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Ultraviolet light, autoimmune disorders and the etiology of malignant lymphomas

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SUMMARY

Malignant lymphomas constitute a clinically and morphologically diverse group of malignancies that may also differ etiologically. The incidence of the most common non-Hodgkin lymphomas (NHL) has increased dramatically worldwide during the past decades. Established risk factors together only explain a minority of the cases, let alone the NHL increase. Observations of a positive link between skin cancer and NHL have fostered the hypothesis that frequent sun exposure could be a risk factor for both malignancies and a contributing factor to the rise in NHL incidence. The aim of this thesis was to test the hypothesis of a positive association between sun exposure and malignant lymphomas, and to evaluate the role of autoimmune and chronic inflammatory disorders, especially rheumatoid arthritis (RA) and celiac disease, in the development of malignant lymphoma subtypes, and lymphomagenic mechanisms in this context.

We performed a population-based case-control study in all of Denmark and Sweden (the Scandinavian Lymphoma Etiology, or SCALE, study) between 1999 and 2002, including 3,740 patients with malignant lymphomas and 3,187 control subjects aged 18 to 74 years. Based on structured telephone interviews, information was collected on history of ultraviolet (UV) light exposure, sun sensitivity, skin cancer history and other potential risk factors. In contrast with the *a priori* hypothesis, frequent sun exposure in Denmark/Sweden and abroad and sun burns at different ages were associated with a statistically significant 30-40% reduction in risk of overall NHL, with clear indications of inverse dose-response trends (all $P_{trends} \leq .003$). There was similar but weaker evidence of inverse associations for Hodgkin lymphoma (HL). Self-reported skin cancer history was associated with a doubling in risks of NHL and HL.

To test the hypothesis that the established excess risk of lymphomas in RA is due to risk factors shared by both disorders, we undertook a retrospective registry-based cohort study of Swedish patients hospitalized with RA (n=76,527) and the first-degree relatives (n=70,290) of a subset of these patients. Relative risks of malignant lymphomas were assessed by matching the respective cohorts with the population-based cancer register. The RA patients had a doubled risk of malignant lymphomas overall, although the excess risk did not persist beyond 20 years of follow-up. First-degree relatives were generally not at increased risk of malignant lymphomas, and thus a prominent role of shared risk factors in RA-related lymphomagenesis was not supported.

To evaluate the spectrum of lymphoma subtypes associated with celiac disease, we re-classified 56 malignant lymphoma cases occurring in a large cohort of patients previously hospitalized for celiac disease (n=11,650). Our results indicated that celiac disease patients are at increased risk, not only of the well-described enteropathy-type T-cell lymphoma, but also of non-intestinal T-cell lymphomas and the common B-cell lymphomas compared to the general population.

Finally, we estimated relative risks of NHL overall and by subtype in association with several autoimmune and chronic inflammatory disorders, disease phenotype and treatment, using self-reported data in SCALE. We confirmed an increased risk of NHL in RA, systemic lupus erythematosus, primary Sjögren's syndrome and celiac disease, but not in type I diabetes, inflammatory bowel disorders, sarcoidosis or psoriasis. The first four disorders were all specifically associated with diffuse large B-cell lymphoma and with a few more uncommon NHL subtypes. Data suggested a tendency towards higher risks in severe and long-standing inflammation, but there was little to support previous notions of risk associated with medical treatments in these conditions.

CONTENTS

LIST OF PAPERS

This thesis is based on the following manuscripts which will be referred to in the text by their Roman numerals:

I. Ekström Smedby K, Hjalgrim H, Melbye M, Torrång A, Rostgaard K, Munksgaard L, Adami J, Hansen M, Porwit-MacDonald A, Anker Jensen B, Roos G, Bach Pedersen B, Sundström C, Glimelius B, Adami H-O.
    Ultraviolet Radiation Exposure and Risk of Malignant Lymphomas.
    Journal of the National Cancer Institute. 2005 Feb;97(3):199-209

II. Ekström K, Hjalgrim H, Brandt L, Baecklund E, Klareskog L, Ekbom A, Askling J.
    Risk of Malignant Lymphomas in Patients With Rheumatoid Arthritis and in Their First-Degree Relatives.
    Arthritis & Rheumatism. 2003 Apr;48(4):963-70.

III. 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

IV. Ekström Smedby K, Hjalgrim H, Askling J, Chang ET, Porwit-MacDonald A, Sundström C, Åkerman M, Melbye M, Glimelius B, Adami H-O.
    Autoimmune and chronic inflammatory disorders and risk of non-Hodgkin lymphoma by subtype.
    Manuscript submitted

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LIST OF ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
BLyS	B-lymphocyte stimulators
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
DMARD	Disease-modifying anti-rheumatic drugs
EBV	Epstein-Barr virus
ETTL	Enteropathy-type T-cell lymphoma
HCV	Hepatitis C virus
HHV-8	Human herpes virus 8
HIV	Human immunodeficiency virus
HL	Hodgkin lymphoma
HLA	Human leukocyte antigen
H. pylori	*Helicobacter pylori*
HTLV-1	Human T-cell lymphotrophic virus-1
IBD	Inflammatory bowel disorders
ICD	International Classification of Diseases
MALT	Mucosa-associated lymphoid tissue
NHL	Non-Hodgkin lymphoma
NK cells	Natural killer cells
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
REAL	Revised European-American Lymphoma classification
SCALE study	Scandinavian Lymphoma Etiology study
SEER Program	Surveillance, Epidemiology, and End Results Program
SIR	Standardized incidence ratio
SV40	Simian virus 40
TH1, TH2	T helper type 1, T helper type 2
UV light	Ultraviolet light
WHO	World Health Organisation

INTRODUCTION

The aim of this thesis was to investigate different aspects of the etiology of malignant lymphomas, especially the role of exposure to ultraviolet (UV) light and autoimmune and chronic inflammatory disorders. There is a focus on non-Hodgkin lymphoma (NHL) and its major subtypes, as NHL is the most common malignancy of the lymphatic system, and its incidence has been increasing rapidly worldwide during the past decades, making it one of the ten most common cancer forms in the world. Chronic lymphocytic leukemia (CLL) is now grouped together with small lymphocytic lymphoma into one NHL entity according to the World Health Organisation (WHO) classification, and is treated as such in papers I and IV, but not in papers II and III. Many previous studies of NHL epidemiology and etiology do not include CLL. Although plasma cell malignancies (plasmocytoma/myeloma) are currently also recognised as NHL subtypes according to WHO, these entities are not under study in this thesis, with one exception (paper II).

The four included papers present results from one case-control study and two cohort studies. Papers I and IV include findings from a population-based case-control study in all of Denmark and Sweden, which is, to our knowledge, the largest case-control study on etiology of malignant lymphomas hitherto performed. Papers II and III involve separate retrospective cohort studies based on several Swedish population-based high-quality health registers.

BACKGROUND

DESCRIPTIVE EPIDEMIOLOGY

Classification of malignant lymphomas

The malignant lymphomas entail considerable heterogeneity with regard to morphological and molecular characteristics as well as clinical course (1). In addition, there is growing evidence of etiologic variation among lymphoma subtypes (2). Traditionally, the two main types considered are non-Hodgkin lymphoma (NHL), which make up around 90% of all cases, and Hodgkin lymphoma (HL), accounting for the remaining 10% percent. NHL arise, with few exceptions, from two distinct types of lymphocytes, the B or T cells, and the heterogeneity is related to the many stages of normal differentiation and maturation of these cells (1). A few rare forms originate from natural killer (NK) cells with close resemblance to T cells, and are thus grouped together with T-cell NHL. Mature B-cell neoplasms comprise over 85% of all NHL, whereas the more uncommon T-cell tumors make up around 12% worldwide (3). In the western world, the dominance of B-cell lymphoma types is even greater (1). HL is distinguished as a separate lymphoma entity based on several features, the most prominent being the presence of characteristic large neoplastic cells (Hodgkin and Reed-Sternberg cells) existing sparsely in the tumors (1). The specific neoplastic HL cells are believed to be of B-cell origin in the vast majority of the cases and therefore, the disorder is now designated as a lymphoma rather than as the previously widely used Hodgkin's disease (1).

The classification of malignant lymphomas has been subject to numerous changes over the years, taking different aspects of the heterogeneity into account. For several decades, lymphomas were classified according to the Kiel classification in Europe and the International Working Formulation in the US, both primarily based on morphologic appearance and, to a lesser extent, clinical behaviour (4). In 1994, the Revised European-American Lymphoma (REAL) classification distinguished lymphomas not only by histology, but also by immunophenotypic, genetic and clinical characteristics (5). This system was further modified into the now universally accepted World Health Organization (WHO) classification where 36 subtypes of NHL (21 of B-cell and 15 of T-cell type) and 5 subtypes of HL are recognised, if entities of uncertain malignant potential are excluded (1). Chronic lymphocytic leukemia (CLL) now belongs to the NHL group according to the REAL and WHO classifications, together with its non-leukemic counterpart small lymphocytic lymphoma (1). However, cancer registration in Sweden and in many other countries is based on the International Classification of Diseases (ICD) where CLL is sorted with other leukemias (6). Although plasma cell malignancies are now recognised as NHL subtypes according to WHO classification, they are not included under the NHL umbrella in this thesis. Plasmocytoma and myeloma are also treated as separate entities in the ICD.

The diagnostic accuracy within the group of malignant lymphomas as well as among lymphomas and other conditions has varied over time (7-10). The most important misclassification in Sweden has been that of NHL as HL. Reclassification studies suggest that a diagnosis of adult HL in the 1970s in Sweden was in fact NHL in about one-third of the cases (7, 8). Although the diagnostic accuracy has improved over time, hematolymphoproliferative malignancies are still among the most challenging cases for clinical pathologists to diagnose.

Incidence

In Sweden in the year 2003, close to 2,000 new cases of NHL (NHL n=1499, CLL n=464), were diagnosed in all age groups (6). Fifty-five percent of the patients were males and 45% females corresponding to a male/female ratio of 1.24. Seventy-seven percent of the patients were diagnosed above the age of 60 years. In the same year, there were only 168 new cases of HL (51% males, 49% females). HL incidence peaks both at 15-34 years and over 60 years of age in developed countries (11), and thus 39% of the HL cases were diagnosed between ages 15 to 34 years and 35% above the age of 60 years in Sweden in 2003.

NHL (excluding CLL) is more common in the developed world, with the highest incidence rates in the US, Australia and New Zealand, and Europe, and the lowest in Eastern and South Central Asia (12). Around the year 2000, the age standardized (world standard) incidence of NHL was estimated at approximately 14 per 100,000 person-years in the US and Canada, 10 per 100,000 in Denmark and Sweden, and 3 per 100,000 in South Central Asia (12). However, the rare T-cell neoplasms are more common in Asia than in other regions. Worldwide, NHL (again excluding CLL) constitutes the tenth most commonly diagnosed malignancy, whereas in the developed world it ranks seven. In Sweden in 2003, malignant lymphomas (NHL and HL) were the eighth most common new cancer diagnoses among males and the tenth most common in females (6). In the US, NHL has climbed to the fifth most frequently diagnosed malignancy in recent years (13). Less is known about the epidemiology of CLL as a separate entity, but the incidence rate of leukemia overall, of which CLL constitutes about 30 to 40%, has been stable in Sweden in recent decades (6). The incidence of CLL is also known to be higher in Caucasians and lower in Asians (14). HL is uncommon worldwide, but interestingly also occurs with higher incidence rates in the western world, and lower in eastern Asia (11). The age standardised incidence of HL around the year 2000 was about 2.3 per 100,000 person-years in the US and Canada, 1.8 per 100,000 in northern Europe and 0.2 per 100,000 in China (12).

The most common NHL subtypes by far in developed countries (disregarding CLL) are diffuse large B-cell lymphoma (about 30%) and follicular lymphoma (about 20%). All other NHL subtypes have a frequency of less than 10% (1). Many subtypes are characterised by a slight preponderance of males, most striking in mantle cell lymphoma (70% males), whereas females predominate in follicular lymphoma (1). HL is divided in two biologically and clinically distinct entities, nodular lymphocyte predominant HL (5%) and classical HL (95%). Classical HL is further divided into four subtypes based on differing clinical and morphological features but with identical tumor cell immune phenotype: nodular sclerosis HL, which is the most common variant in the western world, followed by mixed cellularity and the more rare lymphocyte-rich and lymphocyte-depleted variants. Nodular sclerosis HL is the only subtype without a male preponderance (1).

Time trends

For several decades, there has been a dramatic increase in NHL incidence worldwide, of about 2-4% annually (15). In the 1970s and 1980s, the rapid NHL increase was exceeded only by the increase of lung cancer in women and malignant melanoma in both sexes. The highest increase was observed in Denmark, where the rate doubled between 1970 and 1985 (16). In Scandinavia in general the increase in incidence was apparent already in the 1950s (17), and in Connecticut, USA, even in the 1930's (18). Interestingly, this increase is not limited to developed countries, but has been observed

also in for example India, Japan, Brazil, Singapore and Puerto Rico (19). In the beginning of the 1990s, the rise in incidence began to level off in Sweden (Figure 1) (6), whereas this has not been the case in Denmark (20). In the US, data from the Surveillance, Epidemiology, and End Results (SEER) Program showed a stabilization in overall NHL incidence rates in the early 1990s and then a subsequent decline. However, in population groups at low risk of human immunodeficiency virus (HIV)-infection and acquired immunodeficiency syndrome (AIDS), such as men above the age of 55 years and women of all ages, rate increases were still evident through the 1990s (21). With regard to HL, the overall age adjusted incidence has been stable or slightly declining during the same time period (11), although studies from the US and Nordic countries have noted an increase in HL incidence among adolescents and young adults, especially young women and in particular of the nodular sclerosis subtype, during periods ranging from 1960 to 1997 (11).

Figure 1. Non-Hodgkin lymphoma (NHL) incidence in Sweden 1960 to 2003 in males and females, age-standardized to the Swedish population in the year 2000 (ICD: 200).
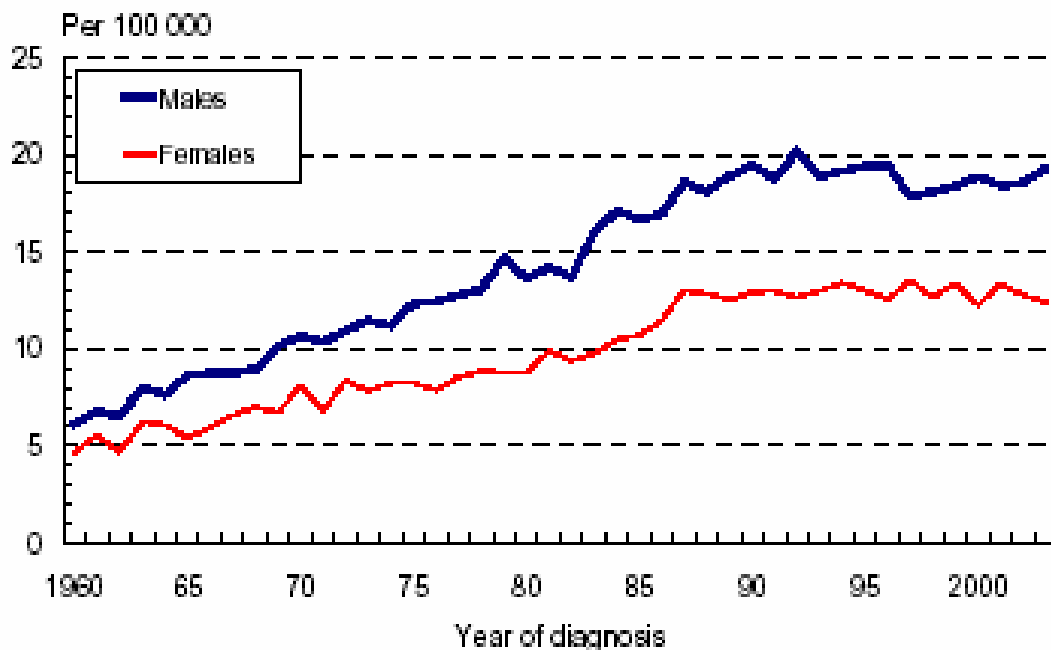
Less is known about time trends for NHL subtypes. Available information comes from studies using US SEER data (4). Thus, between 1974 and 1992, a rapid increase was noted for diffuse large cell lymphoma, partly fuelled by the AIDS epidemic. More modest risk increases were observed for precursor lymphoblastic leukemia/lymphoma, Burkitt's or Burkitt-like lymphoma and follicular lymphoma, whereas no change was noted for CLL/small lymphocytic lymphoma or lymphoplasmacytic lymphoma. For several subtypes such as the mantle cell and marginal zone lymphomas, time trends are difficult to assess due to the recent recognition of these entities as distinct subtypes. Concerning the group of T-cell lymphomas, SEER data have shown an increase of the specific cutaneous type mycosis fungoides, but otherwise epidemiological data are scarce (4). Primary extranodal lymphoma, particularly located in the central nervous system, has increased more rapidly than nodal forms since the 1970s (19). However, a decline in rates of central nervous

system lymphomas has been noted since the mid-1990s in the US, in parallel with the decreasing incidence of AIDS (2).

In 1992, an assembly was organized by the US National Cancer Institute to evaluate the time trends of NHL. At this meeting, it was concluded that the increasing temporal trend was indeed real (10), and that known and suspected risk factors could not explain the observed increase over time (22). Thus, after accounting for the likely effects of misclassification of diagnoses, the inclusion of new entities of NHL, and for established risk factors (see below), it was estimated that close to 50% of the observed increase in both sexes remained unexplained (22). In view of the absence of major breakthroughs concerning the etiology of NHL since then (with the exception of the role of *Helicobacter pylori* in gastric lymphomas that, however, represent few cases of NHL overall), the conclusions from the 1992 meeting are most likely still valid.

