diagnosis then the Kaplan-Meier curve flattens out. This could be due to increased observation and heightened awareness among the treating physicians (diagnosing less severe disease?) but it could also be because the cutaneous manifestations are the presenting symptom of systemic disease.

We have a short follow-up time in this study since the outpatient register is relatively new. In the future it will be possible to follow these patients for a longer period of time and also link them to the PDR in order to see the amounts of prescribed drugs, and if these are topical or systemic, this will hopefully give us an idea of their disease severity.

We believe that the CLE incidence we found is an underestimation: 1) milder CLE cases not getting referred to a specialist and therefore not reported in the register, 2) a delay between onset of symptoms and a correct diagnosis would underestimate the incidence rates we found in that the study was done recently and thus would miss those patients and 3) most patients were diagnosed in outpatient care where the coverage is about 80 %, which leaves out 20 %.

Study III

We found an increased risk for cancer in this nationwide cohort study that included 3,663 CLE patients. The risk increase was especially high for buccal cancer, lymphomas, respiratory cancer and NMSC. Although no causal relationship between potential risk factors and cancer development in CLE patients could be established in this study, a discussion regarding potential explanations for the association between CLE and cancer is included in this section.

Only 10 % of all cancers are caused by germ line mutations; the remaining 90% are associated with environmental factors and somatic mutations. Further, 35 % are linked to dietary factors (mainly obesity), 30 % to smoking and other inhaled pollutants and 20 % to chronic infections (241).

Chronic inflammation and immunologic disturbances

It is widely accepted that inflammation is important in carcinogenesis and an inflammatory microenvironment is a key component of all tumors (241, 242). Chronic inflammatory disease can result in constant B-cell stimulation similar to the immunological disturbances seen in hematological malignancies (192, 198, 205). It has also been suggested that patients with autoimmune diseases have a genetic susceptibility with foci of prematurely aging cells that are prone to transform into cancer cells. However, before they fully transform, they signal “danger” and are detected by the innate immune system (193). Another possible explanation is that certain complex MHC-linked genes predispose to both malignancy and autoimmunity (192, 198).

Consistent local chronic inflammatory stimuli in the skin (such as in DLE with chronic scarring and oral ulcers) may be a part of the explanation for the increased risk of buccal cancer and NMSC. Other inflammatory skin diseases (hidradenitis suppurativa, dermatomyositis and psoriasis) have also been shown to have an increased risk of cancer (195, 213, 243).

Patients with both congenital and acquired immunodeficiencies have an increased incidence of hematopoietic cancers (244). Consequently, the increase we see in this study of lymphomas may be a sign of immunological dysfunction. Other autoimmune diseases (e.g. RA, SLE and SS) are also associated with an increased risk of lymphomas (126, 137).

Infections

Patients with LE might be predisposed to viral infections that are due to innate immune dysfunction and the viral infections might trigger malignancy development. Known oncogenic infections are HPV, EBV, *Helicobacter pylori*, HHV-8, HTLV-1 and HIV (the last three are rare in Sweden) (220).

The increased incidence of lymphomas noted in autoimmune diseases (SLE, RA and SS) may be related to chronic infections with Epstein-Barr, herpes simplex or other oncogenic viruses.

Organ transplanted patients have an excess risk for lymphomas, lip cancer and NMSC. Activated oncogenic viruses and bacteria are thought to be the most important mechanism (220). HPV infections have been shown to be very common in transplanted patients and they have also been found in NMSC in these patients (245).

An increased rate of HPV infections in CLE patients could be one possible explanation to the increased risk of NMSC and buccal cancer. HPVs are small DNA viruses that can infect keratinocytes in skin and mucosa. Thus far, about 120 HPV types have been identified (246, 247). Most humans are infected with different cutaneous HPV types already during childhood (104). HPV is an important risk factor for cancer in the vagina, penis, anus and cervix (220, 248) and since 2007 it is also acknowledged by the International Agency for Research on Cancer (IARC) as an etiologic risk factor for buccal cancer (248, 249). HPV also causes cutaneous warts and both SLE and CLE have been associated with a high prevalence of cutaneous warts. One study showed a prevalence of 12 % in LE patients compared with 2 % in controls, it was not related to immunosuppressive treatment (250).

