

# 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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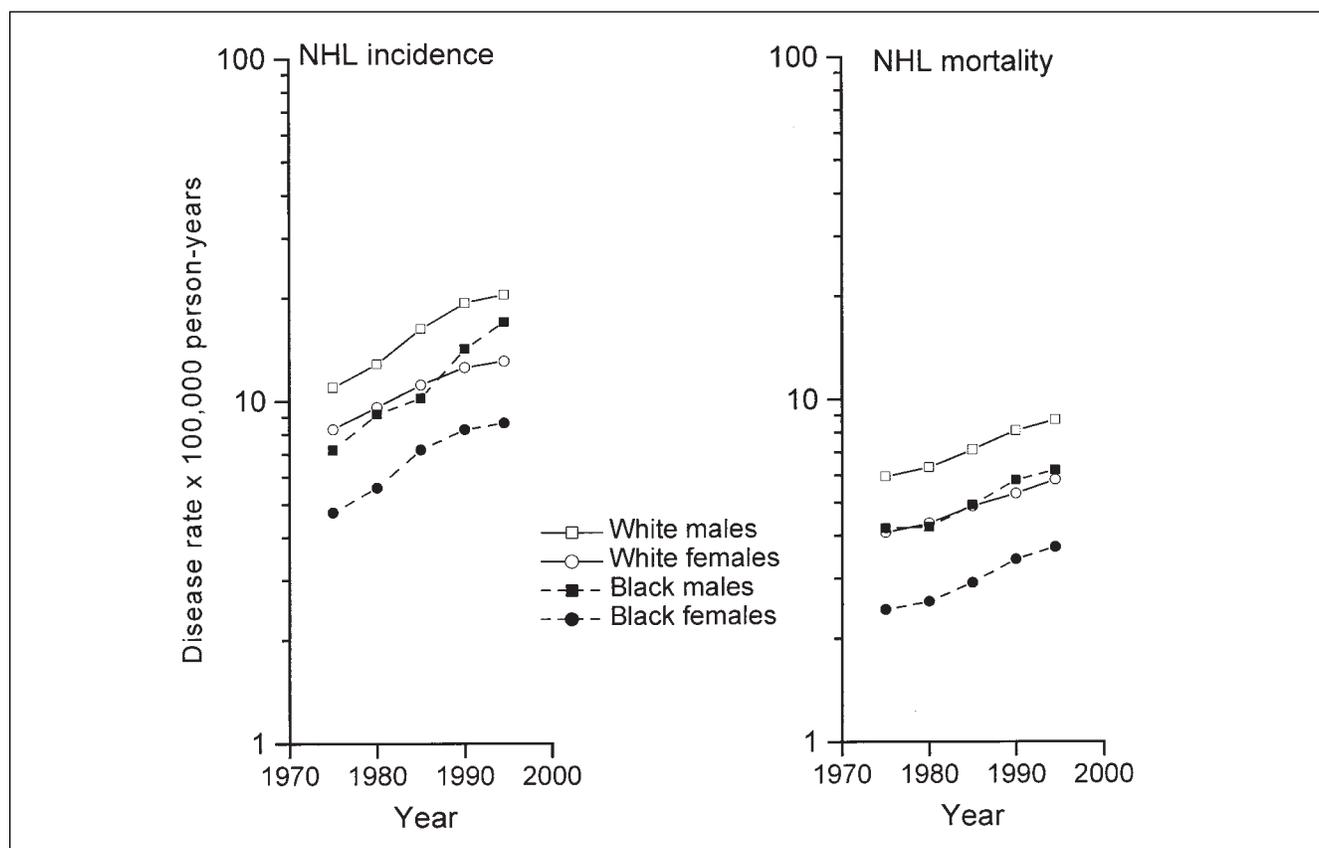
Lymphoma represents a diverse group of neoplasms arising from the lymphopoietic system. Two main groups of lymphomas are Hodgkin disease (HD), characterized by large polynuclear Reed-Sternberg cells, and non-Hodgkin lymphoma (NHL). NHL includes a wide range of subtypes of either B-cell or T-cell lymphomas. 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](http://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](http://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](http://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].

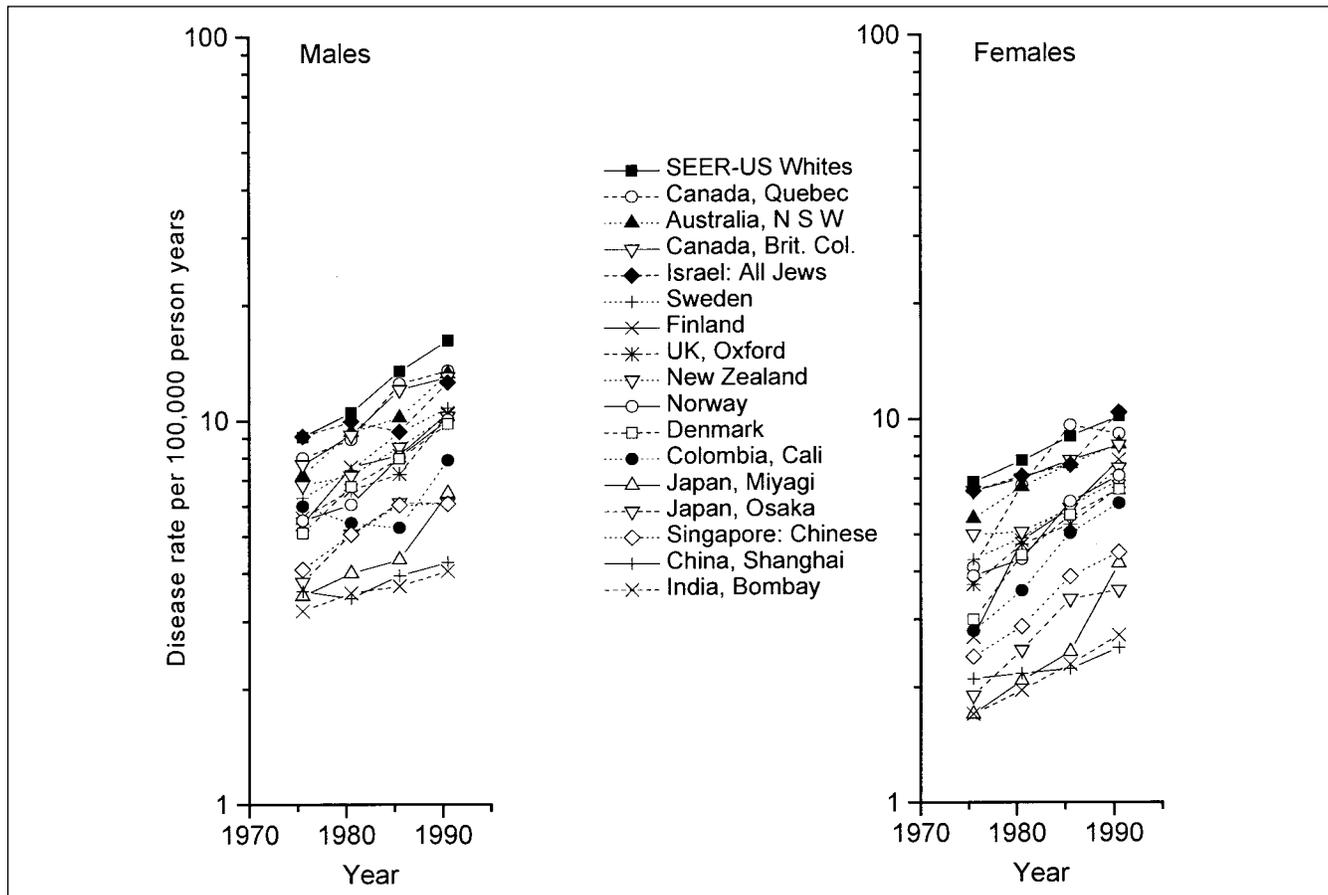
