CEBP Focus: Update on Lymphoma

Altered Immunity as a Risk Factor for Non-Hodgkin Lymphoma

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Abstract

This review examines the association between disorders of immunity, including immune deficiency, atopy, and autoimmune disease, and non-Hodgkin lymphoma (NHL). Immune deficiency is one of the strongest known risk factors for NHL. Risk is increased whether the immune deficiency is congenital, iatrogenic, or acquired. Risk of NHL increases with degree of immune deficiency, and there is no evidence of a threshold. In the profoundly immune deficient, NHL is frequently caused by infection with the ubiquitous EBV. Whether mild, subclinical immune deficiency is related to increased NHL risk is unknown. There is inconsistent evidence that atopic conditions, such as asthma, hayfever, and eczema, characterized by an immune response that is skewed toward Th2, are associated with a decreased risk of NHL. These data come mainly from case-control studies. Concern has been expressed that the association may be due to reverse causality if early symptoms of NHL include a lessening of atopic manifestations. Case-control and cohort studies of people with autoimmune conditions have generally shown that rheumatoid arthritis, systemic lupus erythematosis, and Sjogren's disease are associated with increased NHL risk. It seems to be the intensity of the inflammatory disease rather than its treatment which is related to increased risk of NHL. The study of altered immunity as a cause of NHL in case-control studies is limited by the fact that development of NHL in itself leads to altered immunity. Cohort studies of the role of altered immunity should be a top priority in epidemiologic studies of NHL etiology. (Cancer Epidemiol Biomarkers Prev 2007;16(3):405–8)

Introduction

Lymphoma is a cancer of the immune system and includes more than 20 malignant diseases that originate from B and T lymphocytes. It should thus not be surprising that disorders of function of immune-system cells are associated with risk of malignant transformation. This review focuses on the occurrence of non-Hodgkin lymphoma (NHL) and its relationship to three different abnormalities of the immune system: immune deficiency, atopy, and autoimmune disease.

Immune Deficiency

Immune deficiency is one of the best characterized and strongest known risk factors for NHL. Incidence of NHL in people with congenital or acquired immune deficiency is 50 or more times higher than population rates (1, 2).

Primary/Congenital Immune Deficiency. The primary immune deficiencies constitute a heterogeneous group of disorders with a variable degree of deficiency in B cell and/or T cell function. Malignancy is the second most common cause of death, and NHL is the most common cancer. The NHL subtypes that occur are usually diffuse and often extranodal, and EBV is commonly identified in tumor cells. Burkitt lymphoma occurs only in x-linked lymphoproliferation, and T-cell tumors occur in ataxia-telangiectasia. The relative risk of NHL associated with these conditions varies from 30 to 200 (2).

Iatrogenic Immune Deficiency. Recipients of organ transplants receive a range of immune-suppressive pharmaceutical agents, and the relative risk of NHL after transplantation is 10 to 50 or more. Risk is closely correlated with the degree of immune suppression: the incidence is highest in heart and heart-lung transplant patients in whom it is up to 4% in the first year (3). The risk of NHL is highest in the first year after transplant when iatrogenic immune suppression is most intense. Under these circumstances, EBV is usually, but not always, found in the NHL cells. NHL is often extranodal and occurs relatively frequently in brain (4). It is mostly of diffuse histology, and Burkitt lymphoma is rare.

Acquired Immune Deficiency. The close association of NHL with HIV infection is formally recognized by the fact that NHL is designated an acquired immune deficiency syndrome (AIDS)–defining condition. The majority of NHL cases are of three subtypes. First, primary central nervous system (PCNS) NHL is an EBV-driven lymphoproliferation in profoundly immune-deficient individuals. Second, diffuse large cell or immunoblastic NHL occurs in those with moderately advanced immune deficiency. Third, Burkitt lymphoma tends to occur when immune deficiency is less advanced but can occur at any stage of HIV-related disease (5). EBV has an etiologic role mainly in the severely immune deficient. It is present in tumor cells in almost all cases of PCNS NHL, around half of all diffuse large cell and immunoblastic NHL and around 20% of cases of Burkitt lymphoma (1). Other NHL subtypes occur, but the increase in risk is much less (6). Although risk of lymphoma increases with declining CD4 cell count, recent

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evidence suggests that the risk of NHL remains elevated more than 30-fold above population rates even in those with mild HIV-induced immune deficiency (7). Other risk factors in people with HIV include the duration of severe immune deficiency and markers of B-cell stimulation, including raised serum immunoglobulin G, HIV p24 antigenemia, and elevated levels of B-cell stimulatory cytokines (8, 9).