Cutaneous SCC has been shown to contain HPV DNA in 30-85 %, which can be compared with 15-35 % in normal skin (247, 251). The virus load in skin tumors is low (only 1 out of 20-5000 dysplastic cells have been shown to contain HPV) and studies have proposed HPV as an early pathogen in the development of cutaneous SCC, where the number of HPV infected cells decreases during cancer development (246, 247). The role of HPV in skin cancer is not yet known, although betaPV and unknown HPV subtypes have been hypothesized to be involved in the development (252). Exposure to UV light is the major known risk factor for NMSC but cutaneous HPV types have been proposed to act as cofactors to UV light during early carcinogenesis (247). The association between NMSC and HPV is easily confounded by several factors (e.g. UV light, genetics and immunosuppression) that influence both NMSC and HPV (249). There is one case report in which HPV was found in SCC developing in a patient with DLE (253).

Cervix cancer is a known HPV-induced cancer but we did not notice any increased risk of cervix cancer. SLE was previously thought to be associated with an increased risk of cervical cancers but recently it was concluded that SLE patients have increased susceptibility for being infected with HPV and cervical dysplasia but not for having cervical cancer (113, 114). In a recent meta-analysis that was performed even a decreased risk for cervical cancers was found in SLE patients (237). The immune response in women with SLE seems to be impaired when infected with HPV, which could be due to either immunological abnormalities (e.g. decreased clearance of HPV) or drug exposures (e.g. azathioprin), both of which could be applied to CLE patients (254).

Paraneoplastic disease

Paraneoplastic disease was defined by McLean as the simultaneous occurrence of a dermatosis and development of cancer. The dermatosis, however, may precede the cancer diagnosis by no longer than 2 years and both the dermatosis and the cancer should follow a parallel course (255).

SCLE has been hypothesized as a paraneoplastic disease and a neoplastic antigen with resemblance to the Ro/SSA antigen has been proposed as a mechanism for this phenomenon (182). In this study we found a small increased risk of cancer in SCLE patients during the first year after SCLE diagnosis (HR 3.1 compared with 2.7 in the whole group of CLE patients) but no difference when comparing the occurrence of cancer one year before and one year after CLE diagnosis for SCLE and DLE subsets. These findings are not conclusive to support the theory of SCLE as a paraneoplastic disease thus; there could still be a subgroup of patients where SCLE is a paraneoplastic phenomenon. Our study design did not allow us to study McLean's second criteria.

Traditional risk factors

Smoking induces chronic inflammation, which promotes cancer development (241). Tobacco smoking mostly affects the risk for cancer in the upper aero-digestive tract, oesophagus, lung, kidney and bladder. Smoking is an additional risk factor in the development of both buccal and cervical cancer in patients infected with HPV (256) but smoking is not associated with NMSCs and not a very strong risk factor for lymphomas (257, 258).

Smoking is the leading risk factor for lung cancer and has been suggested to play a role in the development of RA in patients with certain susceptibility genes (259). The incidence of lung cancer is elevated in autoimmune diseases such as SLE and RA (254). A genetic linkage between SLE and lung cancer has been proposed (260) or that the increased lung cancer risk is in part due to the pulmonary fibrosis developing in some patients with SLE and RA and the chronic inflammation that follows might predispose to cancer (205, 261).

Smoking is probably a substantial confounder in this study in that CLE patients (especially DLE) have been shown to smoke more than the general population (147, 169, 170). A Finnish study found that 57 % of DLE patients smoked and 35 % of SCLE patients (262). In the general Swedish population about 15 % are daily smokers (263).