Excess risk of NHL has been observed among patients who are therapeutically immunosuppressed in conjunction with renal [18–21], heart [20,22], or bone marrow transplantation [23•]. Recently, Swerdlow *et al.* [22] assessed the risk of NHL in a cohort of 1,563 patients who underwent cardiothoracic transplantation 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].

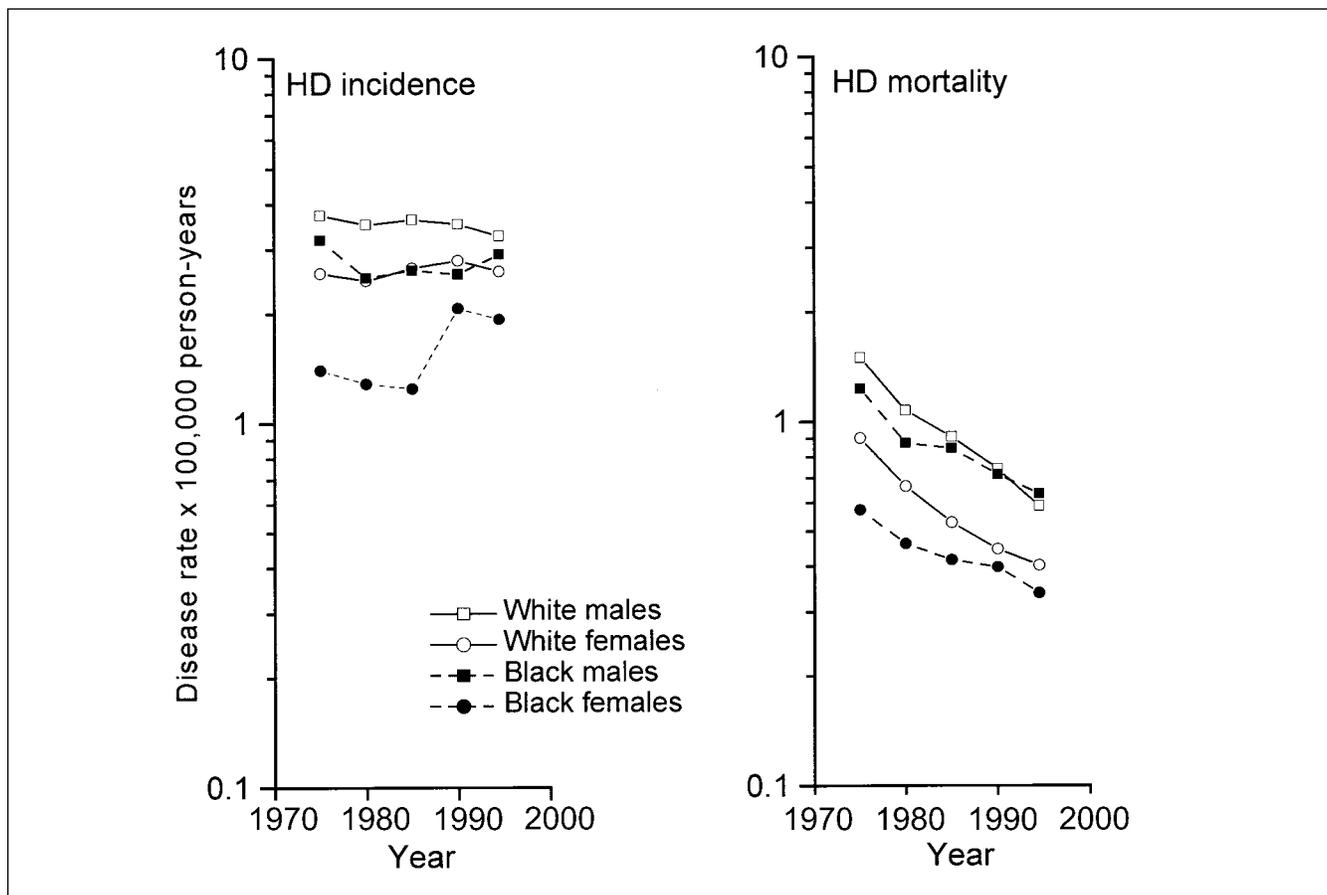
Recent studies confirm the long-observed increased risk of NHL among persons with a family history of lymphoma or hematologic cancer. Zhu *et al.* [27] reported that the risk of NHL was increased among persons with first degree relatives diagnosed with lymphoma (OR = 3.0, 95% CI = 1.7–5.2) or hematologic 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.

