Malignant Lymphomas in Autoimmunity and Inflammation: A Review of Risks, Risk Factors, and Lymphoma Characteristics

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Abstract

Certain autoimmune and chronic inflammatory conditions, such as Sjögren’s syndrome and rheumatoid arthritis (RA), have consistently been associated with an increased risk of malignant lymphomas, but it is unclear whether elevated lymphoma risk is a phenomenon that accompanies inflammatory conditions in general. Likewise, it is debated whether the increased risk identified in association with some disorders pertains equally to all individuals or whether it varies among groups of patients with different phenotypic or treatment-related characteristics. It is similarly unclear to what extent the increased lymphoma occurrence is mediated through specific lymphoma subtypes. This update reviews the many findings on risks, risk levels, and lymphoma characteristics that have been presented recently in relation to a broad range of chronic inflammatory, including autoimmune, conditions. Recent results clearly indicate an association between severity of chronic inflammation and lymphoma risk in RA and Sjögren’s syndrome. Thus, the average risk of lymphoma in RA may be composed of a markedly increased risk in those with most severe disease and little or no increase in those with mild or moderate disease. The roles of immunosuppressive therapy and EBV infection seem to be limited. Furthermore, RA, Sjögren’s syndrome, systemic lupus erythematosus, and possibly celiac disease may share an association with risk of diffuse large B-cell lymphoma, in addition to well-established links of Sjögren’s syndrome with risk of mucosa-associated lymphoid tissue lymphoma and of celiac disease with risk of small intestinal lymphoma. However, there is also obvious heterogeneity in risk and risk mediators among different inflammatory diseases. (Cancer Epidemiol Biomarkers Prev 2006;15(11):2069–77)

Introduction

Over recent decades, the worldwide incidence of malignant lymphomas has increased dramatically (1). In the United States, non-Hodgkin lymphoma (NHL) is now the fifth most commonly diagnosed malignancy (2). The causes of most new cases of lymphoma are poorly understood, as reflected by the relatively few risk factors that have been established (1). Over the years, several studies have linked certain autoimmune and chronic inflammatory conditions, including rheumatoid arthritis (RA), Sjögren’s syndrome, systemic lupus erythematosus (SLE), celiac disease, dermatitis herpetiformis, and chronic thyroiditis to an increased occurrence of lymphoma (3). However, the magnitude of the average lymphoma risk increase in each disorder varies considerably among studies (4). About the exposure, it is unclear whether the increased risk pertains equally to all individuals or varies among groups of patients with different phenotypic or treatment-related disease characteristics, which in turn remain to be defined. About the outcome, it is unclear to what extent the increased lymphoma occurrence is mediated through specific subtypes and whether the relevant subtypes vary among different inflammatory conditions. Another important question is whether elevated lymphoma risk accompanies states of chronic inflammation in general or whether it is specifically linked only to some disorders.

Revealing the nature of lymphomagenesis in relation to autoimmunity/inflammation is important from several points of view. Clinically, we need to learn how to identify individuals who are at substantially increased lymphoma risk and how optimally to intervene against this risk. In particular, we need to understand whether lymphomas arise as a consequence of medical treatment or because of a lack thereof. Considerable clinical concern about the potential lymphomagenicity of the recently introduced immunomodulatory treatments for chronic inflammatory diseases (5, 6) underscores the need for quantification of lymphoma risk based on patient characteristics, especially among patients channeled into treatment with these new drugs. Biologically, although lymphomas complicating defined autoimmune/inflammatory disorders comprise a minority of all lymphomas in the general population, any insights into the nature of this association may shed light on biological pathways of importance that also apply to hitherto unexplained “sporadic” lymphomas.

In this update, we summarize the current knowledge on risks, etiologic and clinical risk factors, and lymphoma subtypes in autoimmunity/inflammation. Importantly and in contrast to previous reviews of selected rheumatologic conditions (4, 7, 8), our update covers inflammation in a broader perspective.

Methodologic Issues

Studies of lymphoma risk in autoimmune/inflammatory disorders are challenging for several reasons. First, autoimmune

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disorders and lymphoproliferative malignancies are both rare in the population, and large patient groups and long observation periods are therefore needed to observe meaningful associations between these disease groups. Registry-based cohort studies, typically based on hospital discharge diagnosis records, may overselect patients with severe disease. Such selection may limit the generalizability of the findings and also obscure the duration of the latency period between the “onset” of the inflammatory disease and cancer development. Although registry-based cohort studies may have adequate statistical power, they seldom provide the opportunity to examine potential confounding factors and effect modifiers. There is also often a lack of detail about the outcome (e.g., lymphoma subtypes by histology or age group). Although case-control studies may offer better information about lymphoma subtypes and covariate exposures of interest, analyses may instead be hampered by low power, control selection bias, and/or differential recall between cases and controls. Population-based registries of incident cases and nested case-control studies in defined cohorts provide the best opportunities for prospective follow-up and assessment of relevant data.

