From the Rheumatology Unit, Department of Medicine Solna,
Karolinska Institutet, Stockholm, Sweden

CHRONIC INFLAMMATION, ANTI-INFLAMMATORY TREATMENT, AND RISK OF MALIGNANT LYMPHOMAS

Karin Hellgren

Karolinska
Institutet

Stockholm 2013

To Arvid, Emil and Janne

ABSTRACT

The aim of this thesis was to investigate the link between malignant lymphomas and chronic inflammation, in particular the associations between inflammatory activity, immune-modulatory treatment and risk of lymphoma development. To address this aim, we used Swedish population-based registers, mandatory cancer reporting and nation-wide clinical registers including the Swedish Rheumatology Register (SRQ).

In study I we investigated whether patients with rheumatoid arthritis (RA) are at increased risk of lymphoma or cancer overall before clinical onset of RA, and if this risk increases with time since RA diagnosis. A cohort of 6,745 incident RA patients (1997-2006) was identified using data from the SRQ. Each cohort member was matched to five population comparator subjects. Relative risks of lymphoma and cancer overall *before* and *after* diagnosis of RA were estimated. We observed no increased risks before diagnosis of RA whereas during the first ten years following diagnosis, the lymphoma risk was almost doubled with a non-significant trend of increasing risks with longer RA disease duration.

In study II with a larger study population and with longer follow-up, we set out to assess whether the lymphoma risk remains elevated in RA patients diagnosed in the last few years and to explore potential risk predictors in relation to disease characteristics and therapy, focusing on the first year following RA diagnosis. Through SRQ, a cohort of 10,367 incident RA patients (1997-2010) was assembled. Each patient was matched to five population comparator subjects. The risk of lymphoma in recently diagnosed RA patients remained increased to the same magnitude as that reported from historical RA cohorts without any change in risk in recent years. The results indicated that inflammatory activity during the 1st year following RA diagnosis correlated with higher lymphoma risk, whereas oral glucocorticoids were associated with a reduced risk. Exposure to tumor necrosis factor inhibitor (TNFi) during the study period was not associated with increased lymphoma risk. Through histopathological classification, we further noted an increased proportion of Hodgkin lymphoma and diffuse large B-cell lymphoma and a decreased proportion of chronic lymphocytic leukemia in RA patients compared with the general population.

In study III the relationship between treatment with glucocorticoids and lymphoma risk in RA patients was investigated in a case-control study. From a nationwide cohort of 74,651 prevalent RA patients 1964-1994, 378 RA patients with lymphoma and 378 matched RA controls were identified. Different aspects of glucocorticoid treatment were abstracted from medical records. Treatment with glucocorticoids, oral as well as intra-articular, was associated with a reduced lymphoma risk.

In study IV the underlying risks of lymphoma in patients with ankylosing spondylitis (AS) and psoriatic arthritis (PsA) were investigated, including risks in relation to disease characteristics and treatment. Nationwide prevalent cohorts of AS (n=8,707) and PsA (n=19,283) 2001-2010 were assembled. Each cohort member was matched to five population comparator subjects. On average, we observed no increased risks of lymphoma in AS or in PsA, although there was a risk increase in PsA patients treated with methotrexate and/or sulfasalazine. Based on small numbers there was no evidence of increased lymphoma incidence following therapy with TNFi in AS or in PsA patients.

LIST OF PUBLICATIONS

I. **Hellgren K**, Smedby K E, Feltelius N, Baecklund E, Askling J.
    Do Rheumatoid Arthritis and lymphoma share risk factors? A comparison of lymphoma and cancer risks before and after the diagnosis of Rheumatoid Arthritis.
    Arthritis & Rheumatism 2010; May; 62 (5):1252–1258.

II . **Hellgren K**, Baecklund E, Backlin C, Sundström C, Smedby K E, Askling J.
    Rheumatoid Arthritis and Risks of Malignant Lymphoma - Are Risks still increased?
    In Manuscript

III. **Hellgren K**, Iliadou A, Rosenquist R, Feltelius N, Backlin C, Enblad G, Askling J, Baecklund E. Rheumatoid arthritis, treatment with corticosteroids and risk of malignant lymphomas: results from a case-control study.
    Annals of Rheumatic Diseases 2010 April; 69(4):654-9.

IV. **Hellgren K**, Smedby K E, Backlin C, Sundström C, Feltelius N, Eriksson JK, Baecklund E, Askling J. Ankylosing Spondylitis, Psoriatic Arthritis, and Risk of Malignant Lymphoma - A Cohort Study.
    In Manuscript

CONTENTS

LIST OF ABBREVIATIONS

ACPA	anti-citrullinated protein antibodies
ACR	American College of Rheumatology
APRIL	cytokine A proliferating-inducing ligand
ARTIS	Anti-Rheumatic Therapies in Sweden
AS	ankylosing spondylitis
BAFF	B-cell activating factor of the TNF family
CCP	cyclic citrullinated peptide
CLL	chronic lymphocytic leukemia
CRP	C-reactive protein
DAS	disease activity score
DLBCL	diffuse large B-cell lymphoma
DMARD	disease modifying anti-rheumatic drugs
EBV	Epstein-Barr virus
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
GC	germinal center
HLA	human leukocyte antigen
HR	hazard ratio
IBD	inflammatory bowel disease
ICD	International Classification of Diseases
IL	interleukin
IRR	incidence rate ratio
MALT	mucosa-associated lymphoid tissue
MTX	methotrexate
NHL	non-Hodgkin lymphoma
NPR	National Patient Register
NRN	national registration number
NSAID	non-steroidal anti-inflammatory drugs
OR	odds ratio
PTLD	post-transplant lymphoproliferative disorder
PsA	psoriatic arthritis
RA	rheumatoid arthritis
ReA	reactive arthritis
RF	rheumatoid factor
RR	relative risk
SIR	standardized incidence ratio
SLE	systemic lupus erythematosus
SLR	Swedish Lymphoma Registry
SS	Sjögren's syndrome
SpA	spondylarthritis
SRQ	Swedish Rheumatology Quality Register
TNFi	tumor necrosis factor inhibitor
WHO	World Health Organization

1 INTRODUCTION

The discipline of Rheumatology has changed dramatically over the last 10-15 years. Today we have the possibility to treat patients with rheumatoid arthritis (RA) and other inflammatory arthritis earlier and more efficiently than ever before. New therapies such as biological agents, increased knowledge on how to best use traditional therapies, as well as better assessment and control of disease activity, are all contributing factors. Nevertheless, much remains to be done. We need to learn more about long-term safety of these new therapies and to improve our knowledge on how to predict, and if possible to prevent the occurrence of different co-morbidities such as malignant lymphomas.

The studies in this thesis investigate the link between malignant lymphoma and chronic inflammation with particular focus on inflammatory activity and immune-modulatory therapy. In three of the studies, we focus on patients with rheumatoid arthritis. In the fourth, we study patients with ankylosing spondylitis and psoriatic arthritis.

1.1 RHEUMATOID ARTHRITIS

1.1.1 Clinical picture and epidemiology

RA is a chronic inflammatory disease characterized by symmetric small joint polyarthritis. The prevalence of RA is approximately 0.5-1% in Western populations and the incidence rate varies between 20-50 cases/100,000 person- years depending on age and sex. [2-3] The usual age of onset is 40-70 years of age and the condition is 2-3 times more common in women. RA typically presents with an insidious onset of symmetric swelling and pain in the small joints of the hands and feet, morning stiffness and fatigue. With time, the local joint inflammation leads to joint destruction with subsequent functional disability and decreased quality of life. Beside the local inflammation, systemic features such as extra-articular organ manifestations may occur. Patients with RA also have a decreased life expectancy mainly due cardiovascular events but also due to other co-morbidities such as malignant lymphomas.[4-5]

1.1.2 Classification criteria

As no single diagnostic test exists, the diagnosis of RA is often based upon classification criteria. The criteria set in widespread international use and also applied in all the studies of this thesis is the American College of Rheumatology (ACR) criteria from 1987 (Table 1).[6] Initially created for research purposes, the ACR criteria have been a useful tool in defining patients with established RA but are more limited in recognizing patients at an early stage of the disease. Thus, updated criteria were issued by the ACR and the European League Against Rheumatism (EULAR) in 2010. These consist of a score-based algorithm where a collective score from four categories are added.[7] The 2010 criteria (Table 2) focus on features at earlier stages of RA rather than defining established disease and also allow for the distinction of RA into two rather specific subsets, anti-citrullinated protein antibodies (ACPA) positive and ACPA negative RA (see section 1.1.3).

Table 1 - The ACR classification criteria for RA (1987)

Criterion
1. Morning stiffness
2. Arthritis of ≥3 joint areas
3. Arthritis of hand joints
4. Symmetric arthritis
5. Rheumatoid nodules
6. Rheumatoid factor
7. Radiographic changes

Patients fulfilling at least 4/7 criteria are classified as having RA. Criteria 1-4 must be present for at least 6 weeks.

Table 2 - The ACR/EULAR scoring criteria for classification of RA (2010)

A. Joint involvement	Score
1 large joint	0
2-10 large joints	1
1-3 small joints	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)	**Score**
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	**Score**
Normal C-reactive protein (CRP) *and* normal erythrocyte sedimentation rate (ESR)	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms	**Score**
<6 weeks	0
≥6 weeks	1

Target population, Patients who 1) have at least 1 joint with definite clinical synovitis (swelling) 2) with the synovitis not better explained by another disease. To be classified as rheumatoid arthritis, an overall score of ≥ 6/10 is required.

1.1.3 Etiology

RA is considered a complex disease where genetic and environmental factors interact with the immune system causing the pathological changes. A family history of RA is associated with an approximately 3-fold increased risk of RA and there is a high concordance of RA between both monozygotic and dizygotic twins further supporting an impact of genetic effects. The strongest genetic risk alleles associated with RA are located in the human leukocyte antigen (HLA) class II region, in particular the HLA-DRB1 locus sharing a defined amino acid sequence, the so called shared epitope (SE).[8] Apart from this, several other susceptibility genes of interest are also identified.[9] However, although HLA-DRB1 SE has been suggested to account for a considerably part of the genetic influence in RA, especially in the ACPA positive subset of RA patients, the majority of the hereditability in RA remains unclear.

Among environmental risk factors, smoking is by far the most established, with an approximate doubling of the RA risk.[10-14] High intensity and longer duration of smoking further increase the risk.[15] Recent studies have also shown an intriguing gene-environmental interaction where smoking and presence of the HLA DRB1-SE risk allele synergistically increase the risk of ACPA.[16] This strengthens the idea of, at least, two distinct subsets of RA (ACPA positive and ACPA negative disease) with mutually different risk factors, clinical course as well as presumably also different molecular pathogenesis.[17] Based on the presence of autoantibodies, RA is traditionally considered an autoimmune disorder. Rheumatoid factor (RF) is present in about 80% of all patients and is associated with a more severe disease course as well as with joint destruction. RF is also shown to precede the onset of the clinical symptoms by many years.[18-20] In recent years, a lot of research has focused on the ACPA. ACPA has a higher specificity for RA than RF and is present in about 60% of the patients at disease onset. As with RF, it is associated with a more severe disease and may be present several years before clinical RA onset.[18, 21] This, together with recent data from animal and molecular studies and the observed gene-environmental interaction between smoking, SE and ACPA, indirectly support a possible causative role of ACPA in the RA pathogenesis.[17]

Hormonal factors also play a role in RA development as illustrated by the gender distribution. For women, RA onset is common at times when sex hormones are fluctuating, such as in the postpartum period and after menopause. [2, 22] Several reports also support a protective effect of oral contraceptives.[22]
Other environmental factors more or less consistently related to risk of RA include alcohol, infections, peridontitis, obesity and dietary factors.[22]

1.1.4 Some aspects of RA pathogenesis

Rheumatoid arthritis is characterized by inflammation of the synovial membrane surrounding the joint. In the synovium, numerous cells of the innate immune system are present and active, including macrophages, dendritic cells and leukocytes. The progression of inflammation (and the subsequent joint damage) is further facilitated by different pathways of the innate immune system and an interaction with adaptive immunity.[23-24] T cells have long been recognized as important players in RA pathogenesis. This is based on several factors, including the pronounced infiltration

of T cells in the synovium, the strong association to HLA class II (HLA being a key molecule responsible for antigen presentation to T cells) and the involvement of T cells in the production of tumor necrosis factor (TNF) and other pro-inflammatory cytokines. However, B cells also play multiple roles in the RA disease process in addition to producing autoantibodies.[25] B cells act as an antigen-presenting cell and produce pro-inflammatory cytokines.[9] Data also support that B cells are necessary for the activation of T cells in the synovial tissue.[26] The pivotal role of B cells is further supported by the fact that depletion of (CD20+) B cells is an efficient therapy in RA.[27]

An important concept in the RA pathogenesis is the mechanisms and the production of pro-inflammatory cytokines[28] such as TNF, interleukin (IL)-6 and IL-1. These cytokines activate leukocytes, synovial fibroblasts and endothelial cells. When released into the circulation, they also mediate acute-phase responses that are responsible for the systemic features seen in the RA clinic, such as fatigue, loss of appetite and fever as well as laboratory measurements of acute-phase reactions, anemia and thrombocytosis. Tumor necrosis factor further induces the production of other cytokines and suppresses regulatory T-cell functions. Interleukin-6 promotes B-cell proliferation and thereby the production of antibodies.[9] The crucial roles of TNF and IL-6 is further confirmed by the successful RA therapies acting by blocking these particular cytokines.

1.1.5 Disease activity

There is no single test available to assess disease activity or level of inflammatory activity in RA. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are commonly used, although neither of these is without limitations. For example, not all RA patients have elevated levels of ESR and CRP despite active disease.[29] ESR can be affected by RF and/or immunoglobulin thereby being a marker of disease severity rather than of inflammation[30]. The acute phase protein CRP may presumably function better as a measure of acute inflammation. Measurements of both ESR and CRP concomitantly probably fulfill the clinical needs in most situations.

The most widespread measure of disease activity (originally developed to describe treatment results in clinical trials) is the 28-joint disease activity score (DAS28).[31] This is a composite index consisting of swollen (0-28) and tender joint counts (0-28), ESR, and the patient's general health assessment on a visual analogue scale (0-100). DAS28 <2.6 is classified as disease remission, DAS28< 3.2 as low active disease, DAS28 3.2-5.1 as moderate active and DAS28 >5.1 as high active disease.[35] In recent years DAS28 has become increasingly used also to evaluate patients at onset and during follow up in the clinical setting. Although the DAS28 score is a useful tool for the clinical evaluation, there are limitations. An overestimation of disease activity may occur if ESR is high (for other medical reasons) or if the patient scores high on the visual analogue scale due to non-RA related causes. Conversely, DAS28 does not include joint counts of the feet, which may underestimate disease activity. A recent study also observed a considerable discrepancy between DAS28 and the physicians' assessment of disease activity.[32] Taking these considerations into account, an optimal clinical evaluation should probably include both DAS28 and the clinicians'

global assessment. Other measures of disease activity not included in the studies in this thesis are different radiographic scores of joint damage and measures of physical function such as the patient-reported Stanford Health Assessment Questionnaire (HAQ).[33]

1.1.6   Management and treatment

There have been major improvements in the management and treatment of RA in the last 10-15 years. Today it is well-established that an early start with disease modifying anti-rheumatic drugs (DMARDs) is crucial in order to prevent joint damage and future disability. The importance of aiming for disease remission or low active disease is well-recognized, although the acceptable level of residual disease activity and the optimal time span for reaching remission remain unclear.[23] The mainstay of initial therapy is methotrexate (MTX), although other DMARDs such as sulfasalazine and leflunomide may be alternatives. If there is a sustained disease activity after 3 months of monotherapy, a combination of therapies should be used. This could imply MTX in combination with one or two other DMARDs or MTX in combination with tumor necrosis factor inhibitor (TNFi). The latter is recommended in the subset of RA patients with poor prognostic factors such as RF and/or ACPA positive disease, early radiographic changes or high disease activity. Apart from TNFi, several other biological agents have more recently been approved and are increasingly used in the treatment of RA ([34-35] serve as general references for this section). The issue of whether oral glucocorticoids should be a part of the initial standard therapy is debated. Data on the beneficial effects with respect to reduced radiographic damage is indeed convincing [36], but there are remaining concerns about potential long-term adverse effects.[37]

It should also be noted that despite the fact that these therapeutic agents have been around for quite a long time, changes in treatment regimen have been gradual. As late as in the mid- to late 90's, therapy guidelines still recommended rheumatologists to initially treat newly diagnosed RA patients with non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy and if DMARD's were indicated, to primarily choose milder agents (such as antimalarial agents) and to use low doses.[38] Consequently patients diagnosed before 2000 (and sometimes even later on) have not benefited from the current treatment recommendations which may affect the disease outcome of these patients in the long term.

1.2   SPONDYLARTHRITIS

Spondylarthritis (SpA) is a heterogeneous group of disorders and can be regarded as a family with interrelated features rather than a single disease with different clinical manifestations. The disorders that make up this group include ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), inflammatory bowel disease related arthritis (IBD-SpA) and undifferentiated spondylarthritis (uSpA). Data on prevalence for the entire SpA-group are limited but is estimated to be about 1-2%.[39] Although there has been a significant increased knowledge on how to classify,[40-41] and how to diagnose and treat patients of the SpA group in recent years, data on underlying etiology, disease course and co-morbidities remain much more limited

than for RA. For the purpose of this thesis, two of the SpA disorders, AS and PsA are described in some more detail.

1.3 ANKYLOSING SPONDYLITIS

1.3.1 Clinical picture and epidemiology

AS is the best-defined disorder of the SpA group and is characterized by chronic inflammation of the sacroiliac joints and spine causing the characteristic inflammatory back pain. Clinical features further include enthesitis, peripheral arthritis (often asymmetrical and of the lower limbs) as well as extra-articular manifestations involving the eyes and sometimes the heart. The inflammatory activity and the structural damage of the spine lead to spinal stiffness and loss of mobility with subsequent functional disability. The prevalence of AS varies considerably with geographic area, estimates range from 0.3 to 0.5% in European populations.[42] There is a strong correlation between the prevalence of AS and the background population frequency of HLA-B27. In Northern Europe the estimated incidence is about 6 cases/100,000 person-years.[43] The usual age of onset is 20-30 years of age and AS is twice as common in men.[44] With respect to co-morbidities, data support an increased risk of cardiovascular events[45-46]. To date, there has been no report of excess risk of cancer overall [47] with the exception of AS patients treated with radiotherapy in whom increased rates of leukemia have been observed.[48]

1.3.2 Classification criteria

The modified New York criteria are the most widely used set of AS criteria since their creation in the 1980's (Table 3)[49]. These criteria require the presence of radiographic sacroiliitis, a feature often occurring rather late in the disease course. In recent years magnetic resonance imaging (MRI) has evolved as a useful diagnostic tool and enables identification of AS patients at an earlier stage of the disease. This, together with the breakthrough of TNFi therapy in this patient population, have strengthened the need for criteria identifying AS patients earlier after onset, and to distinguish those patients for whom biological treatment is indicated. Recently the Assessments of SpondyloArthritis International Society (ASAS) have developed classification and diagnostic criteria for axial spondylarthritis in order to meet this need.[50]

Table 3 - The modified New York criteria for ankylosing spondylitis (1984)

Clinical criteria
●Low back pain and stiffness for more than 3 months that improves with exercise, but is not relieved by rest.
●Limitation of motion of the lumbar spine in the sagittal and frontal planes.
●Limitation of chest expansion relative to normal values correlated for age and sex.
Radiological criterion
●Sacroiliitis grade ⩾2 bilaterally or grade 3–4 unilaterally.

Definite AS if the radiological criterion is associated with at least one clinical criterion

1.3.3 Etiology and pathogenesis

The etiology of AS is unclear, although there is a strong genetic effect i.e. the link to HLA-B27.[51] Data also suggest a role of HLA-B27 in the pathogenesis of AS and in other SpA entities.[39] The strongest evidence of this pathogenic role comes from experimental studies showing that over-expression of HLA-B27 in transgenic rats resulted in gastrointestinal and joint inflammations.[52] Although HLA-B27 is present in approximately 90% of the AS patients [51] it does not explain all genetic susceptibility in AS, suggesting the contribution of other genes.[39] With respect to environmental factors, a possible interaction between different infectious agents and HLA-B27 has been proposed. However, apart from the fact that patients with ReA (usually triggered by bacterial agents) rarely develop AS,[53] there is no clear evidence for any specific infectious agent in the etiology of AS. Smoking has been suggested to worsen the disease course.[54] As in RA, the activation of the pathways of the innate and adaptive immune systems lead to activation and production of pro-inflammatory cytokines where so far TNF seems to play a crucial role.[39]

1.3.4 Management and treatment

The mainstay of therapy for AS has traditionally consisted of NSAIDs in combination with physical therapy. Although NSAIDs remain the first line of pharmacological therapy, the introduction of TNFi has radically improved the treatment possibilities. This is particularly evident for AS patients with isolated spinal disease in whom DMARDs [55-56] have failed in controlling symptoms and disease progression (although sulfasalazine may improve peripheral joint manifestations).[56] The evidence for the efficiency of oral glucocorticoids in AS quite limited.[42] Recently the ASAS international working group published recommendations for the management of patients with AS[57] including guidelines for treatment with TNFi.[58] The guidelines conclude that TNFi should be considered in patients with persistently high disease activity despite treatment trials with ≥2 NSAIDs, and do not recommend the use of DMARDs before or concomitant with TNFi in patients with spinal disease.

The most commonly used measure of disease activity in AS is the Bath Ankylosing Disease Activity Index (BASDAI)[50], which is increasingly used in the clinical setting. This includes six patient-oriented questions based on fatique, overall back and hip pain, peripheral arthritis, enthesitis and duration and intensity of morning stiffness.
With regard to laboratory measures, data have shown a poorer correlation between disease activity and levels of CRP and/or ESR in AS than in RA.[59]

1.4 PSORIATIC ARTHRITIS

1.4.1 Clinical picture and epidemiology

PsA is an inflammatory (usually sero-negative) arthritis associated with psoriasis. The typical presentation is an insidious onset of asymmetric oligoarthritis often including the small joints of hands and/or feet. Other clinical features are enthesitis, tenosynovitis, dactylitis (sausage digit), spinal disease and, as in AS, extra-articular manifestations. PsA occurs in approximately 30% of the patients with psoriasis,[42] corresponding to a prevalence of about 0.2% in Western populations.[60] The annual

incidence is estimated to be 5-7 cases/100.000 person-years.[2, 60-61] The usual age of onset is 40-60 years and PsA is equally common in men and women.

PsA was long considered a milder disease than RA. However, recent data have demonstrated disease progression over time, with associated joint damage and functional impairment resulting in a reduced quality of life similar to that of RA.[62] A decreased life expectancy has been reported primarily due to cardiovascular events.[46] Data on cancer risk in PsA are limited but do not signal any increased risks overall.[63]

1.4.2   Classification criteria

In the 1970's, Wright and Moll described five different subsets of PsA. These subsets included predominantly distal joint disease, arthritis mutilans (a very destructive form), assymetric oligoarthritis (the majority of the patients), polyarthritis (inseparable from RA) and predominantly spinal disease.[64] This division into subsets got a widespread recognition although current data indicate that the majority of the patients with established PsA actually display a polyarthritis.[65-66] The original classification has been followed by several different sets of criteria with rather large variations in the definition of PsA.[67] This has made results from both epidemiological and interventional studies difficult to compare over time.

The latest set of criteria issued is the ClASsification criteria for Psoriatic ARthritis (CASPAR) aiming to distinguish PsA as a distinct entity. The CASPAR criteria are, however, thought to be used for research purposes rather than in a clinical setting. Subsequently the clinical diagnostic of PsA is still based on an overall assessment where several factors need to be taken into consideration, such as presence (or a family history) of psoriasis, type and distribution of joint manifestations, serological factors as well as presence of spinal disease. The diagnostic challenge is primarily to distinguish PsA from RA. For example, how to accurately diagnose a patient presenting with psoriasis, RF and polyarthritis.

1.4.3   Etiology and pathogenesis

Since psoriasis often precedes PsA, it has been hypothesized that some triggering events in the skin activate the innate and the adaptive immune responses resulting in the initiation of the disease process in genetically susceptible individuals. With respect to genetic factors, PsA is associated both with psoriasis-related genes (HLA- cw6) and also with genes prevalent in AS/SpA (HLA B-27), the latter predominately in PsA patients with spinal disease. Other genes have also been proposed to be of importance.[61] With respect to environmental factors, infection-related triggers as well physical traumas have been suggested. Data indicate that smoking may be a risk factor and also associated with a more severe disease and a worse prognosis, similar to the relationship between smoking and RA, although this is not as well explored as in RA.[54] There is also some suggestion of a link between obesity and risk of PsA.[68]
An intriguing mechanism is the association between an increased occurrence of psoriasis and PsA in individuals with Human Immunodeficiency Virus (HIV) infection. Although this could imply a viral trigger for PsA, it could also be related to the

pathogenesis; HIV could change the balance between different types of T cells and lead to the development of PsA.[69]

Evidence strongly supports the importance of T-cell immunity in PsA .The T-cells activation in turn leads to an activation of pro-inflammatory cytokines, in particular TNF [61]. This is also illustrated by the beneficial therapeutical effect seen with TNFi also in PsA. Other biological agents are in the pipeline, for example agents targeting interleukin 12/23 (already approved for psoriasis) and interleukin-17. This further emphasizes the importance of the cytokine cascade in the disease course of PsA.[68]

1.4.4   Management and treatment

Optimal treatment and management of PsA must focus on the different clinical manifestations of the disease and may include non-systemic as well as systemic treatments. MTX is the mainstay in the treatment of joint manifestations although data also support the use of sulfasalazine, cyclosporine and leflunomide. In the case of sustained disease activity despite DMARDs, treatment with TNFi (without continuation of previous DMARDs) should be considered. [42, 70] The definition of active disease is not as well characterized in PsA as in RA, but is in the current treatment guides for PSA defined as "evidence of active arthritis and/or at least moderate disease activity by some composite disease activity measure and/or active disease leading to impaired function".[70] Traditionally the use of oral glucocorticoids in PsA has been restricted in PsA due to a fear of flares of psoriasis. Furthermore, data on efficacy is quite scarce. Despite this, oral glucocorticoids are commonly used in PsA.[70]

With respect to assessments of disease activity in PsA, traditional measures used in RA (DAS scores) and in psoriasis (Psoriasis Area and Severity Index, PASI) have often been applied, however not without limitations. Although the DAS score is useful because it assesses the number of joints affected, the patient's global assessment and includes laboratory measure such as CRP and ESR, it does not account for other manifestations of the PsA disease. Currently the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) has suggested new composite measures on disease activity and on response to therapy with the aim to take different clinical features of PsA into account. However these new measures are not used in a clinical setting and not yet fully validated.[71]

1.5   MALIGNANT LYMPHOMAS

1.5.1   Classification

Malignant lymphomas are a heterogeneous group of disorders deriving from lymphocytes in various stages of differentiation. Depending on the stage of the cell of origin, subtypes with different characteristics are formed. The heterogeneity of the group has made classification a challenge and several systems have been introduced over the years, which, for a long period, rested primarily upon morphological features. With the Revised European-American Lymphoma (REAL) classification issued in 1994 [72], immunological, genetic and clinical characteristics were also taken into account. The REAL classification was further modified into the current, and today internationally accepted, World Health Organization (WHO) classification introduced

in 2001 [73] and updated in 2008.[74] The WHO system divides the lymphomas into more than 40 different subtypes based on morphology, genetics, immune phenotype and clinical features. For all subtypes a cell of origin is identified.