Clinical aspects in brief

The variation in clinical presentation and course, treatment approaches and prognosis among NHL subtypes is considerable, to say the least. In spite of major advances in the understanding of lymphoma biology reflected in the WHO classification, a clinical subdivision into indolent, aggressive and very aggressive lymphoma types is still meaningful. Other aspects considered in the clinical setting are location and disease spread. The standard staging system for NHL and HL is still the same as that proposed for HL at the Ann Arbor conference in 1971 (23). Its main purpose is to distinguish localized (stage I or II) nodal or extranodal presentation from more widespread disease (stage III or IV). It has been estimated that about one-fifth of newly diagnosed NHL patients present with localized extranodal disease, a smaller proportion with localized nodal disease and the majority with generalized nodal or extranodal disease (24).

In 1993, the International Prognostic Index was published, developed from a large number of similarly treated patients with diffuse large B-cell lymphoma. Based on age, performance status, serum lactate dehydrogenase, number of involved extranodal sites, and Ann Arbor stage, patients could be separated into clinically distinct groups with varying prognoses (25). A similar prognostic score has been developed for HL (26). Newer technologies, such as cDNA microarrays, have further distinguished patients into distinct prognostic groups even within histologic subtypes. For example, there appear to be at least two subcategories of diffuse large B-cell lymphoma, a germinal center B-cell type and a less favorable activated B-cell type based on differences in gene expression profiling (27). Also, two clinically distinct forms of CLL are characterized by the presence or absence of somatic hypermutations of the B-cell receptor immunoglobulin variable region genes (28). Thus, the lymphoma classification schemes currently in use will almost certainly be subject to further refinement in the future.

The range of treatment options in lymphoma is large and includes watchful waiting in indolent lymphomas as well as intense chemotherapy and/or radiotherapy in more aggressive types. In recent years, the options have been further diversified to include monoclonal antibodies, either alone or in combination with chemotherapy or other biological agents such as radio-immunoconjugates, and high-dose chemotherapy followed by stem cell transplantation (29).

ETIOLOGY OF MALIGNANT LYMPHOMAS, ESPECIALLY NON-HODGKIN LYMPHOMA

Pathophysiology in brief

B and T lymphocytes are important members of the immune system that above all serve to protect against infectious agents (30). They are the only cells that are able to recognize foreign substances or antigens on their own and consequently they control overall adaptive immune function. In general, B cells produce antibodies with the antigen-bidning capacity, whereas T cells recognize antigen presented by other cells. A variety of different secreted proteins, or cytokines, released by activated T cells (especially of the T helper cell, or CD4+, type) serve to alert and coordinate the local immune response. In order to fulfill the requirements of neverending adaptive recognition and neutralization of a wide range of old and new antigens, the lymphocytes and other immune cells are produced in enormous quantities, many millions per minute, in the bone marrow, and the cell turnover of most cell types is very rapid. The immune cells then migrate and end up in almost all organs in the body, but mainly the lymph nodes and spleen, while some circulate in the lymphatic vessels or in the blood. This explains the diversity in lymphoma locations and why lymphomas easily become widespread. A certain degree of autoimmunity, i.e., response of the immune system to self-antigens, is normal and controlled through continuous elimination primarily of autoreactive T cells. This process is known as immunologic tolerance. In light of the importance of the T cells in controlling B-cell as well as overall immune function, it is perhaps not surprising that the strongest and most well-established risk factors for malignant lymphomas are characterized by dysregulation or suppression of T-cell function (HIV/AIDS, post-organ transplant therapy, see below) that allow for Epstein-Barr virus (EBV)-driven B-cell proliferation and transformation.

As in cancer development in general, neoplastic transformation of T or B cells represents a multistep process with progressive accumulation of genetic lesions that result in clonal expansion and establishment of a solid or leukemic tumor. Mechanisms involve dysregulation of cell growth, cell signaling pathways and programmed cell death (apoptosis). The intricate genetic rearrangements in B-cell immunoglobulin or T-cell receptor genes during the normal differentiation and adaptation of these cells represent vulnerable stages with respect to genetic errors. During these processes, physiologically occurring DNA double-strand breaks pave the way for aberrant chromosomal translocations, which are typical of NHL tumors. In fact, chromosomal translocations have been observed in up to 90% of NHL cases (excluding CLL) (31). These translocations, with or without additional genetic lesions, can precipitate the activation of oncogenes or inactivation of tumor suppressor genes. Oncogenic viruses provide another possible mechanism for genetic lesions, as the introduction of a viral genome in the lymphoid cell may interfere with normal cell growth and regulation. Direct carcinogenesis by environmental factors also needs to be considered in this context.

Although the importance of genetic factors in lymphoma development is evident, the geographically uniform rise in NHL incidence implicates a crucial role of one or several environmental agents in the etiology of NHL. In the search for environmental causes of disease, investigators have quite naturally focused on exposures entailing a disruption of the delicate balance of normal immune function.

Genetic factors

Inherited disorders most commonly associated with an excess risk of NHL include ataxia-telangiectasia, Wiskott-Aldrich syndrome, common variable immunodeficiency, severe combined immunodeficiency, X-linked lymphoproliferative disorder, Nijmegen breakage syndrome, hyper-IgM syndrome and autoimmune lymphoproliferative syndrome (1). It has been estimated that up to 25% of patients with these disorders will develop tumors, primarily B-cell lymphoma, during their lifetime and often already in childhood (32), but as these disorders are exceedingly rare in the population, so are the complicating lymphomas. The mechanisms of lymphomagenesis are related to the underlying disorder and involve loss of T-cell control (Wiskott-Aldrich syndrome), apoptosis defects (autoimmune lymphoproliferative syndrome), abnormal DNA repair function (ataxia-telangiectasia, Nijmegen breakage syndrome), defective T-cell/B-cell interactions (hyper-IgM-syndrome), and perhaps chronic antigen stimulation (common variable immune deficiency) (1). Defective immune surveillance of EBV infection is an important co-factor in lymphoma development in this context.

Familial aggregation of hematopoietic malignancies has been consistently reported implicating a role of genetic susceptibility in lymphoma development. The risk of NHL is increased about 2- to 3-fold in first-degree relatives of patients with lymphoma or hematopoietic cancer (33-38). Higher excess risks of about 7-fold or more have been reported for CLL in first-degree relatives of CLL patients (39) and for HL in first-degree relatives of HL patients (34, 40, 41). It cannot be excluded, however, that familial clustering is attributable to shared environmental exposures rather than genetic predisposition. A few studies have described a tendency toward differential lymphoma risks by type of first-degree relation (33, 36, 38), i.e., higher risk in siblings compared to parents and offspring of index persons with lymphoma or hematopoetic cancer. This may indicate that both shared genetic and environmental factors contribute to the observed overall association.

Studies of common genetic variation that could confer susceptibility to malignant lymphomas in the general population are only beginning to emerge and no strong candidate genes have been identified to date. Specific genes investigated include those encoding for tumor necrosis factor alpha (42) and other cytokines (interleukin-6 (43), interleukin-10 (44)), T-cell antigens (45), the p53 protein (46), DNA repair proteins (47), biotransformation enzymes (48), intermediates of the folate metabolism pathway (49, 50), and human leukocyte antigens (HLA) (14). As in many genetic association studies, however, interpretation is often hampered by the high likelihood of chance findings due to small sample size and thus low statistical power, questionable control selection, failure to reconstruct haplotypes and identify biologically relevant gene-gene and gene-environment interactions, and, finally, failure to recognize lymphoma subtype heterogeneity (51).

Acquired immunosuppression

As is true for the primary disorders of immune dysfunction described above, acquired states of severe immunosuppression constitute strong and well-established risk factors for NHL, but explain few new cases in the general population. Clinical features shared by the majority of immuno-deficiency-related lymphomas are an association with EBV, diffuse large B-cell histology, extra-nodal location especially in the gastrointestinal tract and central nervous system, and aggressive clinical course.

Acquired states of severe immunosuppression associated with lymphoma include HIV infection and AIDS, and post-organ transplant therapy. In HIV-positive patients, aggressive NHL is considered an AIDS-defining condition. Overall NHL risk has been estimated to be increased about 60- to 200-fold in HIV-positive individuals relative to the general population, with low-range risk increases for indolent NHL types and higher excess risk for diffuse large cell NHL, in particular of the immunoblastic type (52). The risk of HL may be increased up to 8-fold (53). A decline in the incidence of AIDS-related lymphomas has been noted since the introduction of highly active antiretroviral therapy (HAART) (54), nevertheless, NHL still accounts for more than 20% of AIDS-related deaths in developed countries (52). The classic model of HIV-associated lymphomagenesis proposes chronic antigenic stimulation of B lymphocytes and macrophages induced mainly by EBV, but also human herpes virus 8 (HHV-8), in the presence of disturbed T-cell function and low CD4 cell counts. However, nearly 50% of AIDS-related lymphomas are negative for EBV or HHV8. Therefore, other factors must also influence HIV-related lymphomagenesis such as genetic abnormalities, cytokine dysregulation and dendritic cell impairment induced by HIV itself (52). Although HIV is not characterized by typical oncogenic potential by insertional mutagenesis, occasional non-random integration of the viral genome could possibly contribute to oncogenic transformation in a subset of patients (55).

A greatly increased relative risk of NHL in conjunction with potent immunosuppressive therapy following renal, liver, heart or bone marrow transplantation has been reported consistently (15). Post-transplant lymphoproliferative disorders comprise a spectrum ranging from early EBV-driven polyclonal proliferations to EBV-positive (80-90%) or EBV-negative malignant lymphomas, predominantly of B-cell origin (56). EBV-negative cases typically occur later than EBV-positive tumors: the majority of cases occurring more than five years after transplantation are EBV-negative. The relative risk of malignant lymphomas increases by about 10- to 20-fold in renal allograft recipients and up to about 200-fold in heart transplant recipients, compared to the general population (57). The pathogenesis of post-transplant lymphoproliferative disorders is complex and multifactorial although drug-induced impaired T-cell immune surveillance in combination with chronic antigenic stimulation exerted by the graft have a central role. Modulating factors include donor and recipient EBV serologic status, type of transplanted organ, underlying disease and type, duration and intensity of the immunosuppressive treatment. Anti-T-cell therapies and T-cell depleted bone marrow transplants are associated with particularly high excess risks of lymphoma (56).

It has been suggested that a minor degree of immunodeficiency also may mediate the development of lymphoma. However, judging from lymphomas occurring in HIV/AIDS and post-transplantation-associated immunodeficiency, it would be predicted that EBV-driven lymphoma most often would be the result. As most lymphomas occurring in the population are not EBV-positive, the HIV/AIDS and post-transplantation settings may not offer ideal causal models for the study of lymphoma etiology in the general population (58).

Infectious agents

Infectious agents consistently associated with malignant lymphomas include the herpesviruses EBV and HHV-8, and the retrovirus human T-cell lymphotrophic virus 1 (HTLV-1). More recent evidence also suggests a role for the hepatitis C virus (HCV), a single-strand RNA virus, whereas the role of simian virus 40 (SV40) of the polyoma virus family remains uncertain. Associated bacteria include *Helicobacter pylori* (*H. pylori*) and perhaps also *Borrelia burgdorferi*.

EBV

Widespread in all human populations, EBV persists in the vast majority of individuals as a lifelong asymptomatic infection of the B-lymphocyte pool. Primary infection with EBV usually occurs in childhood, but if it is delayed until adolescence it presents as infectious mononucleosis in about half of those infected (59). In healthy individuals an equilibrium exists between latent EBV infection and the host's immune system, where continued T-cell surveillance is of special importance. However, with severe immunodeficiency (see above), control mechanisms are impaired which may lead to EBV-driven B-cell proliferation and development of B-cell lymphoma (60). Importantly, EBV-encoded latent genes are capable of transforming B lymphocytes *in vitro* by altering cellular gene transcription and key cell signaling processes (61). Apart from a strong association with lymphomas in immunocompromised hosts, early EBV infection is also associated with Burkitt lymphoma in Africa but infrequently in other parts of the world, and with a few rare but specific types of T- and NK-cell lymphomas (predominantly occurring in Asia). Occasionally, EBV DNA has been found in B-cell tumors other than Burkitt lymphoma in immunocompetent hosts, but only to a small extent (less than 5%), and without evidence of linkage to a specific B-cell NHL type (62). EBV is present in the tumor cells in about 40% of cases with classical HL, especially of mixed cellularity and lymphocyte depleted subtypes, and a pathogenic role of the virus in these cases is plausible (61).

HHV-8

Also called Kaposi sarcoma herpes virus (KSHV), HHV-8 is detected in the majority of primary effusion or body cavity lymphomas. This rare lymphoma type occurs almost exclusively in HIV-infected individuals, but can develop occasionally in the absence of immunodeficiency in areas of high HHV-8 seroprevalence, such as the Mediterranean. Because patients with primary effusion lymphoma are often coinfected with EBV, the delineation of the etiologic role of each virus is difficult (62). However, observations of tumors being monoclonal expansions of a single infected cell support an etiologic role of HHV-8 (63).

HTLV-1

This human retrovirus is causally associated with adult T-cell leukemia/lymphoma in the Caribbean and Japan, where infection is endemic. The virus causes a latent persistent infection in circulating T lymphocytes. Adult T-cell leukemia/lymphoma develops in 2 to 5% of HTLV-1 infected individuals after a long latent period, suggesting a multistage process of T-cell transformation and involvement of additional pathogenetic factors (64). HTLV-1 infection is rare in Europe and the US, but some studies from the US have indicated a possible association between HTLV-1 and mycosis fungoides or Sézary syndrome (1).

HCV

Investigators have reported 2- to 14-fold increased relative risk of B-cell NHL in association with hepatitis C infection, but results are inconsistent (65, 66). Positive associations are mostly reported from geographical areas with high HCV seroprevalence, such as southern and eastern Europe, Japan and southern US, whereas no associations have generally been noted in studies from central and northern Europe, northern US or Canada (66). Thus, it has been estimated that the proportion of B-cell lymphoma cases potentially attributable to HCV infection in countries with a high seroprevalence is about 5 to 10%, but much lower if at all existent in other countries (66, 67). HCV is both lympho- and hepatotrophic and replicates in mononuclear blood cells. A specific HCV protein (E2) may be responsible for chronic antigen-driven polyclonal B-cell proliferation which may lead to lymphoma development in the presence of unidentified genetic or environmental cofactors (68). Interestingly, case reports suggest that low-grade B-cell lymphomas associated with

HCV infection may regress after successful antiviral and interferon therapy (69). Furthermore, various immunologic alterations have been observed with increased prevalence in individuals with chronic HCV infection, such as arthritis, neuropathy and Sjögren's syndrome, but if these links are pathogenetic or merely coincidental is not clear (70). HCV-associated lymphoproliferative lesions also share some molecular characteristics with Sjögren's syndrome-associated lymphomas (71). Mixed cryoglobulinemia, a vasculitic immune complex disorder, develops in a minority of HCV infected individuals and is frequently associated with benign lymphoproliferations in the liver and bone marrow. Overt malignant lymphoma occurs in about 10% of these cases (70).

SV40

The monkey polyoma virus SV40 is known to induce a variety of cancer types in laboratory animals, including lymphomas, by inactivation of the tumor suppressor genes *p53* and *pRB* (72). This virus accidently contaminated the Salk polio vaccine administered during the years 1955 to 1962 (73). However, the infection also exists among recipients of non-contaminated vaccines (31). In a few studies in humans, SV40-specific DNA sequences have been detected in a higher proportion in NHL tumor tissue than in control samples of normal lymphoid tissue or other tumors (74-76). However, several other studies have failed to confirm viral presence in lymphoma lesions (77-81). Furthermore, serum levels of SV40 antibodies were not associated with lymphoma risk in two case-control studies (73, 82). Comparisons of lymphoma risk in recipients of contaminated versus uncontaminated polio vaccine also support no association (83, 84). In conclusion, available evidence for a role of SV40 in NHL etiology is weak.

Helicobacter pylori

This gastric pathogen causes chronic gastritis, and its association with primary gastric lymphoma of the low-grade MALT-type is well established. In one of the first and most important studies, *H. pylori* infection in gastric tissue was detected in over 90% of cases with gastric MALT lymphoma (85). The relative risk of gastric MALT lymphoma has been estimated to be increased about six-fold in association with serologic evidence of *H. pylori* infection (86). *In vitro* studies have shown that B-cell proliferation in response to *H. pylori* is mediated by tumor-infiltrating T cells (87). Clinical trials further support a causal link, as about 75% of gastric MALT lymphomas regress upon eradication of *H. pylori* with antibiotic treatment (88).

Other pathogens

Infection with *Borrelia burgdorferi* has been associated with the development of primary cutaneous B-cell lymphoma in studies from European countries (89). However, no association has been observed in North America (90). The discrepancy may be due to genetic and phenotypic differences between *Borrelia burgdorferi* strains in Europe and the US (90). A bacterial etiology is also suspected for the uncommon immunoproliferative small intestinal disease (also known as alpha chain disease) arising from small intestinal mucosa-associated lymphoid tissue (MALT). Early-stage lesions may respond to antibiotic treatment, and isolation of *Campylobacter jejunei* from tumor tissue was recently reported in a small case series (91). *Chlamydia psittaci* has been linked to ocular adnexal lymphomas (92). In addition, a number of chronic infectious disorders including tuberculosis, malaria, pyelonephritis and herpes zoster have been associated with increased risk of NHL overall in epidemiological studies (93-96). Hence, the number of specific infectious agents found to be associated with lymphoproliferative malignancies is clearly growing, consistent with the idea of chronic immune stimulation as a potential risk factor for lymphomagenesis.

Autoimmune and chronic inflammatory disorders

Excess risks of malignant lymphomas have been consistently reported in association with rheumatoid arthritis (RA), Sjögren's syndrome, systemic lupus erythematosus (SLE), celiac disease, dermatitis herpetiformis, poly- and dermatomyositis, and chronic thyroiditis (97). In most these disorders, however, the mechanisms of lymphomagenesis remain unclear. Other autoimmune and chronic inflammatory disorders occasionally, but not invariably, associated with increased lymphoma risks include diabetes mellitus, psoriasis, sarcoidosis, inflammatory bowel disorders (IBD), systemic sclerosis and Wegener's granulomatosis. However, many studies have only assessed relative risks of lymphomas or leukemias overall, and have not distinguished among lymphoma or leukemia subtypes. Spurious positive associations could also arise due to misclassification, as lymphomas may mimic inflammatory disorders and be accompanied by autoimmune paraneoplastic phenomena (98).