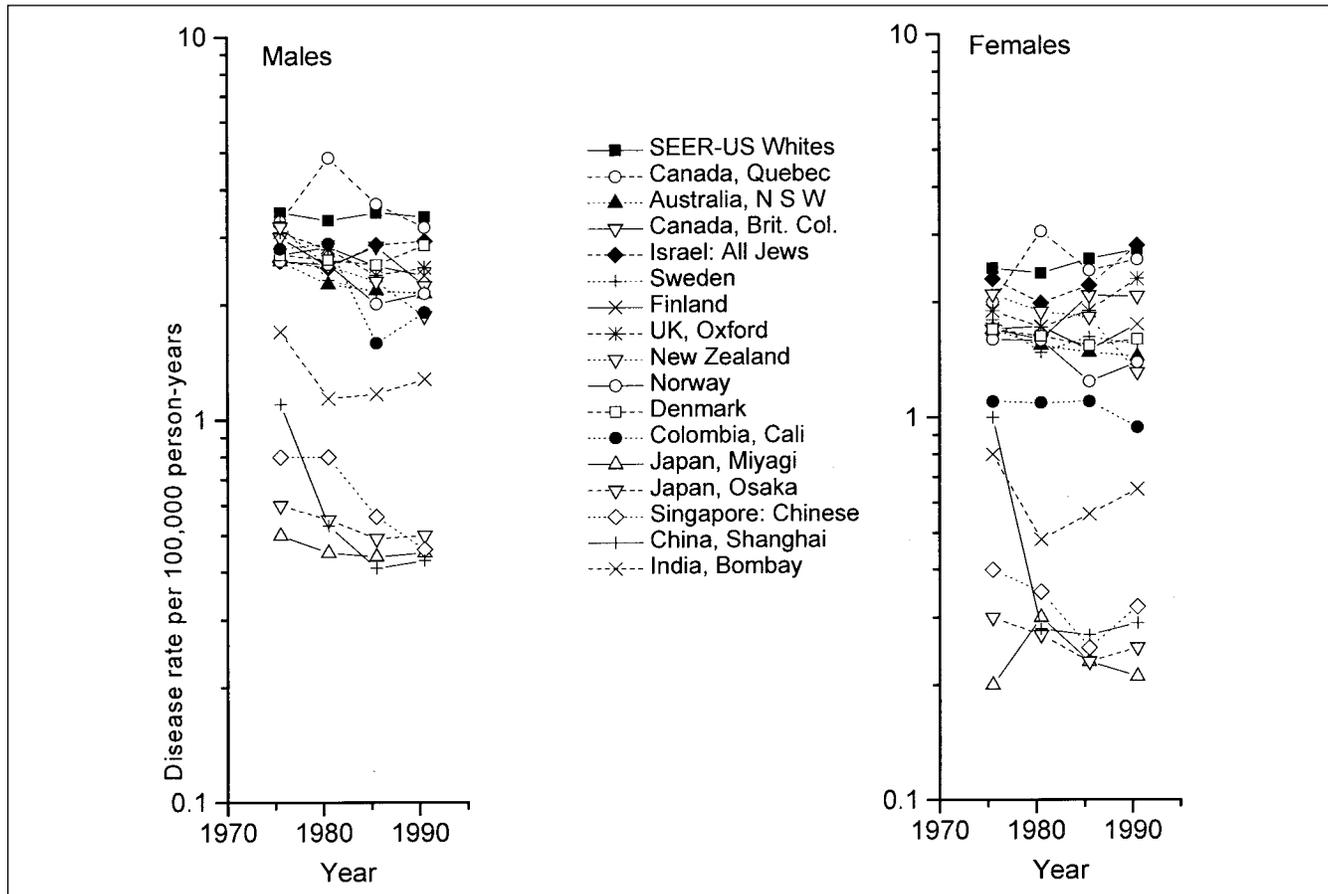
#### Infectious agents other than HIV

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 H<sub>2</sub>-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.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- Of special interest
- Of outstanding interest

- 1 Greenlee RT, Murray T, Bolden S, et al.: Cancer statistics, 2000. *CA Cancer J Clin* 2000, 50:7–33.
- 2 Hartge P, Devesa SS, Fraumeni JF: Hodgkin's and non-Hodgkin's lymphomas. In *Trends in cancer incidence and mortality, cancer surveys, vol. 19/20*. Edited by Doll R, Fraumeni JF, Muir CS. Plainview: Cold Spring Harbour Laboratory Press, 1994:423–453.
- 3 Hartge P: Quantification of the impact of known risk factors on time trends in non-Hodgkin's lymphoma incidence. *Cancer Res* 1992, 52:5566s–5569s.
- 4 Mueller N: Another view of the epidemiology of non-Hodgkin's lymphoma. *Oncology* 1994, 8:83.
- 5 Chassagne-Clement C, Blay JY, Treilleux I, et al.: Epidemiology of non-Hodgkin's lymphoma: recent data. *Bulletin Du Cancer* 1999, 86:529–536.
- 6 Reis LAG, Kosary CL, Hankey BF, et al.: SEER cancer statistics review:1973–1995. Bethesda, MD: National Cancer Institute, 1998.
- 7 Parkin D, Whelan S, Ferlay J, et al.: Cancer incidence in five continents, vol 8. Lyon: IARC Scientific Publication No. 143, 1997.
- 8 Glaser SL SW: Time trends in Hodgkin's disease incidence: the role of diagnostic accuracy. *Cancer* 1990, 66:2196–2204.