Another complicating factor is the close relationship between chronic activation or dysregulation of the immune system and malignant transformation of the same immune cells, resulting in potential bias due to reversed causality (that is, incipient lymphomas causing paramalignant inflammation or malignancy as, for example, RA; ref. 9). Many studies have noted a more pronounced lymphoma risk during the first year of follow-up after autoimmune/inflammatory disease diagnosis or have excluded the first follow-up period, indicating both presence and awareness of this problem.

For this update, we identified all published epidemiologic studies of cohort or case-control design, or case series, through Medline searches using combinations of the following key words: “[the disease in question],” “lymphoma,” “cancer” or “malignancy,” and “risk,” “cohort,” or “case-control.” Rather than doing a formal meta-analysis of all studies encountered, we have summarized the results of the most important studies, with a focus on recent advances. Because of the large number of inflammatory conditions and studies identified through our search, articles cited were prioritized based on the following methodologic characteristics: largest study samples for the condition in question, population-based design, recent publication, or novel finding. Validity was further evaluated based on a well-defined study base, especially for case series.

Malignant Lymphomas

Malignant lymphomas entail considerable heterogeneity with regard to morphologic and molecular characteristics as well as clinical course (10). In addition, there is growing evidence of etiologic variation among lymphoma subtypes (1). The two main types traditionally considered are NHL, which comprises ~90% of all cases, and Hodgkin lymphoma (HL), which accounts for the remaining 10%. Mature B-cell neoplasms comprise >85% of all NHL, and T-cell tumors comprise ~12% worldwide (10). The current WHO classification further distinguishes among close to 40 NHL subtypes (10), including chronic lymphocytic leukemia and plasma cell malignancies, and at least two distinct HL entities (the rare nodular lymphocyte predominant type and the larger group of classic HL further divided in four subcategories).

Worldwide, NHL constitutes the 10th most commonly diagnosed malignancy, whereas in the developed world it ranks 7th. The most common NHL subtypes in western countries are diffuse large B-cell lymphoma (~30% of cases) and follicular lymphoma (~20%). All other NHL subtypes have a frequency of <10% (10). During the second half of the 20th century, there was a dramatic increase in NHL incidence worldwide, of about 2% to 4% annually (1). However, in the beginning of the 1990s, the overall increase in incidence began to level off in most populations. The overall age-adjusted incidence of HL has been stable or slightly declining during the same period (11).

Well-established risk factors for lymphoma include uncommon disorders of strong immune perturbation, such as inherited disorders of immune dysfunction, HIV/AIDS, and organ transplantation. Pathogenic mechanisms in the context of immune dysfunction include suppression or dysregulation of T-cell function, allowing for rapid EBV-driven B-cell proliferation, which results in a high proportion of EBV-positive lymphomas. Other established risk factors include certain infectious agents, a degree of familial aggregation, and some autoimmune disorders (1). Neither confirmed risk factors nor diagnostic improvements or classification changes can, however, fully explain the observed increase in NHL incidence over the past decades (12).

Autoimmune/Inflammatory Conditions Linked to Lymphoma

Rheumatoid Arthritis. Several cohort studies (13-20) and a few case-control studies (21-23) showed increased risks of both NHL and HL in association with RA, with relative risks (RR) typically in the range of 1.5 to 4 (Table 1) regardless of study size or design. Cohort studies that identified prevalent RA patients based on hospitalization (14-17) may have yielded exaggerated RR estimates, as subjects with severe and long-lasting disease may have been overrepresented. However, more recent cohorts of incident RA patients followed from disease onset also reported an ~2-fold increase in risk (19, 20). Higher risk has often been noted in males compared with females (13-16, 18), but this difference was statistically significant only in the hitherto largest cohort study (17).

The approximately doubled lymphoma risk in RA may encompass considerable heterogeneity in risk among subsets of patients. For instance, reports suggest that patients with Felty’s syndrome (splenomegaly and granulocytopenia linked to severe, long-standing seropositive RA) are at a more markedly (5- to 10-fold) increased risk (17, 24). In addition, two recent case-control studies of ~400 RA-associated lymphomas nested in a large, population-based RA cohort, various markers of disease severity (including joint destruction, erythrocyte sedimentation rates, number of affected joints, and cumulated inflammatory load) emerged as independent and strong risk factors (25, 26), with >3 joint regions and presence and awareness of this problem.

Indeed, the emerging pattern in RA thus suggests that the conflation of a more pronounced RR in patients with the most severe disease (25, 26) and little or no increase in those with mild to moderate disease (23).

An alternative explanation for the association between RA and lymphoma risk is the existence of shared genetic and/or environmental risk factors for both conditions. However, in a registry-based cohort study of lymphoma risk in family members of RA patients, parents and siblings were at no or only a marginally increased risk of lymphoma, suggesting that much of the increased lymphoma risk in RA patients is due to factors directly related to the disease or its treatment (17).