Immunosuppressive therapy

We had no information on treatment of CLE in this study. A maximum of 25 % of CLE patients have been reported to be treated with systemic immunosuppressive drugs (27, 264). The majority of the patients are instead treated with local steroids and antimalarials, none of which is associated with increased malignancy risk (254, 265-267). The increased cancer risk in SLE patients is not associated with the use of immunosuppressive therapy, except for hematological cancers and exposure to cyclophosphamide, azathioprine and methotrexat (of which none are first-line therapies for CLE) with a latency period of 5 years (268). The fact that the cancer risk is increased early after CLE diagnosis further supports the view that immunosuppressive therapy is not a strong risk factor in this patient group. However, it remains possible that the minority of CLE patients receiving immunosuppressive therapy could have influenced our overall results in the absence of data collection regarding therapy.

SLE and cancer

Bernatsky et al. (137) have shown in a large multicenter cohort study a slightly increased risk for overall cancer in patients with SLE (SIR 1.15; 95 % CI 1.05-1.27) which was mostly due to the moderate increased risk for lymphomas and lung cancer. The increased risk for cancer in CLE patients that we found remained when excluding patients also diagnosed with SLE. Consequently, comorbidity with SLE could not explain the increased cancer risk we found.

UV exposure

The accumulated UV exposure is a major risk factor for NMSC, with light skin types more affected (247, 269). About two thirds of CLE patients are photosensitive (162) and therefore should avoid the sun, which would mean they would have less SCC. They are advised to be careful regard sun exposure and are instructed to always use UV-protection which could lead to vitamin D deficiency. Vitamin D deficiency has been reported in CLE patients (165, 171) and has been associated with increased risk of cancer.

The incidence of NMSC has increased dramatically during the past decades and it is now the most frequent cancer in the Caucasian population, representing as much as 30 % of total cancers (247). A study by Adami et al. (270) showed a strong association in the general population between lymphomas and NMSC, supporting the idea that UV light may have contributed to the increase in lymphomas incidence seen in recent decades.

Limitations and advantages

A limitation of this study is the absence of information regarding potential confounders (e.g. immunosuppressive treatment, smoking, BMI, alcohol drinking, hormones and UV exposure) that affect cancer risk. On the other hand we were able to adjust for possible confounders such as age, gender and comorbidity with SLE.

Another limitation is the short follow-up time for each individual patient with concern for malignancy to occur; however, this would instead underestimate the cancer risk.

The study design allowed us to study cancers occurring before CLE diagnosis, reflecting that CLE patients have a slightly elevated cancer risk already before being diagnosed with CLE but this risk increase seems to be mainly driven by the patients also being diagnosed with SLE. Only buccal and NMSC were still significantly elevated when excluding patients who were also diagnosed with SLE. When estimating POR on cancers before CLE diagnosis, we could not take into account cancers that occurred before 1958 when the cancer register started. This would potentially underestimate the results. The proportion of cancer cases is higher the year before CLE diagnosis in the CLE cohort than in the control cohort. Explanations for this could be that cancer treatment induces LE disease and that prevalent CLE cases that would not have been registered in the inpatient register if they had not been cared for in hospital for any other reason (e.g. cancer) during the first 4 years of the study before outpatient care were registered.

Study IV

In summary, our results indicate that exposure to certain suspected drugs 0-6 months before SCLE diagnosis is more usual than previously believed. In this population-based, nationwide case-control study we found significantly increased risks for SCLE after exposure to terbinafine, TNF- α inhibitors, antiepileptic, PPIs, thrombocyte inhibitors, ACE-inhibitors and NSAIDs.

Although based on a limited number of cases ($n=4$), a strong association was found between terbinafine exposure and a SCLE diagnosis. On the other hand, no association between other systemic antimycotic drugs and SCLE was noted, indicating a drug-specific association with terbinafine. The underlying mechanisms are unclear but cutaneous adverse reactions are very usual during treatment with terbinafine. It is also a known photo sensitizer and simultaneous involvement with Ro/SSA antibodies has been suggested (271, 272). Our four SCLE patients with a prior exposure of terbinafine all had their exposure during the summer months, which would suggest a photosensitization mechanism. Another possibility is that patients with SCLE were initially misdiagnosed as tinea corporis and treated with terbinafine without a previous positive culture.