- 9 Urba WJ, Longo DL: Hodgkin's disease. *N Eng J Med* 1992, 326:678–687.
- 10 Mueller N: Overview of the epidemiology of malignancy in immune deficiency. *J Acquir Immune Defic Syndr* 1999, 21:S5–S10.
- This article compares patterns of malignancies among immunosuppressed populations to provide insight into viral oncogenesis.
- 11 Knowles DM: Immunodeficiency-associated lymphoproliferative disorders. *Mod Pathol* 1999, 12:200–217.
- 12 Filipovich AH, Mathur A, Kamat D, et al.: Primary immunodeficiencies: genetic risk factors for lymphoma. *Cancer Res* 1992, 52:5465s–5467s.
- 13 Seidemann K, Henze G, Beck JD, et al.: Non-Hodgkin's lymphoma in pediatric patients with chromosomal breakage syndromes (AT and NBS): experience from the BFM trials. *Ann Oncol* 2000, 11 (suppl 1):141–145.
- 14 Cunningham-Rundles C, Bodian C: Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol* 1999, 92:34–48.
- 15 Kersey JH, Shapiro RS, Filipovich AH: Relationship of immunodeficiency to lymphoid malignancy. *Pediatr Infect Dis J* 1988, 7:S10–S12.
- 16 Perry GS, Spector BD, Schuman LM, et al.: The Wiskott-Aldrich syndrome in the United States and Canada (1892-1979). *J Pediatr* 1980, 97:72–78.
- 17 Kinlen LJ: Immunologic factors, including AIDS. In *Cancer Epidemiology and prevention*. Edited by Schottenfeld D, Fraumeni JF. New York: Oxford University Press, 1996.
- 18 Kinlen LJ, Sheil AG, Peto J, et al.: Collaborative United Kingdom-Australasian study of cancer in patients treated with immunosuppressive drugs. *Br Med J* 1979, 2:1461–1466.
- 19 Hoover RN: Lymphoma risks in populations with altered immunity—a search for mechanism. *Cancer Res* 1992, 52:5477s–5478s.
- 20 Opelz G, Henderson R: Incidence of non-Hodgkin lymphoma in kidney and heart transplant recipients. *Lancet* 1993, 342:1514–1516.
- 21 Schwab M, Boswald M, Korn K, Ruder H: Epstein-Barr virus in pediatric patients after renal transplantation. *Clin Nephrol* 2000, 53:132–139.
- 22 Swerdlow AJ, Higgins CD, Hunt BJ, et al.: Risk of lymphoid neoplasia after cardiothoracic transplantation: a cohort study of the relation to Epstein-Barr virus. *Transplantation* 2000, 69:897–904.
- 23 Curtis RE, Travis LB, Rowlings PA, et al.: Risk of lymphoproliferative disorders after bone marrow transplantation: a multi-institutional study. *Blood* 1999, 94:2208–2216.
- A large multicenter study that examined the incidence of and risk factors for posttransplant lymphoproliferative disorders (PTPD). The authors concluded that

factors related to altered immunity and T-cell regulatory mechanisms are predictors of onset of PTPD.

- 24 Scherr PA, Mueller NE: Non-Hodgkin's lymphoma. In *Cancer Epidemiology and prevention*. Edited by Schottenfeld D, Fraumeni JF. New York: Oxford University Press, 1996.
- 25 Tilly H, Rossi A, Stamatoullas A, et al.: Prognostic value of chromosomal abnormalities in follicular lymphoma. *Blood* 1994, 84:1043–1049.
- 26 Warzocha K, Ribeiro P, Bienvenu J, et al.: Genetic polymorphisms in the tumor necrosis factor locus influence non-Hodgkin's lymphoma outcome. *Blood* 1998, 91:3574–3581.
- 27 Zhu K, Levine RS, Gu Y, et al.: Non-Hodgkin's lymphoma and family history of malignant tumors in a case-control study (United States). *Cancer Causes Control* 1998, 9:77–82.
- 28 Biggar RJ, Rabkin CS: The epidemiology of AIDS-related neoplasms. *Hematol Oncol Clin North Am* 1996, 10:997–998.
- 29 Cote TR, Biggar RJ, Rosenberg PS, et al.: Non-Hodgkin's lymphoma among people with AIDS: incidence, presentation and public health burden. AIDS/Cancer Study Group. *Int J Cancer* 1997, 73:645–650.
- 30 Goedert JJ, Cote TR, Virgo P, et al.: Spectrum of AIDS-associated malignant disorders. *Lancet* 1998, 351:1833–1839.
- 31 Tulpule A, Levine A: AIDS-related lymphoma. *Blood Reviews* 1999, 13:147–150.
- 32 Franceschi S, Dal Maso L, La Vecchia C: Advances in the epidemiology of HIV-associated non-Hodgkin's lymphoma and other lymphoid neoplasms. *Int J Cancer* 1999, 83:481–485.
- 33 Grulich AE, Wan X, Law MG, et al.: B-cell stimulation and prolonged immune deficiency are risk factors for non-Hodgkin's lymphoma in people with AIDS. *AIDS* 2000, 14:133–140.
- This is a well-designed case-control study of 219 AIDS-related NHL cases and 219 HIV-infected controls without NHL. The paper concludes that markers of long-standing immune deficiency and B-cell stimulation were related to an increased risk of developing AIDS-related NHL.
- 34 Rabkin CS, Testa MA, Huang J, et al.: Kaposi's sarcoma and non-Hodgkin's lymphoma incidence trends in AIDS clinical trial group study participants. *J Acquir Immune Defic Syndr* 1999, 21:S31–S33.
- 35 Grulich AE: AIDS-associated non-Hodgkin's lymphoma in the era of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 1999, 21:S27–S30.
- 36 Rabkin CS, Yang Q, Goedert JJ, et al.: Chemokine and chemokine receptor gene variants and risk of non-Hodgkin's lymphoma in human immunodeficiency virus-1-infected individuals. *Blood* 1999, 93:1838–1842.