Rheumatoid arthritis
A number of studies, mostly of cohort but also case-control design, have demonstrated increased risks of both NHL and HL in association with RA (94, 97, 99-105). On average, reported excess risks of malignant lymphomas overall range between 1.5- and 4-fold increased, with slightly higher estimates of risk of HL than that of NHL (100, 102, 103, 106). Mortality due to hematolympho-proliferative malignancies in RA is also approximately doubled compared to that in the general population (107). With regard to NHL subtypes, a possible overrepresentation of diffuse large B-cell lymphoma has been described, although not unanimously (108-110). CLL has mostly been studied together with other leukemias in RA, with mixed results (100, 103, 106). In one study where occurrence of CLL was assessed separately, no excess risk was noted (102).

The underlying reasons for the increased lymphoma risk in RA patients remain a matter of debate. Possible factors include chronic inflammation, immunosuppressive treatment, exogeneous agents (i.e., activation of latent EBV infection), and/or genetic or environmental determinants common to both conditions (111). With regard to treatment, particular concern has been raised for the immunosuppressants methotrexate, azathioprine and cyclophosphamide (97), and more recently also for the biological tumor necrosis factor-blocking agents (112). Investigators have reported higher excess risks in RA patients treated with disease-modifying anti-rheumatic drugs (DMARD) compared to patients without such treatment (113), and a positive association between long duration of DMARD use and risk of hematopoietic cancer (114), but neither of these studies could account for variations in disease severity. In a few studies with detailed information on markers of inflammatory activity as well as treatment (104, 115, 116), degree of inflammation was suggested to be more important than treatment. In line with this finding, a more pronounced risk increase of lymphoma has been reported in Felty's syndrome, a complication of severe RA (117). Although the role of EBV is still uncertain, the virus has been detected at low frequency in RA-related lymphomas (108, 115) and is therefore not likely to be of major importance.

Sjögren's syndrome
Patients with Sjögren's syndrome are at increased risk of developing NHL, especially of B-cell type. Reported increases in relative risk range from 4.5- to 44-fold, with higher estimates for primary disease than when secondary to RA, SLE or myositis (97, 106, 118). Case reports and case series have indicated a strong association with MALT lymphomas, especially in the parotid gland (119-121). However, one systematic assessment indicated that the predominance of MALT lymphomas may not be as large as previously believed (122). Local pathogenesis in affected glandular tissue

involves chronic inflammation and T-cell-dependent antigen stimulation. If these mechanisms are responsible also for development of non-organ specific lymphoma is, however, not clear. More severe disease characterized by hypocomplementemia and palpable purpura has been associated with accentuated NHL risks (123, 124), but no association has been reported with immunosuppressive treatment (97). Sjögren's syndrome itself may have a viral pathogenesis, but viruses have not yet been linked to subsequent development of lymphoma (125).

Systemic lupus eryhthematosus
Evidence is accumulating that SLE is associated with an excess risk of malignant lymphomas. Five of nine clinical cohort studies and one case-control study have reported a significantly increased risk of NHL of between 5.4- and 44-fold, whereas an increased risk was suggested in 3 other studies and only one previous report indicated no association (95, 126, 127). The two largest cohort studies based on hospitalized patients with SLE suggested an increase in risk of NHL of about 3- to 5-fold (128, 129). In a review of case reports, malignant lymphomas complicating SLE were often of B-cell NHL type, but HL and plasma cell disorders were also described (130). Only a few SLE patients developing lymphoma were on immunosuppressive treatment with either methotrexate, azathioprine or cyclophosphamide, and thus the role of these drugs appears to be minor (126). As in other autoimmune disorders, lymphomagenic mechanisms coupled with the disease itself may include persistent B-cell stimulation by self-antigens, apoptosis defects and/or other mechanisms (41, 126). EBV has been implicated in the pathogenesis of SLE (131), but it is not known if EBV has a role in the development of malignant lymphomas in SLE patients (130).

Celiac disease and dermatitis herpetiformis
Celiac disease, which is primarily localized to the small intestine, and dermatitis herpetiformis, which affects the skin, are related disorders associated with gluten intolerance, but they also display features common to autoimmune disorders. Increased risks of lymphoproliferative malignancies have been consistently reported in association with these conditions, but risk estimates are unstable. In a large Swedish cohort study of cancer risks linked to hospital discharge diagnoses, celiac patients had a 6-fold excess risk of NHL (132), which is generally lower than that in studies of earlier date (133-135), but in line with more recent studies (136-139). Interestingly, a tendency towards a declining risk of lymphomas in celiac disease was noted over successive calendar periods, from the 1970s to 1995, in this study. With regard to dermatitis herpetiformis, observed increases in lymphoma risk have ranged from 2- to 10-fold in recent studies (132, 140, 141). There is a prevailing hypothesis that early initiation of and total compliance to gluten-free diet therapy may protect against lymphoma in both disorders, but few studies lend direct support to this theory (12, 135). With regard to NHL subtypes, celiac disease has been repeatedly linked to an uncommon form of T-cell lymphoma in the small intestine, referred to as enteropathy-type T-cell lymphoma (ETTL) in the WHO classification. However, in a recent Italian population-based case-control study of NHL, only one of six NHLs in celiac patients was an ETTL (136). The development of intestinal T-cell lymphomas in the area of villous atrophy has been described as a multi-step process of polyclonal to monoclonal T-cell proliferation (142).

Poly- and dermatomyositis
Primarily dermato- but also polymyositis has been associated with a 2- to 4-fold increased risk of hematolymphoproliferative malignancies in both sexes (97, 143). There is little to suggest that immunosuppressive therapy influences lymphoma incidence in these patients (144, 145). In both diseases, lymphoma risk appears to be highest at the time of myositis diagnosis, probably mirroring the fact that these disorders also often occur as paraneoplastic syndromes (97).

Hashimoto's thyroiditis
Clinical cohort studies have estimated risk of NHL to be increased several-fold in association with chronic lymphocytic or Hashimoto's thyroiditis, but with substantial imprecision (146, 147). In these studies, the lymphomas were mainly located in the thyroid gland. Conversely, in two series of patients with thyroid lymphoma, a history of Hashimoto's thyroiditis was noted in about 40% of the patients (148), while over 90% of the cases had evidence of lymphocytic thyroiditis in thyroid tissue adjacent to the tumor (149). Lymphoid tissue is not normally present in the thyroid gland, and thus intrathyroid lymphoid tissue has to be accrued through various pathologic conditions, most notably Hashimoto's thyroiditis, in order for thyroid lymphomas to occur. Chronic antigen stimulation and apoptosis defects are further implicated as local lymphomagenic mechanisms (150). With regard to NHL subtypes, thyroid lymphoma is typically of the indolent MALT type, and can be difficult to distinguish from the inflammatory process itself (151). Occasionally the MALT lymphomas transform to more aggressive diffuse large B-cell tumors (149).

Inflammatory bowel disorders
It is currently believed that the central event in the pathogenesis of IBD (Crohn's disease and ulcerative colitis) is loss of immunologic tolerance against the indigenous enteric flora. However, the intestinal chronic inflammatory process is also characterized by abnormalities in humoral and cell-mediated immune function and autoimmune phenomena (152). In recent years, concern has been raised regarding increased risks of malignant lymphomas in IBD, especially in Crohn's disease, sparked by the introduction of potentially lymphomagenic treatment with tumor necrosis factor inhibitors. In ulcerative colitis, most investigations, including two recent large cohort studies, favor no association with lymphoma risk (153, 154). In Crohn's disease, previous reports are less consistent, with observations of around a two-fold excess risk (155, 156) or of no association (157, 158). The hitherto largest study observed a small risk increase confined to the first five years of follow-up (153), which could reflect a true association although the influence of reverse causality (as intestinal lymphomas may sometimes be mistaken for Crohn's disease) or surveillance bias cannot be entirely excluded. There is no support for an excess risk of HL or CLL in IBD (153). Studies of potential associations between other NHL subtypes or lymphoma location, e.g., gastrointestinal lymphoma, in IBD are lacking.

Psoriasis
Psoriasis is described as a multifactorial disease characterized by broad immune activation, especially of T cells, and influenced by environmental (diet, infections) and genetic components (159). Treatment may include potent immunosuppresive agents and, more recently, tumor necrosis factor inhibitors. Whether psoriasis is associated with an increased risk of malignant lymphomas is not clear. Four studies have observed a 2- to 7-fold increased risk (94, 160) whereas about as many studies have reported no association (95, 160). Yet another investigation noted an association with T-cell lymphoma in particular, but not with lymphomas overall (105).

Other autoimmune and chronic inflammatory disorders
Systemic sclerosis is an autoimmune rheumatic condition involving inflammatory, vascular and fibrotic pathology. Two Swedish cohort studies, including the largest to date, have suggested an increased risk of NHL, whereas two other studies observed no association (161). However, all investigations were limited by small numbers of NHL cases. In other inflammatory disorders with vascular pathology, such as Wegener's granulomatosis, the only large systematic study to date reported a 4-fold increased risk of malignant lymphomas (162). In multiple sclerosis, there is no

support for an excess risk of hematolymphoproliferative malignancies overall (163), although some observations support a shared etiology between multiple sclerosis and HL (164). It has been hypothesized that patients with ankylosing spondylitis are at increased risk of lymphomas, but no association was observed in a recent large study (165).

Associations between diabetes mellitus, regardless of type, and malignant lymphomas have been occasionally described, but the overall picture is that of no association. The few reports on cancer risks in type I (or autoimmune) diabetes have not found increased risks of malignant lymphomas overall, but have not distinguished among lymphoma subtypes (166, 167). In sarcoidosis, a chronic granulomatous condition that may involve an infectious origin and genetic susceptibility (168), case reports have highlighted a possible association with lymphomas, especially HL (169, 170). One large cohort study based on hospital discharge diagnoses found a two-fold excess risk of malignant lymphomas, but significantly increased risks of NHL and HL were confined to the first four years of follow-up (171). As pulmonary or hilar lymphoma may mimic sarcoidosis (172), misclassification could have influenced the results. Two smaller clinical cohort studies failed to observe an overall association (173, 174).

Skin cancer and ultraviolet light exposure

Numerous studies have described increased risks of HL, NHL and CLL following a diagnosis of skin cancer, including malignant melanoma, squamous cell carcinoma and basal cell carcinoma. Conversely, an increased risk of all three forms of skin cancer has been noted following a history of lymphoma (175-182). The latter association has generally been stronger. Several explanations have been proposed, of which exposure to a common environmental risk factor, i.e., ultraviolet (UV) light, has been most widely credited (18, 183, 184). Genetic susceptibility common to the two malignancies, post treatment effects and detection bias are other options. The hypothesis that exposure to UV light increases lymphoma risk, as it increases risk for skin cancer, has been further fuelled by parallel time trends in increasing incidence of skin cancer and NHL (183, 185) and positive correlations between estimated ambient UV-B radiation levels and/or latitude and NHL incidence or mortality. However, results based on such geographical correlations are altogether inconsistent (185-191). Similarly, studies using outdoor occupation as an indicator of chronic UV light exposure have yielded mixed results (192-195). Experimental studies in both humans and animals have shown that UV light exposure can induce systemic immunosuppression and have thus added biological credibility to the UV hypothesis (196, 197).

Allergy

Similar to the incidence of NHL, the incidence of allergic disorders has increased epidemically during the past decades. Interestingly, however, evidence suggests that several allergic conditions are associated with a reduced risk of NHL. A decrease in risk has repeatedly been observed in individuals with allergic skin conditions or with a history of allergy to grass or pollen (93, 198-202). However, the majority of these studies have used self-reported history of allergy, and the distinction between non-allergic conditions and allergy has not always been clear. Allergic reactions may be related to a reduced NHL risk through promotion of B-cell differentiation (199) and/or by skewing the T helper cell immune response towards increased T helper type 2 (TH2) activity (203, 204).

Occupational exposures

According to recent reviews, the role of chemical and agricultural exposures in NHL etiology is still uncertain (2, 31, 205, 206). An increased risk of NHL has been suggested in a variety of occupational groups, such as farmers, pesticide applicators, grain millers, wood and forestry workers and workers in the petroleum, rubber, plastic, and synthetics industries. Of these groups, farmers are most extensively studied, but results remain inconclusive. Potentially hazardous exposures among farmers include pesticides (phenoxy acids and chlorophenol herbicides), benzene and other organic solvents, and allergens. Benzene is a well-known leukemogenic agent (primarily causing acute myeloid leukemia), but current evidence for a causal link with NHL or CLL is insufficient (206).

A positive association between pesticide exposures and NHL and CLL has been observed repeatedly, but not consistently (2, 14). Most concern has been raised for the herbicide 2,4-dichlorophenoxyacetic acid. However, in a review of the effects of this herbicide on cancer risk, Garabrant et al. concluded that epidemiological studies provide weak evidence that 2,4-dichlorophenoxyacetic acid is associated with NHL or HL, and that biologically plausible effect mechanisms are lacking (205). Although the fraction of agricultural workers is small and decreasing in the developed world, domestic use of pesticides is widespread and increasing (2). Therefore, even small risk increases could explain a significant number of NHL cases and thus, further investigations are indeed warranted (2). Another chemical compound of concern is dioxin, which is listed as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC) (207). However, this designation has been criticized partly for being based on observations of increased risks of cancer overall rather than one or a few specific cancer forms (208). Some epidemiological studies have shown increased NHL risk in association with dioxin exposure, but available data are inconsistent (208).

Tobacco smoking

Study results on the possible role of tobacco smoking in NHL etiology are generally conflicting. Most reports have shown no excess risk of NHL overall in tobacco or cigarette smokers (209-213), but there are several exceptions (214-217). Some studies have suggested a specific association with risk of the common follicular NHL subtype (216, 218, 219). In analyses based on the SCALE study, cigarette smoking was associated with an increased risk of follicular lymphoma, but only among women and without evidence of a dose-response trend (220). Tobacco smoking appears to induce the *bcl-2* oncogene translocation (14;18) in peripheral lymphocytes of healthy individuals (221). This translocation is also present in the tumor tissue of 70-95% of follicular lymphomas (1). However, one study that specifically evaluated tobacco use and risk of t(14;18)-positive NHL failed to show any clear association (222). There is some evidence to suggest an association between smoking and HL, mainly among men, but causality has not been established (11).

Alcohol and dietary factors

The role of alcohol in the development of NHL is uncertain. Previous studies of alcohol intake have shown no association, or increased or reduced risk of NHL overall (223). Because dietary habits in western countries have changed dramatically over time, the potential influence of diet on NHL risk

is of interest. Diet could influence NHL risk through changes in energy balance, through direct exposure to dietary carcinogens and anti-carcinogens or by modulating the immune system, although evidence for any biological mechanism is limited. Several investigations, including the SCALE study, have suggested that higher consumption of meat, especially red meat, and dairy products may be associated with increased risk of NHL, and that increased intake of vegetables and fruits may reduce NHL risk (224).

Blood transfusion

Interest in blood transfusions and NHL arose after findings of a positive association in a prospective cohort study in 1993 (225). Blood transfusions may promote lymphomagenesis through transmission of oncogenic viruses, transfusion-associated immunosuppression and/or engraftment of lymphoma cells from a donor with subclinical lymphoma. Four early studies all identified an elevated risk of NHL associated with transfusion of blood products. However, seven subsequent studies, with collectively five times as many study participants as in the first four studies, did not confirm this association (226-228). In general, the early positive studies were less detailed and had less ability to control for potential confounding (228). However, in an update of the first cohort study (229), an increased risk of NHL was still observed after control for potential confounders. Only one study has been able to adjust for possible confounding by transfusion indication. This nested case-control study, based on a cohort of close to 100,000 transfusion recipients, reported no association with type of blood product, amount of blood transfused or latency period and risk of NHL or CLL (230). Thus, although an association between NHL and blood transfusion is biologically plausible, epidemiologic evidence of an association is weak, at most.

Medication

The existing literature concerning use of different drugs and NHL risk is contradictory. Past studies have found a significantly elevated risk of lymphoma in association with use of antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs) and other analgesics, corticosteroids, histamine$_2$-receptor antagonists, psychotropic drugs, anti-convulsants, estrogen replacement therapy, antidepressants or anti-anxiety drugs, amphetamines, and/or digitalis or digitoxin. Conversely, perhaps just as many studies have detected no or even an inverse association between risk of NHL and these same medications (231). As several diseases, including acquired immunosuppression, autoimmune disorders, allergies and infections also appear to be associated with NHL risk, it is difficult to determine whether apparent associations between medications and lymphoma risk are due to the effects of the medications themselves, or rather the underlying disorder. In recent analyses in the SCALE study, lifetime use of antibiotics was positively associated with risk of NHL, but it is unclear whether the association was due to use of the antibiotic drugs *per se*, the infections they were intended to treat or, alternatively, to an underlying susceptibility to infections (231). Other medications evaluated in SCALE, including corticosteroids, histamine$_2$-receptor antagonists, NSAIDs, and anti-convulsants, were not associated with risk of NHL or its major subtypes (231).

Anthropometric measures

The prevalence of obesity has expanded into a global epidemic over recent decades (232), in parallel with the rise in NHL incidence. Several studies have found a significant positive association between obesity and lymphoma incidence or mortality, but most previous investigations have not observed an association (233). Recent results from the SCALE study showed no association between usual adult body mass index and risk of NHL overall, but suggested an increased risk of diffuse large B-cell lymphoma (n=752) among individuals with high body mass index (233). However, in a prospective cohort study, no association was observed with risk of diffuse lymphomas (n=137) (234). Thus, based on available evidence, it appears highly unlikely that the escalation of overweight and obesity worldwide has contributed meaningfully to the increase in incidence of NHL.

Hair dyes

An excess risk of NHL has been proposed in association with use of hair dyes, especially in women and for dark dye colors, but results are not consistent (235, 236). In a recent population-based case-control study, an increased risk of NHL was noted only in relation to hair dye use before 1980 (237). This observation may reflect long duration of use, but it may also relate to the removal of carcinogenic compounds in hair dyes after a warning from the US Federal Drug Adminstration in 1979 (31).