Treatment of RA with disease-modifying antirheumatic drugs, including methotrexate, azathioprine, and other immunosuppressive substances, has been repeatedly suggested as a risk factor for RA-associated lymphomas (27-29). Many studies of disease-modifying antirheumatic drugs, however, did not take into account the close correlation between disease severity and propensity for antirheumatic treatments. More recent
studies with detailed information on markers of inflammatory activity as well as treatment (18, 25, 26, 30) did not substantiate the proposed treatment-related increase in lymphoma risk, with the possible exception of azathioprine (26). Numerous case reports describe lymphoproliferative lesions arising during methotrexate therapy (10). These lymphoproliferations are often EBV positive (about 30-50%; refs. 31, 32) and may regress with methotrexate cessation (31, 33). However, there is little evidence that methotrexate per se (as used to treat inflammatory disorders) increases lymphoma risk (18, 26, 32). In a recent nested case-control study from our group, only 4 of 378 RA-associated lymphomas displayed spontaneous regression, and only 1 of these 4 occurred in a patient exposed to methotrexate (26).

With respect to other anti-inflammatory treatments, such as nonsteroidal anti-inflammatory drugs and systemic corticosteroids, an excess risk of lymphomas has been reported (22, 34-36). As with studies of disease-modifying antirheumatic drugs, most of these investigations are limited by the potential for confounding by indication, as they did not consider the effect of underlying diseases or reasons for treatment (22, 34, 36). In addition, several cohort and case-control studies showed no or inverse associations between use of nonsteroidal anti-inflammatory drugs (22, 26, 37-39), steroids (26, 34, 39, 40), or proxies thereof (41) and lymphoma risk. Thus, current evidence for a role of these medication groups in RA-associated lymphomagenesis is weak. With respect to treatment with tumor necrosis factor (TNF) antagonists, a conspicuous number of lymphomas were observed in the early trials of these drugs (5, 6, 42). These reports also suggested the existence of lymphomas with short latency and exceedingly poor prognosis and of fatal relapses in individuals with a pretreatment history of lymphoma in remission. Although increased risk was also reported in observational cohorts in postmarketing surveillance programs (43), larger cohort studies have thus far not confirmed any treatment-related excess of lymphoma in general (18, 19). Nonetheless, it is still premature to make firm conclusions about the true lymphoma risk in patients treated with TNF antagonists, as available observational studies have included only moderate numbers, not been able to adjust fully for RA disease activity, and not assessed long-term risk or the clinical course of the occurring lymphomas (18, 19).

With regard to NHL subtypes in RA, an increased proportion of diffuse large B-cell lymphoma was described in three of four studies (23, 32, 44, 45). In our recent nested case-control study of 378 RA-associated lymphomas, we noted not only a higher than expected proportion of this subtype but also a much stronger association of RA disease severity with diffuse large B-cell lymphoma (a 100-fold increase in risk; ref. 26). In a recent population-based case-control study with >3,000 NHL cases (23), we also observed a stronger association with diffuse large B-cell lymphoma in cases reporting severe RA disease than in those with mild disease. In addition, associations of RA with NHL risk are typically more pronounced than those with NHL risk (13-17). However, the HL risk in existing studies on this topic (13-17) is likely inflated by a degree of misclassification of NHL as HL, a common problem in the past (46). Thus, the true risk increase of HL in RA remains uncertain. It is also unknown whether RA is associated with any particular subtype of HL by age group, histology, or EBV status, as no studies have determined RR of HL by subtype, most likely due to low statistical power. However, in the large nested case-control study of RA-associated lymphomas (26), the distribution of HL cases according to histologic subtype or EBV status did not differ from that expected. The proportion of EBV is detected at low frequency in RA-related lymphomas in general (25, 26, 44), and although a role for EBV in some cases cannot be dismissed, it is unlikely to be of major importance.

### Sjögren’s Syndrome

Patients with Sjögren’s (sicca) syndrome are at increased risk of developing NHL. Reported RRs range from about 4- to 40-fold and are higher for primary than for secondary disease (15, 23, 47-52). However, risk estimates are generally based on few lymphoma cases and 95% confidence intervals (95% CI) are therefore wide. In the hitherto largest cohort study of hospitalized patients (676 with primary and 709 with secondary Sjögren’s syndrome; ref. 15), an NHL risk of 8.7 (95% CI, 4.3-15) was noted in association with the primary form (Table 1) and of 4.5 (95% CI, 1.5-11) for the secondary form. A recent large prospective cohort study, including 507 incident patients with primary Sjögren’s

### Table 1. Summary of autoimmune/inflammatory disorders consistently associated with risk of malignant lymphomas, including reported RR range, disease-related risk factors, associated lymphoma subtypes, and future research issues

