Epidemiology of lymphomas

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Non-Hodgkin lymphoma (NHL) is the fifth most common cancer in the US, with about 55,000 new cases estimated for the year 2000. According to the new Surveillance, Epidemiology, and End Results (SEER) data from 1973 to 1997, the age-adjusted incidence rates rose by about 80%, with an annual percentage increase of nearly 3%, which is faster than for the majority of cancers. The increasing incidence of NHL is largely unexplained. AIDS-related NHL accounts for some but not all of the increase. The American Cancer Society predicts about 7,400 new cases of Hodgkin Disease (HD) in the year 2000 in the US. The incidence of HD is consistently lower than that of NHL, and has decreased about 16% since the 1970s. Only a small portion of the decrease in HD incidence can be explained by misdiagnosis of HD as NHL. Further research is needed on the cofactors that predispose AIDS cases to lymphoma, as well as other possible causes of NHL such as immunosuppression, genetics, viruses, medical conditions, pesticides, solvents, hair dyes, and diet. Further evaluation of the role of viruses, occupational exposures, and genetics in the etiology of HD should prove valuable. Curr Opin Oncol 2000, 12:383–394 © 2000 Lippincott Williams & Wilkins, Inc.

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Abbreviations

EBV	Epstein-Barr virus
HD	Hodgkin disease
HHV	human herpes virus
HCV	hepatitis C virus
HTLV	human T-cell lymphotropic virus
MALT	mucosa-associated tissue lymphoid
MCPA	4-chloro-2-methyl phenoxyacetic acid
NHL	non-Hodgkin lymphoma
SDF1-3'A	stromal cell-derived factor 1
SEER	Surveillance, Epidemiology, and End Results

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Lymphoma represents a diverse group of neoplasms arising from the lymphopoietic system. Two main groups of lymphomas are Hodgkin disease (HD), characterized by large polynuclear Reed-Sternberg cells, and non-Hodgkin lymphoma (NHL). NHL includes a wide range of subtypes of either B-cell or T-cell lymphomas. NHL is the fifth most common cancer in the US, with about 55,000 new cases estimated for the year 2000 [1]. For several decades, the US and worldwide cancer registries have reported consistent increases in incidence and mortality from NHL [2]. New diagnostic tools, improved registry data, and AIDS-related NHL only partially explain the increase in NHL incidence [3–6].

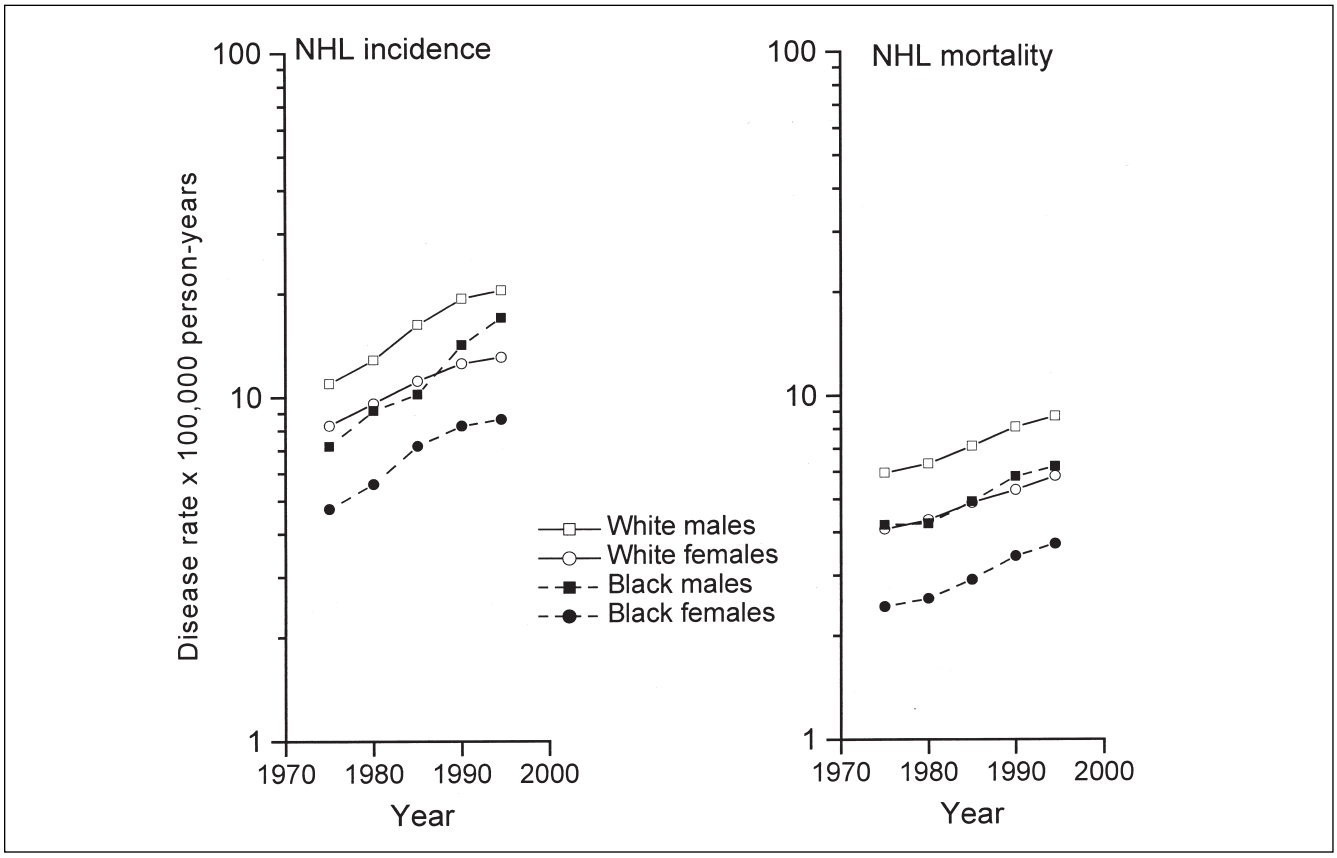
Incidence and mortality trends of lymphoma in the US and worldwide