Other environmental factors

Because pregnancy causes immunologic alterations, it has been suggested that reproductive factors could affect lymphoma incidence. However, no clear picture of any such relationship has emerged (238-240). Evidence is also inconclusive with regard to vaccination history (241). Physical activity could be of importance in lymphomagenesis as exercise is accompanied by transient changes of lymphocyte function. However, four studies found no association between physical activity and NHL risk (2). Exposure to ionizing radiation, either in individuals exposed to therapeutic, diagnostic or occupational radiation or in atomic bomb survivors, does not seem to increase risk of NHL or CLL (14, 15). A few studies have indicated a possible association between non-ionizing radiation such as that emitted by power lines and magnetic fields, and CLL (14), but there is little to suggest an association with other NHL types (15). Acute and chronic psychological stress have suppressive effects on immune function which may affect immune surveillance of developing tumors (242). A relationship between stress and the development of breast cancer has been indicated (243), but if stressful life events affect the development of malignant lymphomas is not known. Exposure measurement is a great challenge in this context, given the complexity of the interaction between personality traits, coping ability and perceived severity of different events.

SUMMARY OF NON-HODGKIN LYMPHOMA ETIOLOGY

In spite of intense research efforts in recent years, the causes of most cases of malignant lymphomas remain poorly understood. Established risk factors for NHL overall, or for one or several NHL subtypes, currently include hereditary immunodeficiency disorders, acquired states of strong immunosuppression (HIV/AIDS, post-organ transplant therapy), some infectious agents (EBV, HTLV-1, HHV-8, *H. pylori*), some autoimmune disorders (RA, Sjögren's syndrome, SLE, myositis, Hashimoto's thyroiditis, celiac disease/dermatitis herpetiformis) and a positive family history of hematolymphoproliferative malignancies. However, these factors together only appear to explain a minority of all new cases. Other probable risk factors include HCV and *Borrelia burgdorferi*, but evidence is still inconclusive for a large number of potentially lymphomagenic exposures. Perhaps the most important breakthrough in recent years was the finding that local *H. pylori* infection is involved in the development of gastric MALT lymphoma, a model that may serve to illustrate the importance of considering biologically plausible risk factors for separate lymphoma entities in future research.

ADDITIONAL NOTES ON HODGKIN LYMPHOMA ETIOLOGY

Several observations on HL epidemiology (e.g., space and time case clustering, diagnostic seasonality) have lead investigators to suspect an infectious etiology in HL, especially among young adults (11). Indirect observations, such as increased risk of HL in association with high social class background, and decreased HL risk in the presence of older siblings (244) and preschool attendance (245), support a role of delayed infections in this age group. Indeed, infectious mononucleosis (which results from delayed EBV infection) has been reported to increase HL risk in young adults (246). EBV has further been implicated in HL etiology in several ways. Antibody titers to EBV and viral capsid antigens are consistently reported to be higher in HL cases compared to controls (247). At the cellular level, EBV antigens have been localized to the HL-specific Reed-Sternberg tumor cells (11), most often in male patients with the mixed cellularity subtype. Recently, serologically verified infectious mononucleosis was also specifically associated with EBV-positive HL, making a causal role of delayed EBV infection probable in young adults (248). With respect to other infectious agents, an increased risk of HL has been observed in association with HIV infection in developed countries, as noted above. Human herpes virus-6 infection has been detected with higher frequency in HL cases than controls, but findings are not consistent (11). Other environmental exposures that may be of importance in HL etiology include tobacco smoking and hormonal factors related to parity and age at first birth (11). In addition, a degree of familial aggregation has been consistently reported. HLA genotypes may be important in determining susceptibility to HL, but specific genotypes have not yet been identified (11).

AIMS

The overall aim of this thesis was to increase our understanding of the etiology of malignant lymphomas, and NHL subtypes in particular, with regard to UV light exposure and autoimmune and chronic inflammatory disorders.

Specifically, the following questions were addressed:

- Is frequent exposure to sun and artificial UV light associated with increased risk of malignant lymphomas overall or any lymphoma subtype? (Paper I)

- What is the level of risk increase of malignant lymphomas (NHL and HL) in patients ever hospitalized with RA, and what is the impact of latency and calendar period on risk estimates? (Paper II)

- Is the increased risk of malignant lymphomas in RA due to genetic or environmental risk factors common to both conditions? (Paper II)

- Is celiac disease associated with lymphoma subtypes other than small intestinal T-cell lymphoma? (Papers III and IV)

- What is the level of risk increase of NHL in any (hospitalized or unhospitalized) patients with RA, Sjögren's syndrome, SLE or celiac disease? (Paper IV)

- Are RA, Sjögren's syndrome and/or SLE associated with specific NHL subtypes? (Paper IV)

- Are diabetes mellitus (type I in particular), psoriasis, IBD and/or sarcoidosis associated with an increased risk of overall NHL or any particular NHL subtype? (Paper IV)

- How is NHL risk affected by autoimmune and chronic inflammatory disease phenotype and treatment with NSAIDs, systemic corticosteroids and specified immunosuppressants, particularly in RA? (Paper IV)

SUBJECTS AND METHODS

SETTING

The studies in this thesis were conducted in Sweden (papers I-IV) and Denmark (papers I and IV). Features that enabled this research included the national registration numbers assigned to all citizens, and existing nationwide high-quality health and population registers based on these registration numbers (see below). The structure of the Swedish health care system, financially and geographically accessible to all citizens, ensures that use of health resources and registration of such use is population-based. Another important prerequisite was the generally high public willingness of Scandinavian residents to participate in research projects.

The Swedish Hospital Discharge Registry (www.sos.se/epc-par)

The Swedish Hospital Discharge Registry holds individualized information on inpatient care by county since 1964, and nationwide since 1987 (249). For every hospital discharge, information on diagnoses and surgical procedures are recorded according to the ICD coding system. Apart from the national registration number and dates of admission and discharge, the register includes up to 8 discharge diagnoses and 6 surgical procedure codes for each hospitalisation. The 7th revision of ICD was used until 1968, the 8th revision between 1969 and 1986, the 9th revision between 1987 and 1996, and the 10th revision since then. The total number of register drop-outs for somatic short-time care in the period 1987 to 1991 has been estimated to be less then 2 percent. Two validation studies of discharge information (in 1986 and 1990) indicated a diagnostic validity of between 85 and 90% overall (249).

The Swedish Cancer Registry (www.sos.se/epc.cancer)

The Cancer Registry holds information on incident cancers since 1958, classified according to the ICD system (6). From the register's inception, it has been mandatory for both clinicians and pathologists to report almost all malignant disorders to the Cancer Registry at the time of diagnosis. One exception is basal cell skin cancer, for which reports became mandatory only in 2003. Since 1982, reports have been sent first to one of six regional oncology centers for quality checks and coding: data are then transferred to the national register. At present, approximately 99% of the registered cases are morphologically verified (6). The completeness of registrations (for all cancer sites) has been estimated at 96%, based on comparisons with other registers (250).

The Swedish Cause of Death Registry (www.sos.se/epc.dors)

The Cause of Death Registry holds information on dates and main causes, as well as complementary causes, of all deaths among Swedish residents since 1952, although a nationwide reporting system for causes of death was first introduced in Sweden already in 1749 (251). The completeness of registrations currently exceeds 99%.

The Swedish Register of Population and Population Changes

This register is maintained by Statistics Sweden and contains official Swedish census data since 1960 in computerized form. The national registration number and current address of residents alive at the end of each year are included. Emigrations have been registered since 1969.

The Swedish Multi-Generation Register

The nationwide Multi-Generation Register was created by Statistics Sweden in the year 2000, and is based on the previous Second-Generation Register that was created in 1994 (252). The register contains information on the national registration numbers of vertical and horizontal first-degree relatives of Swedish residents born in 1932 or later and alive in 1961. Parents who emigrated or died before 1947, as well as siblings who emigrated or died before 1961, are not registered. The completeness with respect to relatives (siblings in particular) deceased during the period 1961 to1990 is also somewhat reduced. Nevertheless, national registration numbers of both parents are identified for at least 83% of all index persons, and for well over 90% of index persons alive in 1991. Non-biological relations (e.g., adoptions) are indicated.

Danish registers

LYFO
The Danish national Lymphoma Registry Organization (LYFO) was initiated in 1991 and collects clinical data on all Danish patients diagnosed with lymphoma (253). Registered information includes date of diagnosis, clinical stage according to the Ann Arbor system (23) and specific organs involved. In addition to the data collection, a random 10% sample of all incident LYFO-registered cases in the country is continuously reviewed by a panel of expert hematopathologists.

The Danish Pathology Register (www.patobank.dk)
All pathology departments in Denmark are connected to this register, which has been functioning in its present form since 1999. Its main purpose is to offer an easily accessible and complete overview of patients' histology for the use of Danish pathologists in their daily clinical work, but the data are also accessible for research purposes. The estimated coverage of the register is close to 100% (personal communication: Inge Gram, Danish pathology register).

STUDY DESIGN

Papers I and IV (the SCALE study)

Study Subjects
Papers I and IV are based on a large case-control study, called the SCALE (Scandinavian Lymphoma Etiology) study, in Denmark and Sweden. The SCALE study base encompassed the entire population between the ages of 18 and 74 years living in Denmark from June 1, 2000, to August 30, 2002 and in Sweden from October 1, 1999, to April 15, 2002. In Denmark, participants in a regional pilot phase study initiated in November 1999 were also included. The source population was further restricted to subjects with sufficient knowledge of the Danish or Swedish language for a telephone interview, and without a history of organ transplantation, HIV infection, or prior hematopoietic malignancy. Individuals with a first, newly diagnosed malignant lymphoma (NHL, including CLL, or HL) according to the REAL (5) and WHO classifications (1) were eligible as case patients. The corresponding ICD-10 codes used were C82-C85, C88.0, C91.3-5, C91.7 (NHL), C91.1 (CLL), and C81 (HL). In both countries, because of the relatively low incidence of HL, the study population also included patients with prevalent HL diagnosed in 1999, before the start of recruitment of incident cases.

For identification of newly diagnosed patients, we set up a system of rapid case ascertainment in both countries. This system consisted of a network of contact physicians in all hospital clinics where malignant lymphomas are diagnosed and treated (internal medicine, hematology, oncology, and clinical pathology), and involved a total of 157 departments (39 in Denmark and 118 in Sweden). Continuous collaboration with the national pathology registry in Denmark and the six regional cancer registries in Sweden ensured complete reporting through the network. Thus, patients were recruited to the study either directly by their treating physician or by mail from the Danish or Swedish study offices after the treating physician's approval was granted. Controls were randomly sampled from the entire Danish and Swedish populations using continuously updated, computerized population registers. A subset of control subjects was sampled every 6 months during the study period, and was frequency-matched within each country on the expected distribution of NHL cases by sex and age (in 10-year intervals). Extra control sampling was performed in the youngest age groups to ensure a minimum 1:1 matching ratio for HL patients in all age groups. All eligible controls were contacted by mail.

Lymphoma classification
In Denmark, review of tumor material took place within the national Lymphoma Registry Organization (LYFO, see above). Within this registry, a random 10% sample of all incident cases in the country is reviewed continuously by a panel of expert hematopathologists. In addition, in all but 20% of the study patients in Denmark the diagnostic tumor specimens had been evaluated primarily by a LYFO-approved senior hematopathologist. In Sweden, samples from all case patients were histopathologically evaluated by one of six senior hematopathologists or cytologists and classified according to the WHO classification (1). Altogether, 70% of all included Swedish patients were reviewed within the study, whereas the remaining 30% had been reviewed already in routine care by one of the six appointed experts. Ambiguous samples were referred to a panel of hematopathologists for final evaluation. The original diagnostic slides could not be retrieved for 35 (1.5% of all) Swedish patients included in the study. In these cases, the written results of the primary morphologic and immunohistochemical investigation were used for diagnostic re-evaluation. For paper IV,

Information on lymphoma location was obtained through the national lymphoma registry organisation in Denmark (253), and six lymphoma registers maintained by the regional cancer registries in Sweden (6).

Exposure information
Information on potential risk factors for lymphoma was collected through a telephone interview based on a standardized and computer-aided questionnaire. All questions were identical in the two countries (except in language), and addressed areas such as current height and normal weight, sun exposure habits, history of autoimmune and chronic inflammatory disorders and specific infections, allergy, medication use, blood transfusions, smoking, travel habits, main occupation, occupational exposure to pesticides and solvents, educational level and family history of cancer. The interviews were performed in Sweden by professional interviewers from Statistics Sweden, and in Denmark by trained medical students. We were unable to blind the interviewers to case or control status, but they were unaware of the specific hypothesis under study and were instructed to treat case patients and control subjects in strictly the same manner. The total number of questions asked varied from 93 to 345, depending on the number of "question loops" entered. Informed consent was obtained from each participant before the interview.

For paper I, we analyzed questionnaire information regarding history of exposure to sun and artificial UV light, host characteristics of sun sensitivity and history of skin cancer. Questions concerning host factors and UV light exposures were adapted from a validated questionnaire previously used in studies of sun-related behaviour in individuals with dysplastic nevus syndrome (254). Recorded host characteristics included natural hair color, eye color and skin sensitivity to sun exposure (also referred to as skin type). Skin sensitivity was defined as the reaction of the skin (without sunscreen protection) to the first sun exposure of the summer season. Four categories were used where skin type I represented the most and type IV the least sun sensitive. Assessment of sun exposure included sunbathing frequency during the summer in Denmark/Sweden 5 to 10 years before interview, and at age 20 years (with 7 response categories ranging from never to 6 to 7 times per week); frequency of sunburns 5 to 10 years before the interview, at age 20 years, and during childhood (with 5 categories from never to 3 times yearly or more); lifetime history of sun vacations abroad (with 6 categories, from never to more than 20 times); and outdoor occupation lasting 1 year or more (ever/never). Sunbathing and sunburns at age 20 years were evaluated only among people 40 or more years old. We also assessed exposure to artificial UV light based on use of solaria (sun beds) or sun lamps. Finally, we recorded history of skin cancer (ever/never), and, if positive, age at diagnosis of skin cancer.

For paper IV, we analysed participants' history of a number of autoimmune and chronic inflammatory disorders, disease characteristics and treatment. The questionnaire included specific questions about medically confirmed diagnoses of each of the following disorders: RA, Sjögren's syndrome, SLE, celiac disease, Crohn's disease and ulcerative colitis (inflammatory bowel disorders, IBD), diabetes mellitus (type I or II), psoriasis and sarcoidosis. Upon confirmation of a disorder, a subset of questions followed, at all times (except for diabetes mellitus) including the age at start of symptoms. For RA we assessed daily drug treatment lasting more than 4 weeks, surgery for RA and degree of daily restraints due to RA. For celiac disease, we assessed age at initiation of a gluten-free diet and dietary compliance. For diabetes mellitus we asked about type (I/II), age at diagnosis and treatment. Type I diabetes was defined as report of type I, age 30 years or younger at diagnosis and treatment with insulin only. For psoriasis, we assessed psoriatic arthritis. In IBD, we asked about surgical treatment. Data on hospital discharges listing RA, SLE, celiac disease and

psoriasis were obtained from population-based and nation-wide Hospital Discharge registers in each country (249, 255).

For all disorders except diabetes, celiac disease and inflammatory bowel disorders, we assessed treatment with systemic corticosteroids and/or immunosuppressive drugs. Immunosuppressive therapy was defined in each sub-question as exposure to any of the following drugs: azathioprine, cyclosporine, methotrexate, cyclophosphamide and chlorambucil, with mentioning of all trademark names currently or historically used in Denmark or Sweden. These drugs were chosen on the basis of their immunosuppressive properties and previously reported associations with cancer (97). In addition, all interviewees were asked about treatments with systemic corticosteroids or cytotoxic/cytostatic/immunosuppressive drugs (oral or intravenous) for any disorder other than those already inquired about specifically. These questions were added a few months after the study start and were asked of approximately 80% of the participating cases and controls. Use of NSAIDs was assessed among all study participants.

Paper II

Study subjects
The cohort of patients with RA was identified in the population-based Swedish Hospital Discharge Register, as all patients with a discharge listing RA between January 1st, 1964, and December 31st, 1999 at age 16 years or older (n=83,737). The ICD codes used were 722 (ICD 7), 712.1, 712.3, 714.93 (ICD 8), 714A-C, 714 W (ICD 9) and M05-6 (ICD 10). Patients were excluded if they had a diagnosis of a related rheumatological disorder (SLE, ankylosing spondylitis or psoriatic arthritis) at any other discharge (n=3,866, 5%). We further excluded 647 (0.8%) subjects due to loss of follow-up or data irregularities, and 2,697 individuals (3%) who died in conjunction with their first discharge with RA. Thus, the final analytical cohort consisted of 76,527 RA patients with information on national registration number, date of first hospital discharge with RA, discharge department, age and sex. First-degree relatives of the RA patients were identified through linkage with the Multi-Generation Register. To overcome certain limitations of this register (see above), linkage was performed with all RA patients born 1932 or later and alive in 1990 (n=15,397). For 477 patients, no first-degree relative could be identified. For the remaining 14,920 patients with RA, we identified a total of 70,650 first-degree relatives. Of these, 2,173 (2.9%) were excluded due to loss of follow-up or data irregularities. Finally, the cohort of first-degree relatives used for analysis consisted of 21,652 parents, 19,546 siblings and 27,279 offspring. This cohort was subsequently linked to the Hospital Discharge Register to obtain information about relatives' inpatient care due to RA and related rheumatological conditions.

Follow-up
Both cohorts were linked to the nationwide and population-based Cancer Register, Cause of Death Register, and Register of Total Population and Population Changes. Through these linkages, we obtained information about all incident cancers, deaths and emigrations. The outcome was defined as malignant lymphomas (NHL, ICD7: 200, 202, and HL, ICD7: 201), CLL (ICD7: 204.1) and multiple myeloma (ICD7: 203). For patients, follow-up started at the first date of discharge with RA. For parents, follow-up started at the last of date of birth of the patient or January 1st, 1961. Siblings and offspring were followed from the last of date of birth or January 1st, 1990. For all individuals, follow-up ended at the first of death, emigration, loss to follow-up, or December 31st, 1999. In the analysis of childhood cancer, we performed analyses of all offspring followed during the period

1961-1999 as well as during the 1990-1999 period only. Since the risk estimates were similar, we present those of the former, and larger, analysis.