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Most reported RR range</th>
<th>Disease-related risk factors</th>
<th>Associated lymphoma subtypes</th>
<th>Future research issues</th>
<th>Selected references</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>1.5-4</td>
<td>Inflammatory activity</td>
<td>Diffuse large B-cell lymphoma</td>
<td>Risk prediction</td>
<td>(18-20, 26)</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>9-16</td>
<td>Hypocomplementemia</td>
<td>MALT lymphoma</td>
<td>Risk prediction</td>
<td>(15, 50, 51, 54, 57)</td>
</tr>
<tr>
<td>SLE</td>
<td>3-7</td>
<td>No data published</td>
<td>Diffuse large B-cell lymphoma</td>
<td>Disease-related risk factors?</td>
<td>(23, 62, 64, 65)</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>3-6</td>
<td>Noncompliance with gluten-free diet?</td>
<td>Enteropathy-type T-cell lymphoma</td>
<td>Effect of gluten-free diet?</td>
<td>(23, 70, 72, 74, 77)</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>2-10</td>
<td>Noncompliance with gluten-free diet?</td>
<td>Enteropathy-type T-cell lymphoma</td>
<td>Effect of gluten-free diet?</td>
<td>(72, 75, 76, 78)</td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis</td>
<td>3-4</td>
<td>No data published</td>
<td>MALT lymphoma</td>
<td>Association confined to thyroid lymphoma?</td>
<td>(79, 80, 82)</td>
</tr>
<tr>
<td>Inflammatory myositis</td>
<td>2-4</td>
<td>Paramalignant phenomenon only?</td>
<td>No data published</td>
<td>Causal association with lymphoma?</td>
<td>(84)</td>
</tr>
</tbody>
</table>

*Confined to the first few years of follow-up.
syndrome (51), noted a 16-fold increased risk of lymphoma in patients fulfilling the diagnostic American-European Consensus Criteria (AECC; ref. 53) but found no risk increase in other sicca patients, suggesting a specificity of the association to strictly defined disease. In this study by Theander et al. (51), the risk was more pronounced with longer follow-up time (>10 years) among the AECC patients. Gender differences in risk have not been robustly evaluated due to the heavy predominance of female patients in Sjögren’s syndrome (23, 48-52).

As in RA, markers of severe Sjögren’s syndrome (e.g., parotid enlargement, hypocomplementemia, and palpalble purpura) are associated with a more pronounced risk of NHL (51, 54, 55). In the only study to evaluate a large range of CD4/CD8 ratios, these factors were the strongest predictors of lymphoma development (51). Specific associations between immunosuppressive treatment and lymphoma risk in Sjögren’s syndrome have been rarely reported (3).

With regard to lymphoma subtypes, case reports and case series have shown a striking occurrence of mucosa-associated lymphoid tissue (MALT) lymphomas, especially those located in the parotid gland, in Sjögren’s syndrome (56, 57). However, more recent and systematic assessments indicate that the predominance of MALT lymphomas may not be as large as believed previously. In two well-defined cohorts of patients with Sjögren’s syndrome, only 6 of 26 (58) and possibly 1 of 12 (51) NHLs were of MALT type. Instead, diffuse large B-cell lymphoma was the most common subtype in both studies (51, 58). Similarly, a recent case-control study (23) showed both a 28-fold increased risk of marginal zone lymphoma (including MALT lymphoma) and an 11-fold increased risk of diffuse large B-cell lymphoma. Conversely, in a series of 33 parotid MALT lymphoma cases, almost half (46%) of the patients had a history of Sjögren’s syndrome (59). Thus, although the association between Sjögren’s syndrome and parotid MALT lymphoma seems indisputable and biologically well-defined (see below), there may also be an association with the more common diffuse large B-cell lymphoma subtype, although putative mechanisms behind such an association remain undefined. No increased occurrence of EBV-positive lymphomas has been reported in patients with Sjögren’s syndrome (56). A role for the hepatitis C virus has been proposed but remains unclear (55, 59).

Systemic Lupus Erythematous. In SLE, 10 of 14 separate studies, mostly of cohort and also of case-control design, reported a significantly 3- to 40-fold increased risk of NHL, and only 4 studies observed no, or only a suggested positive, association (23, 60-63). The largest studies by far, including a cohort of 5,700 patients with hospital discharge diagnoses of SLE (62) and a large, population-based multicenter cohort analysis encompassing the majority of previously published cohort studies (9,500 SLE patients in six countries; ref. 64), showed an overall 3- to 4-fold increased risk of NHL in association with SLE (Table 1). In the multicenter analysis, the excess risk persisted after 10 to 20 years of follow-up and was observed in both sexes (64). Disease-related risk factors responsible for this increase are unknown but under exploration (65). In cohort studies (66, 67) as well as case reports (68), few SLE patients who developed lymphoma were treated with immunosuppressive drugs, such as methotrexate, azathio- prine, or cyclophosphamide. Hence, the role of these drugs in SLE-related lymphoma development does not seem to be pivotal. About lymphoma subtypes in SLE, all NHLs (n = 61) in a review of case reports (68) were of B-cell type, and HL and plasma cell disorders were also described (68). Two recent studies indicate that the proportion of diffuse large B-cell lymphomas is elevated among lymphomas complicating SLE (40-50%) compared with the expected fraction of all NHLs in the general population (25-30%; refs. 23, 65). The role of EBV in SLE-related lymphomas is uncertain (68).