Data covering the period from 1973 to 1996 from the Surveillance Epidemiology, and End Results (SEER) program of the National Cancer Institute indicate that the NHL incidence has been increasing in all four race/sex groups in the US (Fig. 1). According to the new SEER data from 1973 to 1997, the age-adjusted incidence rates rose by about 80%, with an annual percentage increase of nearly 3%, which is faster than for the majority of cancers (www.seer.ims.nci.nih.gov). The NHL curves for mortality also indicate an increase over time (Fig. 1). The SEER data for the period 1973–1997 report an overall increase of 45% with an annual percentage increase of about 1.5% in NHL mortality (www.seer.ims.nci.nih.gov).

According to the data from the World Health Organization International Agency for Research on Cancer [7], the incidence of NHL has risen steadily worldwide (Fig. 2). NHL incidence rates are observed to be higher in developed countries such as Western Europe, North America, and Australia, and lower in South America and Asia, but the rise in incidence is consistent across countries.

The incidence of HD is consistently lower than that of NHL, and has decreased about 16% since 1970s (Fig. 3). The American Cancer Society predicts about 7,400 new cases of HD in the year 2000 in the US (www.cancer.org). Only a small portion of the decrease can be explained by misdiagnosis of HD as NHL [3,8]. By contrast with NHL, HD mortality has shown considerable decreases over time (Fig. 3), by about 65% with an annual percentage decrease of 4%. The main reason for this decline seems to be effective therapy [9]. Figure 4 shows the

Figure 1. Trends in age-adjusted (1970 US standard) non-Hodgkin lymphoma incidence and mortality rates



Data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, 1973–1996.

changes in incidence of HD around the world from the early 1970s to the early 1990s.

Epidemiology of lymphoma

Primary and acquired immunosuppression

The strongest known risk factors for NHL are primary and acquired immunosuppression [10•,11]. Based on a case series, it has been estimated that up to 25% of patients with genetically determined immunodeficiencies will develop primary B-cell lymphomas during their lifetimes [12]. Studies have shown increased risk of NHL among patients with ataxia telangiectasia [13], common variable immune deficiency [14,15], Wiskott-Aldrich syndrome [15,16], and severe combined immunodeficiency [17].