Traditionally lymphomas have been divided into two main groups; non-Hodgkin lymphoma (NHL) accounting for about 90% of all cases and Hodgkin lymphoma (HL) making up for the remaining 10%. Non-Hodgkin lymphomas can further be divided into B-cell and T/NK- cell lymphoma, where the B-cell lymphoma accounts for the majority of the cases (>85%). The most frequent B-cell lymphoma types in Western populations are diffuse large B-cell lymphoma (DLBCL, 30-40%), follicular lymphoma (20-30%) and chronic lymphocytic leukemia (20-30%).[73, 75]

For CLL, the staging system and prognostic factors differ in many aspects from that of other NHL. Thus, although CLL is recognized as a B-cell lymphoma according to the WHO classification, it is sometimes treated as a separate entity. For example many cancer registers (including the Swedish) apply the International Classification of Diseases (ICD) where CLL is included among other leukemias. Further, and of importance for this thesis, CLL is not rarely excluded from studies on the etiology and epidemiology of NHL which may have an impact on the interpretation and comparison of different study results. Plasma cell malignancies (plasmacytoma/myeloma) are also included among the NHL subtypes according to the most recent WHO classification but these entities are not under study in any of the papers of this thesis.

Hodgkin lymphoma is characterized by typical neoplastic cells (Hodgkin and Reed-Sternberg cells) that occur sparsely in the neoplasm. Although it is now known that these cells are primarily of B-cell origin, HL displays several morphological as well as clinical and epidemiological features that distinguishes this entity from other B-cell lymphomas. There are 2 main subtypes of HL, the nodular lymphocyte predominant HL (5%) and the classical HL (95%).[73]

The diagnostic accuracy of lymphoma has varied over the years. The most relevant misclassification in Sweden is that of NHL as HL, where it is estimated that about one third of the diagnosed HL in the 70's actually were NHL.[76-77] Despite major improvements through advances in genetics, technology and not the least in immunohistochemistry, diagnostics of lymphoma remains a challenge for the pathologist as well as for the clinician.

1.5.2 Epidemiology

In Sweden, malignant lymphomas account for approximately 4% of all cancer cases each year.[75] In 2011, about 2,500 new cases were diagnosed (NHL including CLL=2,323, HL=182) and the annual incidence rate in Sweden is estimated to be 29 cases/100,000 person-years. Forty-five percent of the patients were women and the majority were older than 60 years of age at time of diagnosis.[75] Like most tumors, lymphoma becomes more frequent with increasing age, although the various subtypes show relatively different age profiles.[78] Since the 1950's, there have been reports on increasing incidence rates of NHL from several countries including Sweden.[79] Periodically an annual percentage increase of about 3% has been

reported. With regard to subtypes, less information is available on time trends, but an increase has been reported for example for diffuse subtypes such as DLBCLs. Since the early 1990's, the trend of increasing incidence of NHL has stabilized in several countries including Sweden. Still, the reason for this quite remarkable increase during the latter part of the 1900's remains largely unclear [80-81] as only a smaller proportion can be explained by established risk factors and misclassification of diagnoses. Compared with NHL, the incidence rates of HL have been more stable over time.[82]

1.5.3 Clinical aspects, treatment and prognosis

Given the histological and molecular heterogeneity of malignant lymphomas there is a large variation in clinical presentation, clinical course, treatment and prognosis. A more in depth description is beyond the scope of this thesis, however, some brief aspects will be presented.

Beyond the classification of subtypes according to the WHO system, the division of lymphomas into aggressive and indolent forms remains useful from a prognostic point of view. It also has implications for the choice of treatment. Aggressive lymphoma includes DLBCL, follicular lymphoma stage IIIb and peripheral T-cell lymphoma whereas CLL and follicular lymphoma (stage I, II and IIIa) are included in the indolent group. Another important factor for both treatment and prognosis is the localization (nodal or extranodal) and whether the disease is widespread. To distinguish localized (stage I and II) presentation from widespread disease, the Ann Arbor staging system (Table 4) is widely used for both NHL and HL (but not CLL).[83-84] Additionally, in the mid 1990's the International Prognostic Index (IPI) was published. This scoring index separates patients into distinct groups with different prognosis based on five factors; Ann Arbor stage, level of serum lactate dehydrogenase, number of extra nodal sites involved, age, and performance status.[85] Originally IPI was developed on patients with DLBCLs, but a similar index has also been developed for HL[86]and for follicular lymphoma.[87]

Table 4 - Ann Arbor staging classification of lymphoma, modified in Cotswold 1988.

Stage	Area of Involvement
I	Single lymph node group
II	≥ 2 lymph node groups on same side of diaphragm
II	≥ 2 lymph node groups on both sides of diaphragm
IV	Disseminated extranodal involvement
X	Bulk > 10 cm
E	Extranodal extension or single, isolated site of extranodal disease
A/B	B symptoms: weight loss>10%, fever, night sweats

The advances in microarray technology have contributed with further prognostic information. For example, it is now recognized that DLBCL consists of two different subsets, initially distinguished through different gene expression profiling[88]; the germinal center (GC) type and the activated B cell-like (ABC) type (sometimes referred to as the non-GC type). Today, the two subsets can also be separated from one another by using immunohistochemistry technique.[89] The distinction between the GC and non-GC type is important from a prognostic point of view as the non-GC type has a poorer survival.

The heterogeneity of lymphoma results in numerous treatment options and a widely accepted standard treatment exists only for a minority of the patients. For indolent lymphomas, it is sometimes sufficient to treat with a watch-and-wait policy whereas radiotherapy (often in combination with chemotherapy) is used in more aggressive disease. In recent years, biological agents, especially monoclonal antibodies against CD20 B cells,[90] have substantially contributed to an improved prognosis for patients with several different lymphoma subtypes and are increasingly used in the therapeutic arsenal alone or together with chemotherapy. A further treatment alternative in aggressive lymphomas consists of high dose chemotherapy followed by stem cell transplantation.[91]

1.5.4   Some aspects of lymphoma pathogenesis

As for cancer development in general, lymphomas constitute clonal expansions of normal cells, mainly B and T cells. The expansion arises through a multistep process of genetic aberrations that induces a selective growth of the malignant clone and finally the ability to outgrow surrounding cells and tissues.[92] With regard to the more common B-cell lymphomas, recurrent translocations that occur during the different steps of the B-cell differentiation are involved in the initial steps of the malignant transformation. These genetic lesions may in turn deregulate the lymphoid balance in several ways such as by; **i)** enhancing cell growth and proliferation, **ii)** blocking normal cell differentiation, and **iii)** preventing programmed cell death (apoptosis). However these initial translocations alone are not considered sufficient to cause lymphoma development, and further genetic alterations are needed for a complete malignant transformation.[93]

The normal B-cell development includes several different stages and is initiated in the bone marrow with further differentiation in secondary lymphoid tissues such as lymph nodes. In some of these stages of differentiation, the B-cell genome is especially vulnerable for genetic aberrations. For example, both the arrangement of the immunoglobulin genes of the pro-B cells in the bone marrow and disturbances during the response of mature B cells to antigen in the germinal center of the lymph nodes represent such vulnerable processes. Thus, DNA modifications at these stages might predispose to genetic abnormalities leading to lymphoma development. Furthermore, the subtype of lymphoma depends on where in the B-cell stage of differentiation the genetic aberration takes place.[93-94] The dysregulation of B cells may also occur through dysfunction of T-cell mediated immunosurveillance. As already stated in the section on pathogenesis in RA, T cells are of crucial importance in controlling B cells and therefore controlling the overall immune function. This can

be illustrated by the well defined link between risk of lymphoma following HIV/AIDS, a disorder characterized by imbalance between subsets of T cells.[95]

Several biological mechanisms have been suggested to cause the genetic aberrations leading to lymphoma development. One example is oncogenic viruses, where a viral genome would interfere with normal cell growth in the lymphoid cell. Another mechanism is through direct carcinogenic factors that could lead to possibly genetic lesions. A third important biological mechanism (and of interest with respect to the subject of this thesis) could be chronic immune stimulation leading to an increased B-cell proliferation which in turn could increase the risk of genetic aberrations. [96]

1.5.5   Risk factors

1.5.5.1   Genetic factors

A family history of malignant lymphoma is associated with a 1.5 to 4-fold increased risk of NHL.[97-102] Even higher risks have been reported for HL [82, 98, 100, 103] and for CLL.[104] This familial aggregation of lymphoma indicates a role of genetic susceptibility in lymphoma development. Interestingly, some data points towards stronger association of lymphoma risk with siblings than with a parental history of hematopoietic malignancy.[98, 100] Moreover, there are indications that chemical and occupational exposures are associated with an even higher lymphoma risk in patients with a positive family history of cancer.[105-106] This may suggest the contribution of a shared environment in childhood and adolescence or a possible gene-environment interaction for the observed risk association.

With regard to specific genes associated with lymphoma development in the general population, several genetic variants have been identified as potential susceptibility loci.[107] An interesting observation is the increased lymphoma risk associated with susceptibility alleles in pro-inflammatory (TNF and IL-6)[108-110] and regulatory (IL-10)[108] cytokines. Recent studies further observed an association between the HLA class II region and follicular lymphoma.[111-112] This highlights the importance of gene polymorphisms involved in immune function, inflammation, and antigen presentation for the lymphoma development. Other gene polymorphisms that are studied are genes involved in DNA repair/methylation, oxidative stress and hormone regulation.[107]

However, so far the identified susceptibility variants indicate that common genetic variants with low penetrance influence lymphoma risk, presumably with further influence from gene-gene and gene-environment interactions.

1.5.5.2   Inherited and acquired immunodeficiency

Inherited and acquired states of immunodeficiency constitute strong and well-established risk factors for lymphoma even though they altogether only explain a small part of all cases. With regard to inherited conditions, several rare syndromes/disorders are recognized, such as Wiskott-Aldrich syndrome, combined immunodeficiency and X-linked lymphoproliferative syndrome. The relative risk (RR) of developing lymphoma in these conditions is 10-200 times higher than expected and up to 25% of these individuals develop a lymphoma during their life-time.[73]

Although being extremely rare in the population, the inherited immunodeficiency syndromes are important for the understanding of lymphoma etiology overall.
A defective immunosurveillance of Epstein-Barr virus (EBV) seems to be a primary mechanism behind lymphoma development in these conditions.[73]

HIV/AIDS is associated with a highly increased lymphoma risk ranging from 15-400 depending on lymphoma subtype and the population under study.[95] The most common subtypes reported are aggressive NHL including DLBCL and Burkitt lymphoma. Although there are reports of a decreasing trend in HIV/AIDS associated lymphomas with the introduction of antiretroviral therapy,[113-114] malignant lymphomas are still an important cause of mortality in this patient population.[95] Chronic antigenic stimulation resulting in immune dysregulation, genetic aberrations and loss of T-cell immunity against pathogenic viruses such as EBV and Human herpes virus 8 (HHV8) are suggested mechanisms behind HIV/AIDS related lymphomas. Overall, about 50% of all cases are estimated to be EBV-driven.[115]

Long-standing immunosuppressive therapy following organ and bone marrow transplantation has also consistently been associated with risk of malignant lymphoma. The post-transplant lymphoproliferative disorder (PTLD) is a heterogeneous group consisting of different lymphoid proliferations ranging from benign hyperplasia to invasive malignant lymphoma. The majority of lymphomas are of B-cell origin.[116-117] The reported risks of developing PTLD are higher following heart transplantation compared to kidney transplantation.[118-119] A potential explanation is that more intense immunosuppression used in recipients of thoracic organs compared with in renal transplanted patients. The pathogenesis of PTLD is complex, but an interaction between chronic antigenic stimulation induced by the graft and impaired T cell immunosurveillance due to significant immunosuppression are suggested mechanisms. The majority of the patients with PTLD have further EBV-driven positive lymphomas indicating a dysfunctional immune response to a new or re-activated EBV infection.[117] However, not all EBV positive organ transplanted patients develop PTLD, indicating some additional unidentified stimuli other than EBV. Although such factors are not clearly identified, the chronic stimulation of B cells as well as the local cytokine environment may play a role.[116] Clinical characteristics shared by the majority of the immunodeficiency-related lymphomas are an association with EBV, B-cell origin, extranodal localized lymphomas and an aggressive clinical course.[73, 95, 115-116]

1.5.5.3 Infectious agents

Epstein-Barr virus (EBV)
Epstein-Barr virus is a herpes virus with lymphocyte-transforming potential. It is usually acquired in childhood or early adolescence and about 90% of the worlds' population is estimated to be EBV carriers.[116] After primary infection, the virus often persists lifelong in carriers as a latent asymptomatic infection of the B cells. In healthy infected individuals, malignant transformation of EBV-infected B cells is prevented by the presence of an intact T cell-mediated immunity. Thus, in states of severe immunodeficiency this control system may be impaired, leading to uncontrolled B-cell proliferation and sometimes to lymphoma development.[120] On the contrary, EBV infection is also present in lymphomas in immunocompetent

individuals such as (African) Burkitt lymphoma, as well as in some rare T/NK-cell lymphoma.[121] Hodgkin lymphoma is also associated with EBV infection, especially classical HL where EBV is identified in the tumor cells in approximately 40% of cases.[122]

Other infections agents
Two other lymphocyte-transforming viruses also display an association with lymphoma. The human herpes virus 8 (HHV8) is the causative agent of Kaposi's sarcoma but is also associated with primary effusion lymphoma, a rare subset of NHL primarily affecting individuals with HIV/AIDS. Co-infection with EBV is common. The human T lymphotropic virus type I (HTLV-I), a retrovirus, is an established cause of adult T-cell leukemia/lymphoma.[73, 121]

Hepatitis C (HCV) has in several (but not all) studies been associated with an increased risk of NHL by 2- to 10-fold.[123-124] There are substantial differences across studies possibly reflecting both geographically different study populations as well as methodological differences across the studies. The highest risks are reported from geographical areas with high prevalence of HCV in the population. Suggested mechanisms are chronic antigen stimulation leading to B-cell proliferation and to lymphoma development. Other infections suggested to be associated with specific subtypes of lymphoma are; *Helicobacter pylori* and gastric Mucosa-associated lymphoid tissue (MALT) lymphoma, *Campylobacter jejuni* and small intestine NHL.[121]

1.5.5.4 Environmental factors

Lifestyle factors
Studies on smoking and risk of lymphoma have been conflicting.[125] A recent pooled analysis of 9 case-control studies from the International Lymphoma Epidemiology Consortium (InterLymph), noted no increased risk of NHL overall, but a significant increased risk confined to follicular lymphoma.[126] A similar observation was noted in a large Swedish-Danish case-control study, although the increased risk noted for follicular lymphoma was restricted to women.[127] Hodgkin lymphoma has also been associated with increased lymphoma risk although excess risk among smokers has been quite modest. [127-128] For alcohol the association is weak and if anything data indicate a slightly reduced lymphoma risk associated with alcohol consumption.[129-131] With respect to obesity, several studies have observed a positive association, whereas others have not.[132-133] The strongest association reported is of severe obesity and risk of DLBCL.[133] Further, high protein and high fat intake has been associated with a small increased risk of NHL, whereas high vegetable and fruit intake has been reported to reduce the same risk.[134-135] Although the observations with respect to obesity and dietary factors do not explain significant proportion of the lymphoma cases, it may be of interest from an etiological perspective. Obesity may, for example, promote a state of low grade, chronic inflammation and increased production of pro-inflammatory cytokines that in turn deregulate T-cell immunity and promote B-cell proliferation.[132]

Other environmental factors
The link between ultraviolet radiation and risk of NHL has been debated. Initially it was hypothesized that sun exposure might be associated with an increased risk given the elevated risk of lymphoma following a diagnosis of skin cancer (implicated that sun exposure could be a common risk factor for both conditions). However, recent data point to a lymphoma protective effect of sun exposure in particular recreational ultraviolet radiation.[136-137] Potential biological explanations behind this remain unclear, although vitamin D pathways have been proposed as possible mechanisms.

Exposure to moderate to high ionising radiation has consistently been associated with increased risk of leukemia especially for individuals exposed in childhood.[138]
A corresponding risk for lymphoma has not been shown.[139-141]
Several studies have suggested an association between occupational exposure to solvents such as benzene, toluene and xylene, whereas the associations between specific chemicals and/or specific lymphoma subtypes have been inconclusive.[142-144] Another suggested exposure is pesticides. However, a recent published European pooled analysis provided limited evidence for an increased risk of specific lymphoma associated with exposure to pesticides.[145]

1.6   CHRONIC INFLAMMATION AND RISK OF LYMPHOMA

A clear association with lymphoma has consistently been demonstrated for certain, autoimmune/chronic inflammatory conditions and constitutes one of the best-established lymphoma risk factors (apart from severe states of immunodeficiency).
Increased risks are today well-established in patients with Sjögren's syndrome (SS), systemic lupus erythematosus (SLE) and RA. [146-147]Also celiac disease, dermatitis herpetiformis and chronic thyroiditis[148] have repeatedly been associated with lymphoma development. In other diseases, such as inflammatory bowel syndrome, psoriasis, systemic sclerosis[148-151], granulomatosis with polyangiitis (formerly Wegeners granulomatosis),[152-153] sarcoidosis [154-156], and ankylosing spondylitis, data on lymphoma risk are more conflicting, or as for psoriatic arthritis poorly studied. The distribution and the magnitude of increased lymphoma risk varies markedly amongst different studies. In general, earlier and smaller studies of selected (often hospitalized-based) patients have reported higher risks compared with more recent, larger population-based investigations. One explanation for this could be that population-based studies include patients with milder disease.The majority of studies have addressed risks of NHL, but there are evidence of increased risks of HL especially in RA and SLE. Furthermore, evidence is accumulating that the inflammatory response caused by chronic inflammatory conditions may result in a higher risk for specific lymphoma subtypes and to lymphoma development in the target organ of the disease in question such as in SS, celiac disease and thyroiditis[147]

In SS the risk ratios reported range from 2-48[155, 157-161] with an average RR of about 19.[162] Higher risks are generally reported for primary SS than for SS secondary to other autoimmune disorders.[163] There is a strong association specifically with mucosa-associated lymphoid tissue (MALT) lymphoma, which is localized in the target organ, the salivary glands,[73] but increased risks of DLBCL[164] are also observed. In a recent large pooled analysis of case-control studies within the InterLymph consortium, there was a 9-fold increased risk of DLBCL and a 30-fold increased risk of MALT lymphoma.[165] Several clinical characteristics at the time of

the SS diagnosis have been shown to be correlated with future lymphoma development including low C4 complement level, palpable purpura, cryoglobulinemia, splenomegaly, and lymphopenia.[155, 158, 166-167] This indirectly suggests that disease severity and/or disease activity may be of importance for the underlying lymphoma risk in SS.

For SLE, lymphoma risk is overall about 3-6 times higher than in the general population, although some studies have reported even higher risks.[154, 156, 168-175] In the meta-analysis from Zintzaras et al., the pooled SIR was 7.4.[162] Studies have shown that SLE patients have a 3 to 5-fold increased risk for HL also.[171-172, 176] With regard to risk determinants, data indicate that hematological SLE aberrations, sicca symptoms, and pulmonary involvement [177-178] are associated with future risk for lymphoma development. There are also indications of a potential link between high SLE damage score and lymphoma risk[179] whereas immuno-modulatory treatment was unrelated to risk in these studies.[177-179] Additionally the study of Bernatsky et al. [179] noted that the greatest risk of cancer existed earliest in the course of SLE which may suggest that cancer risk is not entirely explained by cumulative exposure to immune-modulatory treatment. Conversely, a very recent case-cohort study of 75 SLE-lymphomas and 4,961 cancer-free SLE controls found higher lymphoma risks with exposure to cyclophosphamide and high cumulative glucocortiocoids, but not with disease activity itself.[180] This illustrates the difficulties with disentangling the effect of a treatment from that of the underlying condition. With regard to NHL subtypes the most commonly occurring form in SLE is DLBCL [154, 165] and in the study of Löfström et al.[178] the majority of these (80%) were the prognostic less favorable non-GC type.

Celiac disease (mainly located in the small intestine) and dermatitis herpetiformis (affecting the skin) are related conditions associated with gluten intolerance. In a recent meta-analysis, Tio et al. observed a pooled RR of about of 2.6 for NHL and an RR of almost 16 for T-cell lymphoma in patients with celiac disease.[181] Furthermore, there is a strong association with the rare enteropathy-associated T-cell lymphoma of the small intestine in patients with celiac disease [73] and also evidence for increased risks of B-cell lymphoma.[154, 182-183] Dermatitis herpetiformis is also associated with an increased risk of lymphoma.[184] Interestingly, some studies have indicated, although not conclusively, that a gluten-free diet may be protective of lymphoma in both conditions.[184-185]

A problematic issue when studying the link between inflammatory conditions and lymphoma risk is that autoimmune rheumatic features may occur in the course of the lymphoproliferative malignancy, sometimes being the first sign of a cancer. These so-called paraneoplastic autoimmune phenomena may lead to misclassification of the undiagnosed lymphoma as an autoimmune disorder. For some inflammatory conditions this issue has turned out to be particularly relevant such as in inflammatory myositis and autoimmune haemolytic anemia. In both of these conditions, increased lymphoma risks have been reported but the lymphomas have typically occurred around the time of the diagnosis of the inflammatory condition.[156, 186]

1.7 RHEUMATOID ARTHRITIS AND LYMPHOMA

In the 1970's, Isomäki et al.[187] presented a study indicating that patients with RA had an increased risk of lymphoma of about 2.7. Since then, this observation has been replicated in several case-control and cohort studies, although with a few exceptions (Table 5). The reported RRs for lymphoma overall range from 1.5-4, with an average RR of about 2.[162, 188] In general, studies including patients hospitalized for RA have observed higher risks than studies of non-hospitalized patients or when the exposure of RA has been self-reported. Data also indicate higher risks in men than in women with RA.[189-191] Although most studies have not shown an excess in cancer deaths overall in RA,[5] mortality due to lymphomas in RA appears to be approximately doubled compared with the general population.[5, 190] Despite increased knowledge on the link between RA and lymphoma in the last 10-15 years, the underlying mechanisms behind this association are not fully understood.[147, 192] Potential risk factors that have been investigated during the years include RA-disease related factors such as inflammatory activity, the immune-modulatory treatment used in RA, and shared genetic (and/or environmental) factors common for both conditions.

1.7.1 Inflammatory activity

Several factors indicate a clear correlation between inflammatory activity and/or disease severity in RA and risk of lymphoma. An early study by Gridley et al.[193] observed a notably higher lymphoma risk in men with Felty's syndrome, a severe complication of long-standing RA. Higher risks seen in patients hospitalized for RA further support an RA-disease related effect, assuming that hospitalized RA patients constitute a group with a more severe disease.[194-195] A problematic issue over the years has been to distinguish effects of treatment from the effects of the RA disease, given the obvious potential for channeling bias. Smaller studies with detailed information on both treatment and disease activity have rarely had the power to address this issue and larger registry-based studies have often had limited access to detailed information on disease characteristics. In some studies, clinical features, indirectly or directly, associated with RA disease activity and/or severity have shown to correlate with lymphoma risk including secondary SS, high ESR, erosive joint history and level of HAQ [163, 189, 196]. However, the strongest evidence for an association between RA disease activity and lymphoma risk is provided by the case-control study by Baecklund et al.[197] including 378 RA patients with lymphomas and 378 RA patients without lymphoma, hospitalized for RA 1964-1994. In this study the RA patients were divided into high, medium and low accumulated disease activity during the entire RA course based on a scoring system including number of swollen and tender joints, ESR, and the doctor's global assessment. The information was abstracted from the medical records and included detailed information on treatment. High active disease was associated with a 71–fold increased risk of lymphoma compared with low active disease whereas moderate activity conferred an RR of almost 8. Conversely, treatment was not related to increased lymphoma risk.[197] However, it must be remembered that the results of this study do not reflect current RA treatment strategies (none of the patients in the study of Baecklund et al. had been treated with TNFi) and cannot easily be compared with RA patients diagnosed and treated today.

Table 5 - Risk of lymphomas in patients with rheumatoid arthritis.