- This article showed that the risk of AIDS-related NHL was associated with polymorphisms in SDF1-3'A, which was related to increased levels of B-cell chemokines.
- 37 Rabkin CS, Sei S: Susceptibility genes for AIDS and AIDS-related lymphoma. *Curr Top Microbiol Immunol* 1998 1999, 246:111–115.
- 38 Baggiolini M: Chemokines and leukocyte traffic. *Nature* 1998, 392:565–568.
- 39 Hsu JL, Glaser SL: Epstein-Barr virus-associated malignancies: epidemiologic patterns and etiologic implications. *Crit Rev Oncol Hematol* 2000, 34:27–53.
- 40 Mueller N: The epidemiology of HTLV-I infection. *Cancer Causes Control* 1991, 2:37–52.
- 41 Blattner WA: Human retroviruses: their role in cancer. *Proc Assoc Am Physicians* 1999, 111:563–572.
- 42 IARC Monographs. Epstein-Barr Virus and Kaposi's sarcoma herpes virus/human herpes virus 8. Lyon: International Agency for Research on Cancer, 1997:82–127.
- 43 Manns A, Hisada M, La Grenade L: Human T-lymphotropic virus type I infection. *Lancet* 1999, 353:1951–1958.
- 44 Arisawa K, Soda M, Endo S, et al.: Evaluation of adult T-cell leukemia/lymphoma incidence and its impact on non-Hodgkin lymphoma incidence in southwestern Japan. *Int J Cancer* 2000, 85:319–324.
- 45 Murphy EL: Evidence among blood donors for a 30-year-old epidemic of human T lymphotropic virus type II infection in the United States. *J Infect Dis* 1999, 180:1777–1783.
- 46 Silvestri F, Pipan C, Barillari G, et al.: Prevalence of hepatitis C virus infection in patients with lymphoproliferative disorders. *Blood* 1996, 87:4296–4301.

- 47 Silvestri F, Barillari G, Fanin R, et al.: Hepatitis C virus infection among cryoglobulinemic and non-cryoglobulinemic B-cell non-Hodgkin's lymphomas. *Haematologica* 1997, 82:314-317.
- 48 Levine AM, Nelson R, Zuckerman E, et al.: Lack of association between hepatitis C infection and development of AIDS-related lymphoma. *J Acquir Immune Defic Syndr* 1999, 20:255-258.
- 49 Alter MJ, Kruszon-Moran D, Nainan OV, et al.: The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med* 1999, 341:556-562.
- 50 Zuckerman E, Zuckerman T, Levine AM, et al.: Hepatitis C virus infection in patients with B-cell non-Hodgkin lymphoma. *Ann Intern Med* 1997, 127:423-428.
- 51 Catassi C, Fabiani E, Coppa GV, et al.: High prevalence of hepatitis C virus infection in patients with non-Hodgkin's lymphoma at the onset. Preliminary results of an Italian multicenter study. *Recenti Prog Med* 1998, 89:63-67.
- 52 Hausfater P, Cacoub P, Rosenthal E, et al.: Hepatitis C virus infection and lymphoproliferative diseases in France: a national study. *Am J Hematol* 2000, 64:107-111.
- 53 Pioltelli P, Gargantini L, Cassi E, et al.: Hepatitis C virus in non-Hodgkin's lymphoma: a reappraisal after a prospective case-control study of 300 patients. *Am J Hematol* 2000, 64:95-100.
- 54 Ohsawa M, Shingu N, Miwa H, et al.: Risk of non-Hodgkin's lymphoma in patients with hepatitis C virus infection. *Int J Cancer* 1999, 80:237-239.
- 55 Dammacco F, Gatti P, Sansonno D: Hepatitis C virus infection, mixed cryoglobulinemia, and non-Hodgkin's lymphoma: an emerging picture. *Leuk Lymphoma* 1998, 31:463-476.
- 56 Carbone A, Cilia AM, Gloghini A, et al.: Primary effusion lymphoma cell lines harbouring human herpesvirus type-8. *Leuk Lymphoma* 2000, 36:447-456.
- 57 Ariad S, Benharroch D, Lupu L, et al.: Early peripheral lymph node involvement of human herpesvirus 8-associated, body cavity-based lymphoma in a human immunodeficiency virus-negative patient. *Arch Pathol Lab Med* 2000, 124:753-755.
- 58 Ascoli V, Scalzo CC, Danese C, et al.: Human herpes virus-8 associated primary effusion lymphoma of the pleural cavity in HIV-negative elderly men. *Eur Respir J* 1999, 14:1231-1234.
- 59 Bouzourene H, Haefliger T, Delacretaz F, et al.: The role of *Helicobacter pylori* in primary gastric MALT lymphoma. *Histopathology* 1999, 34:118-123.
- 60 Takagi A, Watanabe S, Igarashi M, et al.: The effect of *Helicobacter pylori* on cell proliferation and apoptosis in gastric epithelial cell lines. *Aliment Pharmacol Ther* 2000, 14 (suppl 1):188-192.
- 61 IARC monographs on the evaluation of carcinogenic risks to humans, schistosomes, liver flukes and *Helicobacter pylori*. Lyon: IARC, 1994.
- 62 Vineis P, Crosignani P, Sacerdote C, et al.: Hematopoietic cancer and peptic ulcer: a multicenter case-control study. *Carcinogenesis* 1999, 20:1459-1463.
- 63 Wotherspoon AC: *Helicobacter pylori* infection and gastric lymphoma. *Br Med Bull* 1998, 54:79-85.
- 64 Thiede C, Wundisch T, Neubauer B, et al.: Eradication of *Helicobacter pylori* and stability of remissions in low-grade gastric B-cell lymphomas of the mucosa-associated lymphoid tissue: results of an ongoing multicenter trial. *Recent Results Cancer Res* 2000, 156:125-133.
- 65 Wang HH, Myers T, Lach LJ, et al.: Increased risk of lymphoid and nonlymphoid malignancies in patients with lymphomatoid papulosis. *Cancer* 1999, 86:1240-1245.