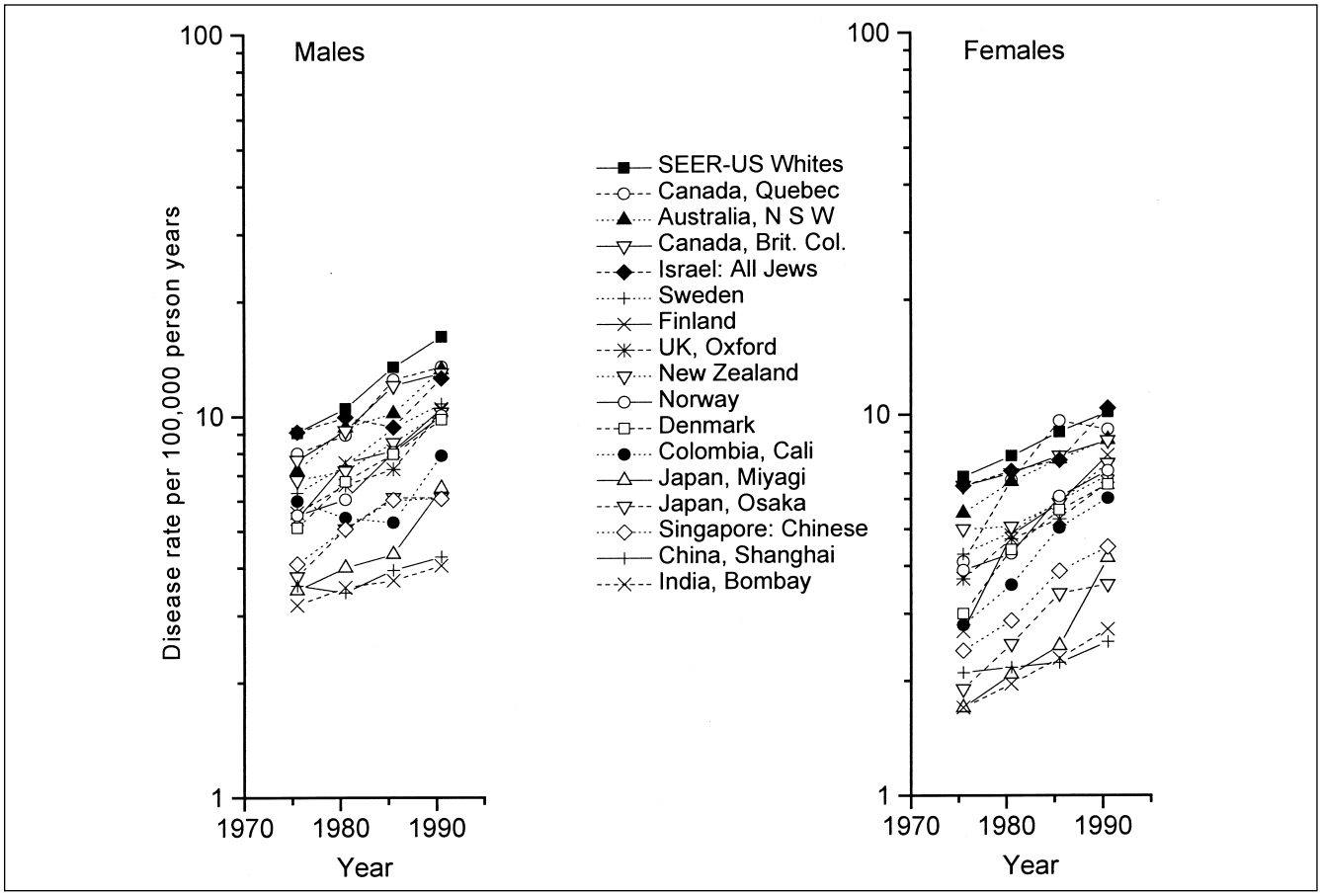
Excess risk of NHL has been observed among patients who are therapeutically immunosupressed in conjunction with renal [18–21], heart [20,22], or bone marrow transplantation [23•]. Recently, Swerdlow *et al.* [22] assessed the risk of NHL in a cohort of 1,563 patients who underwent cardiothoracic transplantation in the UK from 1980 to 1994. There was a significant excess of NHL compared with the expected general population rates (standardized incidence ratio (SIR) = 10.2 [95% CI = 4.6–22.8]). In a study of 18,014 patients who underwent allogeneic bone marrow transplantation in over 200 centers worldwide, 78 patients developed lymphoproliferative disorders, compared with 1.5 cases of NHL expected in the general population (O/E = 51.5; 95% CI = 40.7–64.3) [23•].

Epstein-Barr virus (EBV) appears to be an important factor in the development of lymphomas in patients with primary immunodeficiencies, as well as in those with acquired immunodeficiencies [12]. NHL risk after organ transplantation is believed to result from uncontrolled EBV-transformed B lymphocytes [10,20,22,24].

Genetic factors and family history

The t(14;18)(q32;q21) chromosomal translocation involving the *bcl-2* gene has been observed more than 75% of follicular NHL, and seems to play an important role in tumor progression and survival [25]. Genetic polymorphisms in the tumor necrosis factor locus that influence tumor necrosis factor and lymphotoxin-alpha

Figure 2. Trends in age-adjusted (world standard) non-Hodgkin lymphoma incidence rates



Data from the International Agency for Research on Cancer (IARC), 1973–1992.

(LTalpha) gene expression appear to affect the survival of NHL [26].