			Cohort study design		
Author Year [ref]	Country/ Study period	Setting	Number of RA patients	Number of lymphomas	SIR (95% CI)[1]
Thomas 2000 [190]	Scotland 1981-1996	Hospitalization for RA	Men 7,080 Women 19,543	Men: NHL 30 HL 8 Women: NHL 71 HL 9	Men: NHL 2.4 (1.6–3.4) HL 5.4 (2.4–11) Women: NHL 2.0 (1.6–2.6) HL 3.0 (1.4–5.8)
Ekström 2003 [198]	Sweden 1964-1999	Hospitalization for RA	76,527	535 observed vs. 268 expected	Lymphoma 2.0 (1.8-2.2) NHL 1.9 (1.7-2.1) HL 3.1 (2.4-3.8)
Wolfe 2004 [189]	UK 1999-2002	Rheumatologist based RA diagnosis	18,572	29 observed vs. 15.5 expected	Lymphoma 1.9 (1.3-2.7)
Wolfe 2007 [199]	UK 1998-2005	Rheumatologist based RA diagnosis	19,562	95 observed vs. 52.2 expected	Lymphoma 1.8 (1.5-2.2)
Hemminki 2008 [200]	Sweden 1980 -2004	Hospitalization for RA	42,262	NHL 252 HL 30	NHL 2.2 (2.2-2.5) HL 3.7 (2.5-5.3)
Abásalo 2008 [201]	Spain 1999-2005	Rheumatologist based RA diagnosis	789	NHL 3	NHL 5.4 (1.1-15-7)
Parikh-Patel 2009 [191]	US 1991-2002	Hospitalization for RA	Men 19,239 Women 65,236	Men: NHL 117 HL 10 Women: NHL 208 HL 15	Men NHL 2.1 (1.7–2.5) HL 2.8 (1.3–5.1) Women NHL 1.4 (1.2–1.6) HL 1.6 (0.9–2.7)
Mercer 2013 [202]	UK 2002-2009	Active RA at recruitment	3,771	21 observed vs. 5.51 expected	NHL 3 (1.8-5.1) HL 13 (4.2-30)

Table 5 - Continued

		Case-control design			
Author Year [ref]	Country/ Study period	Setting	Cases/controls	Number of lymphomas	OR (95% CI)[2]
Tavani 2000 [203]	Italy 1983-1992	Hospitalized-based Self reported RA	NHL 429 HL 158 Controls 1,157	NHL 15 HL 4 Controls 28	NHL 1.7 (0.9-3.4) HL 2.4 (0.8-7.3)
Holly 2003 [204]	US 1988-1995	Self-reported RA Random digit to controls	NHL 1,304 Controls 2,402	DLBCL 15 Follicular 14 Controls 47	DLBCL 1.2 (0.7-2.2) Follicular lymphoma 1.6 (0.9-3.0)
Engels 2005 [159]	US 1998-2000	Self-reported RA through interview	NHL 1,321 Controls, 1,057	Cases 48 Controls 34	NHL 1.3 (0.8- 2.1)
Becker 2005 [205]	Germany 1999 -2002	Self-reported RA through interview	710 matched case/control pairs	Cases 11 Controls 18	Overall 0.6 (0.3-1.4) NHL 0.5 (0.2-1.2) T cell lymphoma 4.5 (1.2-17)
Smedby 2006 [154]	Sweden/ Denmark 1999-2002	Self-reported RA 18 - 74 years	NHL 3,055 Controls 3,187	Cases 126 Controls 89	NHL 1.5 (1.1-1.9) DLBCL 1.8 (1.2-2.6) T-cell lymphoma 1.9 (0.9-3.9) CLL 1.4 (0.9-2.2)
Mellemkjaer 2008 [156]	Denmark 1977-1997 Sweden 1964-1998	Hospitalization for RA	NHL 24,728 Controls 55,632	Cases 311 Controls 402	High grade NHL 2,0 (1.2-3.4) Low grade NHL 1.0 (0.7-1.5) T-cell lymphoma 0.5 (0.2-2.0)
Anderson 2009 [155]	US 1993-2002	Age ≥ 67	Lymphoma 44,350 Controls 122,531	Cases 3,289 Controls 1,157	NHL 1.2 (1.1–1.3) DLBCL 1.4 (1.2–1.5) T-cell lymphoma 1.5 (1.1–1.8) CLL 1.1 (1.0–1.2)

[1]SIR= Standardized incidence ratio with 95% Confidence intervals (CI) [2]OR= Odds ratio with 95% CI NHL = Non-Hodgkin lymphoma HL= Hodgkin lymphoma, DLBCL= Diffuse large B-cell lymphoma, NHL = Non-Hodgkin lymphoma HL= Hodgkin lymphoma CLL= Chronic lymphocytic leukemia

Studies assessing whether lymphoma risk increases with time since RA diagnosis have been inconclusive.[148, 198, 206-209] Most reports on this subject have included prevalent rather than incident RA patients making it impossible to assess lymphoma risk as a function of time since onset of RA.[148, 198, 208] In the studies where the patient population has consisted of incident RA or polyarthritis, the number of lymphoma cases has been insufficient to draw reliable conclusions due to low statistical power.[206-207] In one study there was a small, however non-significant, trend suggesting a possible increasing lymphoma risk with long-standing inflammation.[209]

1.7.2 Immune-modulatory treatment

1.7.2.1 Disease modifying anti-rheumatic drugs (DMARD)

With respect to DMARDs, MTX and azathioprine are the two agents most commonly associated with increased lymphoma risks.[73] Several case reports and case series have presented lymphomas in patients treated with MTX as well as reports that a considerably proportion of these lymphomas obtain spontaneous (sometimes complete) remission when treatment is withdrawn.[210-212] However larger population-based studies have failed to show any increased lymphoma risk associated with MTX overall[189, 197, 213-214] although there are exceptions.[206, 215] In some studies, data were too limited to completely explore disease activity [189, 206, 213, 215]. Alternatively, disease activity has been accounted for through indirect measures such as DMARD polytherapy, use of oral glucocorticoids and extra-articular manifestations.[214] Baecklund et al.[197] reported no increased risk with MTX and accounted for disease activity by using a measure of accumulated disease activity (area under the curve, AUC) during the entire RA disease course. Taken together, there is no strong evidence supporting that MTX per se would increase the risk of lymphoma. However, concerns about the impact of MTX in the lymphoma development of the so-called "methotrexate-associated lymphomas" remains.[73] Interestingly, these particular lymphomas often present with a clinical picture similar to those seen in immunodeficient patients including lymphomas of primarily B-cell origin, EBV identified in lymphoma tissue, and extranodal localization.[210-212]

Azathioprine has repeatedly been associated with risk of lymphoma in the post-transplant setting,[73] but also in the setting of RA and inflammatory bowel syndrome (IBD). For RA, older studies have been inconclusive; some have shown increased risk,[216] others have not,[217] again with the problematic issue of distinguishing treatment effects from the risk of the underlying condition. Two more recent studies have also noted that treatment with azathioprine was associated with an increased risk of lymphoma in RA [197] [214], this increase in risk remaining after adjustments for accumulated inflammatory activity in the Swedish study [197]. In the setting of IBD, increased risks following treatment with azathioprine have been presented in several studies.[218-220] Few of these have been able to account for disease severity of IBD.

The carcinogenic effects of cyclophosphamide are well known and increased risks of cancer overall, urinary bladder cancer and acute myeloid leukemia have been reported in patients treated with this agent.[153] For RA patients, evaluations have

been difficult due to lack of power,[221-222] although there is no strong evidence of increased lymphoma development in RA patients due to cyclophosphamide. Furthermore, a recent study assessing cancer risk in association with exposure to cyclophosphamide in patients with Wegener's granulomatosis, did not detect an excess risk of NHL, whereas risk of acute myeloid leukemia was significantly elevated.[153]

With respect to other DMARDs there are, overall, no signals of increased lymphoma risk associated with sulfasalazine, antimalarial agents or cyclosporine, although data are limited. [197, 202]

1.7.2.2 Glucocorticoids

Glucocorticoids have been widely used against RA for more than 50 years, and recently have experienced somewhat of a revival, particularly in the treatment of early RA.[36,223] Despite their extensive use, a comprehensive understanding of their mechanisms of action in RA is still lacking.[224] Previous studies on treatment with glucocorticoids and risk of lymphoma have reported both increased [225-226] as well as non increased risks [159, 209, 227-228] (reviewed in a meta-analysis of Bernatsky et al.[229]). Partly this discrepancy can be explained by various degrees of channeling bias due to the underlying conditions treated with glucocorticoids. In an RA context, data are more limited but also have mixed results.[159, 197, 209] Interestingly, a study by Smedby et al.[209], the increased risk of NHL with respect to glucocorticoids was restricted to patients treated due to underlying RA whereas this risk was not apparent in non-RA patients taking glucocorticoids for other indications. By contrast, the study by Baecklund et al.[197] noted a reduced lymphoma risk associated with oral glucocorticoids in RA patients.

1.7.2.3 TNFi and lymphoma in rheumatoid arthritis

Ever since the approval of TNFi, there have been concerns that the strong immune-modulating effects of these agents may induce development of lymphoma (or other cancers). The potential mechanisms behind this are complex. TNF is a key cytokine in the inflammatory cascade and seems to be of importance for the T-cell mediated immunity. Blocking of the natural functions of TNF might therefore theoretically lead to an impaired T-cell response, decreased tumor surveillance and subsequently to a possible cancer/lymphoma development. On the other hand, the local inflammatory responses mediated by TNF (and other inflammatory mediators) are also suggested to be of importance in the etiology of certain cancer forms. From this perspective, TNFi may instead decrease cancer/lymphoma risk.[230] Additionally, in an RA context, TNFi could potentially reduce lymphoma risk, given their efficiency in lowering inflammatory activity. The net sum of all these mechanisms is obviously complicated.

Data evaluating lymphoma risk in association with TNFi exposure have been inconsistent. In the meta-analysis by Bongartz et al. in 2006 [231] including 3,493 TNFi exposed RA patients and 1,512 placebo treated RA patients indicated an increased occurrence of lymphoma during (and after) end of follow up of the trials, although lymphoma-specific relative risks were not presented. By contrast, two more recent meta-analyses on this subject did not detect any increased lymphoma risk above what

is expected in an RA population.[232-233] Leombruno et al.[232] found a pooled RR of lymphoma of 1.3 (95% CI 0.5 to 3.1) whereas the recent meta-analysis by Lopez-Olivo et al.[233] noted a pooled RR of 2.1 (95% CI 0.6-8.4).

In observational studies, the association between lymphoma and exposure to TNFi has to some extent varied (Table 6). Although the majority of studies have not reported increased risks in TNFi exposed RA patients compared with patients treated with classical DMARDs, there are exceptions. Geborek et al.[234] observed a 5-fold increased lymphoma risk in TNFi exposed RA patients versus non-exposed patients, although risk estimates were imprecise. Pallavacini et al.[235] also noted a substantially higher standardized incidence ratio (SIR) of lymphoma than what would be expected in an RA population overall. Interestingly, in the study by Askling et al.[236] risks of lymphoma were higher in RA patients starting TNFi 1998-2001 versus patients starting 2002 or later. This may suggest that RA patients treated with TNFi in the beginning of the biological era had a more severe disease than RA patients started on TNFi more recently. Assessments of lymphoma subtypes in relation to TNFi exposure are limited and have so far been hampered by the small number of events.[237-238] Furthermore, there are signals of different lymphoma risks depending on the type of TNFi agent received. A recent French study noted higher risks in RA patients treated with the anti-TNF monoclonal antibodies; adalimumab and infliximab than for the TNF-soluble receptor, etanercept.[239] In the publication the authors discuss a potential higher efficacy of the anti-TNF monoclonal-antibodies in inhibiting membrane TNF signalling leading to a decreased immunesurveillance as one possible explanation.

With respect to other biological agents and risk of lymphoma, data are limited but there are no signals of increased risks so far.[233] One particularly interesting agent in this respect is CD20+ B-cell depleting therapy (rituximab). Rituximab is successfully used in therapy for certain lymphomas and also in the treatment of RA (and other inflammatory conditions). This shared treatment further underscores the close link between lymphoma and autoimmunity.[96]

Table 6 - Observational studies of lymphoma risk in patients with rheumatoid arthritis exposed to Tumor Necrosis Factor inhibitor (TNFi).

Author Year [ref]	Country	Study period	Risk vs. general population comparators[1] (95% CI)	Risk vs. TNFi-naïve RA patients[2] (95% CI)
Wolfe 2004 [189]	UK	1999-2002	2.9 (1.7-4.9)	NR
Askling 2005 [207]	Sweden	1999-2003	2.9 (1.3 to 5.5)	1.1 (0.6-2.1)
Geborek 2005 [234]	Sweden	1997-2002	12 (3.7-27)	4.9 (0.9-26)
Setoguchi 2006 [240]	US/ Canada	1994-2004	2.2 (1.7–2.9)[3]	1.1 (0.5-2.4)[4]
Wolfe 2007 [199]	UK	1998-2006	1.8 (1.5-2.2)	1.0 (0.6-1.8)
Askling 2009 [236]	Sweden	1998-2006	2.7 (1.8-4.1)[5]	1.4 (0.8-2.1)
Mariette 2010 [239]	France	2004-2006	2.3 (1.6-3.3)	NR
Pallavicini 2010 [235]	Italy	1999-? NR	6.0 (1.6–15)[6] 5.0 (1.3–13)[6]	NR
Carmona 2011 [238]	Spain	2001-2008	NHL 1.5 (0.3-4.4) HL 5.3 (0.1-29)	NR
Dreyer 2012 [237]	Denmark	2000-2008	NHL 1.9 (0.8-4.5) HL 8.3 (2.1-33) CLL 2.4 (0.8-7.5)	NHL 0.6 (0.2-2.2) HL - CLL 3.1 (0.3-31)

[1]Relative risk expressed as SIR= Standardized incidence ratio, with 95% Confidence interval (CI)
[2] Relative risk, with 95% CI [3]Only including NHL, [4]Including NHL, HL, CLL and myeloma
[5]Compared with a general population comparator group [6]Compared with data in Milan cancer report and Varese Cancer Registry database respectively. NR= Not reported
NHL = Non-Hodgkin lymphoma HL= Hodgkin lymphoma CLL= Chronic lymphocytic leukemia

1.7.3   Shared genetic and/or environmental risk factors

Some of the susceptibility genes implicated in lymphoma pathogenesis have also been proposed as risk genes for RA. [241-243] Hypothetically, it may thus be that the increased lymphoma occurrence in RA is not a cause-and-effect association, but a result of shared genetic factors common for both conditions. However, in studies evaluating the lymphoma occurrence in relatives of RA patients there are no indications of any increased lymphoma risks [148, 198, 244] suggesting that the contribution of shared genetic susceptibility is low. On the other hand, considering the complex genetics of both diseases, and the clustering of lymphomas in the subset of RA patients with the most severe disease [197], it cannot be excluded that shared genetic susceptibility exists but only in the presence of (high) inflammation and/or in addition to immune-modulatory treatment.

Few environmental risk factors shared by lymphoma and RA are recognized. Among infectious agents, EBV is involved in the lymphoma development especially in patients with states of immune-deficiency. There is also a link between EBV and some particular lymphoma subtypes that are commonly observed also in RA such as DLBCL and HL. On the contrary, studies do not indicate that presence of EBV in RA-lymphomas is higher than in lymphomas in the general population. [197, 245] Smoking is identified as a risk factor for RA [10-14] and has also in some studies been associated with lymphoma development.[125] However, this association is not consistent and may not explain the excess risk of lymphoma in RA on a population level.

1.7.3.1 Characteristics of lymphoma in RA

With respect to specific subtypes of lymphoma in RA patients, the majority of studies have assessed risk of lymphoma overall or risk of NHL. Data indicate an even higher risk of HL, although with less precise risk estimates.[190-191, 198, 200, 202-203] Risk of CLL is not as well-investigated and has often been studied together with other leukemias in RA. When assessed separately there are no strong signals of increased risks.[154] Similar evaluations in SLE and SS, have neither reported any increased occurrence of CLL.[154-155, 246]

For RA, DLBCL has so far shown the strongest association. In the study by Baeckund et al. the histopathological classification showed that almost 50% of the RA-lymphomas were of DLBCL-type. Further, these DLBCLs displayed a strong association with disease activity and clinically often presented with extranodal involvement and advanced stages of lymphoma disease.[197] A follow-up study based on the same patient population revealed that 70% of the DLBCLs consisted of the prognostic less favourable non-GC type.[247] In studies assessing lymphoma risk by subtype, two studies observed modestly increased risks of DLBCL in RA [154-155] whereas another study did not detect any specific increased risk.[204] EBV-positive lymphomas seem to be less common in RA and in other inflammatory conditions than in lymphoma-patients with states of immune-deficiency. In one study, including MTX- treated RA patients, 17% of the NHL (3/18) and 71% of the HL (5/7) where EBV-positive.[213] and in the study of Baecklund et al. only 12% of all the RA-lymphomas were EBV-positive.[197] Similar results have been reported from studies assessing the presence of EBV-positive lymphomas in other inflammatory conditions. [178, 245]

In summary, due to the dramatic change in treatment strategies for RA in recent years, aiming at disease remission and low inflammatory activity using new treatment regimens, one could hypothesize that the risk as well as the presentation and clinical course of lymphomas in RA patients may have changed. Data on this subject is limited. Little is known whether the distribution of lymphoma subtypes is different in RA patients diagnosed and treated today compared with the lymphoma distribution reported from historical RA cohorts, i.e. in RA patients with a presumably higher disease activity and higher inflammatory load over time.

1.8 SPONDYLARTHRITIS AND LYMPHOMA

In contrast to RA, data on lymphoma risk in patients with spondylarthritis (SpA) are more limited, but indicate potential differences between different SpA entities.

For AS, previous studies have not observed increased lymphoma risks overall [155-156, 205, 248-249] apart from one retrospective cohort study (published in abstract only) identifying an incidence rate ratio (IRR) of lymphoma of 2.8 among AS patients (Chibata et al. Eular 2004, OP0131). Corresponding data for PsA are scarce and to my knowledge consist of one study assessing cancer risks in PsA patients followed prospectively 1978-2004, reporting a SIR for all hematopoietic malignancies combined of 0.7 (95% CI 0.3–1.8).[63] By contrast, cutaneous psoriasis has repeatedly been linked to increased lymphoma risk,[155, 250-252] in particular T-cell lymphoma,[155, 165, 253] although other studies have failed to observe any excess risk at all.[172, 203, 205] Furthermore, there is some evidence of a link to disease severity and/or to systemic treatment of psoriasis.[254-255]

In IBD patients, available data support that the average risk of lymphoma is similar to or just slightly higher than that of the general population (reviewed in a recent meta-analysis by Pedersen et al.[256]), although increased risk in a subset of patients treated with purin analogs such as azathioprine has consistently been reported.[218-220] The meta-analysis of Kandiel et al. observed a SIR for lymphoma in IBD patients treated with azathioprine of about 4, based on 11 observed lymphomas versus 2.6 expected and with a significant variability in the estimated SIR between the studies.[219] Again, whether this risk was due to the medication itself or to the underlying disease severity could not be fully elucidated.

Recently there has been a particular concern regarding the rare, but aggressive hepatosplenic T-cell lymphoma (HTCL) in patients with IBD. Several cases of HTCL have been presented mainly in young male patients with Crohn's disease, treated with a combination of TNFi and azathioprine.[257] The mechanisms behind this potential association between HTCL development and the combinations of these agents remain unclear.

1.8.1.1 *TNFi and lymphoma in spondylarthritis*

The lymphoma risk associated with TNFi in patients with IBD has been difficult to quantify as most patients are also treated with other immune-modulatory agents including azathioprine. One meta-analysis including 26 studies of different study designs noted an SIR of NHL of about 3.[258] However, the majority of the patients had concomitant or previous exposure to immune-modulatory agents and in a comparison between TNFi exposed patients versus patients treated with immune-modulatory agents alone the RR was 1.7 and did not reach statistical significance. In another meta-analysis of 21 placebo-controlled clinical trials designed to evaluate the safety and efficacy of TNFi therapy for Crohn's disease, there were no differences in the frequency of malignancies between the TNFi exposed and non-exposed group.[259] However, and important to emphasize, clinical trials rarely have enough follow up time to study an outcome such as lymphoma. Nevertheless, in contrast to the more convincing evidence of lymphoma risks in association with purin analogs such as azathioprine in IBD patients, the evidence for an increased risk of TNFi *per se* seems less evident.

In contrast to IBD, patients with AS are often treated with TNFi in mono-therapy, especially AS patients with predominantly spinal disease. Because there is a seemingly non-elevated lymphoma risk in AS overall, this patient population is an ideal model for risk assessments of TNFi therapy. However, so far, data on lymphoma risk in AS and in PsA patients exposed to TNFi have been hampered by small numbers of events making risk estimation difficult. [237, 239, 260] One study, evaluating long term safety of adalimumab, observed an SIR of lymphoma in AS patients of 1.9 and a SIR of almost 6 in PsA patients.[260] Since these estimates were based on 1 lymphoma among 1,684 AS patients and 2 lymphomas among 837 PsA patients, the risk estimates were instable. Another study noted an SIR of lymphoma for AS and PsA combined of 1.9 (0.9-4.0) based on 7 lymphomas in patients with AS or PsA.[239] Thus, there is a need for more stable risk assessments in these patient populations.

1.9   MECHANISMS BEHIND CHRONIC INFLAMMMATION AND RISK OF LYMPHOMA

Proposed mechanisms behind increased lymphoma development in patients with inflammatory conditions include accumulated inflammatory activity *per se*, chronic B-cell stimulation, shared genetic susceptibility and/or environmental factors as well as a possible impact of the treatment.

As discussed in the section 1.5.4, lymphomas arise through a multistep accumulation of genetic aberrations leading to a selective growth advantage of the malignant clone. Recurrent translocations that occur during the different stages of the B-cell differentiation are initial steps of this malignant transformation and are considered necessary but not sufficient. Thus, further genetic and /or environmental stimuli are required for a full malignant transformation. Specific molecular events with a potential to transform an autoimmune B cell into a neoplastic cell remain unidentified, although some potential molecular targets have been proposed. Two such factors are the B-cell activating factor of the TNF family (BAFF) and the cytokine A proliferating-inducing ligand (APRIL). The former, BAFF, plays a vital role in the B-cell maturation and the proper elimination of auto-reactive B cells and increased levels of BAFF are expressed in sera and in inflamed tissues of several inflammatory conditions including SLE, SS and RA. Thus, mechanisms related to BAFF functions and/or levels may constitute a link between autoimmunity and lymphoma.[96, 192] Expression of APRIL is observed in connection with tumors, for example DLBCL, and has the ability to potentiate growth of malignant neoplastic cells. It is also expressed in the sera of some RA and SLE patients. A recent report from Löfström et al.[261] noted a high expression of APRIL in DLBCLs of SLE patients and in a subset of RA patients with high accumulated RA disease activity. The authors concluded that this may indicate an influence of APRIL in the lymphoma development of these particular subsets of rheumatic diseases, alternatively that the observation reflects a dysregulation of APRIL in these patient groups.

Another potentially important link between autoimmunity and lymphoma development is the chronic B-cell stimulation that occurs in the germinal centers (GC). The GC centers are histologically distinct sites within the lymph nodes where intense proliferation of the mature B cells takes place after encountering their specific antigen or T cells. Some of the NHL subtypes, such as DLBCL arise from B cells that have

mutated during the germinal center stages. Furthermore, the GC-reaction is crucial for the anti-body mediated immune responses and is thereby an important mechanism also for autoimmunity. Thus, the development of some particular lymphoma subtypes such as DLBCL in inflammatory conditions characterized by autoantibodies (RA, SLE, SS) may be a result of both the chronic B-cell stimulation and the antigenic drive during the GC reaction.[96] The autoimmune features, such as defective apoptosis may further result in an impaired T-cell immunosurveillance which could enhance a neoplastic development. There is also some evidence of a possible common genetic basis for RA and lymphoma. Recent studies have found genetic variations in the DNA regions (HLA class II) of relevance for both for the risk of RA and the risk of (follicular) lymphoma. This may suggest a possible molecular link between these diseases although this needs to be further elucidated.[111-112]

Additionally, accumulated inflammatory burden and/or disease severity seems to have an impact on the lymphoma development in the inflammatory conditions. As already discussed in previous sections, several studies have shown an association between inflammatory activity, disease severity and risk of lymphoma, particularly in RA, SLE and SS. A potential biological mechanism behind this could be that uncontrolled inflammation creates a microenvironment (for example, a different local cytokine milieu) further enhancing the chronic B-cell stimulation described above. This raises the important question whether the use of anti-inflammatory agents such as NSAIDs and glucocorticoids could reduce the risk of lymphoma and/or prevent lymphoma development in these patients. Although this remains unclear, data on cancer other than lymphoma have provided some potential leads on this subject. It has for example been suggested that the reduced risk of colorectal cancer in RA patients compared with the general population may be due to the increased use of NSAIDs.[188]

With respect to the role of immune-modulatory treatment, one could conclude that although there is no strong evidence that traditional DMARDs *per se* increase the risk of lymphoma, it still remains unclear whether therapy further can modulate the already existing lymphoma risk. Finally, even though there are no strong signals of increased lymphoma risks in RA patients treated with TNFi based on available data, it is premature to make conclusions about the risk associated with TNFi in some of the inflammatory conditions discussed.

2 AIMS

The overall aim of this thesis was to better understand the nature of the association between chronic inflammation and lymphoma development, with particular focus on the role of disease severity, inflammatory activity, and immune-modulatory treatment.

The specific aims were:

i) To assess whether patients with rheumatoid arthritis (RA) have an increased history of lymphoma or other cancer at the time of onset of RA compared with the general population.

ii) To explore whether lymphoma risk in RA remains increased in more recently diagnosed patients with RA and, if so, to further explore predictors of this risk.

iii) To evaluate the nature of a previously observed lymphoma-protective effect of glucocorticoids in RA.

iv) To assess whether the increased lymphoma risk is specific for RA or present also in patients with other chronic inflammation such as ankylosing spondylitis and psoriatic arthritis.

3 METHODS

3.1 SETTINGS

Together with the other Nordic countries, Sweden shares the advantage of access to census registers and nationwide registers on cancer, hospitalization and health care usage of almost 100% coverage. The main holders of these national registers are the National Board of Health and Welfare and Statistics Sweden.

In recent years, an additional type of register has been developed; the quality registers. These latter registers have typically been established within and by the medical profession with the main purpose to evaluate the quality of a given treatment on a group level as well as providing the clinician with individual decision support. The quality registers are increasingly used for research as well, providing more detailed information on both the diagnoses and on characteristics of each patient treated.[262] Chronic diseases, for example RA, with a long follow-up period and a need for continuous evaluation of disease progress are well suited for quality registers. Furthermore, given the dramatic changes in the treatment of inflammatory/rheumatic diseases with the introduction of biological therapies, quality registers have also emerged as an important tool in the safety evaluation of such drugs.