Another unusual exposure, TNF- α inhibitors, also showed a strong positive association with a subsequent SCLE diagnosis. Because we were unable to include in-hospital TNF- α inhibitor treatment, this is probably an underestimation (e.g. only 18 % of infliximab was used in outpatient care settings in 2009) (273). TNF- α therapy can lead to the development of autoantibodies as a side effect, which is known to rarely cause a lupus-like syndrome (64, 274, 275).

We found an increased OR only for exposure to ACE-inhibitors among the antihypertensive drugs. No association between thiazides and the development of SCLE was found, although thiazides are the most common reported drugs to induce SCLE. This lack of association could be due to SCLE being mistaken for a photosensitivity skin reaction, a known side effect of thiazides, and therefore misdiagnosed. One explanation may be that thiazides have a longer latency (from 6 months to 5 years) (63), and our study design prevented us from detecting a possible association.

We found no increased risks for SCLE and exposure to calcium channel blockers, although they are thought to change lymphocyte function, promote production of autoantibodies and cause translocation of Ro antigens from the nucleus and in that way promote induction of SCLE (173). Calcium channel blockers have been associated with rashes and chronic eczema in elderly patients, in certain cases possible misdiagnose of SCLE? (67, 276).

Our estimates remained unchanged after controlling for comorbidity with SLE, suggesting that comorbidity with SLE could not explain our results. Drug-induced SLE is one of the most reported drug-induced autoimmune diseases. Some drugs (TNF- α inhibitors, carbamazepine, ticlopidine and statins) have been associated with the induction of both SCLE and SLE (57, 68, 130, 132, 277, 278).

More than two thirds of the incident SCLE patients (71 %) had a previous exposure to any of the suspected drugs during the 6 months before the SCLE diagnosis. Previous studies have shown an exposed proportion to suspected drugs of 10-12 % during the same time frame (72, 130). The attributable fraction was estimated to 38 %. This means that if a causal relationship between certain suspected drugs and the induction of SCLE exists and no biases influence the results, a non-negligible

proportion of all SCLE cases can be attributed to previous drug exposure. The reported proportion may be overestimated because we were not able to control for all potential confounders (smoking and UV exposure) and because we could not prove a causal relationship between drug exposure and the development of SCLE (partly because we were unable to study re-exposition). DI-SCLE has been proposed by some dermatologists as an under-diagnosed disease entity and as much as 25-30 % might in fact be drug-induced, which is consistent with our results (57).

We found effect modification by age; SCLE patients <50 years of age had a higher relative risk of drug exposure than the older SCLE patients. The higher relative risk among younger SCLE patients were not due to a higher prevalence of “high-risk drugs” in this age group. But SCLE incidence is twice as high after 50 years of age (279) so the absolute excess risk is the same for SCLE patients over and under 50 years of age. Effect modification (EM) is when an exposure has different effect on the outcome in different groups of patients. EM is detected by comparing stratum specific estimates of the measure of effect and when they appear different that is suggestive of EM.

In-hospital drug treatment and over the counter drugs were not included in this study design, which would probably underestimate the results, especially because more cases than controls were cared for in hospital during the study period. On the other hand, most drugs that are introduced during hospital stay (e.g. antibiotics, antihypertensives) would probably also be prescribed at discharge.

It was decided *a priori* that we would only examine associations between drugs that were previously reported of having induced SCLE. This was done to limit the number of comparisons undertaken. A possible publication bias would affect the selection of study drugs and existing associations between SCLE and those drugs not reported would therefore be missed. Even in a large observational study, several of the suspected drugs from case reports are too rarely used to be able to show an association.

A causal relation requires that exposure to the suspected drugs must have occurred before SCLE diagnosis. To make sure that this was the case we only enrolled incident SCLE cases and then searched the PDR retrospectively for drug exposure. Although we carefully checked that the cases had not received a previous diagnosis of SCLE in at least 5 years before the diagnosis in order to make sure that we only included incident SCLE cases, there is of course a possibility that we included some non-incident cases. The date of the first SCLE diagnosis is only an estimation because it does not directly imply when the first symptoms started and both patient and doctor’s delay are crucial here.