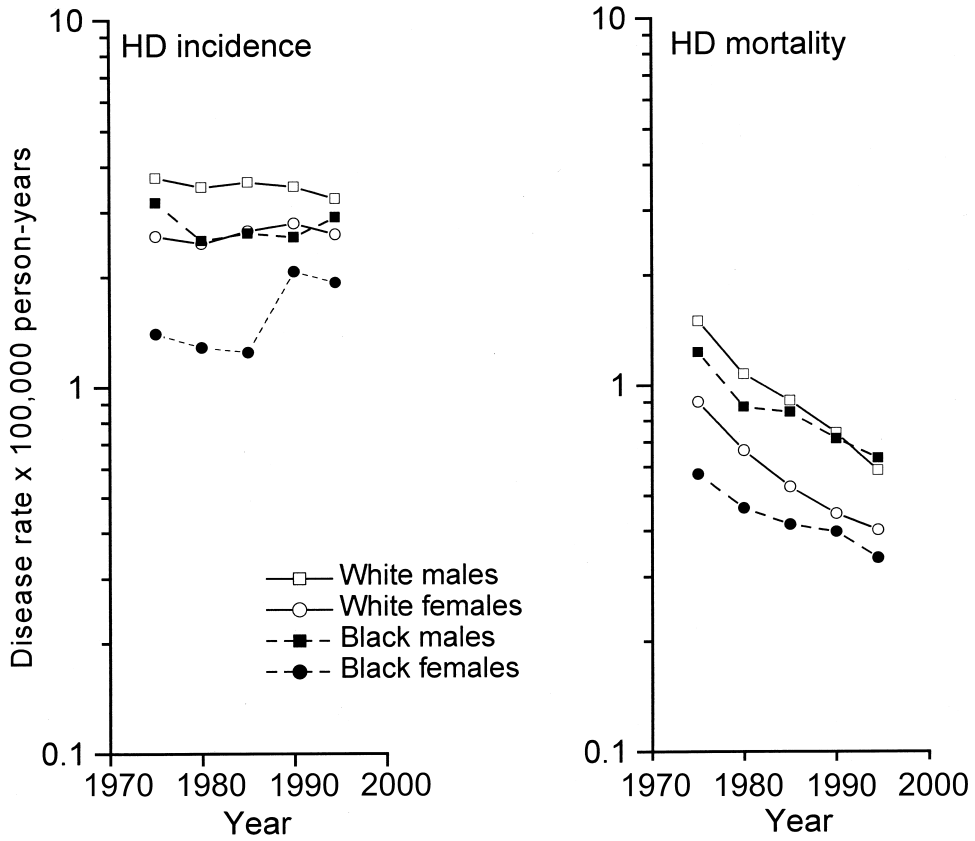
Recent studies confirm the long-observed increased risk of NHL among persons with a family history of lymphoma or hematologic cancer. Zhu *et al.* [27] reported that the risk of NHL was increased among persons with first degree relatives diagnosed with lymphoma (OR = 3.0, 95% CI = 1.7–5.2) or hematologic cancer (OR = 2.0, 95% CI = 1.2–3.4). A large case-control study from the San Francisco Bay area showed that a history of lymphoma among first-degree relatives was found to be associated with NHL among both men and women (OR = 2.1 and OR = 3.0, respectively). Lymphoma, leukemia, or HD in a parent, child, or sibling was associated with increased risk of NHL among women (OR = 1.7, 95% CI = 1.1–2.7).

HIV

Since the mid-1990s, several epidemiologic studies have led to better quantification of the risk of lymphomas among HIV-infected populations [28–30]. The risk of NHL for persons with AIDS is approximately 100–300-fold compared with the general population. The level of risk varies by histologic type of NHL, and is highest for high-grade NHL histologies [31] with a relative risk exceeding 300 [29].

AIDS surveillance data from 17 western European countries indicate that between 1988 and 1997 a total of 7,148 AIDS cases had NHL [32]. The relative risks for NHL in adults with HIV/AIDS ranged between 14 (for low-grade NHL) to over 300 (for high-grade NHL). A case-control study in Sydney, Australia compared 219 patients with AIDS-related NHL with 219 HIV-infected controls without NHL, and concluded that markers of longstanding immune deficiency and B-cell stimulation were related to an increased risk of developing AIDS-related NHL [33•]. The risk of AIDS-related lymphomas seems to decrease with the use of highly active antiretroviral therapy, but the amount of the decline appears to be smaller than that for AIDS-related Kaposi sarcoma [34,35].

Figure 3. Trends in age-adjusted (1970 US standard) Hodgkin disease incidence and mortality rates



Data from the Surveillance Epidemiology, and End Results (SEER) program of the National Cancer Institute, 1973–1996.