Since 1947 each Swedish resident is assigned a unique national registration number (NRN) used by all Swedish national registers which enables linkages across different registers.[263] The Swedish healthcare system is public and tax funded, making it geographically and financially accessible to all residents. All together, these factors create an excellent context for epidemiological research using registry data.

3.2 DATA SOURCES USED

3.2.1 National Registers

3.2.1.1 *The National Patient Register*

The National Patient Register (NPR) is population-based and consists of the Swedish Inpatient Register (also referred to as the Swedish Discharge Register) and the Outpatient Register. The NPR contains information on hospital discharges (defined as at least one overnight hospital stay) by county since 1964 and nationwide since 1987. Since 2001 nationwide data from specialist outpatient care (but not primary care) are also added to the register. Apart from NRN for each individual, the register holds information on all inpatient and outpatient visits with primary and contributory discharge diagnoses as assigned by the physician and coded accordingly to the calendar year-specific International Classification of Disease, ICD 7-10 as well as date of admission and date of discharge.

Validation studies of the Inpatient Register have shown close to 100% completeness. [264] The coverage of the Outpatient Register varies with year and specialty. For 2006 the assessed average coverage for somatic care was almost 80% (lower coverage for private surgical care, and higher for public hospital-based care).[265]

The validity of the correctness of the discharge diagnoses differs from one diagnosis to another. Validation of RA has been shown to have high diagnostic accuracy. In the study by Baecklund et al.[197], the RA diagnosis was manually validated by reviewing

the medical records of > 900 patients recorded with a diagnosis of RA in the NPR observing that more than 90% fulfilled the ACR criteria[6] for RA. With respect to AS and PsA, published data on validity is lacking. However in a pilot study of about 100 diagnosed AS patients we found a diagnostic accuracy of approximately 80% against the modified New York criteria [49] or clinically validated as AS when reviewing the medical records (Karin Hellgren, unpublished data). Among the patients not fulfilling the criteria for AS in this validation, the majority had non-inflammatory back pain (50%) or suffered from another inflammatory condition, mainly RA (20%).

3.2.1.2 The Swedish Cancer Register

The Swedish Cancer Registry was founded in 1958 and covers the whole population. It holds information on all incident cancers, classified according to the ICD system. ICD7 codes are available for all cancer cases from 1958 and the subsequent ICD8-10 codes are available for each time period respectively, such as ICD10 after 1997. For the histological type of cancer, information for the period 1993-2004 is given according to ICD-O/2 and from 2005 ICD-O/3, although the histological information is less complete than the coding of ICD 7-10.

Reporting to the register is compulsory for both clinicians and pathologists resulting in a high completeness. Approximately 99% of the cancer cases on average are morphologically verified.[266]

3.2.1.3 The Cause of Death Register

Already in the 17th century Sweden introduced a nationwide reporting system on cause of death, highlighting a long tradition of keeping records of the inhabitants.[267] Today's Cause of Death Register contains information on dates, main cause as well as contributing causes of deaths among Swedish residents since 1952. The completeness of the register is close to 100%. In 1.8% of the cases (2011)[268] death certificates are not available. However, information on these deaths is still included in the causes of death register but without any medical information.

3.2.1.4 The Register of Population and Population Changes

The Register of Population and Population Changes is maintained by Statistics Sweden and holds census data since 1961.The main information apart from NRN is current addresses of residents alive at the end of the year as well as information on dates of immigration and emigration (available since 1969).

3.2.1.5 The Prescribed Drug Register

Since 2005 (1st July) the Prescribed Drug Register provides data for all dispensed drug prescriptions to the whole population of Sweden including information on age, sex, the prescriber's profession and practice.[269] The register does not include data on drugs used in hospitals, and only partially, drugs that are used in ambulatory care but administered in day-care at hospitals. This implicates that biological therapy given as infusions in hospital or in day care units are not completely captured in the register.

3.2.2 Quality Registers

3.2.2.1 The Swedish Rheumatology Register and the Swedish Biologics Register

The SRQ is maintained by the Swedish Society of Rheumatology and was initially a clinical quality register on patients with RA. The main purpose of the register is to provide rheumatologists with a useful tool to monitor and evaluate their patients both with respect to treatment and to disease control. There are two principal components of the register. The early RA component was initiated in 1995 and includes incident cases of RA defined as < 18 months of symptom duration with RA (≥ 18 years of age, fulfilling the 1987 American Classification of ACR criteria).[6] In 1999 the register expanded by creating the Swedish Biologics Register, ARTIS. This is a register for patients with rheumatic diseases (not only RA) starting biological treatment. In recent years the register has further expanded to include RA (and other rheumatic diseases) with established disease and/or long symptom duration irrespective of treatment.

The SRQ is estimated to include about 60% of newly diagnosed RA from 2007 to 2009 (although the coverage varies with geographical area). This is based on a definition of incident RA as at least two visits with an RA diagnosis in the NPR register, with the 2nd visit within one year, no DMARDS six months before first visit with RA diagnosis and no previous visit with RA. Conversely, of the estimated 50,000 prevalent cases of RA in Sweden in 2010, approximately 50% are included in SRQ, based on a definition of prevalent RA of ≥ 2 visits with RA in the NPR (personal communication Jonas Eriksson unpublished data regarding all the figures above). Currently, about 90% of all patients with RA starting a biological agent are included in ARTIS.[262]

3.2.2.2 Information available in SRQ

At baseline, patients are entered into the register with information on diagnosis, rheumatoid factor (RF) status, number of ACR criteria fulfilled (for RA), previous treatment and disease activity (DAS28)[31]. For incident RA patients, there is also information on date of first symptom of RA and date of diagnosis of RA (i.e. inclusion in the register). The patients are then followed up at pre-specified intervals with respect to disease activity including CRP, ESR, current therapy, and the rheumatologist global assessment of disease activity. All the information is registered by the treating rheumatologist. The patients also fill in their assessment of pain and wellbeing (by using a visual analogue scale) as well as a Health Assessment Questionnaire (HAQ).

3.2.2.3 The Swedish Lymphoma Registry (SLR)

The SLR was set up in 2000 and holds information on all patients ≥16 years, diagnosed with a lymphoma in Sweden. The register contains information on date of diagnosis and subtype of lymphoma. Data are presented in national reports on a regular basis.[78] Compared with the Swedish Cancer Register, the SLR holds more information on lymphoma subtypes according to the WHO classification.[73] The coverage of SLR is approximately 95% of all lymphomas registered in the Swedish Cancer Register.

3.3 STUDY DESIGNS AND STUDY POPULATION

3.3.1 Study I

This study comprises two parts; first we assessed the risk of a history of lymphoma and other cancers *before* RA diagnosis, employing a *case-control design* treating the RA patients as cases and their population comparator subjects as controls. Second we estimated the risk of lymphoma, and other cancers, in relation to time since RA diagnosis employing a matched *cohort design* treating RA patients as the exposed cohort and their comparator subjects as the unexposed cohort (Figure 1).

3.3.1.1 Exposure definition

Through the SRQ we identified a cohort of patients with incident RA (symptom duration < 12 months) from 1997 through 2006 (n=6,745). Each RA patient was individually matched to five population comparator subjects (n=33,657) by linkage to the Swedish Register of Population and Population Changes. Matching variables were gender, year of birth, county of residence and marital status. The comparator subjects had to be alive at the time of the diagnosis of their corresponding RA case.

3.3.1.2 Outcome

By linkage of all RA cases and their comparators subjects to the Swedish Cancer Register between 1958 through 2006, we identified all registered cases of lymphoma and other cancers and their date of diagnosis *before* and *after* the diagnosis of RA. Malignant lymphomas were defined as non-Hodgkin lymphoma (NHL) including chronic lymphocytic leukemia (CLL), and Hodgkin lymphoma (ICD7= 200, 201, 202, 204.1). In the analyses of all other cancers, malignant lymphomas were excluded. Censoring dates for deaths and emigrations were obtained from the Cause of Death Register and the Register of Population and Population Changes respectively.

Figure 1 - Schematic picture of study design in study I.
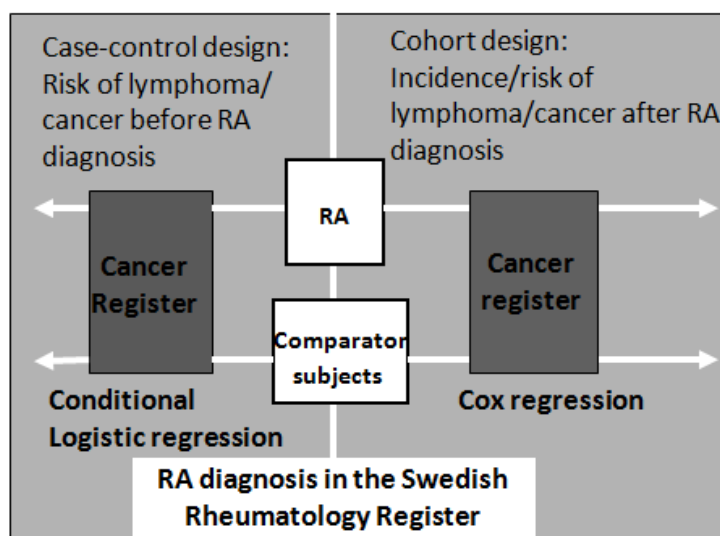
3.3.2 Study II

In this population-based cohort study we assessed whether lymphoma risk remains increased in more recently diagnosed RA, and further explored the determinants of this risk. We also evaluated whether the distribution of lymphoma subtypes among these RA lymphomas is different from the one reported in historical RA cohorts or has changed compared with the distribution that was observed in historical RA cohorts.

3.3.2.1 Exposure definition

Using data from the SRQ we identified a cohort of patients with incident RA (symptom duration ≤ 13 months) from 1997 through 2010 (n=10,367).
By linkage to the Swedish Register of Population and Population Changes each RA patients was matched to five population comparator subjects with respect to gender, year of birth and county of residence (n=49,825). Information on inflammatory activity (DAS28) was abstracted from visit data in SRQ at; **i)** baseline, **ii)** after one year, and **iii)** as a composite measure of DAS28 values during the first year following diagnosis. The composite measure was based on the lowest value of DAS28 at three different time points; **i)** 3 months (encompassing 30 to 150 days), **ii)** 6 months (150 to 270 days), and **iii)** one year (270 to 450 days) post-inclusion. The median number of visits during the 1st year of follow-up in SRQ was 4 (q1-q3=3-4).

Information on therapy with respect to DMARDs and oral glucocorticoids during the first year following RA diagnosis and treatment with TNFi any time during the study period was also abstracted from the SRQ.

3.3.2.2 Outcome

As in study I, lymphomas were identified by linkage to the Swedish Cancer Register 1997-2010. The definition of malignant lymphoma was similar to that of study I. For the identified RA lymphomas (n=45), the pathology reports were collected to enable categorization into lymphoma subtypes. When the initial lymphoma diagnosis had not been confirmed by a hematopathologist and/or not diagnosed according to the WHO classification,[73] the paraffin-embedded lymphoma tissues were reviewed and classified according to the WHO classification by an experienced haematopathologist. This review process was performed in 40 lymphoma cases out of all 45 RA-lymphomas. To compare the distribution of lymphoma subtypes in RA patients with the one in the general population, we used the SLR as reference population.[78]

Subjects with malignant lymphomas occurring before start of follow-up were excluded (24 RA patients and 196 comparator subjects). Information on deaths and emigration was assembled in a similar manner as in study I.

3.3.2.3 Analyses of lymphoma tissue

The nationwide Cancer Register contains information about date of diagnosis, the reporting pathology laboratory as well as a consecutive specimen code number for each diagnosed neoplasm. By using this data, the pathology report and the original slides and paraffin-embedded lymphoma tissue were identified and collected. One

experienced hematopathologist blinded to all clinical information confirmed the lymphoma diagnosis. To review and classify the lymphoma subtypes according to the WHO classification,[73] additional sections from the original slides were cut and routine immunohistochemistry (IH) staining was performed by using panels of antibodies against different antigens (Figure 2).The entire process was performed at the Department of Immunology, Genetics and pathology at Uppsala University. Similar processes have been applied in other studies.[197, 261, 270]

The IH staining was performed in Ventana XT BM module (Ventana medical systems, Tucson, AZ).

Figure 2 - Process of the validation of lymphoma diagnosis including subtype applied in study II, III and IV.
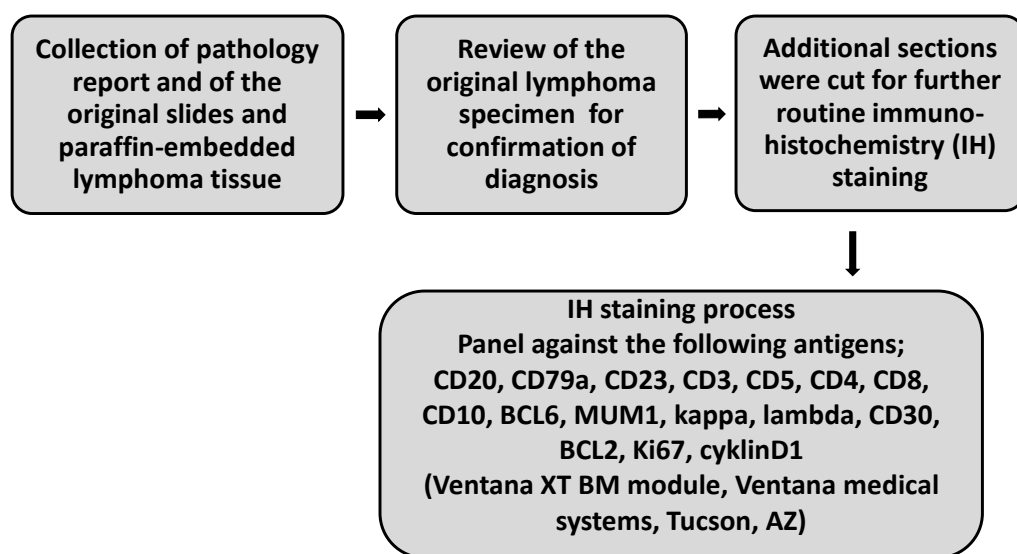
3.3.3 Study III

In this population-based matched case-control study, we sought to further characterize the nature of the association between glucocorticoid treatment and risk of lymphoma in RA.

3.3.3.1 Definition of Cases and Controls

From the NPR (for this study the inpatient register) we identified 74,651 patients with ≥ 1 hospital discharge diagnosis of RA from 1964 through 1994. Through linkage of this entire cohort to Swedish Cancer Register from 1964 through 1995, we identified 424 RA patients who were diagnosed with a malignant lymphoma after the first hospitalization listing RA. From the same underlying cohort we randomly selected three RA patients as potential controls, matched for gender, year of birth, year of first RA-discharge, and county of residence. Among these potential controls the first of the three controls whose medical record could be identified and who fulfilled the ACR criteria [6] for RA was included. The controls had to be alive and lymphoma-free at the diagnosis of their index case. Medical records of cases and controls were reviewed to confirm the RA diagnosis and the lymphoma specimen

were validated, reviewed and (re)classified according to the WHO classification,[73] using the same validation process as described in Figure 2.

After exclusion of cases/controls not fulfilling the inclusion criteria (Figure 3) the final study consisted of 378 RA cases and 378 matched controls.

Figure 3 - Schematic description of case identification in Study III.

424 potential RA-cases with lymphoma

| Not RA n=27 | **Lymphoma diagnosis could not be confirmed n=8** |

| **Medical records not identified n=11** | **Reclassification of lymphoma not possible n=35** |

378 RA cases with lymphoma   **343 RA cases with reclassified lymphomas**
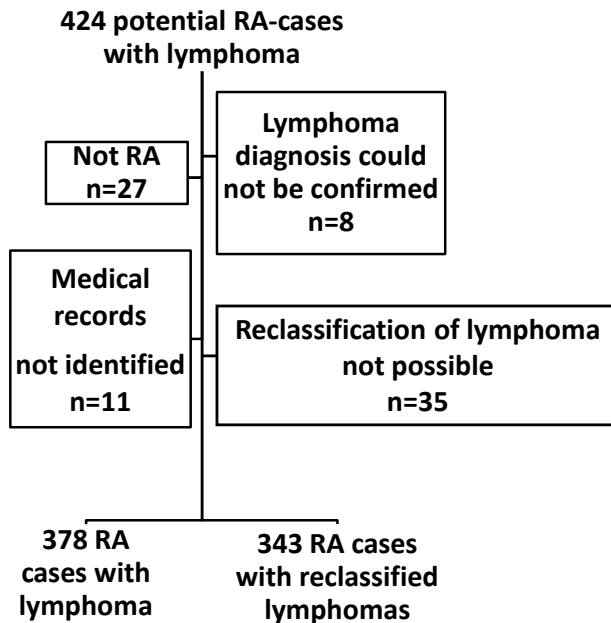
3.3.3.2 Exposure information

Medical records of all hospital stays and all out-patient care were collected. Information on disease characteristics and treatment was abstracted by one of the co-authors (EB) from each individual's medical records, blinded for the case/control status. Controls were followed from onset of RA until the diagnosis of lymphoma of the corresponding case. To assess RA disease activity, we abstracted information on swollen and tender joint counts, ESR and physicians' global assessments as recorded in the medical files. Based on these variables, RA disease activity was scored as inactive, low, medium, or high. Cumulative disease activity for the whole RA period was calculated as the area under the curve (AUC) for the duration in months of the four different levels of disease activity.

Oral treatment was defined as four or more consecutive weeks on a specified drug. The duration of treatment was assessed in months. Treatment with intra-articular glucocorticoids was recorded if ever used and further categorized into two groups; **i)** those who received intra-articular glucocorticoids within one month of onset of arthritis in more than 50% of documented flares and **ii)** the remaining patients i.e. those who, in more than 50% of documented flares had more than one month between arthritis onset and any glucocorticoid injection. Flare was defined as ≥ one inflamed joint confirmed at a physical examination and documented in the medical record.

3.3.3.3   Outcome

The malignant lymphomas were identified and defined in a similar manner as in studies I and II (Figure 2) although CLL was not included. Epstein-Barr virus was search for using EBV-encoded RNA (EBER) *in situ* hybridization. The lymphomas were divided into different stages according to the Ann Arbor classification[83-84] by the information available in the medical records.

3.3.4   Study IV

In this population-based cohort study we assessed the risk of lymphoma in ankylosing spondylitis (AS) and psoriatic arthritis (PsA). We also assessed the overall association between TNFi therapy and lymphoma risk in AS and PsA.

3.3.4.1   Exposure definition

From the NPR (for this study the outpatient register) we identified all individuals with one or more outpatient visit at a rheumatology or internal medicine department from 2001 through 2010, with a diagnosis code for AS (ICD10=M45) or PsA (ICD10=M07.0-3, L40.5). Patients with these codes or the corresponding codes for juvenile disease (M08 and M09) before 18 years of age were excluded. In total, we identified 8,707 patients with AS and 19,283 patients with PsA. Each individual was matched to five population comparator subjects with respect to gender, year of birth and county of residence.

By linkage to the Swedish Prescribed Drug Register we collected information on prescriptions of DMARDs and oral glucocorticoids from 2005 and onwards. Treatment was defined as DMARDs (either of MTX and/or sulfasalazine) or oral glucocorticoids. To be defined as treated we required ≥ 2 prescriptions *within* 6 months as registered in the Prescribed Drug Register. From ARTIS we collected information on start on TNFi during the study period resulting in 1,908 patients with AS (22% of all identified AS patients) and 2,605 patients with PsA (13% of all identified PsA patients) starting their first TNFi 2001-2010.

3.3.4.2   Outcome

The malignant lymphomas were identified and defined in a similar manner as in studies I and II. By using available ICD10 diagnosis codes as registered in the Cancer Register, we further divided the NHLs into subtypes according to the WHO classification.[73] As in the above studies, we assembled information on deaths and emigration in a similar manner as in studies I and II. For lymphomas occurring in patients with AS or PsA treated with TNFi, the lymphoma specimen were collected, reviewed and (re)classified according to the WHO classification using the same validation process as described in Figure 2.

Studies I, II and IV were approved by the Ethics Committee at Karolinska Institutet and study III was approved by the Ethics Committee at Uppsala University.

3.4   STASTISTICAL ANALYSES

3.4.1   Statistical concepts

3.4.1.1   Logistic regression models

Logistic regression is a method for determining the relationship between explanatory (or independent) variables of any kind (continuous, dichotomous or categorical) and a dichotomous (for example RA yes/no) coded dependent variable. The method is often applied in case-control studies. To assess the influence of an explanatory variable on the dependent variable, the odds ratio (OR) is estimated. An OR can be defined as the ratio of the odds of an event occurring in one group to the odds of it occurring in another group. Thus, being a ratio of a ratio, the OR is different from RR (being a ratio of a risk). However OR provides an acceptable approximation for RR when disease incidence is rare (a rule of thumb is a disease prevalence of <10%) the so-called "rare disease assumption". For more common outcomes, the odds ratio overstates the relative risk, sometimes dramatically.

There are two main groups of logistic regression: conditional and unconditional logistic regression. Conditional logistic regression is used if matching of cases to controls has been performed, and unconditional if there has been no matching. When conditional logistic regression is used, the matched pairs are compared to each other. In unconditional logistic regression all cases are compared to all controls.

3.4.1.2   Cox proportional hazard models

Cox regression (or proportional hazards regression) is a method for investigating the effect of several variables upon the time that passes before some specified event occurs. The method is applied in cohort studies. A typical medical example would include covariates such as treatment assignment, as well as patient characteristics such as age, gender, and co-morbidities in order to control for confounding. The Cox regression estimates the hazard ratio (HR) which can be defined as the ratio of the number of new cases of a disease per population at risk per unit time comparing exposed to unexposed. A key assumption of the Cox regression model is the proportional hazard assumption. This means that the survival curves for two strata must have hazard functions that are proportional over time (i.e. constant relative hazard).

3.4.2   Statistical analyses used

In studies I-III we used Cox' proportional hazard model to estimate the hazard ratios expressed as relative risks and to calculate 95% confidence intervals (CI). To test for the proportional hazard assumption we introduced an interaction term between the exposure and the log of follow-up time. In studies I and IV we used conditional logistic regression. Odds ratios were calculated, expressed as RRs with 95% CI. The matching variables were included in all models used. To estimate whether there was a difference between the estimated RRs in the different calendar periods of RA duration in studies I and II we performed a Wald test.

All analyses were performed using the SAS software package, Version 9, SAS institute, Cary, North Carolina, USA.

3.4.2.1 Study I

To assess the risk of having a lymphoma or cancer overall *before* the diagnosis of RA, a first primary lymphoma or other cancer respectively was considered the exposure. All cases of lymphoma or other cancers occurring within 90 days after RA diagnosis (i.e. inclusion in the SRQ) were included in the analysis as these cases were considered as prevalent rather than incident.

To assess the risk of having a lymphoma or cancer overall, in relation *to time since* RA diagnosis, the RA patients were considered as the exposed cohort and the comparator cohort as the unexposed cohort. Time since diagnosis of RA (defined as inclusion date in the SRQ) was used as time-scale. To assess for the risk of lymphoma in relation to time since RA (0-<3, 3-<6 and 6-10 years), we used time-dependent covariates. Patients with a history of a lymphoma or other cancer at the time of the RA diagnosis were excluded.

3.4.2.2 Study II

In study II, RA was the exposure of interest and lymphoma was the outcome. To assess whether lymphoma risk in RA had changed over calendar period of disease onset, we assessed the role of duration of RA (0-<6, 6-14 years) as a function of calendar period (1997-2003, 2004-2010) by using time-dependent covariates. Each cohort member contributed time as person-years from start of follow-up (diagnosis of RA) until lymphoma, death, emigration or end of follow up (31th December 2010) which came first. To avoid that an underlying lymphoma was misclassified as an incident RA, we excluded all person-time and all events during the first 90 days of follow-up.

In the assessments of lymphoma risk in relation to inflammatory activity, DMARDs and oral glucocorticoids during 1st year following RA diagnosis, all person-time and all events with less than one year of follow up were excluded (9,533 RA patients, 41 lymphomas). When estimating lymphoma risk in relation to TNFi, we treated TNFi as a time-varying covariate so that patients contributed to the TNFi-naïve group until start of their first TNFi and to the TNFi exposed group thereafter. In all the treatment analyses we additionally adjusted for inflammatory activity during the 1st year of follow up.

When estimating RRs for subtypes of lymphoma, we used the ICD10 codes as registered in the Swedish Cancer Register. The rationale for this was that through SLR, we only had access to the overall rather than age-specific distributions of subtypes and because the age in SLR was younger that the age in our RA cohort.

3.4.2.3 Study III

The exposure of interest was therapy with glucocorticoids in RA patients in relation to lymphoma risk. The association was assessed overall, adjusted and stratified by the AUC of cumulative disease activity (in quartiles of AUC) and DMARD use (never/ever). We also assessed duration of steroid treatment (more or less than 2 years), timing of first steroid treatment (more or less than five years of RA duration), mode of administration, and intra-articular treatment type (**i** or **ii**, as described in section *3.3.3.2*).

3.4.2.4 Study IV

Main exposures of interest were AS/PsA, and TNFi. The outcome of interest was lymphoma. In all analyses, we excluded all person time and all events during the first 90 days of follow-up in order to exclude underlying lymphomas misclassified as AS or PsA (constituting the reason for the visits that lead to inclusion into the cohorts under study).

Analyses were additionally performed using a stricter definition of the AS/PsA study population, requiring ≥ 2 outpatient visits with AS and PsA, respectively. To further limit the risk of AS/PsA misclassification, the analyses were also performed excluding all patients ever recorded with an RA diagnosis as registered in the outpatient register. Start of follow up was the date of the first outpatient visit for AS and PsA patients and the corresponding date for their comparator subjects until the first of lymphoma, death, emigration or end of follow up (31th December 2010).

When assessing the risk in relation to anti-rheumatic treatment (other than TNFi), start of follow up was defined as date of the 2nd recorded prescription (from the Prescribed Drug Register) of each drug for the AS and PsA patients (and corresponding date for the comparator subjects). The crude incidences of lymphoma in AS and PsA patients exposed to TNFi therapy were calculated counting time from the start of the first TNFi until the first of; lymphoma diagnosis, death, emigration or end of follow-up (31st December 2010). Due to small numbers of events (<5) we abstained from assessing relative risks.