Advantages with this study are that it is population-based (including all incident SCLE cases during a 3-year period in a population of about 9.5 million residents), complete follow-up was ascertained, the exposure was collected independently and ahead of the outcome, we controlled for comorbidity with SLE and we were able to match for some important confounders.

A causal relationship cannot be determined from this study. The underlying pathogenesis is still obscured and the absolute risk for the development of SCLE is small when treating patients with these commonly used drugs.

8.3 Findings and implications

CLE is a severe dermatological disease that causes considerable morbidity to the patients. The findings in this thesis show the importance of an early correct diagnosis and classification of the patient's disease in order to provide appropriate treatment and follow-up to detect possible progression to SLE.

Skin manifestations together with arthritis are the most usual clinical manifestations in SLE patients, where LE-non-specific manifestations are almost twice as usual as LE-specific manifestations. In **study I** we found the Gilliam criteria useful for this type of study, except for the criteria ACLE/malar rash. Malar rash is not well-defined, being easily confused with other common dermatosis. Histopathology is usually lacking and inter-observer concordance is low. Therefore, we suggest that the ACR criteria for SLE concerning skin manifestations should be re-evaluated. One suggestion would be to include only histopathological confirmed CLE as one criterion. The ACR criterion photosensitivity should be re-defined and include a detailed history of PLE in order to make the criteria more specific. Raynaud's phenomenon, which was more common in patients that also displayed CLE, was the most common non-specific manifestation. It is therefore important for dermatologists that meet patients with CLE to ask for symptoms of Raynaud's as a sign of systemic involvement. Non-scarring alopecia is another LE-non-specific manifestation that easily escapes the physician.

In **study II** we present for the first time contemporary population-based incidence figures of CLE and its different subsets together with age- and gender-specific incidence rates and gender distribution. We also showed the short-time probability of receiving an additional diagnosis of SLE. It is also important when analyzing trends, i.e. performing the same study in 10 or 20 years from now and see whether the incidence rates have changed in actual numbers or between genders. Such information can provide important clues about the underlying pathogenesis. Evaluation of prognosis is also essential both for the treating physician so she or he can give correct information to individual patients and in a population-based setting when developing treatment guidelines and recommendations for follow-up. Our study gives an overall picture of CLE disease in Sweden. Such knowledge can serve as a base when planning future studies. In this study we received unidentified data material from EpC but it would be possible in the future to attain identified material and link these data to pathology records, medical charts and serological data.

We found that CLE patients have a substantial risk of receiving an additional diagnosis of SLE. This could be an overestimation that is influenced by detection bias (CLE patients are more carefully examined in general and for SLE symptoms in particular). Still, it is a finding that should alert dermatologists that meet CLE patients to take a thorough medical history, look for systemic symptoms and LE-non-specific cutaneous manifestations and serological findings. CLE patients should be followed carefully and have repeated information about possible triggers, i.e. smoking cessation and avoidance of UV exposure. Nowadays, SLE patients are given antimalarial therapy to a higher extent than previously in order to limit systemic symptoms and complications. It is possible that CLE patients are under-treated as a consequence of dermatological tradition to prefer topical treatment.

In **study III** we showed an increased risk for cancer in CLE patients, especially for buccal cancer, lymphomas, respiratory cancer and NMSC. No causal relationship can be established because our

finding is probably largely influenced by confounding factors (mainly UV exposure and smoking). Buccal and respiratory cancers are especially confounded by smoking.

NMSC and lymphomas are known to be associated to each other for unknown reasons. Exposure to UV light (270) and common genetic mutations (particular the p53 gene)(258) have been suggested. The UV light hypothesis is appealing in that it is a known risk factor for CLE as well.

The hypotheses of an influence of HPV on the increased risk of NMSC and buccal cancer are of course attractive in the sense that vaccination to HPV has been shown to be highly effective in preventing cervical cancer. Our recommendation is that these hypotheses should be study furthered.