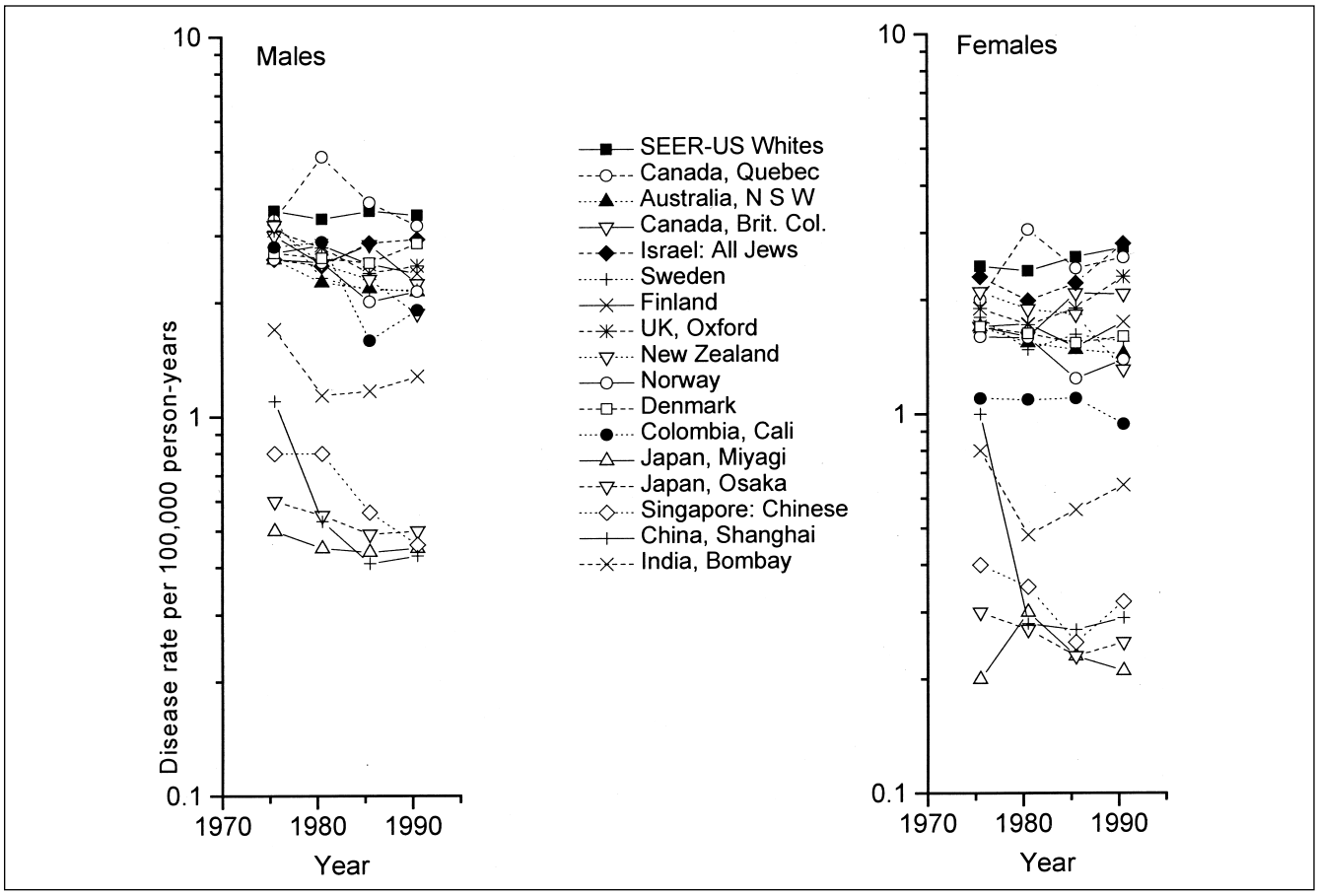
In a recent study among 746 HIV-1 infected patients, Rabkin *et al.* [36•,37] found that the risk of AIDS-related NHL was associated with polymorphisms in stromal cell-derived factor 1 (SDF1-3'A) that produced increased levels of B-cell chemokines. Chemokines are important regulators of normal B-lymphocyte maturation and proliferation [38]. Based on the relative risk models and the reported higher allele frequencies of SDF1-3'A among whites than among blacks, Rabkin and colleagues concluded that the differences in SDF1-3'A allele frequency may partially explain racial differences in AIDS-related NHL in the US.

Infectious agents other than HIV

Epstein-Barr virus [10•,39] and human T-cell lymphotropic virus-I (HTLV-I) [40,41] have been identified as possible etiologic agents for NHL. EBV plays a major role in organ transplant and AIDS-related NHL [10•,24]. Early EBV infection has been consistently associated with African Burkitt lymphomas [42]. Infection with HTLV-I is associated with excess of peripheral T-cell NHL in the Caribbean and Japan [43,44]. However, HTLV infections are rare in the US. [45].

Hepatitis C virus (HCV) has been shown to be associated with NHL [46,47], but the findings of a relation between HCV and NHL are inconsistent [48]. A nationwide survey during 1988–1994 estimated 1.8% seroprevalence of HCV, higher in men than in women, and in blacks than in whites [49]. Recently, several studies have reported higher prevalence of chronic HCV infection in patients with B-cell NHL [50–53]. Oshawa *et al.* [54], from Japan, followed up a total of 2,162 patients from the date of diagnosis of chronic HCV-related hepatitis in Osaka from 1957 to 1997. NHL of the B-cell type developed in four patients, resulting in a relative risk of 2.10 (95% CI = 0.57–5.38). HCV may increase the risk of NHL through the activation of B lymphocytes, resulting in secretion of IgM with rheumatoid factor activity and B-cell stimulation [55].

Figure 4. Trends in age-adjusted (world standard) Hodgkin disease incidence rates



Data from the International Agency for Research on Cancer (IARC), 1973–1992.

Human herpes virus 8 (HHV-8) has been shown to be present in primary effusion lymphoma, which mainly occurs in HIV-infected patients, and is distinguished by effusions in the serous body cavities [56]. Only a few cases of primary effusion lymphoma in HIV-seronegative patients have been reported [57,58].