4 RESULTS

4.1 STUDY I

Risk of lymphoma and cancer overall before diagnosis of RA

Twelve of the RA patients (0.2%) and 89 (0.3% of all comparator subjects) had a history of a malignant lymphoma, resulting in a RR of 0.7 (95% CI 0.4-1.2).

At the time of RA diagnosis, 356 (5.3%) of the RA patients and 2,240 (6.6%) of the general population subjects had a history of *any* other first primary cancer, corresponding to an RR of 0.8 (95% CI 0.7-0.9). RRs for both lymphoma and cancer overall remained virtually similar in stratified analyses according to gender, RF status, age at RA diagnosis, year of RA diagnosis, and time period between lymphoma/cancer diagnosis and RA diagnosis. There was a significantly reduced risk of a history of malignant melanoma and a non-significant reduced risk of lung and breast cancer in the RA patients. A history of colorectal, non-melanoma skin and prostate cancer was equally common among RA patients and their population controls (Table 7).

Table 7 - Relative risk of a history of cancer overall and site-specific malignancies, before the diagnosis of RA in an incident RA cohort (n= 6,745) compared with their matched comparator subjects (n=33,657) 1997-2006.

	RA patients n=6,745	Population controls n=33,657	RR (95% CI)
Cancer overall [1]	356	2,240	0.8 (0.7-0.9)
Breast cancer	95	587	0.8 (0.6-1.0)
Prostate cancer	45	273	0.8 (0.6-1.3)
Colorectal cancer	40	237	0.8 (0.6-1.2)
Malignant melanoma	15	149	0.5 (0.3-0.8)
Non-melanoma skin cancer	14	89	0.8 (0.4-1.4)
Malignant lymphoma	12	89	0.7 (0.4-1.2)
Lung cancer	3	46	0.3 (0.1-1.0)

[1]Not including malignant lymphoma

Risk of lymphoma and cancer overall after diagnosis of RA

After RA diagnosis, 19 lymphomas (crude incidence 65 [95% CI 39-101] per 100,000 person-years) occurred among the 6,720 RA patients compared with 53 lymphomas (crude incidence 37 [95% CI 27-48] per 100,000 person-years) among the 33,063 comparator subjects. The RR of lymphoma was 1.8 (95% CI 1.0-3.0).

There was a suggestive trend of increasing RRs during the first 10 years after diagnosis of RA that was not statistically significant (p =0.15, Figure 4)

Counting from RA diagnosis, 302 of the RA patients, and 1,205 of the comparator subjects were diagnosed with any other first primary cancer (excluding lymphoma), corresponding to a RR of 1.2 (95% CI 1.1-1.4). The overall 20% increased risk was driven by an elevated risk within the first years after RA diagnosis, mainly due to elevated risks for prostate and lung cancer (Figure 4).

Figure 4 - Relative risks of lymphoma and cancer overall as a function of time (years) before and after diagnosis of RA.
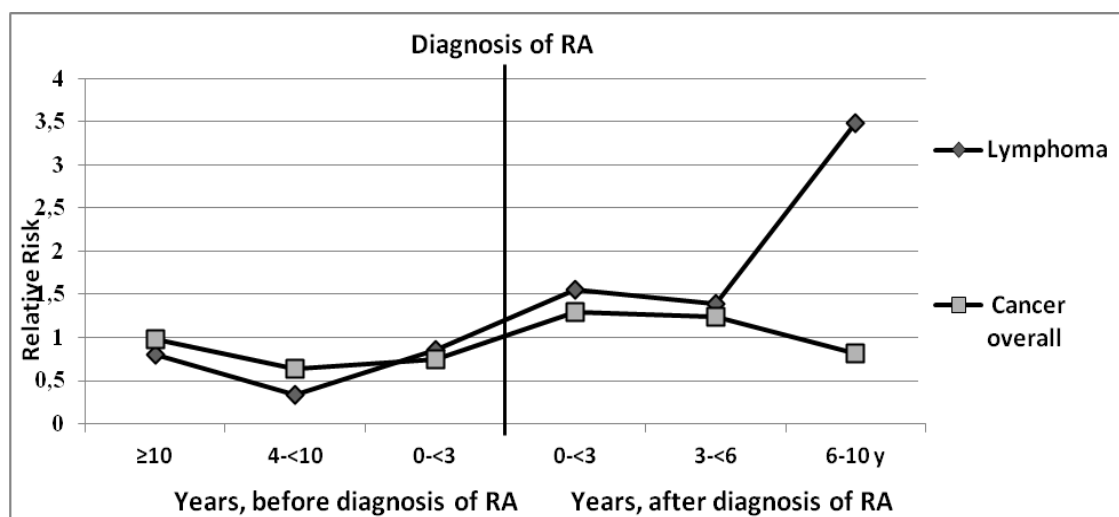
4.2   STUDY II

We identified 45 lymphomas among the RA patients (n=10,367) and 126 lymphomas among the comparator subjects (n=49,825).

Risk of lymphoma in RA patients with respect to disease duration and year of RA onset

Among the RA patients, the crude incidence of lymphoma was 76 [95% CI 56-102] per 100,000 person-years compared with 44 [95% CI 37-34] per 100,000 person-years in the comparator subjects resulting in an RR of lymphoma of 1.7 (95 % CI 1.2-2.4). The point estimate of relative risk of lymphoma was numerically higher 6-14 years after RA onset than during the first 6 years, although the difference did not attain statistical significance (p=0.12). When calendar period of RA diagnosis was added to the model (in one-year bands) no effect of this parameter was observed (p for calendar

period=0.5). A similar pattern was observed when RRs were cross-tabulated according to year of onset and time since RA diagnosis (Table 8).

Table 8 - Relative risks of malignant lymphoma in an incident RA cohort (=10.367) compared with individually matched comparator subjects (=49,825) 1997-2010 with respect to time since RA duration overall, and year of RA onset.

Year of RA diagnosis[1]	Time period since RA diagnosis (years) RR (95% CI) (N lymphomas RA patients/ comparator subjects)		Total follow-up period RR (95% CI)
	0-<6	6-14	
1997-2003	1.3 (0.8-2.3) (14/49)	2.4 (1.4-4.3) (17/32)	1.8 (1.2-2.8) (31/81)
2004-2010	1.5 (0.9-2.8) (13/42)	(1/3)[2]	1.5 (0.8-2.7) (14/45)
Total study period 1997-2010 RR (95% CI)	1.3 (0.9-2.1) (27/91)	2.8 (1.7-4.7) (18/35)	1.7 (1.2 -2.4) (45/126)

[1]Year of inclusion in SRQ [2]We abstained from assessing RR due to small number of events.

Risk of lymphoma in relation to disease characteristics and inflammatory activity
When we estimated the lymphoma risk in mutually exclusive groups of accumulated inflammatory activity (DAS28) during the first year following RA diagnosis we observed a tendency (however non-significant) towards higher risks in the group of patients having a DAS28≥ 3.2 at start and at all the follow-up visits registered in the SRQ during 1st year in comparison to those with a DAS28 at all available visits during the 1st year < 3.2 (with the remainder of the RA cohort as reference group, Table 9).

Risk of lymphoma in relation to anti-rheumatic therapy
Twenty-three out of 41 (56%) of the RA-lymphomas had been treated with MTX during the first year of follow up compared with 6,370 (67%) of the entire RA cohort, resulting in an RR of lymphoma of 0.8 (95% CI 0.4-1.6). On the contrary, treatment with oral glucocorticoids in the first year following RA diagnosis was associated with a non-significant decreased risk of lymphoma; RR= 0.6 (95% CI 0.3-1.0) based on 20 (49%) of the RA lymphomas being treated oral glucocorticoids compared with 6,149 (65%) of the RA cohort as a whole.

Six out of 45 RA lymphomas (13%) had been treated with TNFi anytime during the study period compared to 2,314 (22%) of the entire RA cohort. This yielded an RR of 1.1 (95% CI 0.5-2.8) compared with TNFi-naïve RA patients. Adjusting for inflammatory activity did not appreciably change the results in any of the above analyses (Table 9).

Table 9 - Relative risks of lymphoma in incident RA patients (n=9,533) 1997-2010 with respect to inflammatory activity, use of methotrexate or oral glucocorticoids during first year following RA diagnosis and exposure to TNFi any time during follow- up compared with all other RA patients.

Inflammatory activity during first year following RA diagnosis	N of lymphomas (%) Total = 41	N of RA patients (%) Total =9,533	RR (95% CI)
DAS28≥3.2 at every measure point	9 (22)	1,210 (13)	1.9 (0.9-4.1)
DAS28<3.2 at every measure point	7 (17)	1,311 (14)	1.3 (0.5-2.9)
Remaining group of the RA cohort	25 (61)	7,012 (73)	1 (ref)
Anti-rheumatic therapy during first year following RA diagnosis			
Methotrexate (yes vs. no) during first year following RA diagnosis	23(56)	6,370 (66)	0.8 (0.4-1.6)
Oral glucocorticoids (yes vs. no) during first year following RA diagnosis	20 (49)	6,149 (65)	0.6 (0.3-1.0)
TNFi during follow-up (yes vs.no, time-dependent)[1]	6 (13)	2,314 (22)	1.1 (0.5-2.8)

[1]This analysis was based on the entire RA cohort (=10,367), number of lymphomas=45

Distribution of lymphoma subtypes in patients with contemporary RA
Chronic lymphocytic leukemias comprised a considerably smaller proportion (4%) of all lymphomas in our RA cohort compared with the SLR (24%). However, comparing the incidence to that of the comparator subjects, the decreased risk was not statistically significant; RR for CLL= 0.4 (95% CI 0.1-1.5). Hodgkin lymphomas were more common in the RA cohort (19%) versus SLR (10%) and the historical RA cohort (6%) corresponding to an RR of 6.4 (95% CI 2.2-18) compared with the comparator subjects. The proportion of DLBCLs was 37% compared with 32% in the SLR, both of which were lower than the corresponding proportion in the historical RA cohort (48%).

4.3   STUDY III

Oral glucocorticoid treatment
Of the 373 cases (missing information on glucocorticoids in 5 cases), 183 (49%) subjects and of the 378 controls 217 (57%) subjects had been treated with oral glucocorticoids. The mean duration of RA until lymphoma diagnosis for cases treated with oral glucocorticoids was similar to those who were not treated (treated: 21 years, range 2-54 years, not treated: 19 years, range 1-55 years). Overall treatment with oral glucocorticoids was associated with an RR of lymphoma of 0.6 (95% CI 0.4-0.9) adjusted for DMARD treatment and disease activity as previously reported.[197]

A total duration of oral glucocorticoid treatment less than 2 years was not associated with lymphoma risk (RR=0.9; 95% CI 0.5-1.5), whereas total treatment longer than two

years was associated with a lower lymphoma risk (RR= 0.4; 95% CI 0.3-0.7). The RR of lymphoma was similarly reduced in the group of patients starting oral glucocorticoids within the first 5 years after diagnosis of RA compared with the group of patients starting treatment later in their RA course (RR in both groups = 0.6; 95% CI 0.4-1.0, adjusted for disease activity and DMARD therapy).

Oral glucocorticoid treatment in relation to disease activity
Within each quartile of cumulative RA disease activity, steroid treatment was associated with a lower lymphoma risk. For instance, oral steroid treatment in the highest quartile of disease activity was associated with an RR of 12 (95% CI 5.0-28), compared to an RR of 30 (95% CI 11-76) for the same quartile of disease activity but in the absence of oral steroid treatment.

Oral glucocorticoid treatment in relation to lymphoma characteristics
In the analyses by lymphoma subtype we noted a significantly reduced risk of DLBCL (crude RR=0.6; 95% CI 0.4-0.9) and a non-significantly reduced risk of follicular lymphoma (crude RR=0.7; CI 95% 0.2-2.3) following treatment with oral glucocorticoids, whereas the crude RR for all other subtypes combined was 0.8 (95% CI 0.5-1.3). At the time of lymphoma diagnosis, 84 (22%) of the cases and 125 (26%) of the controls were treated with oral glucocorticoids. The symptoms leading to lymphoma diagnosis, as well as the occurrence of B-symptoms (fever, weight loss, night sweats) were similar for cases on glucocorticoids and not on glucocorticoids, respectively, at the time of lymphoma diagnosis.

Intra-articular glucocorticoids
Overall, treatment with intra-articular glucocorticoids was associated with a decreased lymphoma risk; RR= 0.4 (95% CI 0.2-0.6), adjusted for DMARDs and disease activity. However, this risk reduction was restricted to those patients who received intra-articular glucocorticoids within one month of onset of arthritis in more than 50% of documented flares (group **i**), RR= 0.2 (95% CI 0.1-0.4), whereas the RA patients in group **ii** (i.e. those patients who received intra-articular glucocorticoids after more than one month's delay in more than 50% of reported flares had a RR of lymphoma of 2.6 (95% 1.1-6.2).

4.4   STUDY IV

We identified 14 lymphomas among the AS patients (n=8,707) and 75 lymphomas among the comparator subjects (n=41,092). For PsA we found 45 lymphomas among the patients (n=19,283) and 175 lymphomas among the comparator subjects (n=92,684).

Risk of lymphoma in relation to the general population
The RR of lymphoma in AS patients compared with the comparator subjects was 0.9 (95% CI 0.5-1.6). Excluding all patients ever recorded with a diagnosis code of RA (12% of all AS patients) resulted in a virtually unchanged relative risk. For the patients with PsA, RR of lymphoma was 1.2 (95% CI 0.9-1.7). Excluding all patients ever recorded with a diagnosis code of RA (17% of all PsA patients) yielded an RR of 1.0 (95 % CI 0.6-1.4). Applying a stricter case definition (i.e. demanding ≥ outpatient visits with AS or PsA) resulted in an RR of lymphoma of 0.9 (95% CI 0.5-1.6) for AS and an RR of

1.3 (95% CI 0.9-1.9) for PsA. Subset analyses by gender, age, calendar period and duration of time between start of follow-up until lymphoma diagnosis resulted in RRs largely similar to the overall RR both in AS and in PsA.

Risk of lymphoma in relation to DMARD therapy
Analyses restricted to AS patients who were treated with DMARDs did not reveal any significantly different RRs compared to the overall risk. On the contrary, for the PsA patients, treatment with MTX and/or sulfasalazine was associated with a significantly increased risk of lymphoma compared with the comparator subjects (Table 10). When excluding patients ever recorded with a RA diagnosis code, we observed similar results; RR for DMARDS=1.9 (95% CI 1.1-3.7). Use of oral glucocorticoids was not associated with any increase occurrence of lymphoma neither in AS nor in PsA (Table 10).

Table 10 - Relative risks and crude incidences of lymphoma in the Swedish cohort of AS (n=6,415) and PsA (n=14,088) patients compared with their comparators subjects with respect to anti-rheumatic treatment 2001-2010.

	AS N of lymphomas (N of patients treated)	RR (95% CI)	PsA N of lymphomas (N of patients treated)	RR (95% CI)
Overall	12 (6,415)	0.9 (0.5-1.6)	37 (14,088)	1.3 (0.9-1.9)
DMARDs [1,2]	3 (2,144)	1.2 (0.3-4.3)	15 (7,648)	1.7 (1.0-3.1)
Oral glucocorticoids[1]	0 (1,177)	-	3 (4.082)	0.6 (0.2-2.0)
		Crude incidence/ 100,000 person- years		**Crude incidence/ 100,000 person- years**
Overall	11/6,415	28 (14-50)	37/14,088	44 (31-61)
TNFi	2/1,752	28 (3-102)	5/2,343	52 (17-122)
TNFi -naïve	9/6,146	27 (12-52)	32/13,918	43 (29-61)

All analyses are based on a stricter case exposure definition, i.e. requiring two or more outpatient specialist visits with AS or PsA respectively [1]Treatment defined as ≥ two prescriptions of the drug within 6 months registered in the Prescribed Drug Register 2005-2010. [2]Defined as treatment with either methotrexate and/or sulfasalazine.

Incidence of lymphoma in relation to TNFi therapy
Among the TNFi treated AS patients 2 lymphomas occurred (crude incidence 25 [95% CI 3-93] per 100,000 person-years) compared with 12 lymphomas (crude incidence 27 [95% CI 14-48] per 100,000 person-years) among non-TNFi treated AS patients. Applying a stricter AS-case definition (Table 10) did not change the crude incidence. In both of the 2 AS lymphomas the AS *and* the lymphoma diagnoses could be confirmed from the medical records and from the pathology reports.

For the TNFi treated PsA patients, we observed 8 lymphomas (crude incidence 73 [95% CI 34-144] per 100,000 person-years) compared with 37 lymphomas (crude incidence 37 [95% CI 26-52] per 100,000 person-years) in the comparator subjects. In a second approach, in which we applied a stricter case definition of PsA (i.e. requiring at least 2 outpatient visits with PsA), the crude incidence in the subset treated with TNFi was 52 [95% CI 17-122] per 100,000 person-years (Table 10). However, validation using medical records revealed that 3 out of the original 8 PsA lymphoma patients actually fulfilled the ACR classification criteria [6] for RA *and* were clinically evaluated as RA patients, and thus misclassified as PsA patients in the National Patient Register. In a third approach, we excluded these 3 PsA lymphoma cases from the original numerator and estimated the crude incidence based on all TNFi-treated PsA patients who also had a PsA diagnosis in SRQ (denominator, n=1,987). We then observed a crude incidence of lymphoma of 64 [95% CI 21-151] per 100,000 person-years. Finally, the revalidation of the lymphoma specimens of the remaining 5 PsA lymphoma cases revealed that one of these patients did not have a lymphoma diagnosis. When this patient was excluded from the analysis, this resulted in a lymphoma incidence rate of 52 [95% CI 14-131] per 100,000 person-years.

Distribution of lymphoma subtypes

When categorizing the observed lymphomas into different subtypes according to ICD10 diagnoses registered in the cancer register, we did not find any increased proportion of any specific subtype; apart from a slightly higher proportion of DLBCLs in the AS patients compared with their comparator subjects (based on small numbers in each subgroup of lymphoma). There was no increased proportion of T-cell lymphoma in PsA patients compared with the general population (Table 11).

Table 11 - Distribution of lymphoma subtypes in AS and PsA patients compared with their comparator subjects 2001-2010.

Lymphoma subtypes[1]	AS patients lymphoma N =14 N of lymphomas (%)	General population lymphoma N=75	PsA patients lymphoma N=45	General population lymphoma N=175
B cell				
DLBCL	7 (50)	22 (29)	19(42)	59 (34)
Follicular lymphoma	0 (0)	11 (15)	3 (7)	24 (14)
Other B cell	1 (7)	7 (9)	5 (11)	19 (11)
T cell	1 (7)	3 (4)	1(2)	9 (5)
NHL unspecified	0(0)	6(8)	7 (16)	13 (7)
HL	0(0)	6(8)	5 (11)	5 (3)
CLL	4(29)	20(27)	5(11)	44 (25)
Lymphoma UNS	1(7)	0 (0)	0 (0)	2 (1)

[1]Lymphoma subtype as registered according to ICD10 codes in the Swedish cancer register
DLBCL= Diffuse large B-cell lymphoma, NHL= non-Hodgkin lymphoma, HL= Hodgkin lymphoma, CLL= chronic lymphocytic leukemia

5 GENERAL DISCUSSION

5.1 METHODOLOGICAL ISSUES

5.1.1 Study Design

Choosing the appropriate study design is a give- and-take between validity (whether the study is able to answer the question it is intended to answer) and efficiency. The gold standard for analytic studies is an experimental design. However, for many research questions, an experimental study is considered unethical (such as to expose participants deliberately to a potentially harmful exposure) or inappropriate for other reasons. Thus, in many cases an observational study design is the best or the only choice. Two observational designs commonly used in epidemiology (and in this thesis) are cohort and case-control study designs.

In cohort studies, participants are defined on the basis of a particular exposure. Cohort studies can be prospective (participants are included before or at the time of exposure) or retrospective (the study begins after the exposure). However, also in retrospective designs, information bias (such as recall bias) can be minimized as long as the exposure information is recorded in a prospective manner *and* registered independently of the outcome (this is often the case in register based studies such as the studies in this thesis).

Cohort studies are well-suited to examine disease after rare exposures and to study how the effect of an exposure changes over time. They also allow for the estimation and comparison of incidence rates and allow measures of the absolute risk of developing a disease after an exposure. The design may however require a large number of participants and a sufficiently long period of follow-up time when only a small proportion of the participants at risk actually develops the outcome. This can make them expensive and time-consuming. Loss of follow-up may also be a problem. Here, register-based retrospective cohort studies provide an advantage.

In case-control studies, participants are included on the basis of whether they have developed the disease of interest or not. Exposure is compared between those with the disease (cases) and without (controls) to assess whether an association exists. As in cohort studies, exposure information can be recorded prospectively which is preferable both to minimize recall bias and to ensure that case status and exposure is independent of one another. The major weakness of a case-control study is a proper selection of cases and controls and to avoid bias in assessment of the exposure. Case-control studies have the advantages of being cost-efficient as the number of participants can be smaller. They are well-suited for studying rare diseases, and because entrance into a case-control study is based on disease status, they can examine the association between multiple exposures and the disease of interest. However, they do not allow estimations of multiple diseases associated with one exposure. Furthermore, the data collected in a case-control study cannot be used to calculate the incidence rates, nor absolute risks for disease due to an exposure unless the underlying cohort is known or the exposure prevalence can be estimated.

Studies I, II and IV are cohort studies, with prospectively recorded exposure information, independently from the outcome of interest. In studies I and II, the exposure information was collected from the SRQ, and in study IV from the outpatient register of the NPR. By using population-based information we included large cohorts of exposed individuals allowing us to assess stable risk estimates and (for studies I and II) to estimate relative risks stratified by time period. In study I, we additionally applied a case-control design when assessing the lymphoma/cancer risk before the onset of RA. By incorporating two different designs in the same study, we could estimate risks at different time points before and after diagnosis of RA in order to investigate the possible impact of shared genetic susceptibility or common risk factors behind RA lymphomas.

In study III, the case-control design allowed us to control for a number of potential confounders and to estimate stable risk estimates of some major lymphoma subtypes.

5.1.2 Validity

Validity of a study can be divided into two components, *internal validity (*i.e. can the findings within the study population be trusted or absence of systemic or random errors) and *external validity* (i.e. generalizability of the findings to other populations). The major threats to the internal validity can be classified into three main categories; selection bias, information bias and confounding.

Selection bias
Selection bias is introduced if exposure status influences the selection of cases and controls in a case-control study or if the association between exposure and outcome differs between those that participate in a study versus those that do not participate. In study III, the matched controls were selected from the same underlying prevalent RA-cohort identified within the inpatient register i.e. both cases and controls had at any point been hospitalized with a RA diagnosis. Thus, if a control had developed a lymphoma they would have been a case. Restricting the study to cases and controls who at any point had been hospitalized with RA may have led to a selection of patients with a more severe disease. That would, however, affect the external rather than the internal validity.

In the case-control analysis of study I we assessed the risk of lymphoma or cancer overall before the RA diagnosis the point estimates was just below 1. This could be explained by a bias towards a selection of cancer/lymphoma patients with a good prognosis, i.e. those who die due to their cancer do not have the chance to develop RA. Conversely, it may be that patients with a short life expectancy (for example an advanced cancer) are less likely to be included in a register as SRQ with an intended long follow-up period. This again could lead to a selection of "healthier" RA patients in studies I and II and thereby an underestimation of the true lymphoma risks. Again this would have an impact on the external rather than the internal validity.

In study IV, the exposed (AS and PsA) cohorts were assembled from the outpatient register of the NPR. Since the registration in the NPR is population-based (with outpatient specialist visits accessible to all Swedish residents) the AS and PsA cohorts were recruited from outpatient visits spanning from university hospital

clinics to small outpatient clinics, thereby reducing the risk of choosing patients with a particular phenotype of AS or PsA (for example those with a more complicated and severe disease managed solely at a university hospital). On the other hand, as the outpatient register doesn't hold information on primary care visits, AS or PsA patients managed only at their general practitioner were not included. Furthermore, as no dates of disease onset are available in the NPR, the patients of these cohorts must be considered as prevalent cases.

Detection Bias
A newly diagnosed RA patient is typically subjected to some clinical work up, such as a chest X-ray and blood samples, both for evaluating the RA diagnosis and for preparing for start of DMARD treatment. This may lead to detection of latent diseases such as cancer. Such detection bias is likely to affect risk estimates occurring around and shortly after RA diagnosis. This could partly explain the early increase in overall cancer risk following RA diagnosis in study I, but could not readily explain the persistently increased lymphoma risk seen during a longer follow-up period. Furthermore, a closer surveillance of the RA, AS or PsA patients may potentially lead to an earlier detection of an indolent lymphoma with few symptoms such as a CLL. However, in none of the studies (II and IV) we observed any increased occurrence of CLL. By contrast, increased risks were primarily associated with HL and DLBCL.

Information bias
Information bias can be defined as incorrect measurement of exposure and/or outcome (also called misclassification) and may occur in any study. Misclassification of either exposure or outcome can be differential or non-differential depending on whether measurement error of one variable correlates with the measurement of another variable. Non-differential misclassification is random and will typically dilute an observed association between the exposure and the outcome. Differential misclassification occurs when the misclassification of exposure in a subject is affected by the disease status or vice versa. This can bias the relative risk towards or away from the null. An example of differential misclassification in case-control studies is recall bias (i.e. a patient may overestimate their exposure to a potential harmful risk factor due to their disease status).