- 66 Cerhan JR, Wallace RB, Folsom AR, et al.: Medical history risk factors for non-Hodgkin's lymphoma in older women. *J Natl Cancer Inst* 1997, 89:314-318.
- 67 Hjalgrim H, Frisch M, Ekbohm A, et al.: Cancer and diabetes—a follow-up study of two population-based cohorts of diabetic patients. *J Intern Med* 1997, 241:471-475.
- 68 Cerhan JR, Wallace RB, Folsom AR, et al.: Transfusion history and cancer risk in older women. *Ann Intern Med* 1993, 119:8-15.
- 69 Mariette X: Lymphomas in patients with Sjogren's syndrome: review of the literature and physiopathologic hypothesis. *Leuk Lymphoma* 1999, 33:93-99.
- 70 Mellemkjaer L, Linet MS, Gridley G, et al.: Rheumatoid arthritis and cancer risk. *Eur J Cancer* 1996, 32A:1753-1757.
- 71 Symmons DP, Jones MA, Scott DL, et al.: Longterm mortality outcome in patients with rheumatoid arthritis: early presenters continue to do well. *J Rheumatol* 1998, 25:1072-1077.
- 72 Tavani A, La Vecchia C, Franceschi S, et al.: Medical history and risk of Hodgkin's and non-Hodgkin's lymphomas. *Eur J Cancer Prev* 2000, 9:59-64.
- 73 Vineis P, Crosignani P, Sacerdote C, et al.: Haematopoietic cancer and medical history: a multicentre case control study. *J Epidemiol Community Health* 2000, 54:431-436.
- 74 Holly EA, Lele C, Bracci PM, et al.: Case-control study of non-Hodgkin's lymphoma among women and heterosexual men in the San Francisco Bay Area, California. *Am J Epidemiol* 1999, 150:375-389.
- A comprehensive population-based case-control study of NHL.
- 75 Boice JD: Radiation and non-Hodgkin's lymphoma. *Cancer Res* 1992, 52:S5489-S5491.
- 76 Persson B, Fredrikson M: Some risk factors for non-Hodgkin's lymphoma. *Int J Occup Med Environ Health* 1999, 12:135-142.
- 77 Burnett C, Robinson C, Walker J: Cancer mortality in health and science technicians. *Am J Ind Med* 1999, 36:155-158.
- 78 Wertheimer N, Leeper E: Electrical wiring configurations and childhood cancer. *Am J Epidemiol* 1979, 109:273-284.
- 79 Savitz DA, Wachtel H, Barnes FA, et al.: Case-control study of childhood cancer and exposure to 60hz magnetic fields. *Am J Epidemiol* 1988, 128:21-38.
- 80 Milham S: Increased mortality in amateur radio operators due to lymphatic and hematopoietic malignancies. *Am J Epidemiol* 1988, 127:50-54.
- 81 Coleman M, Beral V: A review of epidemiological studies of the health effects of living near or working with electricity generation and transmission equipment. *Int J Epidemiol* 1988, 17:1-13.
- 82 Repacholi M, Basten A, GebSKI V, et al.: Lymphomas in Ev-Pim1 transgenic mice exposed to pulsed 900 MHz electromagnetic fields. *Radiation Research* 2000, 147:631-640.
- 83 McCormick DL, Ryan BM, Findlay JC, et al.: Exposure to 60 Hz magnetic fields and risk of lymphoma in PIM transgenic and TSG-p53 (p53 knock-out) mice. *Carcinogenesis* 1998, 19:1649-1653.
- 84 Villeneuve PJ, Agnew DA, Miller AB, et al.: Non-Hodgkin's lymphoma among electric utility workers in Ontario: the evaluation of alternate indices of exposure to 60 Hz electric and magnetic fields. *Occup Environ Medicine* 2000, 57:249-257.
- 85 Zahm SH, Blair A: Pesticides and non-Hodgkin's lymphoma. *Cancer Res* 1992, 52:S5485-S5488.
- 86 Zahm SH, Ward MH, Blair A: Pesticides and cancer. *Occupational Medicine—State Of The Art Reviews* 1997, 12:269-289.
- 87 Hoar SK, Blair A, Holmes FF, et al.: Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. *J Am Med Assn* 1986, 256:1141-1147.
- 88 Hardell L, Eriksson M, Lenner P, et al.: Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. *Br J Cancer* 1981, 43:169-176.
- 89 Wingle DT, Semenciw RM, Wilkins K, et al.: Mortality study of Canadian male farm operators: non-Hodgkin's lymphoma mortality and agricultural practices in Saskatchewan. *J Natl Cancer Inst* 1990, 82:575-582.
- 90 Zahm SH, Weisenburger DD, Babbitt PA, et al.: A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. *Epidemiology* 1990, 1:349-356.
- 91 Hardell L, Eriksson M, Degerman A: Exposure to phenoxyacetic acids, chlorophenols, or organic solvents in relation to histopathology, stage, and anatomical localization of non-Hodgkin's lymphoma. *Cancer Res* 1994, 54:2386-2389.
- 92 Cantor KP, Blair A, Everett G, et al.: Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Res* 1992, 52:2447-2455.
- 93 Blair A, Cantor KP, Zahm SH: Non-Hodgkin's lymphoma and agricultural use of the insecticide lindane. *Am J Ind Med* 1998, 33:82-87.

- 94 Pearce NE, Smith AH, Howard JK, et al.: Non-Hodgkin's lymphoma and exposure to phenoxyherbicides, chlorophenols, fencing work, and meat works employment: a case-control study. *Br J Ind Med* 1986, 43:75-83.
- 95 Woods JS, Polissar L, Severson RK, et al.: Soft tissue sarcoma and non-Hodgkin's lymphoma in relation to phenoxyherbicide and chlorinated phenol exposure in western Washington. *J Natl Cancer Inst* 1987, 78:899-910.