Helicobacter pylori has shown to be an important etiologic factor for mucosa-associated tissue lymphoid (MALT) lymphoma [59]. Takagi *et al.* [60] suggested that apoptosis induced by *H. pylori* leads to a hyperproliferative response to gastric epithelial cell antigens. *H. pylori* is recognized as an etiologic agent for peptic ulcer [61]. In a recent population-based case-control study in Italy, Vineis *et al.* [62] found that individuals who reported a diagnosis of peptic ulcer had a relative risk of 5.6 (95% CI = 3.8–8.0) for gastric NHL. Almost all gastric lymphomas were B-cell NHLs of intermediate grade according to the working formulation; the majority belonged to the MALT type. Eradication of *H. pylori* may play a central component of the management and eradication of MALT lymphoma [63,64].

Medical conditions and treatment

Several reports have suggested an association between NHL and medical conditions, including lymphomatoid papulosis [65], diabetes mellitus [66,67], history of blood transfusion [68], and autoimmune disorders such as Sjögren syndrome [69] and rheumatoid arthritis [70,71]. Lymphomas complicating Sjögren syndrome are found to be low grade marginal zone lymphomas, and do not seem to be associated with viruses [69].

In a hospital-based case-control study in Italy [72], positive associations were observed between NHL and pyelonephritis, tuberculosis, malaria, any chronic bacterial diseases, rheumatoid arthritis, and psoriasis. Another study from Italy [73] confirmed the previously observed relations between NHL and lupus erythematosus (OR = 8.4, 95% CI = 1.6, 45), tuberculosis

(OR = 1.6, 95% CI = 1.05, 2.5), and hepatitis (OR = 1.8, 95% CI = 1.4, 2.3). An association was found also between NHL and maternal (OR = 2.8, 95% CI = 1.1, 6.9) or paternal tuberculosis (OR = 1.7, 95% CI = 0.7, 3.9).

A recent large case-control study from the San Francisco Bay area based on 1,281 cases and 2,095 controls, however, showed no evidence for NHL risk associated with autoimmune diseases, diabetes, heart diseases, or blood transfusion [74••]. Among women, a reduced risk for NHL was associated with a history of rubella, whooping cough, cold sores and fever sores, canker sores, and tooth abscess. The same study found an increased risk of NHL with use of cimetidine and other histamine H2-receptor antagonists.

Radiation

There is little evidence for increased risk of NHL due to radiation. A-bomb survivors and persons with therapeutic, diagnostic, or occupational exposure to ionizing radiation have no or only small nonsignificant increases in risk of NHL [24,75]. Recent data are consistent with earlier findings. A pooled analysis of two case-control studies of NHL in Sweden showed a slightly decreased risk of NHL among radiologic workers and among persons who had many diagnostic x-rays [76]. Radiologic technicians in the US were also observed to be at a nonsignificantly decreased risk for NHL [77].

In general, exposure to electromagnetic fields have not been associated with significant increases of NHL in studies of children exposed to 60-Hz fields from power lines [78,79], amateur radio operators [80], or electrical engineers, power linesmen, and power station operators [81]. In 2000, Repacholi *et al.* [82] reported that PIM mice, which carry the pim-1 oncogene and are highly sensitive to lymphoma induction by N-ethyl-N-nitrosourea, exposed to radiofrequency (pulse modulated 900 MHz) magnetic fields developed more lymphomas than controls. McCormick *et al.* [83] exposed PIM mice and TSG-p53 (p53 knockout) mice to 60 Hz magnetic fields and found no evidence of increased risk of lymphoma. Villeneuve *et al.* [84] examined associations between NHL and exposures to 60 Hz fields among Canadian electric utility workers. Various ways of characterizing magnetic and electric fields, such as frequency, waveform, polarization, amplitude, and duration of exposure above threshold intensities were considered. In general, there was no association between indices of exposure to magnetic fields and NHL; however, there was a suggestion of an association with electric field exposure. Times spent above electric field threshold cut-off points 10 and 40 V/m were correlated with NHL incidence. As exposure assessment improves, this suggested link between NHL and electric field exposure should be clarified.

Occupational exposures

In addition to ionizing radiation and electromagnetic fields, pesticides, solvents, and other occupational exposures have been evaluated with respect to the risk of NHL. Pesticides have been associated with NHL in studies of farmers, other pesticide applicators, manufacturing workers, and other exposed populations [85,86]. Persons exposed to phenoxyacetic acid herbicides [87–90], chlorophenols [91], organochlorine insecticides [92,93], and organophosphate insecticides [90,92] were found to be at increased risk of NHL in some, but not all, studies [86,94–96].

Studies published during the past year have continued to provide conflicting evidence for a link between pesticides and NHL. A Swedish case-control study by Hardell and Eriksson [97] observed significantly increased risks for NHL among subjects exposed to herbicides (OR = 1.6), particularly 4-chloro-2-methyl phenoxyacetic acid (MCPA) (OR = 2.7), and fungicides (OR = 3.7). Exposure to insecticides was, at most, only weakly related to NHL. A pooled analysis of two other Swedish case-control studies of NHL showed a decreased odds ratio among farmers, but a 2.6-fold increased risk among persons exposed to phenoxyacetic acid herbicides [76]. Elevated odds ratios for hairy cell leukemia were observed for exposure to farm animals, herbicides, fungicides, and impregnating agents [98]. NHL was not elevated among men exposed to chlorophenols in a US multicenter case-control study [99], nor among female agricultural workers in five rural areas of Italy [100]. In addition, Schiff *et al.* [101] reported that there was no evidence that farming increased the risk of primary central nervous system lymphoma.