Celiac Disease and Dermatitis Herpetiformis. Celiac disease and dermatitis herpetiformis, autoimmune disorders triggered by exposure to gliadin, occur at increased frequency in individuals with other autoimmune conditions (e.g., diabetes and RA). Highly increased lymphoma risks were reported in celiac disease decades ago (69, 70). However, older studies were based on small numbers (69) and patient series in referral clinics (70), resulting in imprecise risk estimation and possible selection of patients with unusual disease characteristics that may entail a higher risk of lymphoma. More recent large, population-based studies of mostly cohort but also case-control design described a lower, albeit still increased, risk of typically between 3- and 6-fold (Table 1; refs. 71-74). As with the largest cohort study of 11,000 hospitalized patients (72), the 6-fold increase in risk (equal in both sexes) was restricted to patients diagnosed as adults and declined over successive calendar periods to a 3-fold excess risk during the 1990s. Whether the apparent discrepancies in risk between older and newer studies and the observed time trend relate to an increasing recognition of mild or silent celiac disease (presumably associated with a lower risk of NHL), a tendency toward earlier age at diagnosis or better management of patients is as yet unknown. Although attractive, the hypothesis that early total compliance to gluten-free diet therapy may protect against lymphomas in celiac disease is supported only by indirect evidence and studies, including very few lymphoma cases (70). With regard to dermatitis herpetiformis, the observed RR of lymphoma ranged from 2 to 10 in recent studies (Table 1; refs. 72, 75, 76).

Traditionally, celiac disease has been linked to an uncommon form of T-cell lymphoma in the small intestine, referred to as enteropathy-type T-cell lymphoma in the WHO classification (10). As with NHL subtypes in Sjögren’s syndrome, however, recent and population-based studies indicate that other and more common lymphoma types, such as non-intestinal T-cell and B-cell NHL (71, 77), and perhaps diffuse large-B-cell lymphomas in particular (23) also occur more often than expected. In dermatitis herpetiformis, occurrence of both B- and T-cell lymphomas has also been described (75, 78).

Hashimoto’s Thyroiditis. Clinical cohort studies have reported a 3- to 4-fold increased risk of malignant lymphoma in association with chronic lymphocytic or Hashimoto’s thyroiditis but with substantial imprecision (Table 1; refs. 79, 80). In the largest study, which included 5,500 female thyroiditis patients (80), all eight lymphomas observed were located in the thyroid gland. Conversely, in two series of patients with thyroid lymphoma, a clinical history of Hashimoto’s thyroiditis was noted in about 40% of the patients (81), whereas >90% of the cases had histologic evidence of lymphocytic thyroiditis in thyroid tissue adjacent to the tumor (82). Thus, although Hashimoto’s thyroiditis undoubtedly confers an increased risk of thyroid lymphoma, it is unclear whether the disease is also accompanied by an increased risk of lymphomas in other locations. Thyroid lymphomas are typically of the indolent MALT type, which occasionally transforms into more aggressive diffuse large-B-cell lymphoma (82).

Polymyositis and Dermatomyositis. Inflammatory myositis (primarily dermatomyositis and less so polymyositis) is associated with a 2- to 4-fold increased risk of NHL (Table 1; refs. 83, 84), although null results have also been reported (85). The increase in risk, however, is not specific for lymphoma but applies to malignancies overall and has been consistently observed to be high around the time of the myositis diagnosis (84, 86, 87). In the largest investigation thus far, a pooled analysis of three Scandinavian cohorts, including 1,500 patients (84), there was no significant risk increase of NHL beyond the first year of follow-up (with five of eight NHLs diagnosed within the first year), and a considerable number of cancer cases also predated the myositis diagnosis. These
observations suggest that inflammatory myositis may occur primarily as a paraneoplastic syndrome (3). Evidence is thus still scarce that the myositis disorders in themselves confer any elevated lymphoma risk. Furthermore, there is little to suggest that immunosuppressive therapy influences lymphoma occurrence in these patients (83, 88).