Even if no causal relationship can be elucidated, the increased morbidity in cancer are an important finding and must be considered in the clinical care of these patients, especially when planning follow-up and providing information to patients. Repeated information to CLE patients about limiting UV exposure is crucial. Every patient should be informed that there is often a latency period between sun exposure and CLE exacerbation of several weeks. We believe that such information could improve compliance. Everyone should use broad-spectrum sun screen (280). It is also important to give individual practical tips on how to limit UV exposure based on occupation and hobbies. For instance a taxi driver could install a UV filter in his or her car and an office worker could change bulbs over his or her desk to limit artificial UV light.

For the dermatologists, the findings in this study show the importance of careful examination of all CLE lesions at each visit and increased suspicion of any changes in the lesion. In addition, if clinically motivated, a new histopathological examination should be performed in order to detect NMSC early. Patients should also be informed that any changes in the lesion or elsewhere should be re-examined so that they are observant themselves.

In **study IV** we were able to confirm previous case reports suggesting an association between intake of certain drugs and development of SCLE. As much as one third of all SCLE cases can be attributed to previous drug exposure. The highest relative risks were found for exposure to terbinafine, TNF- α inhibitors, antiepileptic and PPIs 6 months before SCLE diagnosis.

The absolute risk of developing SCLE after drug intake is very small considering the large number of individuals taking these drugs. Thus, there is no need to avoid needed medication in any patients, even in patients with already existing LE disease. Nevertheless, it is essential to take an accurate drug history in patients with SCLE in order to reveal any potential triggering drugs. DI-SCLE is usually self-healing when the triggering drug is withdrawn. Early identification of these patients would therefore be warranted in order to reduce or eliminate suffering and unnecessary treatment of SCLE.

To deliver optimal health care for patients with CLE and improve their QoL, correct information to the patients about prognosis, comorbidity and other associated risks are of uttermost importance. The studies in this thesis provide a new approach to study CLE by using population-based register data to investigate comorbidity as SLE, cancer and the influence of certain drugs as triggers of SCLE. These studies show only a glimpse of what can be achieved by this approach. No quality register for CLE exists but would provide much knowledge.

- About 25 % of SLE patients have LE-specific cutaneous manifestations and almost twice as many display LE-non-specific cutaneous manifestations.
- DLE is the most common LE-specific manifestation and Raynaud's phenomenon is the most usual LE-non-specific manifestation in SLE patients.
- The ACR criteria for SLE diagnosis should include histopathologically confirmed CLE as one criterion instead of photosensitivity and malar rash, which are not sufficiently defined.
- The incidence of CLE in Sweden is 4.0/100,000 with a female to male ratio of 3:1 and DLE is the most common subset (80 %).
- The probability of receiving an additional diagnosis of SLE is 18 % for the first 3 years after CLE diagnosis; the probability is highest for women and the SCLE subset.
- Patients with CLE have an increased susceptibility to cancer overall and especially buccal cancer, lymphomas, respiratory cancer and NMSC. The risk increase remains when excluding patients also diagnosed with SLE.
- It is very important to try to reduce known risk factors for cancer and CLE by encouraging patients to stop smoking, avoid UV exposure and participate in screening programs. The underlying mechanisms for this cancer susceptibility needs to be further studied.
- The association between certain drugs and the risk of developing SCLE is probably larger than previously believed. We found increased risks of SCLE after exposure to terbinafine, TNF- α inhibitors, antiepileptic and proton pump inhibitors and about one third of SCLE cases can be attributed to a previous suspected drug exposure.
- It is important to carefully screen patients with SCLE for treatment with any potentially triggering drugs. An increased awareness among dermatologists about DI-SCLE would likely save much suffering among affected patients and save them from unnecessary treatment of this often self-healing disease by the withdrawal of the triggering factor.

Do CLE patients with NMSC and buccal cancer have a higher prevalence of HPV infections than other CLE patients? Compare NMSCs from CLE patients compared with NMSCs from control subjects without CLE and compare the frequency of HPV in histopathological specimens.

What characterizes CLE patients with cancer from CLE patients without special concern for smoking, UV exposure, immunosuppressive treatment and genetic similarity?