Misclassification of exposure may be contributing to the inconsistent data across studies of pesticides and NHL. Many studies evaluate general classes of pesticides only, such as phenoxyacetic acid herbicides. The specific pesticides used within the general class may vary in different studies. For example, the most common phenoxyacetic acid herbicide in the US is 2,4-D, whereas MCPA is most common in Sweden. If the activity of these compounds differs, studies reporting on phenoxyacetic acid herbicides as a class could easily contradict each other. Better data on the specific pesticides used, the timing of exposure, and multiple exposures would improve research on pesticides and NHL. Considering genetic polymorphisms in the genes that metabolize pesticides may also clarify the risks associated with NHL in future studies [96].

Occupations other than agriculture that have been associated with NHL include rubber workers, petroleum refining workers, vinyl chloride workers, chemists, dry

cleaners, and aircraft maintenance workers [24]. The etiologic agents responsible for these excess risks have not been identified definitively, but the occupations have in common exposure to organic solvents. Persson and Fredrikson [76] reported an elevated risk of NHL among persons exposed to solvents, white spirits, thinner, aviation gasoline, as well as work as painters. Increased risk associated with exposure to organic solvents and to exhaust fumes was also reported by Nordstrom *et al.* [98]. Increased mortality from NHL was observed among US women employed as clinical laboratory technicians, science technicians, and dental hygienists and assistants [77,102], which is consistent with earlier reports of excess NHL among laboratory workers and chemists [103–108]. Lymphoma was also reported to be elevated among women employed as computer programmers [109], child care workers [109], hairdressers [110], teachers [110], and knitters, bleachers, dyers, and finishers in the textile industry [110]. NHL was not increased among a cohort of concrete workers [111], in contrast to a threefold increase in NHL associated with exposure to concrete dust reported by Siemiatycki *et al.* [112]. No evidence of an increase of NHL was found among populations living close to industrial complexes that include large oil refineries in Great Britain [113].

Lifestyle factors

Cigarette smoking appears to have no or a weak association with NHL. Most previous studies have shown no association [91,114] or only modest increases in risk, often not statistically significant [115–117]. During the past year, results from a large case-control study based on 1,281 cases and 2,095 controls showed no association between NHL and smoking (ex or current) among men or women [74••]. A smaller study from Sweden also found no relation with smoking [76]. Waddell *et al.* [118] did not confirm the observation of Freedman *et al.* [119] that NHL was associated with smoking among young and middle-aged men, but not older individuals. Miligi *et al.* [110] reported OR of 1.3 (95% CI = 1.0–1.6) among women in Italy. Primary central nervous system lymphoma was not significantly elevated among smokers [101] and hairy cell leukemia was nonsignificantly decreased among smokers [98]. Increasing use of marijuana was associated with a significant decrease in NHL [74••].

Several studies have suggested that the use of hair dyes, particularly long-term use of dark permanent dyes, may increase the risk of NHL [120–123], whereas others have reported no increased risk [124,125]. An extension of the follow-up from 7–12 years of mortality experience of women in the American Cancer Society prospective cohort study revealed a slightly higher than expected death rate from NHL among women who used black or brown permanent dye for 10 or more years, based on history of hair dye use at entry to the cohort in 1982 [126]. No association was seen between NHL and hair dye use in a case-control study conducted in Italy; however, no information was available on duration of use [110].

A relation between sunlight exposure and NHL has been suggested by ecological studies of ambient levels of ultraviolet radiation and NHL, correlations between skin cancer and NHL, and other data [127–134]. Evaluations of geographic mortality patterns of NHL and melanoma [135], and residential and occupational exposure in a case-control study [136] do not support the association. A new cohort study from Sweden provides limited support for a modest association of potential sunlight exposure and NHL, based on geographic latitude of residence, but no support for an association based on potential occupational exposure [137].

Physical activity and NHL risk was investigated because acute moderate to intense exercise is accompanied by a transient immunosuppression, and persons who are immunosuppressed because of genetic or acquired immunodeficiency states have a higher risk of NHL [138]. A pooled analysis of occupational data from three case-control studies found no association between NHL and occupational physical activity measured by energy expenditure or sitting time [138]. Research on nonoccupational physical activity, which in the US is likely the more important component of daily activity than occupational activity, may still be warranted given the laboratory evidence linking physical activity and altered immune function, an important factor in the etiology of NHL. Significantly elevated risks of NHL were observed among men and women with body mass indices of 30 or higher in a case-control study in the San Francisco Bay Area [74••].