Similarities and Differences. Profound immune deficiency, of whatever cause, is associated with the loss of EBV-specific CTLs and frequently results in EBV-driven malignant proliferations presenting as NHL. Because EBV is essentially ubiquitous, the main determinant of EBV-associated NHL risk seems to be the intensity of immune suppression. Milder but measurable immune deficiency is associated with a less dramatic increase in NHL risk, and NHL in those immune-deficient states is mostly unrelated to EBV infection; the cause in these situations remains elusive. Possibilities include as-yet unidentified lymphotrophic viruses and dysregulation of control of B-lymphocyte replication. Why Burkitt lymphoma should be relatively common in the setting of AIDS, but uncommon in the setting of other immune-deficient states is unknown.

Whether or not subtle, subclinical, immune deficiency is a risk factor for NHL is a key question in lymphoma research. Unfortunately, measures of immune function after a diagnosis of NHL probably do not reflect the state of the immune system before NHL. For this reason, this question can probably only be addressed by measuring genetic determinants of immune function or by measuring immune function years before NHL development in longitudinal studies. Another approach that has been recently used in studies of Hodgkin lymphoma is to examine immune phenotypes in identical twins of patients (10).

Atopic Conditions and Associated Factors

Atopic conditions are caused by hypersensitivity to environmental allergens and are characterized by an immune response that is skewed toward a T-helper type 2 (Th2)–dominant response (associated with immunoglobulin E antibody production). A recent review of the role of atopy in NHL concluded that there was no clear association between a history of allergy to specific substances and risk of NHL, although a protective effect for childhood leukemia, pancreatic cancer, and brain tumors was observed (11). Case-control studies that have reported risks for eczema, asthma, or hayfever are summarized in Table 1. For eczema, there is a wide range of associations with NHL risk, including three studies with statistically significantly decreased risk, one study with a statistically significantly increased risk, and four studies with no association. For hayfever, the evidence is more consistent: three studies found a statistically significantly decreased risk, and four reported nonsignificant reductions in NHL risk. For asthma, two studies reported a statistically significantly decreased risk, and six studies reported nonsignificant odds ratios of around 1 or less. There is thus some inconsistent evidence of an inverse association between atopy and NHL risk.

A potential concern with case-control studies of the link between NHL and atopic conditions is that the onset of NHL may have changed manifestations of atopy. There has been at least one hospital series reporting that NHL patients may experience a decrease in allergic symptoms as a result of developing NHL (12). Unfortunately, there are few prospective studies that can address this question, and those that exist tend to be too small to be conclusive. Prospective studies based on biomarkers have reported no association between total serum immunoglobulin E (13) or skin hypersensitivity (14) and subsequent NHL risk. A recent Swedish linkage study found a statistically significant 4-fold increased risk of NHL among women diagnosed as atopic by skinprick testing (15).

An intriguing recent addition to the hypothesis that allergy may protect against NHL has been the finding that only, and other first-born, children may have a lower risk of NHL (16), and conversely, that later born children or children with

Table 1. Atopic conditions and risk of NHL in case-control studies

Study author, year, and location*	Type of case-control study	Cases (*n*)	Odds ratio and 95% CI
Eczema			
Cartwright (1988), United Kingdom (1)	Hospital based	437	1.6 (1.1–2.4)
Bernstein (1992), USA (2)	Population based	619	0.6 (0.4–1.0)
Doody (1992), USA (3)	Population based	100	1.9 (0.6–5.8)
Vineis (2000), Italy (4)	Population based	1,388	1.2 (0.9–1.6)
Fabbro-Peray (2001), France (5)	Population based	445	0.5 (0.3–0.7)
Zhang (2004), USA women (6)	Population based	601	1.3 (0.9–1.9)
Becker (2005), Germany (7)	Population based	554	0.7 (0.5–1.0)
Grulich (2005), Australia (8)	Population based	704	0.8 (0.6–1.1)
Hayfever			
Doody (1992), USA (3)	Population based	100	0.5 (0.2–1.2)
Bernstein (1992), USA (2)	Population based	619	1.0 (M), 1.0 (F)
Vineis (2000), Italy (4)	Population based	1,388	0.7 (0.5–1.0)
Zhang (2004), USA women (6)	Population based	601	1.0 (0.8–1.4)
Becker (2005), Germany (7)	Population based	554	0.6 (0.4–0.9)
Grulich (2005), Australia (8)	Population based	704	0.7 (0.5–0.8)
Bracci (in press), USA (9)	Population based	1,304	0.7 (0.6–0.8)
Asthma			
Cartwright (1988), United Kingdom (1)	Hospital based	437	0.8 (0.4–1.5)
Holly (1999), USA (10)	Population based	701 M 580 F	M 0.9 (0.6–1.2) F 0.8 (0.5–1.2)
Tavani (2000), Italy (11)	Hospital based	429	0.8 (0.5–1.4)
Fabbro-Peray (2001), France (5)	Population based	445	0.8 (0.5–1.3)
Zhang (2004), USA women (6)	Population based	601	1.0 (0.7–1.4)
Becker (2005), Germany (7)	Population based	554	0.4 (0.2–0.8)
Grulich (2005), Australia (8)	Population based	704	0.7 (0.5–0.8)
Lee (2006), US (12)	Population based	668	0.9 (0.6–1.4)