Paper III

Study subjects

Study subjects with celiac disease and subsequent lymphoma were identified from a pre-existing cohort of individuals with celiac disease recorded in the Hospital Discharge Register (132), and matched with the Cancer Register. This cohort consisted of all patients discharged with a diagnosis of celiac disease between January 1st, 1964, and December 31st, 1995 (n=11,605). The ICD codes used were 286.00 (ICD 7), 269.00, 269.98 (ICD 8) and 579A (ICD 9). Upon linkage with the Swedish Cancer Register, 77 patients with malignant lymphomas had been identified, including NHL (ICD 7: 200, 202) or HL (ICD 7: 201), but not CLL (ICD 7: 204.1). Seven of these were diagnosed at autopsy. Following written consent from all living patients, we collected medical files of each case and extracted diagnostic details about the celiac disease and the malignant lymphoma. Upon review of medical records, eight patients did not have celiac disease and were thus excluded. In another three patients, celiac disease was not confirmed with certainty due to atypical symptoms and/or lack of duodenal biopsies. Overall, the diagnosis of celiac disease could be confirmed in 66 patients, primarily through typical findings in duodenal biopsies (n=64) or a combination of typical symptoms, prompt effect of gluten-free diet and relapse of symptoms upon gluten provocation (n=2).

Reclassification

Original tumor slides and paraffin embedded tissue blocks for the lymphoma were retrieved for all but eight patients (seven of whom were diagnosed at a hospital that did not participate). The condition of the tumor material precluded a reliable review for two patients (both diagnosed at autopsy). Thus, final histopathological review and reclassification were performed in 56 lymphoma patients (56/66, 85%). This process included re-evaluation of original slides in order to select appropriate blocks with preserved tumor areas and cutting of new sections from these areas for routine- and immunostainings. The new slides were stained with hematoxylin-eosin, according to May-Grünwald-Giemsa and with a panel of antibodies for lymphoma subtyping. With respect to antibodies, all slides were stained with the B-cell antibody CD20 and the T-cell antibodies CD3 and CD45^{RO}. For further subtyping, antibodies were used when appropriate (based on the WHO classification criteria (1)) from the following panel: CD2, CD5, CD10, CD15, CD23, CD30, Kappa, Lambda, Mib-1 (Ki-67), granzyme, perforin, cyclin D1, TIA-1, Cam5.2, MNF116 and myelo-peroxidase. The slides were then reviewed by an experienced hematopathologist (Måns Åkerman) who, blinded to all clinical data, reclassified the malignant lymphomas according to the WHO (1).

STATISTICAL METHODS

Papers I and IV

Using unconditional logistic regression, we calculated odds ratios (OR), with 95% confidence intervals (CI), as measures of relative risk. All analyses were adjusted for the matching factors age (in 5-year intervals), sex, and country. Confounders were considered based on prior knowledge of potential risk factors for NHL (241), as well as on changes in estimates of relative risk comparing models with and without additional covariates.

In paper I, due to small numbers, we collapsed the upper two categories of the variables concerning sunbathing and sunburns at different ages, and use of solaria/sun lamps, and intermediate categories in the analyses of hair and eye color, sunbathing, sun vacations abroad, and use of solaria/sun lamps. Regarding eye color, brown and black color were collapsed into the referent category. Statistical significance of independent variables and interaction effects was tested by the likelihood ratio test. We tested for trend across categories of some exposure variables by assigning equally spaced values (e.g., 1, 2, 3, 4) to the categories and treating them as continuous variables in the regression analysis.

In paper IV, a reported diagnosis of any autoimmune/inflammatory disorder was excluded if symptoms began less than two years before lymphoma diagnosis (or interview for controls). In the analyses of treatment stratified on RA, drug use initiated less than two years before lymphoma diagnosis or interview was also disregarded. Multivariable adjustment for treatment, as well as a number of other covariates changed estimates 6% or less and were therefore not included in the final model. We calculated the population attributable fraction for four disorders using the following formula: (prevalence of exposure x (OR-1))/(prevalence of exposure x (OR-1)+1) x 100 (256-260).

Papers II and III

We assessed risks of overall cancer and of malignant lymphomas using the standardized incidence ratio (SIR). SIRs were calculated by dividing the observed number of cancers with that expected. Expected numbers were calculated as the product of sex-, age-, and calendar period-specific person-years of follow-up in the underlying cohorts and the corresponding incidence of the same malignancy in the general population. Ninety five % CIs were calculated assuming a Poisson distribution for the observed cases (261). In paper II, p-values for difference were calculated in a multivariate Poisson regression model, including age, with the expected rates as offset: the p-value for trend in follow-up time was calculated in a linear model. In paper III, the expected numbers of cases of NHL subtypes (i.e., T- and B-cell NHL, primary gastrointestinal NHL and non-intestinal NHL) were estimated using information from previous studies (including SCALE) on their respective proportions (11,19-22), as national rates are only available for overall NHL, CLL and HL. P-values for trends over calendar periods were calculated using Poisson regression.

RESULTS

RESULTS OF THE SCALE STUDY DATA COLLECTION (Papers I and IV)

Altogether, 6,927 individuals (3,740 patients with malignant lymphomas and 3,187 controls) participated in the study (Table 1). Approximately 37% of the participants were from Denmark, and 63% were from Sweden. Among the case patients, 3,055 had NHL (including CLL), 618 HL and 67 unspecified lymphoma. Participation rates among eligible subjects were 83% among all cases (81% for NHL and 90% for HL), and 71% among controls. The main reason for non-participation was early death among cases (n=279, 6%), whereas unwillingness was most frequent (n=718, 16%) among controls. Most of the HL patients were newly diagnosed during the study period (n=508, 82%), but 18% (n=111) were diagnosed in 1999, prior to study start and were thus recruited as prevalent cases. The median duration of the interview was 25 minutes among cases (range: 12 to 121 minutes) and 26 minutes among controls (range: 12 to 106 minutes). Most patients (82%) with incident lymphoma were interviewed within 6 months after the date of the diagnostic biopsy (median interval: 2.8 months; range: 0 to 40 months). Among the patients with prevalent HL, the median time from biopsy to interview was 13 months (range: 1 to 50 months).

Table 1. Characteristics of participants in the Scandinavian Lymphoma Etiology (SCALE) study

	Controls	All malignant lymphomas*	All NHL	NHL subtypes							HL
				Diffuse large B-cell	CLL[†]	Follicular	T-cell	Mantle cell	Marginal zone	Lympho-plasma-cytic	
Number of participants											
	3187	3740	3055	796	752	586	204	148	117	116	618
Country of residence											
Denmark	1186 (37)	1393	1075 (35)	283 (36)	296 (39)	222 (38)	77 (38)	54 (36)	49 (42)	50 (43)	254
Sweden	2001 (63)	2347	1980 (65)	513 (64)	456 (61)	364 (62)	127 (62)	94 (64)	68 (58)	66 (57)	364
Sex											
Male	1767 (55)	2184 (58)	1819 (60)	474 (60)	480 (64)	279 (48)	128 (63)	112 (76)	57 (49)	75 (65)	333 (54)
Female	1420 (45)	1556 (42)	1236 (40)	322 (40)	272 (36)	307 (52)	76 (37)	36 (24)	60 (51)	41 (35)	285 (46)
Age[§] (years)											
18-24	123 (4)	158 (4)	35 (1)	12 (2)	0	5 (1)	11 (5)	0	0	0	122 (20)
25-34	189 (6)	269 (7)	89 (3)	38 (5)	4 (0.5)	14 (2)	18 (9)	1 (1)	3 (3)	1 (1)	177 (29)
35-44	264 (8)	329 (9)	210 (7)	81 (10)	17 (2)	54 (9)	28 (14)	3 (2)	5 (4)	3 (3)	114 (18)
45-54	597 (19)	670 (18)	588 (19)	143 (18)	138 (18)	141 (24)	38 (19)	26 (18)	22 (19)	16 (14)	65 (11)
55-64	906 (28)	1105 (30)	1011 (33)	247 (31)	257 (34)	206 (35)	54 (26)	52 (35)	41 (35)	48 (41)	72 (12)
65-74	1108 (35)	1209 (32)	1122 (37)	275 (35)	336 (45)	166 (28)	55 (27)	66 (45)	46 (39)	48 (41)	68 (11)
median	59	59	60	60	63	57	55	63	62	62	36
(range)	(18-76)	(18-74)	(18-74)	(19-74)	(30-74)	(22-74)	(18-74)	(34-74)	(26-74)	(28-74)	(18-74)

* All malignant lymphomas included cases with non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL) and 67 cases of unspecified lymphoma
[†] Chronic lymphocytic leukemia
[§] Age at diagnosis for cases and interview for controls

ULTRAVIOLET LIGHT EXPOSURE (Paper I)

Host characteristics of sun sensitivity

Hair and eye color were not convincingly associated with risk of malignant lymphomas. A U-shaped association between skin sensitivity to sun (skin type) and lymphoma risk was observed for both NHL and HL. Subjects whose skin often burns on first seasonal sun exposure (type II) consistently had the lowest relative risk compared with subjects whose skin seldom burns (type IV). For subjects with even more sensitive skin (type I), the risk estimates approached unity.

Exposure to sun and artificial ultraviolet light

In multivariable analyses, increasing frequency of sunbathing during summer in Denmark/Sweden and increasing number of sun vacations abroad were associated with a decreasing risk of NHL (Table 2). Individuals with a history of sunbathing 4 times a week or more (both during the period 5 to 10 years before interview and at age 20 years) or a lifetime total of 20 or more sun vacations abroad had an approximately 30% lower risk of all NHL than individuals without such sunbathing or vacation histories. Increasing annual frequency of sunburns during all time periods assessed was also inversely associated with risk of all NHL. The association was most pronounced for exposure at 20 years of age; individuals in the highest category of sunburn frequency (twice a year or more) at that age experienced a statistically significant 40% decrease in their risk of NHL compared with those who had no sunburns (Table 2). These risk reductions were statistically significant, as were the inverse trends (all $P_{trend} \leq .003$).

We observed reductions in risk of HL of the same magnitude, but these estimates were based on smaller numbers and did not reach statistical significance (Table 2). Similar results were observed for all major B-cell NHL subtypes, but the data for T-cell lymphoma were less clear. Frequent use of solaria or sun lamps was associated with a marginally significant 20% reduced risk of NHL and a significant 30% reduction in risk of HL. Ever having had an outdoor occupation for one year or more was associated with a slightly increased relative risk of NHL (OR=1.2, 95% CI 1.0-1.3), compared with never having worked outdoors, but this association was weakened after additional adjustment for occupational exposure to pesticides. Mutual adjustment for all other UV light exposure measures in subjects 40 years of age or older (not all variables were assessed in subjects younger than 40 years) resulted in attenuation of a few estimates. Mainly, the negative associations between risk of NHL and sunbathing or sunburns during the period 5 to 10 years before interview or solaria/sun lamp use were weakened, whereas estimates for exposures at 20 years of age and in childhood, as well as for number of sun vacations abroad, remained unchanged.

Analyses of interaction

Results did not vary by skin type, age or sex. However, the relative risk of NHL was significantly lower in Sweden than in Denmark in association with sunburns 5 to 10 years before interview and at age 20 years, but not in childhood. Importantly, though, negative associations were seen in both countries. For all other UV exposure variables, there was no effect modification by country.

Table 2. Relative risk* of all non-Hodgkin lymphoma (NHL), major NHL subtypes and Hodgkin lymphoma (HL) according to selected sun exposure variables

	All NHL	NHL subtypes				HL
		Diffuse large B-cell	**CLL**[†]	**Follicular**	**T-cell**	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Sun vacations abroad						
Never	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
1-5 times	1.0 (0.9-1.1)	0.9 (0.8-1.2)	0.9 (0.7-1.1)	1.2 (0.9-1.5)	0.9 (0.6-1.3)	0.8 (0.6-1.0)
6-20 times	0.9 (0.8-1.0)	0.8 (0.6-1.0)	0.9 (0.7-1.1)	1.0 (0.7-1.2)	0.7 (0.5-1.1)	0.7 (0.5-0.9)
>20 times	0.7 (0.6-0.8)	0.7 (0.5-0.9)	0.6 (0.5-0.8)	0.7 (0.5-1.0)	0.6 (0.3-1.0)	0.8 (0.6-1.2)
	P_{trend}<.0001	P_{trend}=.001	P_{trend}=.002	P_{trend}=.04	P_{trend}=.02	P_{trend}=.06
Sun bathing at 20 yrs of age[§]						
Never	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
≤once/week	0.8 (0.7-0.9)	0.9 (0.7-1.2)	0.7 (0.6-0.9)	0.6 (0.4-0.8)	1.5 (0.9-2.6)	0.8 (0.5-1.2)
2-3 times/week	0.7 (0.6-0.9)	0.8 (0.6-1.0)	0.6 (0.5-0.8)	0.7 (0.5-0.9)	0.9 (0.5-1.6)	0.6 (0.4-1.0)
≥4 times/week	0.7 (0.6-0.9)	0.7 (0.5-1.0)	0.7 (0.5-0.9)	0.6 (0.5-0.9)	1.3 (0.8-2.3)	0.9 (0.6-1.4)
	P_{trend}=.001	P_{trend}=.01	P_{trend}=.009	P_{trend}=.06	P_{trend}=.95	P_{trend}=.84
Sun burns at 20 yrs of age[§]						
Never	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
<1/years	1.0 (0.9-1.2)	1.0 (0.8-1.2)	1.1 (0.9-1.3)	1.0 (0.8-1.3)	1.2 (0.8-1.8)	0.9 (0.7-1.3)
1/year	0.8 (0.7-0.9)	0.8 (0.6-1.1)	0.8 (0.6-1.1)	0.7 (0.6-1.0)	1.0 (0.6-1.6)	0.8 (0.5-1.1)
≥2/year	0.6 (0.5-0.8)	0.5 (0.4-0.7)	0.7 (0.5-1.0)	0.7 (0.5-1.0)	0.5 (0.2-1.0)	0.8 (0.5-1.3)
	P_{trend}<.0001	P_{trend}<.001	P_{trend}=.03	P_{trend}=.009	P_{trend}=.19	P_{trend}=.14

* Multivariable odds ratios (OR) and 95% confidence intervals (CI) adjusted for age (in 5-year intervals), sex, country and skin type
[†] Chronic lymphocytic leukemia
[§] Restricted to subjects 40 years of age and older (case patients, n=3,177; control subjects, n=2,751)

Skin cancer

A self-reported previous diagnosis of skin cancer was associated with an approximately doubled risk of NHL. With respect to NHL subtypes, the risk of T-cell lymphoma was increased four-fold, whereas we found no association between skin cancer and risk of diffuse large B-cell lymphoma. In analyses stratified according to time between diagnosis of skin cancer and of malignant lymphomas, risk estimates were highest within the first 5 years after skin cancer diagnosis. With an interval of more than 5 years, risks of all NHL, CLL, and follicular lymphoma approached unity, whereas the risks of T-cell lymphomas and HL remained statistically significantly increased. Multivariable adjustment for skin type and total number of sun vacations abroad increased a few risk estimates slightly. Further adjustment for other UV light exposure measures, smoking, educational level, occupational exposure to pesticides, autoimmune disorders, family history of cancer, and history of blood transfusions did not change the results.

RHEUMATOID ARTHRITIS (Paper II)

Patients

Among the 76,527 patients with RA, there was no excess risk of cancer overall whereas the risk of malignant lymphomas was increased two-fold (Table 3). If the first year of follow-up after hospital discharge with RA was excluded, the SIR remained at 1.8 (95% CI 1.7-2.0). The relative risk of HL was higher than that of NHL (Table 3), but SIRs for CLL and multiple myeloma were not elevated (data not shown). Patients with a discharge diagnosis of Felty´s syndrome had a five-fold increased risk of malignant lymphomas. In RA, the lymphoma risk was highest within the first year of follow-up, then decreased with increasing follow-up time (Table 3). Significantly elevated risks of malignant lymphomas overall could be observed up to 20 years after the date of first discharge with RA (p for trend <0.0001), but then reached unity. The doubled risk persisted through all calendar periods from 1964 to 1999 (Table 3).

Table 3. Relative risk* of malignant lymphomas, non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma (HL) in RA patients and their first-degree relatives overall and according to selected characteristics

	Malignant lymphomas		NHL		HL	
	Obs	SIR (95% CI)	Obs	SIR (95%CI)	Obs	SIR (95% CI)
All patients with RA	535	2.0 (1.8-2.2)	458	1.9 (1.7-2.1)	77	3.1 (2.4-3.8)
Calendar period of 1st RA discharge						
1964-1969	47	1.9 (1.4-2.6)	35	1.7 (1.2-2.4)	12	3.3 (1.7-5.7)
1970-1979	220	2.0 (1.8-2.3)	184	1.9 (1.7-2.2)	36	2.9 (2.1-4.1)
1980-1989	185	1.9 (1.6-2.2)	163	1.8 (1.5-2.1)	22	3.1 (1.9-4.7)
1990-1999	83	2.2 (1.8-2.8)	76	2.2 (1.7-2.7)	7	3.4 (1.4-7.0)
Time from 1st RA discharge†						
<1 year	87	3.6 (2.9-4.5)	72	3.4 (2.7-4.3)	15	5.2 (2.9-8.6)
1-4 years	164	2.1 (1.8-2.4)	136	1.9 (1.6-2.3)	28	3.2 (2.1-4.6)
5-9 years	124	1.8 (1.5-2.1)	109	1.7 (1.4-2.1)	15	2.2 (1.2-3.7)
10-19 years	139	1.9 (1.6-2.2)	124	1.8 (1.5-2.2)	15	2.7 (1.5-4.5)
20+ years	21	1.0 (0.6-1.5)	17	0.9 (0.5-1.4)	4	3.5 (0.9-8.9)
First-degree relatives without RA	230	1.1 (0.9-1.2)	200	1.1 (1.0-1.3)	30	0.9 (0.6-1.2)
Type of relation						
Parents (n=21,652)	192	1.1 (1.0-1.3)	170	1.1 (1.0-1.3)	22	0.9 (0.6-1.3)
Siblings (n=19,546)	24	0.8 (0.5-1.3)	23	0.9 (0.6-1.4)	1	0.3 (0.01-1.7)
Offspring (n=27,279)	14	1.2 (0.6-1.9)	7	1.2 (0.5-2.4)	7	1.1 (0.5-2.4)

* Standardized incidence ratio (SIR) with 95% confidence interval (CI)
† To end of follow-up

First-degree relatives

Among the 68,477 first-degree relatives without discharge diagnoses of RA, or related disorders, the risk of cancer overall or of malignant lymphomas was not increased (Table 3), nor was the risk of CLL or multiple myeloma (data not shown). Slightly elevated risk estimates were observed in subgroups, such as all parents (Table 3), relatives of patients discharged from a rheumatology department and female relatives (data not shown), but the estimates were not statistically significant. Moreover, there was no evidence of excess risk of malignant lymphomas among relatives with more than one family member with RA, among relatives of patients diagnosed with both RA and lymphoma, or relatives of patients with Felty's syndrome. First-degree relatives who themselves had a discharge diagnosis of RA in the Hospital Discharge Register during the study period were at an increased risk of malignant lymphomas similar to that of other RA-patients. In an analysis of childhood cancer (ages 0-14 years) among offspring, there was no risk increase of malignancies overall. However, we observed a significantly increased risk of HL (SIR=3.2, 95% CI 1.0-7.4, n=5).