Although validation studies of the population-based NPR show that the majority of the diagnoses are correct [264], there is a certain degree of misclassification of diagnoses. This became evident in study IV where confirmation of the PsA diagnoses in the patients exposed to TNFi (and developing a lymphoma) turned out to be correct in 5/8 (63%) of the PsA-cases when we validated the diagnosis against the medical records. However, in study IV we also had access to information from ARTIS, enabling estimations of lymphoma incidences rates in rheumatologist-diagnosed AS and PsA diagnoses of patients receiving TNFi. In study IV, we also tried to reduce potential misclassification bias both by applying a stricter exposure definition i.e. requiring at least 2 outpatient visits with AS/PsA diagnosis as well as excluding all patients ever recorded with a diagnosis code for RA (given the obvious but challenging overlap between these two diagnosis). This resulted in largely similar relative risks. Nevertheless, the potential misclassification of exposure remains a limitation of study IV. Furthermore, to avoid including an underlying undiagnosed lymphoma (which could be the reason for the visits that lead to inclusion in the

cohorts under study) we excluded all person-time and all events during the first 90 days of follow-up.

As for the outcome status (in all studies) and the exposure information (in the first part of study I), this was register-based information from the Swedish Cancer Register which has a high validity, although it must be remembered that misclassification to some extent exists in all registers.

Confounding

The definition of a confounder is a factor that is associated with both the disease and the exposure but not an effect of the exposure. When unequally distributed among exposed/non-exposed or cases/controls, a confounder may bias the relative risk away from or towards the null. There are several methods to control for confounding in a study design (randomization, restriction, matching) and in the statistical analyses (stratification and adjustment). However, to successfully control for confounding requires that the confounder a) is a priori known b) is measurable. In register-based studies information on potential confounders is often limited.

In studies I and II, we could adjust for the matching variables in statistical models and stratify by RF, age and calendar period of onset in RA as well as duration of RA disease. We did not have information about lifestyle factors such as smoking; information that probably would influence the observation of increased RR of lung cancer following RA diagnosis since smoking is a common risk factor for both conditions.[11, 271-273] The same holds for study IV, where we could adjust only for the matching variables and some basic characteristic of the AS/ PsA diseases. On the other hand, few risk factors shared by lymphoma and RA (besides immune-suppression) are established.[147]

A particular type of confounding, confounding by indication (or sometimes called channeling bias) arises from the fact that individuals who take a medication are different from those who do not. In the studies of this thesis, this can be illustrated by the challenge to assess the link between therapy, inflammatory activity and lymphoma risk in RA, since patients receiving systemic treatment have a more active and/or a more severe disease. This emphasizes the importance of taking both disease severity and treatment into account. In study II, we had access to visit data in the SRQ that enabled for adjustments for inflammatory activity during the first year following RA diagnosis in the treatment analyses performed. In study III, the extensive data collected on characteristics of the RA disease, treatment and disease severity enabled us to evaluate several possible confounders of the association between glucocorticoids and risk of lymphoma in RA, taking accumulated inflammatory activity and concomitant DMARD therapy into account.

In study III, cases and controls were matched on age, gender and residency as well as year of first RA hospitalization. In this matching procedure, we could not match for the exact RA duration, as date of onset was not available when selecting the study population. This resulted in a small but significant difference in the duration of RA in the cases and the controls (+3 years in the cases). To take this difference into account, the lymphoma risk associated with different groups of accumulated inflammatory activity (high, moderate, low) was stratified for disease duration, which resulted in largely similar RRs of lymphoma.

Reverse causation

A hematopoietic (or some other) malignancy can sometimes present with a clinical picture similar to RA or PsA (maybe less likely AS) for example oligo/polyartrthritis, high ESR or B-symptoms. This paraneoplastic phenomenon may be misclassified as incident RA or as some other inflammatory condition instead of the not yet diagnosed malignancy. Just as detection bias, reverse causation is likely to affect the risk estimates in studies with short follow-up time. To account for the possible effects of reverse causation, analyses in studies I, II and IV excluded all events and all person-time the first 90 days of follow-up.

External validity

In study III the patient population consisted of hospitalized RA patients that were followed from 1964-1994. These observations are therefore not generalizable to RA patients diagnosed and treated today. By contrast, the patient population under study in studies I and II probably better reflects today's RA patients, since this population consisted of incident RA patients with a rheumatologist based diagnosis according to the ACR criteria,[6] although a certain selection of patients, as already described, cannot be ruled out. The same is true for the findings in study IV, although the AS and PsA populations assembled from the outpatient register were less well defined compared with the RA population assembled from the SRQ.

5.1.3   Precision

Precision in epidemiologic measurements corresponds to the reduction of random error i.e. the influence of chance. Statistical techniques such as p values and confidence intervals can be used to quantify the degree of precision of observed estimates. The confidence levels were set to 95% in all studies. In the cohort studies (I-II, IV) the large cohort sizes contributed to enhance precision and to produce stable risk estimates in the analyses overall. However when an outcome is rare, such as assessing RRs per lymphoma subtype in study II, precision tended to be low despite the underlying large cohort size. This was also notable in the analyses of lymphoma risk in relation to inflammatory activity the first year following RA diagnosis in study II. However the observed tendency that higher inflammatory activity may be associated with an increased lymphoma risk is less likely due to chance alone as this finding corroborates previous reports.[197, 201] Due to sparse data in some of the analyses in study II and IV we abstained from calculating RRs when numbers of event were less than five.

5.2   FINDINGS AND IMPLICATIONS

Risk of lymphoma before diagnosis of RA and risk of cancer overall

In study I we reported that a history of lymphoma or cancer overall was not more common than expected in RA patients compared with the general population. By studying the risk of lymphoma before diagnosis of RA we could reduce the impact of disease severity or accumulated burden of disease as well as other possible factors that influence the risk of lymphoma in established RA. Our results indirectly support that the *major* driving forces for lymphoma risk in RA are not shared genetic susceptibility or risk factors common for both diseases but instead points to RA disease-related factors or disease severity as important determinants behind

lymphoma development in RA. This is further supported by previous studies assessing overall occurrence of lymphomas in first-degree relatives of patients with RA which do not occur more often than expected.[148, 198, 244]

On the other hand, in the light of the accumulation of lymphoma in a subset of RA patients [197,274] and the complex genetics of both diseases, our findings do not exclude that individual clustering due to shared genetic or common risk factors may be of importance for some particular lymphomas among a subset of RA patients. Given the study design, a true shared etiology between RA and lymphomas may still exist but may be confined to lymphomas diagnosed at high ages (i.e. with onset after the typical age at diagnosis of RA), to lymphomas with poor prognosis (i.e., had the patients survived the lymphoma, they would have gone on to develop RA), or to indolent lymphomas where repeated chemotherapy would prevent emerging RA from becoming clinically manifested. It may also be that an underlying genetic susceptibility exists but becomes important only in the presence of inflammation and/or in addition to immune-modulatory treatment.

With respect to a history of cancer other than lymphoma in patients with newly diagnosed RA, we observed no increased risk overall, although we found an early increase in cancer risk following RA diagnosis, probably partly a consequence of cancer surveillance and detection around the time of RA diagnosis. Furthermore the risk increase was mainly driven by elevated risks for prostate and lung cancer whereas the risk for breast, colorectal and skin cancer was non-elevated. Our observation is generally consistent with results from other studies on RA and risk of cancer showing that RA patients are at increased risk of certain (but not all) types of cancer [188, 201-202, 275-276]. Apart from being important for patient counselling this may also be of etiological significance. In the therapy of several cancer forms, treatment such as chemotherapy and anti-hormonal therapy is often used. Our observation of a non-increased risk of RA following a diagnosis of a cancer may thereby suggest that perturbations induced by chemo- or anti-hormonal therapy are not major risk factors for RA. Conversely, one could speculate whether the effect of, for example, chemotherapy through apoptosis in various tissues could postpone or even prevent a later RA development.[277-278]

Risk of lymphoma following RA diagnosis
In studies I and II we observed that risk of malignant lymphoma remains increased to the same extent in incident RA patients diagnosed from 1997 up until 2010 as the one reported in historical cohorts [159, 190, 197, 199] (an approximately doubling of the expected risk). We also found a trend (although non-significant) that risk increases with disease duration. Furthermore, in study II we could not demonstrate any tendency towards declining risk in recent years when RA disease duration was taken into account. Given the radical changes in RA therapy and management over the last decade, with both earlier and more aggressive treatment [34], this observation is somewhat counterintuitive. There may be several explanations, but regardless of which, it is from a clinical point of view, important to point out that clinicians need to be aware of lymphoma development in RA patients.

One explanation may be that the therapeutic regimens may still not suppress accumulated inflammatory activity efficiently enough to decrease the lymphoma risk in RA. Studies I and II included RA patients diagnosed and treated in the late 1990's, a time period where therapy standards were not as intense as in the last 5-10 years. On the other hand, in study I we observed a similar level of risk among RA patients diagnosed after 2000 as that reported for the entire study period 1997-2006. It is also important to emphasize that despite our efforts to monitor the risk for a sufficiently long time span, the follow-up period may still be too short to reveal a possible decline in the elevated lymphoma risk in recently diagnosed RA patients.

In study II, our observation that a higher DAS28 (but not exposure to MTX or glucocorticoids) in the first year following RA diagnosis was associated with a higher lymphoma risk, adds some evidence for the role of chronic inflammation or the RA disease itself, rather than treatment, behind lymphoma development.[147, 154, 197] However, the results are limited by the decreasing availability of information on DAS28 with increasing disease duration in SRQ, i.e., we did not have the possibility to adjust for inflammatory activity during the entire RA disease duration which naturally would have been a better measure of disease severity. Despite this limitation, our result may serve as an indication that we need to be attentive to patients with high disease activity already early in their RA disease course. Regarding MTX, we found nothing to support that the treatment should be associated with an increased lymphoma risk in itself which is consistent with earlier data.[189, 197, 199]

In regard of lymphoma risk in relation to exposure of TNFi (study II), we observed that TNFi-treated RA patients did not have any higher risk of lymphoma compared with patients not treated with TNFi (based on 6 exposed lymphomas). This is consistent with the increasing number of studies suggesting that TNFi therapy does not markedly increase the lymphoma risk in RA above the one already present (Table 6, section 1.7.2.3)

With respect to lymphoma subtypes (study II), we observed a higher proportion of DLBCL compared with that of the general population but still lower compared to the estimate previously reported from a Swedish historical RA cohort, in which DLBCL comprised almost 50% of all lymphomas (not including CLL).[197] An increased proportion of DLBCL has also been shown in other studies [154-155] with some exception.[204] Conversely, we found an increased proportion of HL and a decreased proportion of CLL compared with that of the general population. Previous data do not support any especially low or high proportion of CLL in RA. [154-155] As for HL, studies have typically shown a quite pronounced increased risk in RA.[190-191, 198, 200, 202-203, 244] However, register-based studies spanning earlier time periods must be interpreted with caution as a significant proportion of NHL have been misclassified as HL which may inflate risk estimates of both HL and NHL.[76-77] This was however not the situation in study II in which we used the current WHO classification [73] and also (re)classified the majority (40/45) of the identified RA lymphomas. One explanation of the low proportion of CLL among the RA lymphomas in study II may be that an incipient CLL may go undetected longer if masked by an alternative explanation for a mild leukocytosis such as treatment with oral glucocorticoids, and/or long-standing

inflammation. Alternatively, anti-rheumatic treatment (as already mentioned) may postpone or even prevent a CLL to emerge.[277-278]

Furthermore, and important to emphasize, although a lower proportion of DLBCL than previously reported may suggest a less skewed distribution of lymphoma subtypes in contemporary RA, this is challenged by the observation of a higher than expected proportion of Hodgkin lymphoma. Thus we cannot exclude that the remaining increase in lymphoma risk is an effect of a switch from disease- to treatment-related lymphoma risks, i.e. that we have exchanged one lymphoma risk for another. This remains however a speculation.

Oral glucocorticoids and risk of lymphoma
In study III we found that oral glucocorticoids were associated with a decreased lymphoma risk in prevalent RA patients diagnosed 1964-1994. In study II we could to some extent confirm this finding as we noted a borderline risk reduction associated with treatment with oral glucocorticoids the first year after RA onset in incident RA patients diagnosed 1997-2010. In both studies, we were to some extent able to adjust for inflammatory activity; in study III for the entire RA course and in study II for DAS28 during the first year following RA diagnosis. The consistency of our findings is interesting because the two RA cohorts vary widely with respect to study periods and therefore in RA disease control and use of anti-rheumatic therapies.
As already discussed, evaluations of lymphoma risk in association with glucocorticoids in RA have been inconclusive [159, 209].

Our observations in studies II and III suggest that not only may glucocorticoids be used safely (with respect to lymphoma risk) in RA patients; they may even have the potential to reduce the lymphoma risk in this patient population. Glucocorticoids have potent anti-inflammatory effects. Thus, the most obvious interpretation of our observation is that glucocorticoids efficiently lower inflammatory activity, the so far strongest risk factor for lymphoma in RA patients. This interpretation is supported by our observation of a particularly lowered lymphoma risk among those patients that received intra-articular glucocorticoids consistently as flare therapy (in study III), and the fact that adjustment for accumulated disease activity did not attenuate the association in studies II and III. A second explanation is that our finding is due to a better rheumatologic management rather than to properties of the glucocorticoids themselves. This is particularly relevant in study III where the study population consisted of "historical" RA patients not benefitting from today's more proactive and guideline-based RA management. However, it is unlikely that this fully explains the results of study II, which included contemporary and more recently diagnosed RA patients receiving anti-rheumatic therapy to a large extent.

A third explanation of the inverse association found is that the lymphoma "protective effect" of the glucocorticoids is mediated through other mechanisms than anti-inflammatory properties. Glucocorticoids induce apoptosis in immune cells including lymphatic cells [279-280] and are therefore used frequently in high doses in various lymphoma/leukemia regimens.[281] Whether this or a similar mechanism would apply also to the typically lower but longer glucocorticoid therapies used in RA is unclear, although successfully administered intra-articular steroids result in high

synovial exposure to glucocorticoids that in turn might "control" emerging clonal B-cell populations. This remains, however, a speculation. If such a potential mechanism of the glucocorticoids is relevant for the development of lymphomas in non-RA patients remains unclear.

AS/PsA and risk of lymphoma
In study IV, we found that AS was not associated with an increased lymphoma risk overall. This finding is consistent with previously published studies.[148, 155, 205, 248-249] The large AS cohort size assembled in our study enabled us to perform additional analyses with respect to DMARDs and oral glucocorticoids, as well as excluding patients ever recorded with a diagnosis code for RA. These sensitivity analyses did not appreciably change the results.

For PsA, the interpretation of our results is more complex. Overall we found a borderline increased lymphoma risk of 20% compared with the general population although this risk disappeared when we excluded all patients in the PsA cohort ever recorded with a diagnosis code for RA. We further noted a significantly increased lymphoma risk restricted to PsA patients treated with DMARDs (defined as methotrexate and/or sulfasalazine), possibly reflective of a patient group where systemic treatment is indicated and thereby with a more severe disease.

Clinically it is sometimes difficult to distinguish between RA and PsA, at least the PsA phenotype characterized by small-joint polyarthritis (as illustrated by the diagnostic uncertainty of the PsA diagnosis observed in our validation of the medical records). A significant proportion of patients with PsA (in study IV 17%) were at some occasion (correctly or incorrectly) diagnosed also as RA. Although the average RR of lymphoma approximated 1 when these patients were excluded, a truly increased lymphoma risk in a particular subset of PsA patients (i.e. those with an RA-like disease) is therefore difficult to rule out, as is a risk increase in those patients with the most severe PsA. Furthermore, based on the available information in study IV, we cannot exclude that the excess lymphoma risk seen in DMARD-exposed PsA patients is due to the DMARD treatment itself. Reports on the underlying lymphoma risk in PsA are few. A literature search resulted in one published study assessing cancer risk in prospectively followed PsA patients 1978-2004, reporting a non-increased SIR for all hematopoietic malignancies combined.[63] Our study is the first to our knowledge to assess lymphoma risk separately in PsA and adds an important baseline assessment of lymphoma occurrence in this population.

The apparent discrepancy between increased risk of lymphoma in RA compared with a seemingly non-increased risk in AS and a potentially slightly increased risk in a subset of PsA may have several explanations. As already discussed, the underlying mechanisms behind lymphoma development in inflammatory conditions are complex. RA, unlike AS and PsA, is characterized by activated autoimmune and stimulated B cells. This together with systemic inflammation gives rise to a state of chronic immune stimulation, which is one of several possible biological mechanisms linking autoimmunity to lymphoma development. Another explanation may be that the accumulated burden of systemic inflammation is less pronounced in AS and PsA compared with RA.

With respect to treatment with TNFi, we found no increased lymphoma incidence rates in AS or in PsA after accounting for misclassification of RA as PsA. As stated earlier, evaluations on lymphoma risks in AS and PsA following TNFi exposure are limited and risk assessments have been difficult due to the small number of events. [237-239, 260, 282]Thus, although study IV adds to the knowledge on this field and is the largest study (so far) to evaluate this association; we still did not have the power to assess robust risk estimates. It may also be that exposure to TNFi (or to combinations of therapies including TNFi) may lead to development of particular subsets of lymphoma. In recent years there have been unsettling reports on hepatosplenic T-cell lymphoma in young patients with IBD treated with a combination of TNFi and azathioprine.[257] There is also some evidence of an increased proportion of in particular T-cell lymphoma in psoriasis.[155, 165, 253]

In study IV, the distribution of lymphoma subtypes corresponded on average to the one expected in the general population, apart from a slightly higher proportion of DLBCL in AS (based on small numbers). By contrast, and reassuringly, there was no increased proportion of T-cell lymphoma neither in PsA nor in AS.

6   CONCLUSIONS

i) A history of malignant lymphoma or cancer overall preceding the diagnosis of RA is not more common than expected in the general population.

ii) The risk of malignant lymphoma remains increased in incident RA patients diagnosed during the last 5-10 years, and is similar in magnitude to that reported from historical cohorts.

iii) With respect to risk determinants for future lymphoma development, high inflammatory activity during the first year following RA diagnosis may be of importance.

iv) Treatment with oral glucocorticoids appears to be associated with a decreased lymphoma risk both in prevalent historical RA patients diagnosed 1964-1994 and in incident more contemporary RA patients diagnosed 1997-2010 treated with oral glucocorticoids during first year following RA diagnosis.

v) The distribution of lymphoma subtypes in RA patients is different from that of the general population, with a smaller proportion of chronic lymphocytic leukemia and a higher proportion of Hodgkin lymphoma and diffuse large B-cells lymphoma.

vi) The average risk of lymphoma in AS and PsA is no different from the one in the general population, although an increased risk in a subset of patients with PsA cannot be excluded.

vii) Regarding the RA, AS and PsA populations under study in this thesis, the occurrence of lymphoma was not more common in patients treated with TNFi than in TNFi-naïve patients.

7 FUTURE PERSPECTIVES

Based on the findings in studies I-IV, some relevant future research questions are raised:

i) *What exact mechanisms are the driving forces behind the persistent lymphoma risk in contemporary RA patients?* This may be addressed in studies with the possibility to abstract information on accumulated inflammatory activity and therapy during the entire RA disease course, thus ideally with a prospective approach. Such a study design should also include histopatological, genetic and molecular investigations of the lymphoma specimen, as well as samplings from sera and from inflamed tissue such as lymph nodes and synovial fluids.

ii) *Is the potential lymphoma "protective" effect of oral glucocorticoids restricted to RA patients or applicable also in other conditions?* One way of approaching this would be to study the lymphoma occurrence in other conditions treated with longstanding and/or high doses of oral glucocorticoids.

iii) *Have today's modern and more intense RA therapy regimens replaced one lymphoma risk for another?* Future risk evaluations in RA (and other inflammatory conditions) following exposure to TNFi should not only focus on the lymphoma risk *overall* but also need to further characterize the lymphoma subtypes of these patients.

iv) *Is there an association with disease severity or longstanding chronic inflammation and lymphoma risk in PsA similar to what is seen in RA?* This requires a study including information on disease activity/inflammatory activity and immune-modulatory therapy to be able to account for both potential treatment effects and the effect of disease severity on the lymphoma risk.

v) *What is the risk of lymphoma (or other co-morbidities) following exposure to TNFi in patients with AS and PsA?* Reaching more reliable risk estimates on lymphoma risk in these patient populations may warrant international collaboration in order to assemble sufficiently large study populations given such a rare outcome as lymphoma.

vi) *What distinguish lymphomas in inflammatory conditions from the lymphomas in the general populations?* One way to better understand the etiology behind lymphomas in inflammatory conditions may be to characterize the differences (or similarities) between the lymphoma tissues in patients with inflammatory conditions versus those without such a condition. This would preferably also include assessments of the levels and function of the B cells in order to better understand the impact of inflammation and the extent of a dysregulated immune system.

8 ACKNOWLEDGEMENTS

9 REFERENCES

1.   Harris JC. Art and images in psychiatry. La Cortisone. Arch Gen Psychiatry. 2010 Apr;67(4):317.
2.   Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. Semin Arthritis Rheum. 2006 Dec;36(3):182-8.
3.   Eriksson JK, Neovius M, Ernestam S, Lindblad S, Simard JF, Askling J. Incidence of Rheumatoid Arthritis in Sweden - a nationwide population-based assessment of incidence, its determinants, and treatment penetration. Arthritis Care Res (Hoboken). 2012 Dec 19.
4.   Levy L, Fautrel B, Barnetche T, Schaeverbeke T. Incidence and risk of fatal myocardial infarction and stroke events in rheumatoid arthritis patients. A systematic review of the literature. Clin Exp Rheumatol. 2008 Jul-Aug;26(4):673-9.
5.   Naz SM, Symmons DP. Mortality in established rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2007 Oct;21(5):871-83.
6.   Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988 Mar;31(3):315-24.
7.   Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010 Sep;62(9):2569-81.
8.   Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. Arthritis Rheum. 1987 Nov;30(11):1205-13.
9.   McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011 Dec 8;365(23):2205-19.
10.   Uhlig T, Hagen KB, Kvien TK. Current tobacco smoking, formal education, and the risk of rheumatoid arthritis. J Rheumatol. 1999 Jan;26(1):47-54.
11.   Symmons D, Harrison B. Early inflammatory polyarthritis: results from the norfolk arthritis register with a review of the literature. I. Risk factors for the development of inflammatory polyarthritis and rheumatoid arthritis. Rheumatology (Oxford). 2000 Aug;39(8):835-43.
12.   Wolfe F. The effect of smoking on clinical, laboratory, and radiographic status in rheumatoid arthritis. J Rheumatol. 2000 Mar;27(3):630-7.
13.   Stolt P, Bengtsson C, Nordmark B, Lindblad S, Lundberg I, Klareskog L, et al. Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population based case-control study, using incident cases. Ann Rheum Dis. 2003 Sep;62(9):835-41.
14.   Carlens C, Hergens MP, Grunewald J, Ekbom A, Eklund A, Höglund CO, et al. Smoking, use of moist snuff, and risk of chronic inflammatory diseases. Am J Respir Crit Care Med. 2010 Jun 1;181(11):1217-22.
15.   Costenbader KH, Feskanich D, Mandl LA, Karlson EW. Smoking intensity, duration, and cessation, and the risk of rheumatoid arthritis in women. Am J Med. 2006 Jun;119(6):503 e1-9.
16.   Klareskog L, Stolt P, Lundberg K, Källberg H, Bengtsson C, Grunewald J, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum. 2006 Jan;54(1):38-46.
17.   Klareskog L, Rönnelid J, Lundberg K, Padyukov L, Alfredsson L. Immunity to citrullinated proteins in rheumatoid arthritis. Annu Rev Immunol. 2008;26:651-75.
18.   Nielen MM, van Schaardenburg D, Reesink HW, van de Stadt RJ, van der Horst-Bruinsma IE, de Koning MH, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. Arthritis Rheum. 2004 Feb;50(2):380-6.

19. Aho K, Heliovaara M, Maatela J, Tuomi T, Palosuo T. Rheumatoid factors antedating clinical rheumatoid arthritis. J Rheumatol. 1991 Sep;18(9):1282-4.

20. Nielsen SF, Bojesen SE, Schnohr P, Nordestgaard BG. Elevated rheumatoid factor and long term risk of rheumatoid arthritis: a prospective cohort study. BMJ. 2012;345:e5244.

21. Rantapää-Dahlqvist S, de Jong BA, Berglin E, Hallmans G, Wadell G, Stenlund H, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. Arthritis Rheum. 2003 Oct;48(10):2741-9.

22. Karlson EW, Deane K. Environmental and gene-environment interactions and risk of rheumatoid arthritis. Rheum Dis Clin North Am. 2012 May;38(2):405-26.

23. McInnes IB, O'Dell JR. State-of-the-art: rheumatoid arthritis. Ann Rheum Dis. 2010 Nov;69(11):1898-906.

24. Huang QQ, Pope RM. The role of toll-like receptors in rheumatoid arthritis. Curr Rheumatol Rep. 2009 Oct;11(5):357-64.

25. Dorner T, Burmester GR. The role of B cells in rheumatoid arthritis: mechanisms and therapeutic targets. Curr Opin Rheumatol. 2003 May;15(3):246-52.

26. Takemura S, Klimiuk PA, Braun A, Goronzy JJ, Weyand CM. T cell activation in rheumatoid synovium is B cell dependent. J Immunol. 2001 Oct 15;167(8):4710-8.

27. Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med. 2004 Jun 17;350(25):2572-81.

28. Firestein GS. Immunologic mechanisms in the pathogenesis of rheumatoid arthritis. J Clin Rheumatol. 2005 Jun;11(3 Suppl):S39-44.

29. Pincus T, Sokka T. Laboratory tests to assess patients with rheumatoid arthritis: advantages and limitations. Rheum Dis Clin North Am. 2009 Nov;35(4):731-4, vi-vii.

30. Wolfe F. Comparative usefulness of C-reactive protein and erythrocyte sedimentation rate in patients with rheumatoid arthritis. J Rheumatol. 1997 Aug;24(8):1477-85.

31. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995 Jan;38(1):44-8.

32. Wolfe F, Michaud K, Pincus T, Furst D, Keystone E. The disease activity score is not suitable as the sole criterion for initiation and evaluation of anti-tumor necrosis factor therapy in the clinic: discordance between assessment measures and limitations in questionnaire use for regulatory purposes. Arthritis Rheum. 2005 Dec;52(12):3873-9.

33. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980 Feb;23(2):137-45.

34. Smolen JS, Landewe R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis. 2010 Jun;69(6):964-75.

35. http://www.svenskreumatologi.se/kunder/srf/sites/default/files/49/Guidelines_for_the_Management_of_Rheumatoid_Arthritis.pdf.