*Numbers are references added to the supplementary data.

Table 2. Auto-immune conditions and risk of NHL

Study author, year, and location*	Type of study †	Risk estimate (OR/RR and 95% CI)
Rheumatoid arthritis		
Gridley (1993), Sweden ‡ (13)	Cohort, Population based	1.9 (1.3–2.6)
Kauppi (1997), Finland ‡ (14)	Cohort, Population based	2.2 (1.5–3.1)
Tavani (2000), Italy (11)	CC, Population based	1.7 (0.9–3.4)
Ekstrom (2003), Sweden ‡ (15)	Cohort, Population based	1.9 (1.7–2.1)
Becker (2005), Germany (7)	CC, Population based	0.7 (0.3–1.4)
Engels (2005), United States (16)	CC, Population based	1.3 (0.8–2.1)
Zintzaras (2005), multinational (17)	Meta-analysis, cohorts	3.9 (2.5–5.9)
Smedby (2006), Denmark/Sweden (18)	CC, Population based	1.5 (1.1–1.9)
Systemic lupus erythematosis		
Gridley (1993), Sweden ‡ (13)	Cohort, Population based	1.9 (1.3–2.6)
Vineis (2000), Italy (4)	CC, Population based	8.4 (1.6–45)
Bjornadal (2002), Sweden ‡ (19)	Cohort, Population based	2.9 (2.0–4.0)
Bernatsky (2005), multinational ‡ (20)	Cohort, ?Population based	3.6 (2.6–4.9)
Engels (2005), United States (16)	CC, Population based	4.2 (1.2–15)
Zintzaris (2005), multinational (17)	Meta-analysis, cohorts	7.4 (3.3–17)
Smedby (2006), Denmark/Sweden (18)	CC, Population based	4.6 (1.0–22)
Sjogren's syndrome		
Kauppi (1993), Finland ‡ (14)	Cohort, Population based	8.7 (4.3–16)
Fabbro-Peray (2000), France (5)	CC, Population based	5.1 (0.9–28)
Engels (2005), United States (16)	CC, Population based	13 (1.7–100)
Zintzaris (2005), multinational (17)	Meta-analysis, cohorts	19 (10–37)
Smedby (2006), Denmark/Sweden (18)	CC, Population based	6.1 (1.4–27)
Psoriasis		
Hannuksela-Svahn (2000), Finland ‡ (21)	Cohort, Population based	2.2 (1.4–3.4)
Tavani (2000), Italy (11)	CC, Hospital based	2.5 (0.8–7.3)
Vineis (2000), Italy (4)	CC, Population based	1.2 (0.8–1.8)
Gelfand (2003),United Kingdom (22)	Cohort, GP based	3.0 (1.8–4.8)
Smedby (2006), Denmark/Sweden (18)	CC, Population based	1.2 (0.9–1.5)

*Numbers are references added to the supplementary data.
†CC = Case-control study.
‡Based on data linkage between patients hospitalized with the disease and population-based cancer data.

larger numbers of siblings have a higher risk (17). There is a well-described inverse relationship between risk of atopic conditions and indicators of early-life exposure to infections such as higher birth order (18). According to the ''hygiene hypothesis,'' a delay in early infection with commensal and pathogenic microbes leads to a persistent Th2-dominant immune response. This response is characterized by high antibody titers and a high risk for the subsequent development of atopic conditions (18, 19). Thus, the inverse association between NHL risk and being an only, or other first-born, child is consistent with a protective effect of atopy on NHL risk (16). However, it is equally possible that the relationship between sibship size and birth order and NHL risk is due to other factors, such as direct effects of early infection that are independent of any effect on Th1/Th2 balance.