CELIAC DISEASE (Paper III)

Upon tumor review, 55 of 56 patients with verified celiac disease and subsequent lymphoma were classified as NHL, and one case as HL. Thirty cases (55%) were of primary gastrointestinal origin whereas 25 cases (45%) had no evidence of gastrointestinal involvement upon routine clinical and radiological examination. Compared to the expected numbers in the base cohort of celiac patients, the observed numbers corresponded to a more than 6-fold increased risk of all NHL, an unaltered risk of HL, a 24-fold increased risk of intestinal NHL, and a more than 3-fold increased risk of non-intestinal NHL (Table 4). Female sex was more common among B- than T-cell NHL (75% versus 43%) and among non-intestinal lymphomas (67% versus 42% among primary intestinal NHL).

Table 4. Observed number of cases and relative risk* of non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL) and NHL subtypes according to immunophenotype (B/T) and intestinal/non-intestinal location.

		Observed cases	SIR (95% CI)
NHL		55	6.6 (5.0-8.6)
HL		1	1.0 (0.02-5.6)
NHL:	**B-cell**	16	2.2 (1.3-3.6)
	T-cell	37	51 (35-68)
	Uns	2	8.1 (1.0-29)
	Intestinal	30	24 (16-35)
	Non-intestinal	25	3.6 (2.3-5.2)

* Standardized incidence ratio (SIR) with 95% confidence interval (CI)

B-cell lymphoma

Sixteen NHL cases were of B-cell lineage, corresponding to an approximately doubled risk among celiav patients compared to the general population (Table 4). If the first year of follow-up was excluded, the relative risk remained doubled. Five cases (31%) were of primary gastrointestinal origin (four in the small intestine and one in the gastric ventricle). Observed numbers of intestinal B-cell NHL were increased compared to expected numbers of all intestinal NHL (5 observed intestinal B-cell NHL cases versus a maximum of 1.2 expected, p<0.05). Likewise, observed numbers of non-intestinal B-cell NHL were increased compared to all non-intestinal NHL (11 observed non-intestinal B-cell NHL cases versus a maximum of 7 expected (statistically non-significant)). The most common subtype among the B-cell NHL cases was diffuse large B-cell lymphoma (n=7). No clear temporal trend was observed over successive calendar periods (Table 5). Seven patients (six women and one man) were previously diagnosed with other autoimmune or infectious disorders at the time of celiac disease diagnosis: five had thyroid disorders with either hyper- or hypothyroid function (of which one also had a history of sarcoidosis), and two had a history of tuberculosis.

T-cell lymphoma

With 37 observed cases, the relative risk of T-cell lymphoma was increased 50-fold among hospitalized celiac patients (Table 4). Exclusion of the first year of follow-up had little impact on the relative risk. Twenty-three cases (62%) were of primary gastrointestinal origin (22 in the small intestine and one in the colon) and 14 (38%) presented in non-intestinal sites. The observed number of intestinal T-cell NHL was substantially increased compared to the expected number of all intestinal NHL overall (23 observed cases versus a maximum of 1.2 expected p<0.01). With regard to non-intestinal T-cell NHL, the number was also clearly increased compared to non-intestinal NHL overall (14 observed cases versus a maximum of 0.8 expected p<0.01). Nineteen (51%) of the T-cell lymphomas were of the ETTL subtype (all with small intestinal location). Six cases were classified as anaplastic large cell lymphomas (all non-intestinal), and ten cases as unspecified peripheral T-cell lymphomas (including 4 with intestinal involvement). Over successive calendar periods, the relative risk of T-cell lymphoma decreased (p for linear trend=0.004, Table 5). The decrease over time was indicated among both intestinal and non-intestinal T-cell lymphomas.

Table 5. Observed number of cases and relative risk* of all non-Hodgkin lymphoma (NHL) and B-cell/T-cell NHL in celiac disease over successive calendar periods

	All (n=55)		**B-cell** (n=16)		**T-cell** (n=37)	
	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)
1970-79	6	11 (4.1-24)	0	undefined	5	103 (33-240)
1980-89	31	9.3 (6.3-13)	9	3.1 (1.4-5.8)	21	70 (43-107)
1990-95	18	4.1 (2.4-6.5)	7	1.8 (0.7-3.7)	11	28 (14-50)

* Standardized incidence ratio (SIR) with 95% confidence interval (CI)

AUTOIMMUNE AND CHRONIC INFLAMMATORY DISORDERS (Paper IV)

Rheumatoid arthritis

Self-reported RA (126 NHL cases and 89 controls) was associated with a statistically significant 50% increased relative risk of NHL overall, comprised of excess risks of diffuse large B-cell (n=39) and lymphoplasmacytic lymphoma (n=8) (Table 6). We observed increased risks of both extranodal (OR=1.7, 95% CI 1.1-2.5, n=36) and nodal NHL (OR=1.4, 95% CI 1.0-1.9, n=84). In analyses according to RA phenotype, relative risks of overall NHL and diffuse large B-cell lymphoma were most increased in categories implying severe disease. With respect to RA treatment, we found a modestly increased risk of NHL following use of NSAIDs and corticosteroids, and a more pronounced risk increase in ever users of any of the studied immunosuppressants. In participants without RA, there were no associations between ever use of these medication types and NHL risk.

Primary Sjögren's syndrome

Primary Sjögren's syndrome was associated with a 6-fold increased relative risk of NHL overall, due to an excess of diffuse large B-cell (n=5), marginal zone (n=3) and lymphoplasmacytic lymphomas (n=1) (Table 6). However, these subtype-specific analyses were hampered by small numbers. Six cases had extranodal disease spread (2 in the parotid gland) (extranodal NHL OR=13, 95% CI 2.5-63, nodal NHL OR=4.8, 95% CI 1.0-24). None of the primary Sjögren's syndrome patients reported previous treatment with the specified immunosuppressants.

Systemic lupus erythematosus

SLE was associated with a more than 4-fold increased relative risk of NHL overall, comprised of increased risks of diffuse large B-cell (n=3), marginal zone (n=2) and lymphoplasmacytic lymphomas (n=1) (Table 6). However, again, small numbers rendered estimates imprecise. Five of 8 lymphomas were located in extranodal sites (extranodal NHL OR=12, 95% CI 2.3-63, nodal NHL OR=2.8, 95% CI 0.5-17). One SLE patient reported previous treatment with immunosuppressants.

Celiac disease

Celiac disease was associated with a doubled risk of NHL overall, due to a nearly 20-fold excess risk of T-cell lymphoma (n=8), and a close to 3-fold increased risk of diffuse large B-cell lymphoma (n=6) (Table 6). Ten lymphomas involved extranodal sites, of which 5 were located in the gastrointestinal tract. This corresponded to a substantial excess risk of gastrointestinal NHL (OR=12, 95% CI 3.8-37, n=5) whereas an increased risk of non-gastrointestinal lymphoma was only suggested (OR=1.7, 95% CI 0.7-4.0, n=13). Statistically significantly increased risks of overall NHL, diffuse large B-cell, T-cell and gastrointestinal lymphomas were confined to those in whom gluten-free diet therapy was initiated in adulthood, and those who reported total diet compliance.

Inflammatory bowel disorders, diabetes mellitus, sarcoidosis and psoriasis

Crohn's disease and ulcerative colitis, whether surgically treated or not, were not significantly associated with risk of overall NHL, any NHL subtype studied, or gastrointestinal lymphoma. Type I diabetes was associated with a statistically significantly increased risk of CLL (n=7), and a borderline significant risk of mantle cell lymphoma (n=2), but not with risk of NHL overall. A self-reported diagnosis of psoriasis or psoriatic arthritis, immunosuppressive therapy for, or a hospital discharge with psoriasis, were not associated with risk of overall NHL, any subtype or cutaneous lymphoma. Sarcoidosis was not associated with risk of NHL or its major subtypes.

Population attributable fraction

The fraction of all NHL cases in the population attributable to RA, primary Sjögren's syndrome, SLE and celiac disease was estimated at 3.5% in total (0.5% for RA, 2.5% for primary Sjögren's syndrome, 0.2% for SLE, and 0.3% for celiac disease). For diffuse large B-cell lymphoma, the total population fraction attributable to these autoimmune conditions rose to 6.6%. Celiac disease was estimated as being responsible for 39% of all intestinal T-cell lymphomas in the population.

Table 6. Relative risk* of non-Hodgkin lymphoma (NHL) overall and subtypes in relation to history of selected autoimmune and chronic inflammatory disorders (excluding disease duration less than two years before lymphoma diagnosis/interview)

	All NHL	NHL subtypes						
		Diffuse large B-cell	CLL[†]	Follicular	T-cell	Mantle cell	Marginal zone	Lympho-plasma-cytic
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Rheumatoid arthritis								
no	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
yes	**1.4 (1.1-1.9)**	**1.8 (1.2-2.6)**	1.4 (0.9-2.1)	1.0 (0.6-1.6)	1.8 (0.9-3.7)	1.2 (0.5-3.0)	1.3 (0.5-3.4)	**2.4 (1.1-5.1)**
Primary Sjögren's syndrome								
no	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
yes	**6.1 (1.4-27)**	**11 (2.1-58)**	2.0 (0.2-24)	4.0 (0.6-29)	undefined	undefined	**28 (4.4-176)**	**16 (1.4-185)**
Systemic lupus erythematosus								
no	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
yes	**4.6 (1.0-22)**	**6.2 (1.0-37)**	2.8 (0.2-40)	2.2 (0.2-26)	undefined	undefined	**30 (3.7-233)**	**20 (1.2-352)**
Celiac disease								
no	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
yes	**2.1 (1.0-4.8)**	**2.8 (1.0-8.0)**	0.5 (0.1-4.0)	0.4 (0.1-3.6)	**17 (6.3-46)**	3.3 (0.4-28)	undefined	3.4 (0.4-28)

* Odds ratios (OR) and 95% confidence intervals (CI) adjusted for age (in 5-year intervals), sex and country
[†] Chronic lymphocytic leukemia

DISCUSSION

METHODOLOGICAL CONSIDERATIONS

Study design

In epidemiology, studies of cohort or case-control design are commonly used. The choice of study design is often a trade-off between validity (the probability that study results will reflect true associations in the population) and efficiency (best use of time and money).

Cohort studies are well suited for investigations of rare exposures and provide opportunities for assessment of multiple outcomes. In contrast, case-control studies are preferable for studies of rare outcomes, and permit assessment of multiple exposures. Prospective cohort studies can provide great detail in exposure assessment but are often extremely costly with regard to both time and money. Retrospective cohort studies, on the other hand, can take advantage of registry-based data and permit low-cost handling of large sample sizes. However, lack of exposure detail puts a limit on exposure assessment and control of confounding. When properly carried out, case-control studies provide information that mirrors what could be learnt from a cohort study, but in a more efficient way using sampling (262). A crucial step is therefore the sampling or selection of individuals as controls. The controls need to represent the source population, i.e., the population that generates the cases and preferably also the case person-time experience, and the selection should be made independently of exposure. If these prerequisites are met, and no biases are operating, the measured relative risk (odds ratio) in a case-control study approximates the incidence rate ratio obtained in a cohort study (262).

Given that malignant lymphomas are rare, and that causes are mostly unknown, the case-control study design is suitable for investigating the etiology of this disease. Thus, we undertook a large population-based case-control study to test the hypothesis of an association between lymphoma risk and sun exposure on one hand (paper I), and an array of autoimmune and chronic inflammatory disorders on the other (paper IV). The case-control design permitted us to control for a number of potential confounding factors, as well as perform detailed analyses of risks associated with major lymphoma subtypes. However, studying risk of malignant lymphomas in relation to autoimmune and chronic inflammatory disorders is challenging, as most of these disorders represent rare exposures. In order to achieve more stable risk estimates of the relative risk of cancer and of malignant lymphomas in RA, and the possible impact of shared genetic or environmental risk factors in RA-related lymphomagenesis, we undertook a retrospective cohort study which allowed identification of very large cohorts of exposed individuals (paper II). We also used the retrospective cohort study design for unbiased identification of lymphoma types complicating celiac disease (paper III).

Validity

Internal validity, or absence of systematic errors, applies to the source population under study, and is a prerequisite for external validity, or generalizability of the findings to other populations. Some possible sources of systematic errors in the studies included in this thesis are discussed below.

Selection bias

In a case-control study, selection bias can be introduced in different ways. The importance of selecting controls that are representative of the population generating the study cases has been discussed previously. If control selection is performed by means of, for example, hospital admittance lists, random-digit telephone dialing or member lists of health insurance companies, the resulting sample may not be representative of the source population with regard to socioeconomic status or other life-style factors that are related to their probability of being selected and, perhaps, also directly or indirectly related to the exposure under study. However, control selection in SCALE was based on continuously updated and complete population registers, and thus all Danish and Swedish residents had an equal probability of being sampled, within the defined age limits. Bias in case-control studies can also be introduced by self-selection through differing participation rates between cases and controls. Patients may be more motivated than randomly selected, healthy individuals, to take part in studies about possible causes of their disease. If non-participation among controls is directly or indirectly associated with the investigated exposure, the exposure distribution among participating controls may no longer reflect that of the source population and person-time that gave rise to the cases. In SCALE, 71% of all eligible controls chose to participate, which was lower than the participation rate among eligible case patients (83%). The proportion of participating controls is high in an international perspective, but those who participated obviously represent a selection from the original sample.

Previous studies have indicated that non-participation may be linked to low socioeconomic status and morbidity (263). In paper I, a high total number of sun vacations abroad was associated with high educational level among the controls, but a high frequency of sun tanning in Denmark/Sweden was more common among those with low educational level. Thus, a potential over-selection of study controls with higher educational level/socioeconomic status than the source population could have biased some results away from the null, but other results toward the null. Therefore, such selection bias does not offer a plausible explanation for all of our findings, given the consistency across different sun exposure variables observed in paper I. In paper IV, eligible cases and controls with autoimmune and chronic inflammatory disorders may have been more likely than those without such disorders to decline participation due to poor health. However, prevalences of the studied disorders among the participating controls were not lower than expected based on previously reported population prevalences. Failure to include cases with severe co-morbidity could have led to underestimation of lymphoma risks in some disorders or an inability to distinguish small risk increases in others.

In papers II and III, we used the Swedish Hospital Discharge Register for identification of patients. As not all individuals diagnosed with a disorder such as RA or celiac disease are hospitalized during the course of their disease, the use of hospital discharges introduces a likely selection for patients with particular characteristics. Although patients may be hospitalized for a variety of different reasons, including diagnostic investigations that require inpatient care or for concomitant disorders, it is possible that hospitalized patients represent a group with on average more severe and/or longlasting disease than in the general population. However, since the discharge registration is prospective and population-based in Sweden (with hospital admission being financially and geographically accessible to all), this restriction should be unrelated to outcome (lymphoma risk) and does therefore not threaten the internal validity although it could affect the external validity or generalizability of the results. Thus, if RA or celiac disease severity is associated with lymphoma

risk, the results for these hospitalized groups may not be generalizable to the entire group of patients in the population. However, if the proportion of hospitalized patients is high, results may provide good approximations of the overall risk. In paper II, we estimated to have identified approximately 75% of all patients diagnosed with RA during the study period. In paper III, it was more difficult to estimate the proportion of patients identified, as the proportion of all true celiac patients eventually diagnosed most likely have changed considerably over time. Assuming a true prevalence of celiac disease in Sweden of around 1/200 (264), the 9,204 celiacs who were alive in 1994 in our study would represent around 23% of the total pool of true celiacs, but a higher proportion of all patients diagnosed with celiac disease. The threshold for hospitalisation in Sweden, irrespective of diagnosis, was rather low in the 1970s and early 80s compared to the 1990s. Therefore, the study populations in paper II and III may represent gradually more limited proportions of all diagnosed patients over time.

In paper II, we used the Multi-Generation Register to identify first-degree relatives of RA patients. As this register is incomplete for some periods in the past, we only matched a subset of the RA patients, and we further restricted the time of follow-up to periods for which data in the register are complete. Thus, we aimed to avoid a selection bias due to survival that could have influenced early registration.

Detection bias
Hospitalization for RA could be precipitated by an incipient lymphoma or a new RA diagnosis may lead to closer health surveillance and thereby increased risk of detecting latent cancers. Such detection bias is likely to affect risk estimates of malignancies occurring with a short latency period. Indeed, in paper II, the relative risk of malignant lymphomas was highest within the first year after a first hospital discharge with RA, but the persistence of an excess risk during 20 years of follow-up cannot readily be explained by these mechanisms. Exclusion of the first year of follow-up had little impact on overall risk estimates. Closer surveillance could primarily lead to earlier detection of indolent lymphoma types with few symptoms, such as low-grade follicular lymphoma or CLL. However, RA was not associated with risk of CLL in paper II, nor with risk of CLL or follicular lymphoma, but rather with risk of high-grade or diffuse large B-cell lymphoma, in paper IV. In paper III, we did not include patients diagnosed with celiac disease subsequent to a lymphoma diagnosis, in order to avoid undue overrepresentation of lymphoma types (e.g., intestinal T-cell lymphomas) that would prompt investigation of celiac disease.