**Inflammatory Bowel Disorders.** In ulcerative colitis, most investigations favor no association with lymphoma risk (89-93). In the two largest and population-based cohort studies, including ~40,000 patients in total, the risk of lymphoma was close to unity [standardized incidence ratio (SIR), 1.1; 95% CI, 0.5-2.2 (92) and SIR, 1.0; 95% CI, 0.8-1.3 (93)]. In Crohn’s disease, reports are somewhat less consistent. In a population-based cohort of ~3,000 Crohn’s disease patients, a 2-fold excess risk of lymphoma was observed (SIR, 2.4; 95% CI, 1.2-5.0; ref. 91). A significant 2-fold risk increase was also reported for lymphoproliferative and myeloid malignancies in another twice as large cohort (94), but there was no separate assessment of lymphoma risk. Neither of these studies analyzed risk by duration of follow-up; therefore, the effect of possible initial misclassification cannot be evaluated. Several other reports are, however, consistent with no association (89, 92, 95, 96). The hitherto largest study, based on 20,000 patients, observed a 30% increased risk of lymphoma (SIR, 1.3; 95% CI, 1.0-1.6; ref. 93) excluding the first year of follow-up, but after 5 years the association approached unity. Thus, the result may reflect a true association as well as reversed causality or surveillance bias. We conclude that, to date, there is little to suggest a true excess risk of NHL, HL, chronic lymphocytic leukemia, or gastrointestinal lymphoma in ulcerative colitis, whereas an increased risk in subsets of patients with Crohn’s disease cannot formally be excluded (23, 93). Nevertheless, any overall increase in NHL risk in Crohn’s disease seems to be of much smaller magnitude than in, for example, RA and SLE.

**Psoriasis and Spondylarthropathies.** In psoriasis, several studies observed a statistically significant 2- to 8-fold increased risk of lymphoma (97-99), whereas others described no association (23, 100). Interestingly, practically all studies assessing risk by NHL subtype described a severalfold increased risk of T-cell lymphoma overall (22) or mycosis fungoides (101, 102). In the largest study by far, including ~150,000 patients with mild disease and 4,000 patients with severe psoriasis from the UK General Practice Research Database (103), there was a 4-fold excess risk of cutaneous T-cell lymphoma associated with mild disease and a >10-fold risk increase with severe disease but no significant association with other NLHS in either group. An increased risk of HL was also noted in both groups (RR, 1.4 and 3.2, respectively). Limitations of the investigation were the short follow-up time (median, 4-6 years) and the lack of evaluation of the effect of latency. Although evidence is indeed accumulating that psoriasis is associated with risk of cutaneous T-cell lymphomas in particular, possibly driving the association with increased risk of lymphoma overall in some studies, potential inflation of risk due to misclassification cannot be disregarded, as cutaneous T-cell lymphomas may initially mimic benign skin disorders, such as psoriasis (104). For other spondylarthropathies, data are scarce, with the exception of ankylosing spondylitis. In a cohort study of ~3,000 patients, an ~3-fold excess risk of lymphoma was reported based on the occurrence of 7 NHL cases (SIR, 2.9; 95% CI, 1.4-5.6), but latency was not evaluated (105). In addition, a 70% increased mortality due to NHL was observed in a historical cohort of 15,000 irradiated ankylosing spondylitis patients, but there was also a 30% increase in overall cancer mortality (106). In a recent registry-based case-control study, including 50,000 lymphoma patients and 93,000 matched population controls, there was no association between hospitalization for ankylosing spondylitis and risk of NHL or HL (risk of lymphoma overall, 1.0; 95% CI, 0.6-1.7; ref. 107). Thus, although a positive association between ankylosing spondylitis and lymphoma cannot be refuted, any association is likely to be of lower magnitude than that between, for example, RA and lymphoma risk.

**Other Autoimmune Disorders.** In systemic sclerosis, two cohort studies, including close to 1,000 hospitalized patients (108, 109), suggested a moderately increased risk of NHL or hematopoietic malignancy overall, whereas two other equally large clinical cohort studies observed no association (110, 111). However, each of these investigations was limited by small case numbers (about two cases of NHL or hematologic malignancies per study) and low precision (108-111). Hence, there is no conclusive evidence for an increased risk of NHL in systemic sclerosis. The only large-scale study of cancer risk in the rheumatic vasculitides reported a 4-fold excess lymphoma risk (SIR, 4.2; 95% CI, 1.8-8.3) in 1,000 patients hospitalized with Wegener’s granulomatosis (112). However, there was no significantly increased risk beyond the first year of follow-up; thus, misclassification of the positive association could be due to misclassification. In multiple sclerosis, studies have consistently shown no excess risk of lymphoma or hematopoietic malignancy (113-115). Associations between diabetes mellitus and malignant lymphomas have been described occasionally (116), but the overall picture is that of no association (117, 118). Two cohort studies with a total of 50,000 patients diagnosed with diabetes before age 30 years (predominantly type 1/autoimmune diabetes) showed no excess risk of lymphoma (118, 119) but did not distinguish among lymphoma subtypes. In sarcoidosis, a chronic granulomatous condition that may involve an infectious origin and genetic susceptibility, case reports have highlighted a possible association with HL (120). One large cohort study based on ~9,000 patients found a 2-fold excess risk of lymphoma overall (SIR, 1.9; 95% CI, 1.3-2.7), but significantly increased risks of both NHL and HL were confined to the first 4 years of follow-up (121). As pulmonary or hilar lymphoma may mimic sarcoidosis, misclassification may have influenced the results. Two smaller cohorts with a total of 800 sarcoidosis patients and only one complicating lymphoma did not observe excess risk of lymphoma, although less than one case was expected (122, 123). In conclusion, an excess risk of lymphoma in sarcoidosis cannot be excluded, but current evidence is weak.