Diet

NHL has been linked to increased consumption of animal protein [139,140], fat [140,141], milk [141,142], vegetables and fruits [143], nitrate in drinking water [144], as well as decreased consumption of whole-grain bread or pasta [142]. The data are not consistent, however, with some studies reporting no association with animal protein [145] or milk [140,145]. A new report on diet and NHL among women in the Nurses' Health Study found that greater intake of beef, pork, or lamb was associated with a significantly higher risk of NHL [146•]. Meat preparation methods that increase formation of heterocyclic amines were not associated with significantly elevated risk. Law *et al.* [147] found no evidence of an association between NHL and current levels of nitrate in drinking water. Historical levels of nitrate were not available.

Alcohol consumption has been linked to an increased risk [148], decreased risk [149,150], and no relation [115,141,142,151–153] to NHL. A decreased risk of NHL in association with alcohol consumption was reported among both genders in a case-control study [74••] and a prospective cohort study of women [154]. In both studies, protective effects were observed for all types of alcoholic beverages.

Epidemiology of Hodgkin disease

Viruses

The virus linked most strongly with HD is EBV [155,156]. Evidence supporting the association comes from a variety of investigations, including epidemiologic, serologic, and molecular biologic studies. The monoclonal episomes have been detected in Reed-Sternberg cells, and viral proteins with oncogenic potential are expressed. The link appears stronger for the mixed cellularity and nodular sclerosis histologic subtypes [157,158]. This year the association of HD with EBV was reported among cases in Sweden, although not as strong as might have been expected [158], and in a developing country, Turkey [159].

Armstrong *et al.* [160] postulated that HD can be divided into three entities: an EBV-associated disease, usually of mixed cellularity, among children; an EBV-associated disease, usually of mixed cellularity, among older adults; and an entity that is not EBV-associated, occurring among young adults, usually with nodular sclerosis histology. Some other virus may play a role in the third entity among young adults [161], possibly HCV, as suggested in a report from Southern Turkey [162]. Space-time clustering, which provides support for an infectious etiology, was observed for young adult nodular sclerosis HD cases in the UK [163], but not among cases aged 0–24 in New Zealand [164].

Cytomegalovirus and lymphotropic human herpesvirus type 6 have also been evaluated and do not appear to be related to risk of HD [155,156].

Immune dysfunction

The development of HD is affected by overstimulation of immunity and by immunosuppression. A five- to sixfold increased risk of HD among allogeneic bone marrow transplantation recipients supports the link between overstimulation of cell-mediated immunity, exposure to EBV, and HD [165]. In a study from Australia [35], people with AIDS had an 18-fold increase in the incidence of HD, with the highest risk around the time of AIDS diagnosis, suggesting an association with immunodeficiency. An English cohort of persons infected with HIV experienced a 22-fold increase in the incidence of HD [166]. In contrast, the risk for HD did not appear to be increasing over time in the population of Zimbabwe, which has had dramatic increases in AIDS and AIDS-related malignancies [167].

Genetics

Immune responses to infectious agents may be influenced by genetic variation in the HLA class II region, with some loci increasing susceptibility and others increasing resistance to HD. Taylor *et al.* [168] observed a higher risk of HD associated with the *DPB1*0301* allele of the HLA-DPB1 locus and a decreased risk associated with *DPB1*0201*. The *DPB1*0301* association was greatest in women with histologic subtypes other than nodular sclerosis HD, whereas the decreased risk associated with *DPB1*0201* was greatest in women with nodular sclerosis HD. Among men, increased risk for lymphocyte-predominant and mixed cellularity HD was associated with the alleles **2001* and **3401*, respectively. Associations with the amino acids coded by these regions support their possible role in the development of HD. There is little evidence for genetic susceptibility to HD other than in relation to immunosuppression [156], except for the increased risk in identical twins of persons with HD.

Medical conditions and treatment

A small but not statistically significant elevated risk of HD was observed among a cohort of patients in Finland who underwent total polyethylene-on-metal knee arthroplasty [169].

Occupational exposures

The occupation most consistently associated with HD is woodworking [170]. Other occupations involving chemical exposures, notably solvents and pesticides, have been linked to HD but with more conflicting data [170,171]. Recent studies reported excess HD among men employed in the cotton industry in Poland [135] and among women employed as hairdressers in the US [109]. In Great Britain, risk for HD increased with proximity of residence to industrial complexes that included major oil refineries, but there is little other epidemiologic evidence linking HD to the petrochemical industry [113].

Conclusions

The increasing incidence of NHL is largely unexplained. AIDS-related NHL accounts for some but not all of the increase. The incidence of HD is consistently lower than that of NHL, and has decreased about 16% since 1970s. Only a small portion of the decrease can be explained by misdiagnosis of HD as NHL. Further research is needed on the cofactors that predispose AIDS cases to lymphoma, as well as other possible causes of NHL such as immunosuppression, genetics, viruses, medical conditions, pesticides, solvents, hair dyes and diet. Further evaluation of the role of viruses, occupational exposures, and genetics in the etiology of HD should prove valuable.

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