36. Kirwan JR, Bijlsma JW, Boers M, Shea BJ. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane Database Syst Rev. 2007(1):CD006356.

37. Hoes JN, Jacobs JW, Boers M, Boumpas D, Buttgereit F, Caeyers N, et al. EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis. 2007 Dec;66(12):1560-7.

38. Wilske KR, Healey LA. Challenging the therapeutic pyramid: a new look at treatment strategies for rheumatoid arthritis. J Rheumatol Suppl. 1990 Nov;25:4-7.

39. Dougados M, Baeten D. Spondyloarthritis. Lancet. 2011 Jun 18;377(9783):2127-37.

40.   Amor B, Dougados M, Mijiyawa M. [Criteria of the classification of spondylarthropathies]. Rev Rhum Mal Osteoartic. 1990 Feb;57(2):85-9.

41.   Dougados M, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A, et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. Arthritis Rheum. 1991 Oct;34(10):1218-27.

42.   Klippel John H SJH, Crofford Leslie J, White Patience H Editors. Primer on the Rheumatic Diseases. 13th Edition ed: Springer; 2008.

43.   Bakland G, Nossent HC, Gran JT. Incidence and prevalence of ankylosing spondylitis in Northern Norway. Arthritis Rheum. 2005 Dec 15;53(6):850-5.

44.   Zochling J, Smith EU. Seronegative spondyloarthritis. Best Pract Res Clin Rheumatol. 2010 Dec;24(6):747-56.

45.   Mathieu S, Gossec L, Dougados M, Soubrier M. Cardiovascular profile in ankylosing spondylitis: a systematic review and meta-analysis. Arthritis Care Res (Hoboken). 2011 Apr;63(4):557-63.

46.   Papagoras C, Voulgari PV, Drosos AA. Atherosclerosis and cardiovascular disease in the spondyloarthritides, particularly ankylosing spondylitis and psoriatic arthritis. Clin Exp Rheumatol. 2013 Feb 7.

47.   Prati C, Claudepierre P, Pham T, Wendling D. Mortality in spondylarthritis. Joint Bone Spine. 2011 Oct;78(5):466-70.

48.   Smith PG. The 1957 MRC report on leukaemia and aplastic anaemia in patients irradiated for ankylosing spondylitis. J Radiol Prot. 2007 Dec;27(4B):B3-B14.

49.   van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 1984 Apr;27(4):361-8.

50.   Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis. 2009 Jun;68 Suppl 2:ii1-44.

51.   Brewerton DA, Hart FD, Nicholls A, Caffrey M, James DC, Sturrock RD. Ankylosing spondylitis and HLA 27. Lancet. 1973 Apr 28;1(7809):904-7.

52.   Hammer RE, Maika SD, Richardson JA, Tang JP, Taurog JD. Spontaneous inflammatory disease in transgenic rats expressing HLA-B27 and human beta 2m: an animal model of HLA-B27-associated human disorders. Cell. 1990 Nov 30;63(5):1099-112.

53.   Leirisalo-Repo M, Helenius P, Hannu T, Lehtinen A, Kreula J, Taavitsainen M, et al. Long-term prognosis of reactive salmonella arthritis. Ann Rheum Dis. 1997 Sep;56(9):516-20.

54.   Braun J, Sieper J, Zink A. The risks of smoking in patients with spondyloarthritides. Ann Rheum Dis. 2012 Jun;71(6):791-2.

55.   Chen J, Veras MM, Liu C, Lin J. Methotrexate for ankylosing spondylitis. Cochrane Database Syst Rev. 2013;2:CD004524.

56.   Chen J, Liu C. Is sulfasalazine effective in ankylosing spondylitis? A systematic review of randomized controlled trials. J Rheumatol. 2006 Apr;33(4):722-31.

57.   Zochling J, van der Heijde D, Burgos-Vargas R, Collantes E, Davis JC, Jr., Dijkmans B, et al. ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis. 2006 Apr;65(4):442-52.

58.   Braun J, Davis J, Dougados M, Sieper J, van der Linden S, van der Heijde D. First update of the international ASAS consensus statement for the use of anti-TNF agents in patients with ankylosing spondylitis. Ann Rheum Dis. 2006 Mar;65(3):316-20.

59.   Spoorenberg A, van der Heijde D, de Klerk E, Dougados M, de Vlam K, Mielants H, et al. Relative value of erythrocyte sedimentation rate and C-reactive protein in assessment of disease activity in ankylosing spondylitis. J Rheumatol. 1999 Apr;26(4):980-4.

60.   Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of psoriatic arthritis: a systematic review. J Rheumatol. 2008 Jul;35(7):1354-8.

61.   Haroon M, Fitzgerald O. Pathogenetic overview of psoriatic disease. J Rheumatol Suppl. 2012 Jul;89:7-10.

62.   Husted JA, Gladman DD, Farewell VT, Cook RJ. Health-related quality of life of patients with psoriatic arthritis: a comparison with patients with rheumatoid arthritis. Arthritis Rheum. 2001 Apr;45(2):151-8.

63.   Rohekar S, Tom BD, Hassa A, Schentag CT, Farewell VT, Gladman DD. Prevalence of malignancy in psoriatic arthritis. Arthritis Rheum. 2008 Jan;58(1):82-7.

64.   Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum. 1973;3(1):55-78.

65.   Gladman DD, Shuckett R, Russell ML, Thorne JC, Schachter RK. Psoriatic arthritis (PSA)--an analysis of 220 patients. Q J Med. 1987 Feb;62(238):127-41.

66.   Madland TM, Apalset EM, Johannessen AE, Rossebo B, Brun JG. Prevalence, disease manifestations, and treatment of psoriatic arthritis in Western Norway. J Rheumatol. 2005 Oct;32(10):1918-22.

67.   Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006 Aug;54(8):2665-73.

68.   Mease P. Update on treatment of psoriatic arthritis. Bull NYU Hosp Jt Dis. 2012;70(3):167-71.

69.   Chandran V, Raychaudhuri SP. Geoepidemiology and environmental factors of psoriasis and psoriatic arthritis. J Autoimmun. 2010 May;34(3):J314-21.

70.   Gossec L, Smolen JS, Gaujoux-Viala C, Ash Z, Marzo-Ortega H, van der Heijde D, et al. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. Ann Rheum Dis. 2012 Jan;71(1):4-12.

71.   Helliwell PS, Fitzgerald O, Fransen J, Gladman DD, Kreuger GG, Callis-Duffin K, et al. The development of candidate composite disease activity and responder indices for psoriatic arthritis (GRACE project). Ann Rheum Dis. 2012 Jul 13.

72.   Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood. 1994 Sep 1;84(5):1361-92.

73.   Jaffe ESHN SH, Vardimir JW (ed.). World Health Organization classification of tumours: pathology and genetics of haematopoetic and lymphoid tissues. Geneva: IARC Press: 2001.

74.   Swerdlow SH CE, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; . 2008.

75.   http://www.socialstyrelsen.se/publikationer2012/2012-12-19.

76.   Dige U, Johansson H, Lenner P, Norberg B, Roos G. Hodgkin's disease in northern Sweden 1971-1981. I. A histopathological reevaluation of 223 cases. Acta Oncol. 1991;30(5):593-6.

77.   Martinsson U, Glimelius B, Sundström C. Lymphoma incidence in a Swedish county during 1969-1987. Acta Oncol. 1992;31(3):275-82.

78.   Register SL. http://swedishlymphoma.se.

79.   Muller AM, Ihorst G, Mertelsmann R, Engelhardt M. Epidemiology of non-Hodgkin's lymphoma (NHL): trends, geographic distribution, and etiology. Ann Hematol. 2005 Jan;84(1):1-12.

80.   Baris D, Zahm SH. Epidemiology of lymphomas. Curr Opin Oncol. 2000 Sep;12(5):383-94.

81.   Chiu BC, Weisenburger DD. An update of the epidemiology of non-Hodgkin's lymphoma. Clin Lymphoma. 2003 Dec;4(3):161-8.

82.   Cartwright RA, Watkins G. Epidemiology of Hodgkin's disease: a review. Hematol Oncol. 2004 Mar;22(1):11-26.

83.   Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res. 1971 Nov;31(11):1860-1.

84.   Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol. 1989 Nov;7(11):1630-6.

85.   A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med. 1993 Sep 30;329(14):987-94.

86.		Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med. 1998 Nov 19;339(21):1506-14.

87.		Solal-Celigny P, Roy P, Colombat P, White J, Armitage JO, Arranz-Saez R, et al. Follicular lymphoma international prognostic index. Blood. 2004 Sep 1;104(5):1258-65.

88.		Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature. 2000 Feb 3;403(6769):503-11.

89.		Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood. 2004 Jan 1;103(1):275-82.

90.		Keating GM. Rituximab: a review of its use in chronic lymphocytic leukaemia, low-grade or follicular lymphoma and diffuse large B-cell lymphoma. Drugs. 2010 Jul 30;70(11):1445-76.

91.		Ayala E, Tomblyn M. Hematopoietic cell transplantation for lymphomas. Cancer Control. 2011 Oct;18(4):246-57.

92.		Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011 Mar 4;144(5):646-74.

93.		Nogai H, Dorken B, Lenz G. Pathogenesis of non-Hodgkin's lymphoma. J Clin Oncol. 2011 May 10;29(14):1803-11.

94.		Ekström-Smedby K. Epidemiology and etiology of non-Hodgkin lymphoma--a review. Acta Oncol. 2006;45(3):258-71.

95.		Dal Maso L, Franceschi S. Epidemiology of non-Hodgkin lymphomas and other haemolymphopoietic neoplasms in people with AIDS. Lancet Oncol. 2003 Feb;4(2):110-9.

96.		Tarella C, Gueli A, Ruella M, Cignetti A. Lymphocyte transformation and autoimmune disorders. Autoimmun Rev. 2012 Dec 4.

97.		Altieri A, Bermejo JL, Hemminki K. Familial risk for non-Hodgkin lymphoma and other lymphoproliferative malignancies by histopathologic subtype: the Swedish Family-Cancer Database. Blood. 2005 Jul 15;106(2):668-72.

98.		Chang ET, Smedby KE, Hjalgrim H, Porwit-MacDonald A, Roos G, Glimelius B, et al. Family history of hematopoietic malignancy and risk of lymphoma. J Natl Cancer Inst. 2005 Oct 5;97(19):1466-74.

99.		Zhang Y, Wang R, Holford TR, Leaderer B, Zahm SH, Boyle P, et al. Family history of hematopoietic and non-hematopoietic malignancies and risk of non-Hodgkin lymphoma. Cancer Causes Control. 2007 May;18(4):351-9.

100.		Wang SS, Slager SL, Brennan P, Holly EA, De Sanjose S, Bernstein L, et al. Family history of hematopoietic malignancies and risk of non-Hodgkin lymphoma (NHL): a pooled analysis of 10 211 cases and 11 905 controls from the International Lymphoma Epidemiology Consortium (InterLymph). Blood. 2007 Apr 15;109(8):3479-88.

101.		Goldin LR, Landgren O, McMaster ML, Gridley G, Hemminki K, Li X, et al. Familial aggregation and heterogeneity of non-Hodgkin lymphoma in population-based samples. Cancer Epidemiol Biomarkers Prev. 2005 Oct;14(10):2402-6.

102.		Chatterjee N, Hartge P, Cerhan JR, Cozen W, Davis S, Ishibe N, et al. Risk of non-Hodgkin's lymphoma and family history of lymphatic, hematologic, and other cancers. Cancer Epidemiol Biomarkers Prev. 2004 Sep;13(9):1415-21.

103.		Goldin LR, Pfeiffer RM, Gridley G, Gail MH, Li X, Mellemkjaer L, et al. Familial aggregation of Hodgkin lymphoma and related tumors. Cancer. 2004 May 1;100(9):1902-8.

104.		Goldin LR, Bjorkholm M, Kristinsson SY, Turesson I, Landgren O. Elevated risk of chronic lymphocytic leukemia and other indolent non-Hodgkin's lymphomas among relatives of patients with chronic lymphocytic leukemia. Haematologica. 2009 May;94(5):647-53.

105.		Zhu K, Levine RS, Brann EA, Gu Y, Caplan LS, Hall I, et al. Risk factors for non-Hodgkin's lymphoma according to family history of haematolymphoproliferative malignancies. Int J Epidemiol. 2001 Aug;30(4):818-24.

106.		Paltiel O, Schmit T, Adler B, Rachmilevitz EA, Polliack A, Cohen A, et al. The incidence of lymphoma in first-degree relatives of patients with Hodgkin disease

and non-Hodgkin lymphoma: results and limitations of a registry-linked study. Cancer. 2000 May 15;88(10):2357-66.

107.	Skibola CF, Curry JD, Nieters A. Genetic susceptibility to lymphoma. Haematologica. 2007 Jul;92(7):960-9.

108.	Rothman N, Skibola CF, Wang SS, Morgan G, Lan Q, Smith MT, et al. Genetic variation in TNF and IL10 and risk of non-Hodgkin lymphoma: a report from the InterLymph Consortium. Lancet Oncol. 2006 Jan;7(1):27-38.

109.	Skibola CF, Bracci PM, Nieters A, Brooks-Wilson A, de Sanjose S, Hughes AM, et al. Tumor necrosis factor (TNF) and lymphotoxin-alpha (LTA) polymorphisms and risk of non-Hodgkin lymphoma in the InterLymph Consortium. Am J Epidemiol. 2010 Feb 1;171(3):267-76.

110.	Vasku JA, Vasku A, Goldbergova M, Vasku V. Heterozygote AG variant of -596 A/G IL-6 gene polymorphism is a marker for cutaneous T-cell lymphoma (CTCL). Clin Immunol. 2004 Dec;113(3):256-60.

111.	Conde L, Halperin E, Akers NK, Brown KM, Smedby KE, Rothman N, et al. Genome-wide association study of follicular lymphoma identifies a risk locus at 6p21.32. Nat Genet. 2010 Aug;42(8):661-4.

112.	Smedby KE, Foo JN, Skibola CF, Darabi H, Conde L, Hjalgrim H, et al. GWAS of follicular lymphoma reveals allelic heterogeneity at 6p21.32 and suggests shared genetic susceptibility with diffuse large B-cell lymphoma. PLoS Genet. 2011 Apr;7(4):e1001378.

113.	Engels EA, Pfeiffer RM, Goedert JJ, Virgo P, McNeel TS, Scoppa SM, et al. Trends in cancer risk among people with AIDS in the United States 1980-2002. AIDS. 2006 Aug 1;20(12):1645-54.

114.	Franceschi S, Lise M, Clifford GM, Rickenbach M, Levi F, Maspoli M, et al. Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV Cohort Study. Br J Cancer. 2010 Jul 27;103(3):416-22.

115.	Kaplan LD. HIV-associated lymphoma. Best Pract Res Clin Haematol. 2012 Mar;25(1):101-17.

116.	Taylor AL, Marcus R, Bradley JA. Post-transplant lymphoproliferative disorders (PTLD) after solid organ transplantation. Crit Rev Oncol Hematol. 2005 Oct;56(1):155-67.

117.	Andreone P, Gramenzi A, Lorenzini S, Biselli M, Cursaro C, Pileri S, et al. Posttransplantation lymphoproliferative disorders. Arch Intern Med. 2003 Sep 22;163(17):1997-2004.

118.	Krynitz B, Edgren G, Lindelof B, Baecklund E, Brattström C, Wilczek H, et al. Risk of skin cancer and other malignancies in kidney, liver, heart and lung transplant recipients 1970 to 2008--a Swedish population-based study. Int J Cancer. 2013 Mar 15;132(6):1429-38.

119.	Engels EA, Pfeiffer RM, Fraumeni JF, Jr., Kasiske BL, Israni AK, Snyder JJ, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA. 2011 Nov 2;306(17):1891-901.

120.	Wagner-Johnston ND, Ambinder RF. Epstein-Barr virus-related lymphoproliferative disorders. Curr Hematol Malig Rep. 2007 Oct;2(4):249-54.

121.	Engels EA. Infectious agents as causes of non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev. 2007 Mar;16(3):401-4.

122.	Young LS, Rickinson AB. Epstein-Barr virus: 40 years on. Nat Rev Cancer. 2004 Oct;4(10):757-68.

123.	Matsuo K, Kusano A, Sugumar A, Nakamura S, Tajima K, Mueller NE. Effect of hepatitis C virus infection on the risk of non-Hodgkin's lymphoma: a meta-analysis of epidemiological studies. Cancer Sci. 2004 Sep;95(9):745-52.

124.	Dal Maso L, Franceschi S. Hepatitis C virus and risk of lymphoma and other lymphoid neoplasms: a meta-analysis of epidemiologic studies. Cancer Epidemiol Biomarkers Prev. 2006 Nov;15(11):2078-85.

125.	Zhang Y, Dai Y, Zheng T, Ma S. Risk Factors of Non-Hodgkin Lymphoma. Expert Opin Med Diagn. 2011 Nov 1;5(6):539-50.

126.	Morton LM, Hartge P, Holford TR, Holly EA, Chiu BC, Vineis P, et al. Cigarette smoking and risk of non-Hodgkin lymphoma: a pooled analysis from the International Lymphoma Epidemiology Consortium (interlymph). Cancer Epidemiol Biomarkers Prev. 2005 Apr;14(4):925-33.

127.   Hjalgrim H, Ekström-Smedby K, Rostgaard K, Amini RM, Molin D, Hamilton-Dutoit S, et al. Cigarette smoking and risk of Hodgkin lymphoma: a population-based case-control study. Cancer Epidemiol Biomarkers Prev. 2007 Aug;16(8):1561-6.

128.   Briggs NC, Hall HI, Brann EA, Moriarty CJ, Levine RS. Cigarette smoking and risk of Hodgkin's disease: a population-based case-control study. Am J Epidemiol. 2002 Dec 1;156(11):1011-20.

129.   Morton LM, Zheng T, Holford TR, Holly EA, Chiu BC, Costantini AS, et al. Alcohol consumption and risk of non-Hodgkin lymphoma: a pooled analysis. Lancet Oncol. 2005 Jul;6(7):469-76.

130.   Kroll ME, Murphy F, Pirie K, Reeves GK, Green J, Beral V. Alcohol drinking, tobacco smoking and subtypes of haematological malignancy in the UK Million Women Study. Br J Cancer. 2012 Aug 21;107(5):879-87.

131.   Besson H, Brennan P, Becker N, De Sanjose S, Nieters A, Font R, et al. Tobacco smoking, alcohol drinking and Hodgkin's lymphoma: a European multi-centre case-control study (EPILYMPH). Br J Cancer. 2006 Aug 7;95(3):378-84.

132.   Skibola CF. Obesity, diet and risk of non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev. 2007 Mar;16(3):392-5.

133.   Willett EV, Skibola CF, Adamson P, Skibola DR, Morgan GJ, Smith MT, et al. Non-Hodgkin's lymphoma, obesity and energy homeostasis polymorphisms. Br J Cancer. 2005 Oct 3;93(7):811-6.

134.   Chang ET, Smedby KE, Zhang SM, Hjalgrim H, Melbye M, Ost A, et al. Dietary factors and risk of non-hodgkin lymphoma in men and women. Cancer Epidemiol Biomarkers Prev. 2005 Feb;14(2):512-20.

135.   Talamini R, Polesel J, Montella M, Dal Maso L, Crovatto M, Crispo A, et al. Food groups and risk of non-Hodgkin lymphoma: a multicenter, case-control study in Italy. Int J Cancer. 2006 Jun 1;118(11):2871-6.

136.   Kricker A, Armstrong BK, Hughes AM, Goumas C, Smedby KE, Zheng T, et al. Personal sun exposure and risk of non Hodgkin lymphoma: a pooled analysis from the Interlymph Consortium. Int J Cancer. 2008 Jan 1;122(1):144-54.

137.   Bertrand KA, Chang ET, Abel GA, Zhang SM, Spiegelman D, Qureshi AA, et al. Sunlight exposure, vitamin D, and risk of non-Hodgkin lymphoma in the Nurses' Health Study. Cancer Causes Control. 2011 Dec;22(12):1731-41.

138.   Wakeford R. The risk of childhood leukaemia following exposure to ionising radiation-a review. J Radiol Prot. 2013 Mar;33(1):1-25.

139.   Eheman CR, Tolbert PE, Coates RJ, Devine O, Eley JW. Case-control assessment of the association between non-Hodgkin's lymphoma and occupational radiation with doses assessed using a job exposure matrix. Am J Ind Med. 2000 Jul;38(1):19-27.

140.   Berrington de Gonzalez A, Darby S. Risk of cancer from diagnostic X-rays: estimates for the UK and 14 other countries. Lancet. 2004 Jan 31;363(9406):345-51.

141.   Kim CJ, Freedman DM, Curtis RE, de Gonzalez AB, Morton LM. Risk of non-Hodgkin lymphoma after radiotherapy for solid cancers. Leuk Lymphoma. 2012 Dec 31.

142.   Vineis P, Miligi L, Costantini AS. Exposure to solvents and risk of non-Hodgkin lymphoma: clues on putative mechanisms. Cancer Epidemiol Biomarkers Prev. 2007 Mar;16(3):381-4.

143.   Cocco P, t'Mannetje A, Fadda D, Melis M, Becker N, de Sanjose S, et al. Occupational exposure to solvents and risk of lymphoma subtypes: results from the Epilymph case-control study. Occup Environ Med. 2010 May;67(5):341-7.

144.   Wang R, Zhang Y, Lan Q, Holford TR, Leaderer B, Zahm SH, et al. Occupational exposure to solvents and risk of non-Hodgkin lymphoma in Connecticut women. Am J Epidemiol. 2009 Jan 15;169(2):176-85.

145.   Cocco P, Satta G, Dubois S, Pili C, Pilleri M, Zucca M, et al. Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study. Occup Environ Med. 2013 Feb;70(2):91-8.

146.   Tarella C, Passera R, Magni M, Benedetti F, Rossi A, Gueli A, et al. Risk factors for the development of secondary malignancy after high-dose chemotherapy and autograft, with or without rituximab: a 20-year retrospective follow-up study in patients with lymphoma. J Clin Oncol. 2011 Mar 1;29(7):814-24.

147.	Smedby KE, Askling J, Mariette X, Baecklund E. Autoimmune and inflammatory disorders and risk of malignant lymphomas-an update. J Intern Med. 2008 Dec;264(6):514-27.

148.	Mellemkjaer L, Pfeiffer R, Engels E, Gridley G, Wheeler W, Hemminki K, et al. Autoimmune disease in individuals and close family members and susceptibility to non-Hodgkin's lymphoma. Arthritis Rheum. 2008 Mar;58(3):657-66.

149.	Chatterjee S, Dombi GW, Severson RK, Mayes MD. Risk of malignancy in scleroderma: a population-based cohort study. Arthritis Rheum. 2005 Aug;52(8):2415-24.

150.	Hill CL, Nguyen AM, Roder D, Roberts-Thomson P. Risk of cancer in patients with scleroderma: a population based cohort study. Ann Rheum Dis. 2003 Aug;62(8):728-31.

151.	Szekanecz E, Szamosi S, Horvath A, Nemeth A, Juhasz B, Szanto J, et al. Malignancies associated with systemic sclerosis. Autoimmun Rev. 2012 Oct;11(12):852-5.

152.	Knight A, Askling J, Ekbom A. Cancer incidence in a population-based cohort of patients with Wegener's granulomatosis. Int J Cancer. 2002 Jul 1;100(1):82-5.

153.	Faurschou M, Sorensen IJ, Mellemkjaer L, Loft AG, Thomsen BS, Tvede N, et al. Malignancies in Wegener's granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. J Rheumatol. 2008 Jan;35(1):100-5.

154.	Smedby KE, Hjalgrim H, Askling J, Chang ET, Gregersen H, Porwit-MacDonald A, et al. Autoimmune and chronic inflammatory disorders and risk of non-Hodgkin lymphoma by subtype. J Natl Cancer Inst. 2006 Jan 4;98(1):51-60.

155.	Anderson LA, Gadalla S, Morton LM, Landgren O, Pfeiffer R, Warren JL, et al. Population-based study of autoimmune conditions and the risk of specific lymphoid malignancies. Int J Cancer. 2009 Jul 15;125(2):398-405.

156.	Mellemkjaer L, Pfeiffer RM, Engels EA, Gridley G, Wheeler W, Hemminki K, et al. Autoimmune disease in individuals and close family members and susceptibility to non-Hodgkin's lymphoma. Arthritis Rheum. 2008 Mar;58(3):657-66.

157.	Varoczy L, Payer E, Kadar Z, Gergely L, Miltenyi Z, Magyari F, et al. Malignant lymphomas and autoimmunity-a single center experience from Hungary. Clin Rheumatol. 2012 Feb;31(2):219-24.

158.	Theander E, Henriksson G, Ljungberg O, Mandl T, Manthorpe R, Jacobsson LT. Lymphoma and other malignancies in primary Sjogren's syndrome: a cohort study on cancer incidence and lymphoma predictors. Ann Rheum Dis. 2006 Jun;65(6):796-803.

159.	Engels EA, Cerhan JR, Linet MS, Cozen W, Colt JS, Davis S, et al. Immune-related conditions and immune-modulating medications as risk factors for non-Hodgkin's lymphoma: a case-control study. Am J Epidemiol. 2005 Dec 15;162(12):1153-61.

160.	Zhang W, Feng S, Yan S, Zhao Y, Li M, Sun J, et al. Incidence of malignancy in primary Sjogren's syndrome in a Chinese cohort. Rheumatology (Oxford). 2010 Mar;49(3):571-7.

161.	Lazarus MN, Robinson D, Mak V, Moller H, Isenberg DA. Incidence of cancer in a cohort of patients with primary Sjogren's syndrome. Rheumatology (Oxford). 2006 Aug;45(8):1012-5.

162.	Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. Arch Intern Med. 2005 Nov 14;165(20):2337-44.

163.	Kauppi M, Pukkala E, Isomaki H. Elevated incidence of hematologic malignancies in patients with Sjogren's syndrome compared with patients with rheumatoid arthritis (Finland). Cancer Causes Control. 1997 Mar;8(2):201-4.