Autoimmune Disease

Autoimmune diseases comprise a heterogeneous group of conditions associated with a failure of the immune system to recognize self and consequent inflammatory disease. In contrast to allergic disease, it has generally been agreed that autoimmune conditions are mediated by an overactive Th1 arm of the immune system. More recently, there has been considerable debate about the role of Th2 in autoimmune conditions and the relative Th1/Th2 balance, especially in those mediated by autoantibodies, such as systemic lupus erythematosis (SLE) and rheumatoid arthritis.

Much of the evidence on the association between autoimmune disease and NHL comes from clinical cohort studies of relatively small numbers of people diagnosed with autoimmune disease. In the past decade, knowledge in this field has been greatly enriched by several Scandinavian population-based linkage studies that have linked hospital discharge data for autoimmune disease with cancer-registry data. Although there have been several case-control studies, the relative rarity of most autoimmune conditions means that only very large studies have been able to contribute. Table 2 summarizes data from case-control studies and population-based cohort studies on the association between rheumatoid arthritis, SLE, Sjogren's syndrome, and psoriasis and risk of NHL.

The association between NHL and autoimmune disease is best described for rheumatoid arthritis; increased risk has been widely described, although there has been some controversy over whether NHL risk is related to the disease process itself, or to therapy with immune-suppressive medications such as steroids and azathioprine. Population cohort linkage studies in Sweden and Finland have described consistent modest (of the order of 2-fold) increases in NHL risk (Table 2). These studies include only patients who have been hospitalized, and therefore, the results may not be generalizable to all people with rheumatoid arthritis. However, they have the major advantage of only including confirmed rheumatoid arthritis, whereas diagnostic confusion over this condition likely makes self-reported diagnosis relatively inaccurate in case-control studies. Recent data suggest that it is the intensity of inflammatory disease rather than immune-suppressive therapy that is most closely related to NHL risk (20). Further evidence that it is not steroid medication that leads to increased risk among those with rheumatoid arthritis came from a Swedish linkage study of patients with giant cell arteritis and polymyalgia rheumatica. Both these conditions require therapy with a few years of high-dose steroids, but were associated with a reduced rather than an increased risk of NHL (21).

Although there are fewer data, several other autoimmune diseases have been shown to be associated with increased NHL risk. Systemic lupus erythema nodosum (SLE) has been associated with relative risks in the order of 2 to 8 in

cohort and case-control studies (Table 2), and the increase was confined to diffuse large cell NHL in the largest case-control study (22). Sjogren's syndrome was associated with 5-fold or greater increased risk of NHL in published studies (Table 2), and this was limited to diffuse B-cell and marginal-zone lymphomas. Increased risks have also been reported for NHL localized to the parotid gland, suggesting the importance of local immune factors (22). A smaller and inconsistent increase has been reported for psoriasis (Table 2). For celiac disease, overall risk is only slightly raised, but there is a marked increase in T-cell lymphoma (22, 23). The data are mainly null or mixed for other autoimmune diseases.

Summary and Research Directions

It is clear that immune deficiency and certain specific autoimmune disorders markedly increase the risk of NHL. The possibility that atopy is associated with reduced risk of NHL needs to be confirmed in cohort studies, or in case-control studies that include information on distant, as well as recent, history of atopic disease.

The impact of immune deficiency and autoimmune disease on the well-described secular increase in NHL incidence rates in the second half of the 20th century (24, 25) is less clear. However, as the population-attributable risk associated with autoimmune conditions has been estimated to be <5% (22), it seems unlikely that these conditions have made a major contribution to the increase. Of more interest is the potential role of mild immune deficiency. Immune deficiency is a very strong risk factor for NHL, and there is no evidence of a threshold below which there is no increased risk in immune-deficient states such as early HIV disease (7). Therefore, the potential exists that a highly prevalent, subclinical form of immune deficiency might be associated with a substantial proportion of NHL. The investigation of minor variations in immune function as a risk factor for specific types of NHL in cohort studies should be a top priority in NHL research. This should include immunoepidemiologic investigations of abnormalities of, and natural variation in, cellular, humoral, and innate immunity.

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