- 96 Georgellis A, Kolmodin-Hedman B, Kouretas D: Can traditional epidemiology detect cancer risks caused by occupational exposure to pesticides? *J Exp Clin Cancer Res* 1999, 18:159-166.
- 97 Hardell L, Eriksson M: A case-control study of non-Hodgkin lymphoma and exposure to pesticides. *Cancer* 1999, 85:1353-1360.
- 98 Nordstrom M, Hardell L, Magnuson A, et al.: Occupational exposures, animal exposure and smoking as risk factors for hairy cell leukaemia evaluated in a case-control study. *Br J Cancer* 1998, 77:2048-2052.
- 99 Garabedian MJ, Hoppin JA, Tolbert PE, et al.: Occupational chlorophenol exposure and non-Hodgkin's lymphoma. *J Occup Environ Med* 1999, 41:267-272.
- 100 Settimi L, Comba P, Carrieri P, et al.: Cancer risk among female agricultural workers: a multi-center case-control study. *Am J Ind Med* 1999, 36:135-141.
- 101 Schiff D, Suman VJ, Yang P, et al.: Risk factors for primary central nervous system lymphoma: a case-control study. *Cancer* 1998, 82:975-982.
- 102 Petralia SA, Dosemeci M, Adams EE, et al.: Cancer mortality among women employed in health care occupations in 24 US states, 1984-1993. *Am J Ind Med* 1999, 36:159-165.
- 103 Li F, Fraumeni JF, Mao Y: Cancer Mortality among chemists. *J Natl Cancer Inst* 1969, 43:1159-1164.
- 104 Searle CE, Waterhouse JAH, Herman BA: Epidemiologic study of the mortality of British chemists. *Br J Cancer* 1978, 38:192-193.
- 105 Olin GR, Ahlboma A: The cancer mortality among Swedish chemists graduated during 3 decades: a comparison with the general population and with a cohort of architects. *Environ Res* 1980, 22:154-161.
- 106 Carpenter L, Beral V, Roman E, et al.: Cancer in laboratory workers. *Lancet* 1991, 338:1080-1081.
- 107 Belli S, Comba P, Desantis M, et al.: Mortality study of workers employed by the Italian National Institute of Health, 1960-1989. *Scan J Work Environ Health* 1992, 18:64-67.
- 108 Dosemeci M, Alavanja M, Vetter R, et al.: Mortality among laboratory workers employed at the United States Department of Agriculture. *Epidemiology* 1992, 3:258-262.
- 109 Robinson CF, Walker JT: Cancer mortality among women employed in fast-growing US occupations. *Am J Ind Med* 1999, 36:186-192.
- 110 Miligi L, Seniori CA, Crosignani P, et al.: Occupational, environmental, and life-style factors associated with the risk of hematolymphopoietic malignancies in women. *Am J Ind Med* 1999, 36:60-69.
- 111 Knutsson A, Damber L, Jarvholm B: Cancers in concrete workers: results of a cohort study of 33 668 workers. *Occup Environ Medicine* 2000, 57:264-267.
- 112 Siemiatycki J, Richardson L, Gerin M, et al.: Associations between several sites of cancer and 9 organic dusts: results from an hypothesis generating case-control study in Montreal, 1979-1983. *Am J Epidemiol* 1986, 123:235-249.
- 113 Wilkinson P, Thakrar B, Walls P, et al.: Lymphohaematopoietic malignancy around all industrial complexes that include major oil refineries in Great Britain. *Occup Environ Medicine* 1999, 56:577-580.
- 114 Zahm SH, Weisenburger DD, Holmes FF, et al.: Tobacco and non-Hodgkin's lymphoma: Combined analysis of three case-control studies (United States). *Cancer Causes & Control* 1997, 8:159-166.
- 115 Franceschi S, Serraino D, Bidoli E, et al.: The epidemiology of non-Hodgkin's lymphoma in the northeast of Italy: a hospital-based case-control study. *Leuk Res* 1989, 13:465-472.
- 116 Brown LM, Everett GD, Gibson R, et al.: Smoking and risk of non-Hodgkin's lymphoma and multiple-myeloma. *Cancer Causes Control* 1992, 3:49-55.
- 117 Linet MS, McLaughlin JK, Hsing AW, et al.: Is cigarette smoking a risk factor for non-Hodgkin's lymphoma or multiple myeloma: results from the Lutheran brotherhood cohort study. *Leuk Res* 1992, 16:621-624.
- 118 Waddell BL, Blair A, Zahm SH: Re: "Relation of cigarette smoking to non-Hodgkin's lymphoma among middle-aged men" [letter]. *Am J Epidemiol* 1999, 150:661-662.
- 119 Freedman DS, Tolbert PE, Coates R, et al.: Relation of cigarette smoking to non-Hodgkin's lymphoma among middle-aged men. *Am J Epidemiol* 1998, 148:833-841.
- 120 Zahm SH, Weisenburger DD, Babbitt PA, et al.: Use of hair coloring products and the risk of lymphoma, multiple myeloma, and chronic lymphocytic leukemia. *Am J Public Health* 1992, 82:990-997.
- 121 Cantor KP, Blair A, Everett G, et al.: Hair dye use and risk of leukemia and lymphoma. *Am J Public Health* 1988, 78:570-571.
- 122 Linos A, Kiamouris C, Foukanelis T, et al.: A case-control study of non-Hodgkin's lymphoma. *Am J Epidemiol* 1994, 139:S46-S46.
- 123 Thun MJ, Altekruse SF, Nambodiri MM, et al.: Hair dye use and risk of fatal cancers in United States women. *J Natl Cancer Inst* 1994, 86:210-215.
- 124 Grodstein F, Hennekens CH, Colditz GA, et al.: A prospective study of permanent hair dye use and hematopoietic cancer. *J Natl Cancer Inst* 1994, 86:1466-1470.
- 125 Holly EA, Lele C, Bracci PM: Hair-color products and risk for non-Hodgkin's lymphoma: a population-based study in the San Francisco Bay area. *Am J Public Health* 1998, 88:1767-1773.