164.	Voulgarelis M, Ziakas PD, Papageorgiou A, Baimpa E, Tzioufas AG, Moutsopoulos HM. Prognosis and outcome of non-Hodgkin lymphoma in primary Sjogren syndrome. Medicine (Baltimore). 2012 Jan;91(1):1-9.

165.	Ekström Smedby K, Vajdic CM, Falster M, Engels EA, Martinez-Maza O, Turner J, et al. Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a

pooled analysis within the InterLymph Consortium. Blood. 2008 Apr 15;111(8):4029-38.

166.   Skopouli FN, Dafni U, Ioannidis JP, Moutsopoulos HM. Clinical evolution, and morbidity and mortality of primary Sjogren's syndrome. Semin Arthritis Rheum. 2000 Apr;29(5):296-304.

167.   Baimpa E, Dahabreh IJ, Voulgarelis M, Moutsopoulos HM. Hematologic manifestations and predictors of lymphoma development in primary Sjogren syndrome: clinical and pathophysiologic aspects. Medicine (Baltimore). 2009 Sep;88(5):284-93.

168.   Mellemkjaer L, Andersen V, Linet MS, Gridley G, Hoover R, Olsen JH. Non-Hodgkin's lymphoma and other cancers among a cohort of patients with systemic lupus erythematosus. Arthritis Rheum. 1997 Apr;40(4):761-8.

169.   Björnådal L, Löfström B, Yin L, Lundberg IE, Ekbom A. Increased cancer incidence in a Swedish cohort of patients with systemic lupus erythematosus. Scand J Rheumatol. 2002;31(2):66-71.

170.   Bernatsky S, Boivin JF, Joseph L, Rajan R, Zoma A, Manzi S, et al. An international cohort study of cancer in systemic lupus erythematosus. Arthritis Rheum. 2005 May;52(5):1481-90.

171.   Parikh-Patel A, White RH, Allen M, Cress R. Cancer risk in a cohort of patients with systemic lupus erythematosus (SLE) in California. Cancer Causes Control. 2008 Oct;19(8):887-94.

172.   Vineis P, Crosignani P, Sacerdote C, Fontana A, Masala G, Miligi L, et al. Haematopoietic cancer and medical history: a multicentre case control study. J Epidemiol Community Health. 2000 Jun;54(6):431-6.

173.   Cibere J, Sibley J, Haga M. Systemic lupus erythematosus and the risk of malignancy. Lupus. 2001;10(6):394-400.

174.   Ragnarsson O, Gröndal G, Steinsson K. Risk of malignancy in an unselected cohort of Icelandic patients with systemic lupus erythematosus. Lupus. 2003;12(9):687-91.

175.   Bernatsky S, Ramsey-Goldman R, Labrecque J, Joseph L, Boivin JF, Petri M, et al. Cancer risk in systemic lupus: An updated international multi-centre cohort study. J Autoimmun. 2013 Feb 11.

176.   Bernatsky S, Ramsey-Goldman R, Isenberg D, Rahman A, Dooley MA, Sibley J, et al. Hodgkin's lymphoma in systemic lupus erythematosus. Rheumatology (Oxford). 2007 May;46(5):830-2.

177.   King JK, Costenbader KH. Characteristics of patients with systemic lupus erythematosus (SLE) and non-Hodgkin's lymphoma (NHL). Clin Rheumatol. 2007 Sep;26(9):1491-4.

178.   Löfström B, Backlin C, Sundström C, Ekbom A, Lundberg IE. A closer look at non-Hodgkin's lymphoma cases in a national Swedish systemic lupus erythematosus cohort: a nested case-control study. Ann Rheum Dis. 2007 Dec;66(12):1627-32.

179.   Bernatsky S, Joseph L, Boivin JF, Gordon C, Urowitz M, Gladman D, et al. The relationship between cancer and medication exposures in systemic lupus erythaematosus: a case-cohort study. Ann Rheum Dis. 2008 Jan;67(1):74-9.

180.   Bernatsky S, Ramsey-Goldman R, Joseph L, Boivin JF, Costenbader KH, Urowitz MB, et al. Lymphoma risk in systemic lupus: effects of disease activity versus treatment. Ann Rheum Dis. 2013 Jan 8.

181.   Tio M, Cox MR, Eslick GD. Meta-analysis: coeliac disease and the risk of all-cause mortality, any malignancy and lymphoid malignancy. Aliment Pharmacol Ther. 2012 Mar;35(5):540-51.

182.   Catassi C, Fabiani E, Corrao G, Barbato M, De Renzo A, Carella AM, et al. Risk of non-Hodgkin lymphoma in celiac disease. JAMA. 2002 Mar 20;287(11):1413-9.

183.   Smedby KE, Åkerman M, Hildebrand H, Glimelius B, Ekbom A, Askling J. Malignant lymphomas in coeliac disease: evidence of increased risks for lymphoma types other than enteropathy-type T cell lymphoma. Gut. 2005 Jan;54(1):54-9.

184.   Askling J, Linet M, Gridley G, Halstensen TS, Ekström K, Ekbom A. Cancer incidence in a population-based cohort of individuals hospitalized with celiac disease or dermatitis herpetiformis. Gastroenterology. 2002 Nov;123(5):1428-35.

185.   Holmes GK, Prior P, Lane MR, Pope D, Allan RN. Malignancy in coeliac disease--effect of a gluten free diet. Gut. 1989 Mar;30(3):333-8.

186.   Andras C, Ponyi A, Constantin T, Csiki Z, Szekanecz E, Szodoray P, et al. Dermatomyositis and polymyositis associated with malignancy: a 21-year retrospective study. J Rheumatol. 2008 Mar;35(3):438-44.

187.   Isomäki HA, Hakulinen T, Joutsenlahti U. Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis. J Chronic Dis. 1978;31(11):691-6.

188.   Smitten AL, Simon TA, Hochberg MC, Suissa S. A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. Arthritis Res Ther. 2008;10(2):R45.

189.   Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. Arthritis Rheum. 2004 Jun;50(6):1740-51.

190.   Thomas E, Brewster DH, Black RJ, Macfarlane GJ. Risk of malignancy among patients with rheumatic conditions. Int J Cancer. 2000 Nov 1;88(3):497-502.

191.   Parikh-Patel A, White RH, Allen M, Cress R. Risk of cancer among rheumatoid arthritis patients in California. Cancer Causes Control. 2009 Aug;20(6):1001-10.

192.   Martin DN, Mikhail IS, Landgren O. Autoimmunity and hematologic malignancies: associations and mechanisms. Leuk Lymphoma. 2009 Apr;50(4):541-50.

193.   Gridley G, Klippel JH, Hoover RN, Fraumeni JF, Jr. Incidence of cancer among men with the Felty syndrome. Ann Intern Med. 1994 Jan 1;120(1):35-9.

194.   Tennis P, Andrews E, Bombardier C, Wang Y, Strand L, West R, et al. Record linkage to conduct an epidemiologic study on the association of rheumatoid arthritis and lymphoma in the Province of Saskatchewan, Canada. J Clin Epidemiol. 1993 Jul;46(7):685-95.

195.   Prior P, Symmons DP, Hawkins CF, Scott DL, Brown R. Cancer morbidity in rheumatoid arthritis. Ann Rheum Dis. 1984 Apr;43(2):128-31.

196.   Baecklund E, Ekbom A, Sparen P, Feltelius N, Klareskog L. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study. BMJ. 1998 Jul 18;317(7152):180-1.

197.   Baecklund E, Iliadou A, Askling J, Ekbom A, Backlin C, Granath F, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum. 2006 Mar;54(3):692-701.

198.   Ekström K, Hjalgrim H, Brandt L, Baecklund E, Klareskog L, Ekbom A, et al. Risk of malignant lymphomas in patients with rheumatoid arthritis and in their first-degree relatives. Arthritis Rheum. 2003 2003 Apr;48(4):963-70.

199.   Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. Arthritis Rheum. 2007 May;56(5):1433-9.

200.   Hemminki K, Li X, Sundquist K, Sundquist J. Cancer risk in hospitalized rheumatoid arthritis patients. Rheumatology (Oxford). 2008 May;47(5):698-701.

201.   Abasolo L, Judez E, Descalzo MA, Gonzalez-Alvaro I, Jover JA, Carmona L. Cancer in rheumatoid arthritis: occurrence, mortality, and associated factors in a South European population. Semin Arthritis Rheum. 2008 Jun;37(6):388-97.

202.   Mercer LK, Davies R, Galloway JB, Low A, Lunt M, Dixon WG, et al. Risk of cancer in patients receiving non-biologic disease-modifying therapy for rheumatoid arthritis compared with the UK general population. Rheumatology (Oxford). 2013 Jan;52(1):91-8.

203.   Tavani A, La Vecchia C, Franceschi S, Serraino D, Carbone A. Medical history and risk of Hodgkin's and non-Hodgkin's lymphomas. Eur J Cancer Prev. 2000 Feb;9(1):59-64.

204.   Holly EA, Bracci PM. Population-based study of non-Hodgkin lymphoma, histology, and medical history among human immunodeficiency virus-negative participants in San Francisco. Am J Epidemiol. 2003 Aug 15;158(4):316-27.

205.   Becker N, Deeg E, Rudiger T, Nieters A. Medical history and risk for lymphoma: results of a population-based case-control study in Germany. Eur J Cancer. 2005 Jan;41(1):133-42.

206.   Franklin J, Lunt M, Bunn D, Symmons D, Silman A. Incidence of lymphoma in a large primary care derived cohort of cases of inflammatory polyarthritis. Ann Rheum Dis. 2006 May;65(5):617-22.

207.	Askling J, Fored CM, Baecklund E, Brandt L, Backlin C, Ekbom A, et al. Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. Ann Rheum Dis. 2005 Oct;64(10):1414-20.

208.	Thomas E, Brewster D, Black R, Macfarlane G. Risk of malignancy among patients with rheumatic conditions. Int J Cancer. 2000 2000 Nov;88(3):497-502.

209.	Smedby K, Hjalgrim H, Askling J, Chang E, Gregersen H, Porwit-MacDonald A, et al. Autoimmune and chronic inflammatory disorders and risk of non-Hodgkin lymphoma by subtype. J Natl Cancer Inst. 2006 2006 Jan;98(1):51-60.

210.	Rizzi R, Curci P, Delia M, Rinaldi E, Chiefa A, Specchia G, et al. Spontaneous remission of "methotrexate-associated lymphoproliferative disorders" after discontinuation of immunosuppressive treatment for autoimmune disease. Review of the literature. Med Oncol. 2009;26(1):1-9.

211.	Hoshida Y, Xu JX, Fujita S, Nakamichi I, Ikeda J, Tomita Y, et al. Lymphoproliferative disorders in rheumatoid arthritis: clinicopathological analysis of 76 cases in relation to methotrexate medication. J Rheumatol. 2007 Feb;34(2):322-31.

212.	Miyazaki T, Fujimaki K, Shirasugi Y, Yoshiba F, Ohsaka M, Miyazaki K, et al. Remission of lymphoma after withdrawal of methotrexate in rheumatoid arthritis: relationship with type of latent Epstein-Barr virus infection. Am J Hematol. 2007 Dec;82(12):1106-9.

213.	Mariette X, Cazals-Hatem D, Warszawki J, Liote F, Balandraud N, Sibilia J. Lymphomas in rheumatoid arthritis patients treated with methotrexate: a 3-year prospective study in France. Blood. 2002 Jun 1;99(11):3909-15.

214.	Bernatsky S, Clarke AE, Suissa S. Hematologic malignant neoplasms after drug exposure in rheumatoid arthritis. Arch Intern Med. 2008 Feb 25;168(4):378-81.

215.	Buchbinder R, Barber M, Heuzenroeder L, Wluka AE, Giles G, Hall S, et al. Incidence of melanoma and other malignancies among rheumatoid arthritis patients treated with methotrexate. Arthritis Rheum. 2008 Jun 15;59(6):794-9.

216.	Silman AJ, Petrie J, Hazleman B, Evans SJ. Lymphoproliferative cancer and other malignancy in patients with rheumatoid arthritis treated with azathioprine: a 20 year follow up study. Ann Rheum Dis. 1988 Dec;47(12):988-92.

217.	Singh G, Fries JF, Spitz P, Williams CA. Toxic effects of azathioprine in rheumatoid arthritis. A national post-marketing perspective. Arthritis Rheum. 1989 Jul;32(7):837-43.

218.	Armstrong RG, West J, Card TR. Risk of cancer in inflammatory bowel disease treated with azathioprine: a UK population-based case-control study. Am J Gastroenterol. 2010 Jul;105(7):1604-9.

219.	Kandiel A, Fraser AG, Korelitz BI, Brensinger C, Lewis JD. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. Gut. 2005 Aug;54(8):1121-5.

220.	Beaugerie L, Brousse N, Bouvier AM, Colombel JF, Lemann M, Cosnes J, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Lancet. 2009 Nov 7;374(9701):1617-25.

221.	Baker GL, Kahl LE, Zee BC, Stolzer BL, Agarwal AK, Medsger TA, Jr. Malignancy following treatment of rheumatoid arthritis with cyclophosphamide. Long-term case-control follow-up study. Am J Med. 1987 Jul;83(1):1-9.

222.	Radis CD, Kahl LE, Baker GL, Wasko MC, Cash JM, Gallatin A, et al. Effects of cyclophosphamide on the development of malignancy and on long-term survival of patients with rheumatoid arthritis. A 20-year followup study. Arthritis Rheum. 1995 Aug;38(8):1120-7.

223.	Kirwan J, Power L. Glucocorticoids: action and new therapeutic insights in rheumatoid arthritis. Curr Opin Rheumatol. 2007 May;19(3):233-7.

224.	Buttgereit F, Straub R, Wehling M, Burmester G. Glucocorticoids in the treatment of rheumatic diseases: an update on the mechanisms of action. Arthritis Rheum. 2004 Nov;50(11):3408-17.

225.	Kato I, Koenig K, Shore R, Baptiste M, Lillquist P, Frizzera G, et al. Use of anti-inflammatory and non-narcotic analgesic drugs and risk of non-Hodgkin's lymphoma (NHL) (United States). Cancer Causes Control. 2002 2002 Dec;13(10):965-74.

226.	Zhang Y, Holford T, Leaderer B, Zahm S, Boyle P, Morton L, et al. Prior medical conditions and medication use and risk of non-Hodgkin lymphoma in Connecticut United States women. Cancer Causes Control. 2004 2004 May;15(4):419-28.

227.	Beiderbeck A, Holly E, Sturkenboom M, Coebergh J, Stricker B, Leufkens H. No increased risk of non-Hodgkin's lymphoma with steroids, estrogens and psychotropics (Netherlands). Cancer Causes Control. 2003 2003 Sep;14(7):639-44.

228.	Chang E, Smedby K, Hjalgrim H, Schöllkopf C, Porwit-MacDonald A, Sundström C, et al. Medication use and risk of non-Hodgkin's lymphoma. Am J Epidemiol. 2005 Nov;162(10):965-74.

229.	Bernatsky S, Lee J, Rahme E. Non-Hodgkin's lymphoma--meta-analyses of the effects of corticosteroids and non-steroidal anti-inflammatories. Rheumatology (Oxford). 2007 2007 Apr;46(4):690-4.

230.	Balkwill F. TNF-alpha in promotion and progression of cancer. Cancer Metastasis Rev. 2006 Sep;25(3):409-16.

231.	Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006 May 17;295(19):2275-85.

232.	Leombruno JP, Einarson TR, Keystone EC. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. Ann Rheum Dis. 2009 Jul;68(7):1136-45.

233.	Lopez-Olivo MA, Tayar JH, Martinez-Lopez JA, Pollono EN, Cueto JP, Gonzales-Crespo MR, et al. Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy: a meta-analysis. JAMA. 2012 Sep 5;308(9):898-908.

234.	Geborek P, Bladström A, Turesson C, Gulfe A, Petersson IF, Saxne T, et al. Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. Ann Rheum Dis. 2005 May;64(5):699-703.

235.	Pallavicini FB, Caporali R, Sarzi-Puttini P, Atzeni F, Bazzani C, Gorla R, et al. Tumour necrosis factor antagonist therapy and cancer development: analysis of the LORHEN registry. Autoimmun Rev. 2010 Jan;9(3):175-80.

236.	Askling J, Baecklund E, Granath F, Geborek P, Fored M, Backlin C, et al. Anti-tumour necrosis factor therapy in rheumatoid arthritis and risk of malignant lymphomas: relative risks and time trends in the Swedish Biologics Register. Ann Rheum Dis. 2009 May;68(5):648-53.

237.	Dreyer L, Mellemkjaer L, Andersen AR, Bennett P, Poulsen UE, Juulsgaard Ellingsen T, et al. Incidences of overall and site specific cancers in TNFalpha inhibitor treated patients with rheumatoid arthritis and other arthritides - a follow-up study from the DANBIO Registry. Ann Rheum Dis. 2012 Sep 17.

238.	Carmona L, Abasolo L, Descalzo MA, Perez-Zafrilla B, Sellas A, de Abajo F, et al. Cancer in patients with rheumatic diseases exposed to TNF antagonists. Semin Arthritis Rheum. 2011 Aug;41(1):71-80.

239.	Mariette X, Tubach F, Bagheri H, Bardet M, Berthelot JM, Gaudin P, et al. Lymphoma in patients treated with anti-TNF: results of the 3-year prospective French RATIO registry. Ann Rheum Dis. 2010 Feb;69(2):400-8.

240.	Setoguchi S, Solomon DH, Weinblatt ME, Katz JN, Avorn J, Glynn RJ, et al. Tumor necrosis factor alpha antagonist use and cancer in patients with rheumatoid arthritis. Arthritis Rheum. 2006 Sep;54(9):2757-64.

241.	Skibola C, Curry J, Nieters A. Genetic susceptibility to lymphoma. Haematologica. 2007 2007 Jul;92(7):960-9.

242.	Rothman N, Skibola C, Wang S, Morgan G, Lan Q, Smith M, et al. Genetic variation in TNF and IL10 and risk of non-Hodgkin lymphoma: a report from the InterLymph Consortium. Lancet Oncol. 2006 2006 Jan;7(1):27-38.

243.	Wang S, Cozen W, Cerhan J, Colt J, Morton L, Engels E, et al. Immune mechanisms in non-Hodgkin lymphoma: joint effects of the TNF G308A and IL10 T3575A polymorphisms with non-Hodgkin lymphoma risk factors. Cancer Res. 2007 May;67(10):5042-54.

244.	Landgren O, Engels EA, Pfeiffer RM, Gridley G, Mellemkjaer L, Olsen JH, et al. Autoimmunity and susceptibility to Hodgkin lymphoma: a population-based case-control study in Scandinavia. J Natl Cancer Inst. 2006 Sep 20;98(18):1321-30.

245.	Hoshida Y, Tomita Y, Zhiming D, Yamauchi A, Nakatsuka S, Kurasono Y, et al. Lymphoproliferative disorders in autoimmune diseases in Japan: analysis of clinicopathological features and Epstein-Barr virus infection. Int J Cancer. 2004 Jan 20;108(3):443-9.

246.	Landgren O, Engels EA, Caporaso NE, Gridley G, Mellemkjaer L, Hemminki K, et al. Patterns of autoimmunity and subsequent chronic lymphocytic leukemia in Nordic countries. Blood. 2006 Jul 1;108(1):292-6.

247.	Baecklund E, Backlin C, Iliadou A, Granath F, Ekbom A, Amini RM, et al. Characteristics of diffuse large B cell lymphomas in rheumatoid arthritis. Arthritis Rheum. 2006 Dec;54(12):3774-81.

248.	Feltelius N, Ekbom A, Blomqvist P. Cancer incidence among patients with ankylosing spondylitis in Sweden 1965-95: a population based cohort study. Ann Rheum Dis. 2003 Dec;62(12):1185-8.

249.	Askling J, Klareskog L, Blomqvist P, Fored M, Feltelius N. Risk for malignant lymphoma in ankylosing spondylitis: a nationwide Swedish case-control study. Ann Rheum Dis. 2006 Sep;65(9):1184-7.

250.	Hannuksela-Svahn A, Pukkala E, Laara E, Poikolainen K, Karvonen J. Psoriasis, its treatment, and cancer in a cohort of Finnish patients. J Invest Dermatol. 2000 Mar;114(3):587-90.

251.	Gelfand JM, Shin DB, Neimann AL, Wang X, Margolis DJ, Troxel AB. The risk of lymphoma in patients with psoriasis. J Invest Dermatol. 2006 Oct;126(10):2194-201.

252.	Söderberg KC, Jonsson F, Winqvist O, Hagmar L, Feychting M. Autoimmune diseases, asthma and risk of haematological malignancies: a nationwide case-control study in Sweden. Eur J Cancer. 2006 Nov;42(17):3028-33.

253.	Morales MM, Olsen J, Johansen P, Kaerlev L, Guenel P, Arveux P, et al. Viral infection, atopy and mycosis fungoides: a European multicentre case-control study. Eur J Cancer. 2003 Mar;39(4):511-6.

254.	Margolis D, Bilker W, Hennessy S, Vittorio C, Santanna J, Strom BL. The risk of malignancy associated with psoriasis. Arch Dermatol. 2001 Jun;137(6):778-83.

255.	Stern RS. Lymphoma risk in psoriasis: results of the PUVA follow-up study. Arch Dermatol. 2006 Sep;142(9):1132-5.

256.	Pedersen N, Duricova D, Elkjaer M, Gamborg M, Munkholm P, Jess T. Risk of extra-intestinal cancer in inflammatory bowel disease: meta-analysis of population-based cohort studies. Am J Gastroenterol. 2010 Jul;105(7):1480-7.

257.	Subramaniam K, D'Rozario J, Pavli P. Lymphoma and other lymphoproliferative disorders in inflammatory bowel disease: A review. J Gastroenterol Hepatol. 2013 Jan;28(1):24-30.

258.	Siegel CA, Marden SM, Persing SM, Larson RJ, Sands BE. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. Clin Gastroenterol Hepatol. 2009 Aug;7(8):874-81.

259.	Peyrin-Biroulet L, Deltenre P, de Suray N, Branche J, Sandborn WJ, Colombel JF. Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials. Clin Gastroenterol Hepatol. 2008 Jun;6(6):644-53.

260.	Burmester GR, Panaccione R, Gordon KB, McIlraith MJ, Lacerda AP. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. Ann Rheum Dis. 2012 Jul 6.

261.	Löfström B, Backlin C, Pettersson T, Lundberg IE, Baecklund E. Expression of APRIL in diffuse large B cell lymphomas from patients with systemic lupus erythematosus and rheumatoid arthritis. J Rheumatol. 2011 Sep;38(9):1891-7.

262.	Neovius M, Simard J, Sundström A, Jacobsson L, Geborek P, Saxne T, et al. Generalisability of clinical registers used for drug safety and comparative effectiveness research: coverage of the Swedish Biologics Register. Ann Rheum Dis. 2011 Mar;70(3):516-9.

263.	Personal identity number -its design and use at Statistics Sweden. Statistics Sweden, Background facts, Population and Wellfare Statistics, . 2007:1.
264.	Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.
265.	Socialstyrelsen. www.socialstyrelsen.se Kvalitet och innehåll i patientregistret 2008.
266.	Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol. 2009;48(1):27-33.
267.	Causes of death 2007. Official Health and Diseases 2009.
268.	http://www.socialstyrelsen.se/register/dodsorsaksregistret.
269.	Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf. 2007 Jul;16(7):726-35.
270.	Baecklund E, Sundström C, Ekbom A, Catrina AI, Biberfeld P, Feltelius N, et al. Lymphoma subtypes in patients with rheumatoid arthritis: increased proportion of diffuse large B cell lymphoma. Arthritis Rheum. 2003 Jun;48(6):1543-50.
271.	Vessey MP, Villard-Mackintosh L, Yeates D. Oral contraceptives, cigarette smoking and other factors in relation to arthritis. Contraception. 1987 May;35(5):457-64.
272.	Hernandez Avila M, Liang MH, Willett WC, Stampfer MJ, Colditz GA, Rosner B, et al. Reproductive factors, smoking, and the risk for rheumatoid arthritis. Epidemiology. 1990 Jul;1(4):285-91.
273.	Voigt LF, Koepsell TD, Nelson JL, Dugowson CE, Daling JR. Smoking, obesity, alcohol consumption, and the risk of rheumatoid arthritis. Epidemiology. 1994 Sep;5(5):525-32.
274.	Baecklund E, Natkunam Y, Backlin C, Iliadou A, Askling J, Ekbom A, et al. Expression of the human germinal-centre-associated lymphoma protein in diffuse large B-cell lymphomas in patients with rheumatoid arthritis. Br J Haematol. 2008 Apr;141(1):69-72.
275.	Chen YJ, Chang YT, Wang CB, Wu CY. The risk of cancer in patients with rheumatoid arthritis: a nationwide cohort study in Taiwan. Arthritis Rheum. 2011 Feb;63(2):352-8.
276.	Cibere J, Sibley J, Haga M. Rheumatoid arthritis and the risk of malignancy. Arthritis Rheum. 1997 Sep;40(9):1580-6.
277.	van Dongen H, van Aken J, Lard L, Visser K, Ronday H, Hulsmans H, et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2007 May;56(5):1424-32.
278.	Wöhrer S, Troch M, Zwerina J, Schett G, Skrabs C, Gaiger A, et al. Influence of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone on serologic parameters and clinical course in lymphoma patients with autoimmune diseases. Ann Oncol. 2007 Apr;18(4):647-51.
279.	Moalli P, Rosen S. Glucocorticoid receptors and resistance to glucocorticoids in hematologic malignancies. Leuk Lymphoma. 1994 Nov;15(5-6):363-74.
280.	Frankfurt O, Rosen ST. Mechanisms of glucocorticoid-induced apoptosis in hematologic malignancies: updates. Curr Opin Oncol. 2004 Nov;16(6):553-63.
281.	Zwick C, Gleissner B, Pfreundschuh M. Aspects of chemotherapy schedules in young and elderly patients with aggressive lymphoma. Clin Lymphoma Myeloma. 2007 Dec;8 Suppl 2:S43-9.
282.	Haynes K, Beukelman T, Curtis JR, Newcomb C, Herrinton LJ, Graham DJ, et al. Tumor necrosis factor alpha inhibitor therapy and cancer risk in chronic immune-mediated diseases. Arthritis Rheum. 2013 Jan;65(1):48-58.