Misclassification
Incorrect measurement of exposure and/or outcome (also called information bias or misclassification) can occur in any study. Misclassification of either exposure or outcome can be differential or non-differential, depending on whether measurement of one variable is related to measurement of the other. Recall bias, a form of differential misclassification that is of concern in case-control studies, is discussed below in a paragraph of its own. Although validation studies of the population-based Hospital Discharge Register show that the majority of the diagnoses are indeed correct, there is a certain degree of erroneous registration. This was evident in paper III where confirmation of the celiac disease diagnoses was sought through medical files, and was confirmed with certainty in 66 of 77 patients (86%). Although data on hospital discharges were collected after the occurrence of cancer in papers II and III, the actual registration antedated the cancer diagnoses. Thus, exposure information was registered independently of outcome, and any exposure

misclassification would therefore have been non-differential between individuals who did and did not subsequently develop lymphoma. The effect of non-differential exposure misclassification of a dichotomous exposure is generally to dilute any differences between outcome groups, leading to underestimation of true effects. However, there are exceptions to this rule, for example, for risk estimates of in-between categories of categorical exposure variables. Differential misclassification of outcome can arise in cohort studies if follow-up is incomplete and the loss is related to exposure. In our retrospective cohort studies, registration of outcome was independent of exposures and follow-up was almost entirely complete, minimizing the possibility of differential loss to follow-up.

Self-reported diagnoses of autoimmune and chronic inflammatory disorders analyzed in paper IV could be incorrect. False positive reports could be due to patients having disorders with names similar to those asked about, or due to erroneous diagnoses made by doctors. False negative reports can arise due to lapses of memory. We tried to improve measurement accuracy by asking only about disorders definitely diagnosed by a doctor, and by always mentioning existing and accurate alternative disease terms. Although misclassified reporting of previous disorders could be differential (for example due to recall bias, see below), we found positive associations between only some disorders and NHL risk overall where this was expected, and not with most disorders studied, which speaks against differential misclassification as the only explanation for our findings. A certain degree of false-positive reporting among both cases and controls could have acted to bias our estimates toward the null through non-differential (equal proportions of misclassified reports among cases and controls) or differential mechanisms (a higher proportion of misclassification among controls than cases).

Recall bias
Differential recollection of exposure between cases and controls is always a concern in case-control studies, as patients' recollection may be influenced by a search for causes of their disease. Although the effect of differential recollection is unpredictable, more concern is generally raised upon findings of positive associations between exposures and disease risk. It is difficult to conceive that case patients would underestimate their exposure to presumably harmful risk factors due to their disease status, and that this could explain the observed inverse association between sun exposure history and lymphoma risk in paper III, even more so as the inverse association was stronger for exposure early in life. In paper IV, recall bias is an unlikely explanation for positive associations with some disorders but not with others.

In SCALE, we aimed to limit differential reporting by not giving participants information in advance about the type of questions to be asked during the interview, so that they would not prepare their answers beforehand. Furthermore, interviewers were instructed to treat cases and controls in the same way as far as possible, and to interview equal numbers of cases and controls. The concern for recall bias in well-designed and properly conducted case-control studies may be exaggerated if one trusts results from two previous large Scandinavian case-control studies where a second control group of patients with cancer types not under study was used in parallel with population controls (265, 266). The more general problem of accurately remembering and reporting exposures affects all individuals to some extent, and tends to be non-differential between cases and controls.

Reverse causality
Autoimmune phenomena can occur during the course of hematopoietic malignancies. Such paraneoplastic phenomena can be mistaken for and registered as autoimmune disorders if the

underlying malignancy is not yet diagnosed. Such reverse causality would primarily influence risk estimates for short follow-up time. To explore the possible effects of this bias on overall risk estimation, we performed analyses with and without exclusion of the first year of follow-up both in papers II and III. Because the estimates excluding the first year of follow-up were similar to overall results, making a large impact of such reverse causality (and/or detection bias, see above) unlikely, the overall analyses were presented. In all analyses in paper IV, we excluded participants reporting autoimmune and chronic inflammatory disorders with symptoms beginning less than two years before lymphoma diagnosis (or interview for controls) in order to avoid inflation of relative risks due to such misclassification. In analyses of treatment, we also excluded treatment use during less than two years before lymphoma diagnosis (or interview) to allow for a plausible latency time, and to avoid including treatment of symptoms that could in fact due to incipient lymphoma, or even to the diagnosed lymphoma.

Confounding
Factors other than the actual exposure under investigation can sometimes explain the observed association between exposure and outcome. For a third factor to have this effect, however, it has to fulfill the criteria of being independently associated with the exposure on one hand, and with outcome on the other, and it must also not be affected by either the exposure or the outcome. These stipulations imply that the third factor must be associated with the exposure in the source population, not just in diseased individuals; that it must be associated with the outcome in the unexposed (or reference) group; and that it cannot constitute an intermediate step between exposure and disease. In registry-based studies, available information on potential confounders is limited. Thus, in papers II and III we were not able to adjust for any confounders other than age, sex and calendar period (through standardization). However, few risk factors for RA and celiac disease, as well as for malignant lymphomas, are known, and thus the possibilities of confounding of these study results are difficult to evaluate.

We know that some autoimmune disorders (e.g., RA, celiac disease, Sjögren's syndrome, autoimmune thyroiditis) tend to aggregate in individuals and in families (106, 267, 268). Thus it is possible that some of the observed associations in papers II and III were influenced by autoimmune disorders other than those under study. In paper II, slight increases in risk of lymphoma in a few subgroups of first-degree relatives, such as all parents, all women and all relatives to patients discharged from a department of rheumatology, could have been due an overrepresentation of other autoimmune disorders among family members of patients with RA. In paper III we observed a surprisingly high frequency of history of thyroid disorders in celiacs who had developed B-cell lymphoma (5/16). There were also two patients with B-cell NHL cases who had previously had tuberculosis, which could influence NHL risk due to long-standing inflammation. However, autoimmune thyroiditis has primarily been associated with thyroid lymphomas, of which there were none in paper III, and the association between tuberculosis and NHL is uncertain. Hence, the observation of a more than two-fold increased risk of B-cell NHL in celiac disease patients cannot readily be explained only on the basis of the co-existence of these disorders.

An advantage in our case-control study was the extensive collection of data on a number of potential risk factors for malignant lymphomas. Thus, we were able to evaluate several possible confounders of the associations between sun exposure on one hand, and autoimmunity and chronic inflammation on the other, and risk of malignant lymphomas. Controls were frequency-matched to the expected

distribution of cases by age in 10-year intervals, sex and country in order to achieve efficient adjustment for these factors, as they were likely to be important confounders in analyses of many exposures. In statistical models of lymphoma risk in association with different UV light exposure measures in paper I, only the addition of skin type had some effect on relative risk estimates, after adjusting for the matching variables. As it is plausible that skin type may affect suntanning habits (i.e., if sun exposure just causes pain and blisters, then you are likely to avoid it), and it was also independently related to lymphoma risk, skin type was added to the multivariable model.

We also evaluated changes in risk estimates with addition of covariates occasionally, but not invariably, associated with lymphoma risk in the literature. Additional adjustment in paper I for hair and eye color, educational level, blood transfusions, smoking, family history of cancer, and autoimmune disorders conferred only marginal changes in relative risk estimates. However, adjustment for occupational exposure to pesticides attenuated the observed positive association between outdoor exposure and lymphoma risk and was thus included in the analytic model for this exposure variable. Many of the same potential confounders, and treatment were evaluated in paper IV, but were not included in the final model, as they caused only marginal changes in risk estimates.

External validity
If the results reported in this thesis are not subject to any major biases or threats to the internal validity, the findings are likely to be valid for populations beyond Sweden (and Denmark). In paper I, the fact that inverse associations between frequent sun exposure and lymphoma risk were indicated for all four skin types may imply that these findings are generalizable to other Caucasian populations. However, due to the population homogeneity in the Nordic countries with respect to ethnicity, results cannot be readily extrapolated to non-Caucasian ethnic groups.

Precision

Precision in risk estimation corresponds to the degree of random error, i.e., the influence of chance, or data variation that cannot be explained in other ways. The role of chance can be roughly reflected statistically by p-values and/or the width of confidence intervals. The confidence level was set to 95% in all papers in this thesis. In registry-based cohort studies such as in paper II, the large size of the studied cohorts acted to enhance precision and allowed for stable risk estimation. However, if the outcome is rare, as in paper III where relative risks were evaluated for lymphoma subtypes, precision can be low in spite of the large size of the founding cohort. Likewise, precision in a case-control study is dependent in part on exposure frequency. Hence, precision is greater in the analysis of a common exposure such as in paper I, compared to uncommon exposures such as those investigated in paper IV. In the latter study, lymphoma subtype analyses were sometimes hampered by small numbers. However, observed positive associations with NHL overall in paper IV were unlikely to be due to chance alone, in light of the consistency with previous reports. Also, the large sample size of the SCALE study, which included more participants than any previous case-control study of lymphoma, helped to improve the precision of risk estimates. In general, the role of chance increases with an increasing number of comparisons and analyses performed, and chance can never be excluded as a potential explanation for observed results.

FINDINGS AND IMPLICATIONS

Exposure to ultraviolet light and risk of malignant lymphomas

In contrast with previous beliefs, our results indicated that UV light exposure is associated with a reduced risk of malignant lymphomas, primarily NHL. High frequency of sunbathing, domestically or abroad, as well as high frequency of sunburns at age 20 years or in childhood was associated with a statistically significantly reduced relative risk of NHL of about 30-40%. There was similar, albeit weaker evidence of an inverse association between various UV light exposure measures and risk of HL. We also observed an approximately 2-fold increased risk of both NHL and HL following self-reported history of skin cancer, which is consistent with numerous registry-based cohort studies (175, 179, 269, 270).

Previous studies exploring a possible relationship between sun exposure and lymphomas (ecologic observations and studies of outdoor occupation) have often been taken to support the hypothesis of a positive association, although in fact results have been largely inconsistent and exposure measurements likely subject to substantial misclassification (183, 185-195, 271). Given the indirect nature of almost all previously published reports on this matter, the primary strength of our study lies in the detailed and individual assessment of exposure. Other strengths include the population-based design, the complete and rapid case ascertainment, and the thorough and uniform classification of malignant lymphomas. Limitations include the possibilities of selection bias due to differing participation rates between cases and controls, recall bias and misclassification of self-reported data. However, none of these biases, nor residual confounding or chance appears to offer a plausible explanation for the overall findings in view of the consistency of the results across different exposure variables, strong indications of a dose-response trend, and similar results in separate analyses by country and by skin type. Furthermore, our findings are supported by recent data from a smaller Australian case-control study, in which high levels of sun exposure, measured as number of hours spent outdoors, were also unexpectedly found to be inversely associated with risk of NHL overall (272).

Possible biological mechanisms behind the observed association include UV light-induced systemic immune modulation and photo-initiation of activated vitamin D production. Both of these mechanisms are modified by skin type, and would thus be consistent with the observed variation in lymphoma risk by skin type. Significant immune alterations have been observed in humans after exposure to the equivalent of 1 hour of noonday summer sunlight at mid-latitudes. Hence, it has been concluded that solar UV exposure is likely to be of biological relevance to the effectiveness of the human immune system. As the penetration of UV radiation, especially UV-B, into the body is poor, a variety of factors, such as UV-induced DNA damage, are believed to initiate a complex cascade of events that ultimately lead to systemic immunosuppression. Although incompletely known, effects appear to include a downregulation of antigen presenting activity, increased levels of suppressor T cells (NK cells and/or T regulatory type 1 cells), and a tilting toward a TH2-type immune response (197, 273). Clinically relevant short-term effects include suppression of contact hypersensitivity and delayed hypersensitivity (197, 274). These observations were previously taken to support the hypothesis of an increased lymphoma risk in association with sun exposure, but long-term effects that may be of relevance for lymphoma development are far from clear (197, 275). Interestingly,

allergic disorders, also tentatively associated with a reduced risk of lymphomas, may also be characterized by a predominance of a TH2-type immune response (204).

The ability to convert provitamin D to the active 1,25-dihydroxyvitamin D_3, which is dependent on exposure to UV-B, is much reduced at northern latitudes, and populations living far from the equator are at increased risk of vitamin D deficiency during the winter months (276). Active vitamin D promotes cell differentiation and has an anti-proliferative effect on a variety of cell lines including those derived from the hematopoietic system (277). Ecologic studies have demonstrated that mortality rates of several cancer forms are inversely associated with regional UV-B exposure (190). In accordance with these findings, vitamin D deficiency has been associated with increased occurrence of several common cancer forms, including those of the prostate, colon, breast, and ovary (278). Furthermore, treatment with vitamin D analogs has led to tumor regression in follicular low-grade lymphomas. Interestingly, vitamin D is also suggested to have a role in T helper cell function and maintenance of immune tolerance, and vitamin D deficiency has been linked to increased occurrence of several autoimmune disorders including RA (279). Nevertheless, it remains to be clarified whether the observed inverse association between UV exposure and lymphoma risk is mediated by vitamin D, systemic UV-induced immune modulation, both these mechanisms or by totally different ones.

If these results are confirmed in future studies and if, ideally, the mechanisms can be elucidated, the findings could have implications for clinical lymphoma management as well as for the general population in a broader public health perspective. Elucidation of the underlying biological mechanisms could perhaps lead to the development of new treatment strategies for lymphoma. From a public health point of view, integration of the current findings into previous knowledge of UV-related skin carcinogenesis is more complicated. However, in view of accumulating evidence of beneficial effects of UV exposure on the development of several cancer forms as well as other chronic disorders, it might soon be time for an estimation of the net effect of UV light exposure on cancer and health in the population.

In light of the observed inverse association between UV light exposure and risk of NHL, the link between skin cancer and malignant lymphomas is indeed puzzling. According to our study and previous results, NHL risk appears to be highest within a few years after skin cancer diagnosis and approaches unity with longer follow-up time (175, 177, 181, 270). This observation argues for a role of shared predisposing factors such as acquired dysfunction of the cellular immune system or of DNA repair that would lead to increased occurrence of both cancers. However, part of such a phenomenon could also be explained by detection bias. Further support for this theory is rendered by reports of skin cancer patients being at increased risk of not only NHL, but also of carcinomas in the upper aerodigestive tract, breast, kidney, lung, and brain (176-178, 269, 280): and by a worse prognosis in skin cancer patients diagnosed with second cancers of several types (NHL, breast, prostate, colon and lung cancer) than in individuals with the same cancer forms as a primary malignancy (281, 282). Our results further indicated that the association with skin cancer may be differential according to subtype of malignant lymphoma. As this has not been described before, the observed pattern of associated subtypes needs confirmation.

Rheumatoid arthritis and risk of malignant lymphomas

In the cohort study of patients with hospital discharge diagnoses of RA (paper II), we found a close to 2-fold increased risk of overall NHL, and a 3-fold increased risk of HL. Risk estimates were marginally lower when the first year of follow-up was excluded. In our case-control study (paper IV) the relative risk of NHL was increased by about 50% following a self-reported history of RA. The discrepancy in the magnitude of the relative risk between the two studies can be due to several factors. The restriction to hospital discharge diagnoses in the first study most likely led to an assembly of RA patients with more severe disease than patients in general. If lymphoma risk is associated with RA disease severity and not treatment, as indicated in study IV as well as in a few other studies (115, 116), a higher risk estimate in paper II is biologically feasible.

In paper IV, self-reported diagnoses of RA may have been subject to a certain degree of misclassification. The RA prevalence among our controls (2.8%) corresponded, after adjustment for age and sex, to a population prevalence of 1.5%, which is in the upper range of previous reports (257, 283). Thus, some degree of false positive reporting could have occurred among controls as well as cases, which most likely could have led to an attenuation of the observed association. Although the participation rate among the NHL cases was relatively high (81%), patients with severe RA complicated by a high grade lymphoma may have declined participation due to physical incapacitation or early death. Such a selection could also have acted to lower the observed relative risk, but could have been counteracted by a similar selection mechanism among controls. Taken together, the relative risk of NHL in association with RA overall in Sweden (and Denmark) may be slightly higher than that observed in paper IV and slightly lower than that in paper II. Both studies indicated that time of follow-up was of relevance for overall assessment of lymphoma risk, and that longer follow-up time was not necessarily associated with a more pronounced risk of lymphoma. A possible interpretation of this finding is that disease intensity is a more important determinant of lymphoma risk than duration, and that the proportion of patients with mild disease, and perhaps lower lymphoma risk is higher among those followed for a long time.

In paper II, the observation of no prominent risk increase among relatives of RA patients (except for an increased risk of HL in childhood) indicates that genetic susceptibility or environmental risk factors common to both conditions are unlikely to be major determinants of lymphomagenesis in RA patients. It also implies that a positive family history of RA, or of both RA and lymphoma, does not facilitate the identification of RA patients prone to lymphoma development. However, we were not able to distinguish between NHL subtypes in this respect. In light of the findings described in paper IV and previous reports, it would have been of special interest to assess the risk of diffuse large B-cell lymphoma in the first-degree relatives of RA patients. Family history of RA may be of importance for risk of HL in childhood through common susceptibility genes or environmental factors.