Does early treatment (especially antimalarials) of CLE lower the risk of progression to SLE? Can progression to SLE be prevented by avoiding known triggers?

Is there a difference in the prevalence of Ro/SSA autoantibodies in SCLE patients with DI-SCLE and the idiopathic form? Is there a predisposition of certain genotypes in DI-SCLE?

Data from outpatient care and the PDR only span from 2001 and 2005, respectively, but when they have been available for a longer period, it would be of interest to include only incident CLE cases and estimate the risk of cancer and other comorbidities.

Kutan lupus erythematosus (hudlupus) är en kronisk svår hudsjukdom med varierande symptom och svårighetsgrad. Lupus betyder varg på latin och sjukdomens namn kommer troligen från att man förr i tiden tyckte att utslagen påminde om röda vargbett. Eftersom hudlupus är en ovanlig sjukdom har det tidigare varit svårt att samla ihop ett större antal patienter för att undersöka prognos och samsjuklighet. I Sverige finns ett flertal hälsoregister där information från både slutna och öppna vård registreras. Från dessa register har vi nu kunnat samla ihop data från ett stort antal patienter med hudlupus. Denna avhandling baserar sig på fyra studier som kort beskrivs nedan.

I den första studien undersökte vi förekomsten av hudsymtom hos 260 patienter med den systemiska formen av lupus (SLE). Vi undersökte vilka hudsymtom dessa patienter hade och hur olika hudsymtomen kunde kopplas samman med förekomsten av s.k. autoantikroppar (antikroppar mot kroppens egna vävnader) i blodet och symptom från andra organ i kroppen såsom exempelvis ledvärk. Vi fann att det var väldigt vanligt med hudsymtom bland SLE patienter och att de som även hade hudlupus hade mindre ledengagemang och mindre inflammation i hjärt- och lungsäck än de övriga patienterna. Förekomsten av autoantikroppar skiljde sig också åt mellan dem som hade hudlupus och de som inte hade det.

I andra studien studerade vi förekomsten av hudlupus i Sverige och i vilken utsträckning patienter med hudlupus även drabbas av SLE. Via Patientregistret i Sverige samlade vi in alla patienter som nyinsjuknat i hudlupus 2005-2007, totalt 1088 patienter. Ca 380 människor insjuknar i hudlupus varje år i Sverige, tre gånger fler kvinnor än män och medelåldern vid insjuknande är 54 år. Av dem som diagnosticerats med hudlupus har cirka en fjärdedel av patienterna redan en SLE diagnos och under de första tre åren efter att ha fått diagnosen hudlupus insjuknar cirka ytterligare 18 % i SLE.

I tredje studien undersökte vi om patienter med hudlupus har större risk för cancer än normalbefolkningen. Alla patienter som diagnostiserats med hudlupus 1997-2007 i Sverige togs fram via Patientregistret, 3,663 patienter. Patientregistret länkades sedan med Cancerregistret och Dödsorsaksregistret för att undersöka cancer förekomsten. Vi fann att risken för cancer i munhåla, viss typ av hudcancer, lymfom och lungcancer var cirka fyra gånger högre hos patienter med hudlupus. Detta kan dels förklaras med att dessa patienter röker i en högre utsträckning än friska. Andra orsaker kan vara att de är mer känsliga för UV-ljus och vissa virusinfektioner än människor utan denna hudsjukdom.

I fjärde studien studerade vi i hur stor uträkning hudlupus utlöses av vissa läkemedel. Alla som insjuknat i en speciell form av hudlupus, SCLE, 2006-2009 togs fram via Patientregistret, 234 patienter. Data från Patientregistret länkades sedan med Läkemedelsregistret för att få information om uthämtade läkemedel. Vi fann samband mellan uthämtning av flera stycken olika läkemedel och en efterföljande diagnos av hudlupus och i cirka en tredjedel av SCLE fallen tros ett samband med läkemedel finnas. Med hjälp av svenska register har unika data kunnat samlas in, som kommer att vara till hjälp i vården av patientgruppen med CLE i framtiden.

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