**Nonautoimmune Inflammatory Conditions.** Several infectious agents have been specifically linked to certain subtypes of lymphoma. These agents include the viruses HIV, EBV, human T-cell lymphotrophic virus-1, human herpes virus-8 (1), and hepatitis C virus (124) and the bacteria *Helicobacter pylori* (125), *Borreliarburgdorferi* (126), and most recently also *Chlamydia psittaci* (127) and *Campylobacter jejuni* (128). Most of these agents are believed to exert their lymphoma-generative mechanisms primarily or partially through chronic immune stimulation (124, 126, 128-130). Infection-related systemic activation of the immune response, as observed in tuberculosis, malaria, herpes zoster, pneumonia, or pylonephritis, was suggested as a risk factor for lymphoma in some studies (21, 60, 131, 132). Excess lymphoma risk in association with frequent use of antibiotics may reflect similar mechanisms (39). Chronic bronchitis is another inflammatory state that was associated with NHL risk in one study (133). However, asthma, similarly characterized by airway inflammation and hyperreactivity, is more consistently associated with NHL risk along with other allergic disorders (134). Thus, although a biological association is plausible, available data are yet insufficient to establish or exclude a general link between nonautoimmune inflammation and lymphoma risk.
Common Mechanisms of Lymphogenesis

The Role of Antigens. In normal B-cell development and differentiation, the development of antigen recognition through modification and selection of cell surface immunoglobulin receptors is of central importance. The processes of immunoglobulin variable-(diversity)-joining gene recombinase and somatic hypermutation serve to increase receptor affinity for external or self-antigens (135). These genetic rearrangements also provide patterns of clonality that can be detected in immunoglobulin gene analyses. Reciprocal chromosomal translocations involving the immunoglobulin loci are a hallmark of most mature B-cell lymphomas and lead to dysregulated expression of proto-oncogenes important in cell proliferation, differentiation, and/or survival (e.g., c-myc, bcl-2, or bcl-6; ref. 10).

In Sjögren’s syndrome, Hashimoto’s thyroiditis, and celiac disease, mechanisms of development of specific lymphoma types in the affected organs are well documented. In Sjögren’s syndrome and Hashimoto’s thyroiditis, lymphogenesis is attributed to local T-cell-dependent antigen-driven proliferation of B cells that eventually become monoclonal and develop into primarily low-grade MALT lymphoma (136, 137). Sustained antigenic drive during lymphoma transformation is implied by the presence of selected immunoglobulin variable gene mutations and clonal heterogeneity in the hypervariable regions within the tumor cells (136). Similarly, small intestinal T-cell lymphoma (i.e., enteropathy-type T cell) in celiac disease is suggested to develop from intraepithelial autoreactive T-cell infiltrates through polyclonal and monoclonal proliferations of cells with aberrant immune phenotypes (138). Other lines of evidence for the pathogenic importance of antigenic drive come from studies of H. pylori –associated gastric MALT lymphoma (129) and of hepatitis C virus–associated lymphoma (124), in which early lymphomatous lesions may regress on eradication of the antigen stimulus (124, 139). In chronic lymphocytic leukemia, molecular genetic studies indicate that malignant transformation could originate in B-cell precursors reactive to self-antigens (140).

With respect to the evolution of lymphomas without a clear connection to chronically inflamed sites, local antigen stimulation may still be of importance. In celiac disease, clonal lymphocytes are capable of disseminating into the bloodstream and disseminating to extralymphatic sites (138). This may also be true for transforming B cells in Sjögren’s syndrome (141, 142). Nonmalignant B-cell subpopulations in the parotid gland of Sjögren patients have been shown to transform to overt lymphomas in extralymphatic sites, such as the lung and gastric ventricle (142, 143). In RA, ectopic germinal center formation in the synovium provides an ideal setting for continuous immune stimulation (144), and nonrandom use of immunoglobulin heavy chain genes and somatic mutation patterns indicative of antigen-driven selection have been observed in synovial cells of affected patients (145). In a recent case report, an aggressive RA-associated lymphoma was traced back to an antedating nodal oligoclonal lymphoproliferation (146). Interestingly, the neoplastic cells had significant sequence homology with B-cell lymphomas arising in Sjögren’s syndrome and hepatitis C virus–associated mixed cryoglobulinemia, suggesting a possible common pathogenic pathway.