In spite of the increasing use of immunosuppressive drugs for treatment of RA in recent decades, we did not observe an increase in relative risk of malignant lymphomas in paper II over successive calendar periods. In paper IV, we were able to investigate the role of a group of specified immunosuppressants more directly. Although we did not have detailed information on the specific drug(s) used, we did have information on duration of and indication for use. An increased risk of

NHL in association with use of any of the specified drugs was observed in RA patients, but not in individuals without RA. Based on reported treatment indications, we have no reason to believe that the RA patients received higher doses of the specified drugs than individuals without RA. Rather, the opposite was more likely, since about one-third of the individuals without RA reported treatment with immunosuppressive therapy for previous non-hematopoietic malignancies, which normally implies higher doses than those used for chronic inflammatory illnesses. Indeed, even a history of receiving potent chemotherapy for previous non-hematopoietic malignancies *per se* did not confer an excess risk of NHL among the individuals without RA. This suggests that the level of drug-induced immune suppression is not a major lymphoma risk determinant in RA, and that immunosuppressive drug use in RA patients may be a marker of other determinants of lymphoma risk, such as disease severity. However, due to the somewhat rough assessment of immunosuppressant use in paper IV, we cannot exclude that any of these drugs may individually have some influence on RA lymphomagenesis. With regard to use of NSAIDs and systemic corticosteroids, there was likewise little to suggest a prominent role of these drugs in RA-related lymphomagenesis or otherwise.

The findings presented in this thesis add to the evidence that lymphoma risk in RA is primarily due to factors related to the disease itself and severity of inflammation, rather than treatment or shared risk factors such as genetic susceptibility (or activation of latent EBV infection, although the latter was not studied within the scope of the present papers). If disease severity governs the increase in lymphoma risk, the relative risk in any group of RA patients will depend heavily on the average degree of inflammatory activity in the group. Thus, rather than determining the average relative risk of lymphoma in all RA patients, it will be more important to learn to identify RA patients at greatest risk of these malignancies for closer clinical surveillance and appropriate treatment. Exact mechanisms of lymphomagenesis in association with autoimmunity and inflammation also remain to be elucidated (see below). In addition, potential lymphomagenic properties of treatment with the recently introduced tumor necrosis factor blockers need to be better determined in studies that also account for disease severity.

Celiac disease and risk of malignant lymphomas

Celiac disease and associated malignant lymphoma types were investigated using two different approaches. In paper III, we defined a cohort of patients with hospital discharge diagnoses of celiac disease, whereas self-reports of the disease among NHL cases and controls were used in paper IV. In analyses of relative risks of histopathological and anatomical subtypes of NHL, we had more power in paper III to assess relative risks of a few subtypes, whereas relative risks could be elaborated in relation to distinct lymphoma subtypes according to WHO, and to more detailed celiac disease characteristics, in paper IV. In both studies, we observed increased relative risks of overall NHL, T-cell NHL and NHL with intestinal involvement, but estimates were generally higher in paper III than in paper IV. However, in paper III we found tendencies toward decreasing risks of all NHL, T-cell NHL and perhaps also intestinal lymphoma over successive calendar periods from the 1960s to the 1990s. Therefore, even lower estimates for the period 1999 to 2002 (as in paper IV) fit with this decreasing trend.

In the cohort study, we found significantly increased risks of B-cell NHL and non-intestinal NHL, whereas excess risks of these subtypes were not statistically significant in the case-control study. Explanations for the discrepancy in the relative risks of these more common lymphoma types might include differing disease characteristics between hospitalized celiac disease patients and celiacs in general, between patients diagnosed during the two different time periods under study, and/or lower precision in paper IV. Interestingly, however, we observed a statistically significant excess risk of diffuse large B-cell lymphoma in the case-control study, which could well have driven the association with B-cell NHL overall observed in paper III. Thus, both studies clearly indicated excess risks of other and more common lymphoma types than the rare ETTL and other intestinal T-cell lymphomas in celiac disease. This new knowledge has implications for the clinical surveillance of celiac disease patients.

Whether the biological mechanisms responsible for the increased risk of intestinal T-cell lymphoma are partly the same for T-cell NHL overall in celiac disease is not clear, but not unlikely. However, a risk increase of the more common B-cell lymphomas, perhaps confined to diffuse large B-cell lymphoma, is probably due to other mechanisms. While intestinal T-cell lymphomas are thought to arise due to mucosal T-cell proliferation evolving from polyclonal to monoclonal stages, B-cell lymphoma development may be triggered by factors related to the systemic autoimmune features of celiac disease. This notion is indirectly supported by the observation in paper IV that celiac disease, RA, SLE and Sjögren's syndrome shared a common association with diffuse large B-cell lymphoma.

Are there any biologically plausible explanations for a tendency toward decreased risks of all NHL, T-cell lymphoma and perhaps also intestinal lymphomas in celiac patients over time? Patterns of celiac disease incidence in Sweden and in several other countries have changed dramatically in recent decades. While the incidence based on diagnosed cases has increased, this apparent rise may largely be due to an increasing number of mild or silent cases diagnosed (284). Thus, the seemingly decreasing lymphoma risk in diagnosed cases over successive calendar periods may be due to an increasing proportion of patients with mild celiac disease that may have lower lymphomagenic potential. Another interesting hypothesis stipulates that early initiation of a gluten-free diet and complete diet compliance would lower the long-term risk of lymphoma. This theory has gained widespread credibility, although available evidence is not impressive (135). Observations of no excess risk of lymphoma in celiacs diagnosed in childhood (paper III, (132)) may offer indirect support for this idea. However, self-reported subtotal diet compliance was not associated with higher risk increases than total compliance in paper IV: rather, the contrary was observed. Hence, this matter needs further investigation.

Other autoimmune and chronic inflammatory disorders and risk of non-Hodgkin lymphoma

In our large case-control study, we confirmed previous reports of increased NHL risk in primary Sjögren's syndrome and SLE, whereas we observed no excess risk in type I (or type II) diabetes mellitus, inflammatory bowel disorders, psoriasis or sarcoidosis (paper IV). Positive associations with Sjögren's syndrome and SLE appeared to be confined to diffuse large B-cell and marginal zone lymphoma and perhaps also lymphoplasmacytic lymphomas, although subtype analyses were

hampered by small numbers. Only one case patient with SLE and no participants with primary Sjögren's syndrome reported use of any of the specified immunosuppressants. Thus, an important role of this type of treatment in lymphomagenesis in these disorders seems highly unlikely, which is in accordance with others' observations (97).

The observed risk increase of NHL overall in association with primary Sjögren's syndrome and SLE was consistent with or slightly lower than in previous reports, although reported relative risk estimates have varied greatly. Again, most other studies have been confined to patients with a hospital discharge diagnosis of the disorder in question, and thus their study populations may be characterized by more severe disease and higher excess risks of lymphomas than patients in general. With respect to NHL subtype distribution, interpretations based on previous case series of SLE or Sjögren patients with lymphoma, mostly of the MALT type, are hampered due to the possibility of selection bias (119, 120, 285, 286). In one recent study of lymphoma occurrence in a well-defined cohort of 460 Sjögren patients, only 6 out of 24 NHL cases were MALT lymphomas (122), which is in line with our result of 3 out of 12 NHL cases being of the MALT type in primary Sjögren's syndrome. A possible excess risk of lymphomas with diffuse large B-cell histology has not been noted before in Sjögren's syndrome, but was indicated in one study of SLE (285). An identical NHL subtype pattern in primary Sjögren's syndrome and SLE, as we observed, is perhaps not surprising in view of an existing biological relationship between the two disorders (287).

In type I diabetes, we observed no increased risk of NHL overall, but we found a statistically significant excess risk of CLL and a borderline significant increase in risk of mantle cell lymphoma (based on two cases). However, the number of patients with type I diabetes was small and observed associations with CLL and mantle cell lymphoma were dependent upon the study's definition of type I diabetes. In paper IV we used a strict definition based on reported type, 30 years or younger at diagnosis, and treatment with only insulin. In exploratory analyses based solely on self-report of type I diabetes, the observed NHL subtype associations disappeared. Previous studies of hematopoietic cancer in type I diabetes are few, and have not shown any association with malignant lymphoma or leukemia based on registry data (167, 288). Although these previous results do not preclude the possibility of NHL subtype-specific associations, our results could also have been due to chance.

We did not observe an increased risk of overall NHL or any subtype in psoriasis patients. Previous reports are inconsistent, and some suggest an excess risk of T-cell lymphoma in particular (94, 160). However, cutaneous T-cell lymphoma may mimic psoriasis (289) and go undiagnosed for many years, which could lead to false positive associations. Our negative results for inflammatory bowel disorders are consistent with recent large studies (153, 154, 156, 290), although no previous investigations distinguished among histopathological or anatomical subtypes of NHL. However, it is also possible that ulcerative colitis and Crohns disease are differentially linked to lymphoma risk. The present results and the majority of previous studies strongly suggest no association with ulcerative colitis (153, 154, 156), whereas a small excess risk of lymphomas in Crohn's disease cannot be entirely excluded (153).

An important limitation in paper IV was the use of self-reported diagnoses and the lack of validation of autoimmune disorders, other than matching with hospital discharge diagnoses for SLE and psoriasis (as well as for RA and celiac disease). Although numbers of hospitalized patients were few, results based on hospital discharge diagnoses pointed in the same direction as those based on self-

reports. Furthermore, study control prevalences were in line with reported population prevalences for most investigated disorders after taking differences in age and sex distribution into account (259, 260, 291-294). The estimated fraction of NHL cases in the population due to RA, primary Sjögren's syndrome, SLE and celiac disease together was low (3.5%). However, understanding the mechanisms of lymphomagenesis in these patients may be of benefit for a larger number of individuals.

Potential and established biological mechanisms in autoimmunity-related lymphomagenesis

In view of the results of papers II, III and IV, a summary of possible lymphomagenic mechanisms in association with autoimmunity and chronic inflammation may be warranted.

In Sjögren's syndrome, Hashimoto's thyroiditis and celiac disease, mechanisms of development of specific lymphoma types in the affected organs have been studied in detail. In both Sjögren's syndrome and Hashimoto's thyroiditis, lymphoma development has been attributed to T-cell dependent antigen-driven proliferation of B cells that eventually become monoclonal and develop into primarily low-grade MALT-lymphoma (125, 150). Sustained antigenic drive by infectious agents or self-antigens during lymphoma transformation is implied by the presence of selected immunoglobulin variable gene mutations and clonal heterogeneity in the hypervariable regions within the tumors (150). In addition, continuous T-cell-dependent antigenic drive appears to be crucial for the development of MALT lymphomas in the gastric ventricle, as early lymphomatous lesions regress upon eradication of the antigen stimulus, i.e. *H. pylori* (295). In this context, acquisition of particular chromosomal translocations in the reactive B-cells marks the loss of dependence on the bacteria. The same mechanism could apply to MALT lymphomas developing in association with other infectious agents such as HCV or Borrelia burgdorferi. Similarily, small intestinal T-cell lymphomas (i.e., ETTL) in celiac disease are suggested to develop from intraepithelial autoreactive T-cell infiltrates through polyclonal and monoclonal proliferations of such lymphocytes with aberrant immune phenotypes (142).

With respect to development of nodal or extranodal lymphomas without a clear connection to the chronically inflamed sites, local mechanisms may still be of importance. In celiac disease, the clonal lymphocytes are capable of disseminating into the bloodstream and to distant sites (142). This may also be true for transforming B cells in Sjögren's syndrome (121). Malignant lymphomas could perhaps also develop due to persistent B-cell stimulation by self-antigens on a systemic level. Adverse genetic events during sustained B-cell proliferation could be enhanced by acquired resistance to apoptosis in autoimmune disorders (41). In RA and SLE, apoptotic resistance is increased and mediated by enhanced Bcl-2 expression, activation of nuclear factor kappaB (NFκB) by inflammatory cytokines and growth factors, and abnormalities in expression of B lymphocyte stimulators (BLyS, a recently recognized member of the tumor necrosis factor family) (41, 296, 297). Patients with systemic autoimmune disorders have increased amounts of BLyS in serum or synovial fluid (298), and B-cell activating factors have been implicated in the growth and survival of B-cell malignancies (299).

Furthermore, some cytokines, specifically interleukins 6 and 10, appear to be important in the development of both autoimmunity and malignancy. Interleukin-10 mediates autoantibody production and may function as an autocrine growth factor in B-cell lymphomas (300). With regard to interleukin secretion overall, the balance between two T helper cell types, TH1 and TH2, with different cytokine profiles, is a recurrent theme in reports on autoimmunity and lymphoma. It has been stated that an excessive TH1 response would be associated with autoimmune disorders in general (58, 301) and that the ratio of TH1 to TH2 responses could affect the risk of developing lymphoproliferative disorders (58). However, RA, sarcoidosis and psoriasis have been associated with accumulation of TH1 lymphocytes, SLE primarily with a TH2 response (302), and Sjögren's syndrome with high serum levels of both TH1 and TH2 cytokines (303). Thus, in view of our results in paper IV and previous reports, an altered TH1/TH2 balance does not in itself appear to explain why some but not other autoimmune disorders are associated with increased occurrence of malignant lymphomas.

Another factor of relevance for B-cell lymphomagenesis in particular may be an inherent genetic vulnerability of these cells during the elaborate molecular genetics of the normal adaptive immune system. The processes of immunoglobulin variable-diversity-joining (V(D)J) gene recombination, somatic hypermutation and isotype switching require repeated remodeling of B-cell DNA (304), with the possible consequence of translocation of oncogenes to the immunoglobulin loci (chromosome 14q32). Indeed, such translocations are common in various lymphoma subtypes (1). The process of somatic hypermutation in the immunoglobulin variable region genes of B lymphocytes takes place in the germinal centers of lymphoid tissue after antigen encounter and serves to increase the affinity for that specific antigen. Most B-cell lymphoma subtypes appear to arise from cells that are in or have passed through this germinal center stage of development, but about 50% of CLL cases and most mantle cell lymphomas arise from cells with unmutated variable region genes indicating that they have not passed through the germinal center stage. A link between some autoimmune disorders and NHL that excludes unmutated NHL subtypes could imply that T-cell-dependent germinal center B-cell adaptation to antigen may be relevant for autoimmune lymphomagenesis. Indeed, RA patients have been shown to display oligoclonal B-cell expansions with non-random use of certain sets of immunoglobulin heavy-chain genes and patterns of somatic mutation indicative of antigen-driven selection (111). Similarily, selected use of immunoglobulin variable genes and somatic hypermutation patterns have been observed in some lymphoma subsets, for example in MALT lymphomas (see above). However, antigenic drive does not explain the observed link of autoimmune disorders with diffuse large B-cell lymphoma in particular, but not with all other subtypes arising from germinal center or post-germinal center stages of lymphocyte differentiation.

In line with the above discussion, excess risk of malignant lymphomas in some autoimmune and chronic inflammatory disorders but not in others may relate to individual and disease-related degree of B-cell proliferation and antigenic drive, degree of apoptotic resistance and other differences in susceptibility to adverse genetic events during immunoglobulin rearrangement and somatic hypermutation, perhaps specifically in relation to T-helper cell function. If one or several of these potential mechanisms in autoimmunity-related lymphomagenesis is relevant for the development of lymphomas in individuals not diagnosed with such disorders is an open question.

FUTURE RESEARCH

In spite of what can be learnt from the present studies, the "old" and most important questions with regard to lymphoma etiology remain unsolved. Hence, we are still ignorant of the causes of the majority of new lymphoma cases, of environmental agents contributing to the dramatic increase in NHL incidence in the past decades, and of factors underlying the increase in incidence of HL among young adults. In light of the extreme heterogeneity of this malignancy group, as reflected in the WHO classification and further underlined by the recent characterization of more sub-entities with DNA microarray techniques, one clue to this mystery most certainly lies in strict definition of homogeneous lymphoma subtypes in future etiologic studies. Elucidation of susceptibility genes for lymphoma subtypes and investigation of potential gene-gene and gene-environment interactions in carefully designed studies will hopefully help disentangle some etiological mechanisms in the years to come. For such efforts, clinical, epidemiologic and genetic competence will need to be combined. Areas of interest in genetic susceptibility and gene-environment interactions include different aspects of DNA repair and immune function in response to infectious agents, UV light exposure, allergy, smoking, dietary habits and pesticide exposure, just to mention a few.

In the smaller perspective, the following questions are relevant based on the present studies:

- What are the biological mechanisms that explain the observed inverse association between sun exposure and lymphoma?

- What is the nature of the link between skin cancer and malignant lymphomas (or some lymphoma subtypes)?

- What are the biological mechanisms of lymphomagenesis in RA?

- What are the biological mechanisms of the development of nodal or non-localized NHL in Sjögren's syndrome, SLE and celiac disease?

- If disease severity can be confirmed as the major determinant of lymphoma risk in the context of RA, does this imply that early initiation of potent treatment in patients with severe RA confers a reduced risk of lymphoma for these patients?

- Does early initiation of and compliance to a gluten-free diet in celiac disease confer a decreased risk of lymphoma, or for one or several NHL subtypes in particular?

CONCLUSIONS

- Frequent exposure to UV light appears to be associated with a reduced relative risk of NHL, and perhaps also HL. Mechanisms are unclear but could include UV light-induced systemic immune modulation or photo-activation of vitamin D production.

- The risks of NHL and HL are increased by about 2-fold following any kind of skin cancer. Skin cancer history may be differentially associated with NHL subtypes. The nature of the link between the two malignancy groups remains to be elucidated, as the previously popular hypothesis involving frequent UV light exposure has been rejected.

- RA is associated with increased risks of both NHL and HL, and of diffuse large B-cell lymphoma in particular.

- Development of NHL in RA appears to be linked to disease severity and antigenic drive, rather than treatment or risk factors common to both disorders, including genetic susceptibility.

- Celiac disease is associated with an increased risk of malignant lymphomas not only of the intestinal T-cell type, but also of more common non-intestinal T-cell and B-cell NHL types (perhaps diffuse large B-cell lymphoma in particular).

- Relative risks of overall NHL and T-cell NHL in celiac disease may have decreased in recent decades in Sweden. However, the role of gluten-free diet therapy in this context is not clear.

- Primary Sjögren's syndrome and SLE are associated with markedly increased relative risks of NHL, perhaps primarily of diffuse large B-cell and marginal zone lymphomas, that are not confined to parotid or lacrimal gland locations. Lymphomagenesis in these disorders may thus involve local inflammation as well as systemic mechanisms related to autoimmunity.

- We did not observe an overall increased risk of NHL in association with type I (or type II) diabetes mellitus, inflammatory bowel disorders, psoriasis or sarcoidosis. Small overall risk increases may have been missed due to low statistical precision.

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