Other Mechanisms. It is conceivable that sustained antigen-driven B-cell proliferation may increase the risk of adverse genetic events, ultimately leading to the emergence of a neoplastic clone. The effect of such events could be enhanced by acquired resistance to apoptosis in autoimmune disorders (147). In RA and SLE, apoptotic resistance is increased and mediated by Bcl-2 expression, activation of nuclear factor-κB by inflammatory cytokines and growth factors, and abnormalities in the expression of B-cell activating factor (BAFF/BLyS, a member of the TNF superfamily; refs. 147, 148). Patients with Sjögren’s syndrome, RA, and SLE have increased levels of BAFF in serum and synovial fluid (149), and BAFF levels in Sjögren’s syndrome patients correlate with the level of disease-specific autoantibodies (149). B-cell activating factors have also been implicated in the growth and survival of B-cell malignancies (150). In one study, serum levels of BAFF were on average 3-fold higher in follicular lymphoma patients than in controls (151). Other cytokines of potential importance include (IL)-6 and IL-10 and TNF-α. IL-10 mediates autoantibody production and may function as an autocrine growth factor in B-cell lymphomas (152). Apart from being a key inflammatory mediator in RA and other inflammatory diseases, TNF is also a growth factor for lymphoma. Recently, in a pooled analysis within a large lymphoma study consortium (InterLymph; ref. 153), genetic variation in the TNF-α and IL-10 genes was associated with an up to 2-fold increased risk of diffuse large B-cell lymphoma, the subtype particularly associated with several autoimmune disorders in other studies (23, 25, 51, 65). Interestingly, variation in TNF-α and related receptor genes may also increase susceptibility to SLE and Sjögren’s syndrome (154). In another study, IL-10 and IL-4 polymorphisms were modestly but significantly associated with NHL risk (155), leading the authors to speculate that abnormalities in the T helper (TH) cell type 2 immune response enhance lymphogenesis. Autoimmune disorders are also associated with alterations in the TH cell response, although in various ways. RA, sarcoidosis, and psoriasis are characterized by accumulation of TH1 lymphocytes, SLE by a TH2 response (156), and Sjögren’s syndrome by high serum levels of both TH1 and TH2 cytokines (157). Therefore, an altered TH1/TH2 balance does not in itself explain why some but not other autoimmune disorders are associated with increased lymphoma occurrence.

Clinical Aspects

Little is known about whether the clinical behavior of lymphomas complicating autoimmune disorders is different from that of lymphomas in general. In one study of 33 RA-associated NHLs (predominantly diffuse large B-cell NHL), median survival time from lymphoma diagnosis was as short as 6 months (45), indicating a worse outcome than for NHL or diffuse large B-cell lymphoma in general (158). However, in another study of 65 RA lymphoma cases and 1,500 non-RA lymphoma controls (159), RA was inversely associated with death from lymphoma or its treatment (hazard ratio, 0.60; 95% CI, 0.37-0.98) but positively associated with death from other causes. These disparate results may relate in part to advances in lymphoma diagnostics and treatment over time, as the larger study was more recent. A possible misclassification of cause of death as unrelated to lymphoma in the latter study could also have concealed a worse outcome of RA lymphomas. Thus, this question remains to be further investigated. Accordingly, it is also unclear whether these patients should be treated differently following lymphoma diagnosis. For obvious reasons, treatment with monoclonal anti-CD20 antibodies (rituximab), which has become part of standard therapy for patients with CD20+ lymphomas (160) and is currently being introduced for the treatment of several autoimmune disorders, is an option that may strike two birds with one stone.

Conclusions

The association between several autoimmune and inflammatory disorders and risk of malignant lymphomas is now well established. In addition, evidence is accumulating, particularly from studies of RA and Sjögren’s syndrome, that the increased
lymphoma risk in these patient groups is mainly due to high inflammatory activity and severity of disease, rather than treatment, in a subgroup of patients. Here, two distinctions are particularly important to keep in mind. First, there is the distinction between the average risk in a group of patients and the risk confined to a particular subgroup, as exemplified by the indication that a minority of RA patients with severe disease may account for the majority of the doubled overall lymphoma burden in RA. Second, there is the distinction between relative and absolute risks. Even a highly increased RR, such as the 50-fold excess risk of enteropathy-type T-cell in celiac disease, translates to a very small absolute risk expressed in terms of the percentage of all patients with celiac disease. On the other hand, extrapolations from available risk data suggest that high-risk subsets of patients, such as those with severe RA, may face a 10% or greater life-time risk of developing lymphoma.

An important challenge over the coming years will be to define algorithms for the identification of autoimmune/inflammatory patients at high risk of lymphoma, to evaluate their pretreatment lymphoma risk profile, and to quantify this risk in absolute terms. Another important issue will be to assess whether the new immunomodulatory treatments increase, decrease, or do not affect the short- and long-term clinical occurrence and course of malignant lymphomas in patients otherwise prone to lymphoma development. Additional research is also needed to further explore biological mechanisms and understand the interplay between genetic susceptibility to lymphoma, such as common variation in IL genes outlined above, and inflammatory activity. With respect to “sporadic” lymphomas, it is important to understand whether also frequent short periods of common but non-autoimmune inflammation or inflammation in response to infection confers an increase in risk, perhaps primarily in genetically susceptible individuals. If so, lymphomagenesis in autoimmune inflammation may serve as a model for a much larger proportion of patients.

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References


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