- 126 Altekruse SF, Henley SJ, Thun MJ: Deaths from hematopoietic and other cancers in relation to permanent hair dye use in a large prospective study (United States). *Cancer Causes Control* 1999, 10:617-625.
- 127 Cartwright R, McNally R, Staines A: The increasing incidence of non-Hodgkin's lymphoma (NHL): the possible role of sunlight. *Leuk Lymphoma* 1994, 14:387-394.
- 128 Melbye M, Adami HO, Hjalgrim H, et al.: Ultraviolet light and non-Hodgkin's lymphoma. *Acta Oncologica* 1996, 35:655-657.
- 129 Bentham G: Association between incidence of non-Hodgkin's lymphoma and solar ultraviolet radiation in England and Wales. *Br Med J* 1996, 312:1128-1131.
- 130 McMichael AJ, Giles GG: Have increases in solar ultraviolet exposure contributed to the rise in incidence of non-Hodgkin's lymphoma? *Br J Cancer* 1996, 73:945-950.
- 131 Adami J, Frisch M, Yuen J, et al.: Evidence of an association between non-Hodgkin's lymphoma and skin cancer. *Br Med J* 1995, 310:1491-1495.
- 132 Frisch M, Melbye M: New primary cancers after squamous cell skin cancer. *Am J Epidemiol* 1995, 141:916-922.
- 133 Hall P, Rosendahl I, Mattsson A, et al.: Non-Hodgkin's lymphoma and skin malignancies: shared etiology. *Int J Cancer* 1995, 62:519-522.
- 134 Levi F, Randimbison L, Te VC, et al.: Non-Hodgkin's lymphomas, chronic lymphocytic leukaemias and skin cancers. *Br J Cancer* 1996, 74:1847-1850.
- 135 Hartge P, Devesa SS, Grauman D, et al.: Non-Hodgkin's lymphoma and sunlight. *J Natl Cancer Inst* 1996, 88:298-300.
- 136 Freedman DM, Zahm SH, Dosemeci M: Residential and occupational exposure to sunlight and mortality from non-Hodgkin's lymphoma: composite (threefold) case-control study. *Br Med J* 1997, 314:1451-1455.
- 137 Adami J, Gridley G, Nyren O, et al.: Sunlight and non-Hodgkin's lymphoma: a population-based cohort study in Sweden. *Int J Cancer* 1999, 80:641-645.
- 138 Zahm SH, Hoffman-Goetz L, Dosemeci M, et al.: Occupational physical activity and non-Hodgkin's lymphoma. *Med Sci Sports Exercise* 1999, 31:566-571.
- 139 Cunningham A: Lymphomas and animal-protein consumption. *Lancet* 1976, 2:1184-1186.
- 140 Chiu B, Cerhan J, Folsom A, et al.: Diet and risk of non-Hodgkin's lymphoma in older women. *J Am Med Assn* 1996, 275:1315-1321.
- 141 Tavani A, Pregnolato A, Negri E, et al.: Diet and risk of lymphoid neoplasms and soft tissue sarcomas. *Nutr Cancer* 1997, 27:256-260.
- 142 Franceschi S, Serraino D, Carbone A, et al.: Dietary factors and non-Hodgkin's lymphoma: a case-control study in the northeastern part of Italy. *Nutr Cancer* 1989, 12:333-341.
- 143 Negri E, Lavecchia C, Franceschi S, et al.: Vegetable and fruit consumption and cancer risk. *Int J Cancer* 1991, 48:350-354.

- 144 Ward MH, Mark SD, Cantor KP, et al.: Drinking water nitrate and the risk of non-Hodgkin's lymphoma. *Epidemiology* 1996, 7:465-471.
- 145 Ward MH, Zahm SH, Weisenburger DD, et al.: Dietary factors and non-Hodgkin's lymphoma in Nebraska (United States). *Cancer Causes Control* 1994, 5:422-432.
- 146 Zhang S, Hunter DJ, Rosner BA, et al.: Dietary fat and protein in relation to risk of non-Hodgkin's lymphoma among women. *J Natl Cancer Inst* 1999, 91:1751-1758.
- This article examined the possible association between intake of specific types of dietary fat and protein and risk of NHL.
- 147 Law G, Parslow R, McKinney P, et al.: Non-Hodgkin's lymphoma and nitrate in drinking water: a study in Yorkshire, United Kingdom. *J Epidemiol Community Health* 1999, 53:383-384.
- 148 De Stefani E, Fierro L, Barrios E, et al.: Tobacco, alcohol, diet and risk of non-Hodgkin's lymphoma: a case-control study in Uruguay. *Leuk Res* 1998, 22:445-452.
- 149 Brown LM, Gibson R, Burmeister LF, et al.: Alcohol-consumption and risk of leukemia, non-Hodgkins lymphoma, and multiple-myeloma. *Leuk Res* 1992, 16:979-984.
- 150 Nelson RA, Levine AM, Marks G, et al.: Alcohol, tobacco and recreational drug use and the risk of non-Hodgkin's lymphoma. *Br J Cancer* 1997, 76:1532-1537.
- 151 Cartwright RA, McKinney PA, O'Brien C, et al.: Non-Hodgkin's lymphoma: Case control epidemiological study in Yorkshire. *Leuk Res* 1988, 12:81-88.
- 152 Armenian HK, Hoover DR, Rubb S, et al.: Risk factors for non-Hodgkin's lymphomas in acquired immunodeficiency syndrome (AIDS). *Am J Epidemiol* 1996, 143:374-379.
- 153 Tavani A, Negri E, Franceschi S, et al.: Smoking habits and non-Hodgkin's lymphoma: a case-control study in northern Italy. *Preventive Medicine* 1994, 23:447-452.
- 154 Chiu BCH, Cerhan JR, Gapstur SM, et al.: Alcohol consumption and non-Hodgkin's lymphoma in a cohort of older women. *Br J Cancer* 1999, 80:1476-1482.
- 155 Mueller NE: Hodgkin's disease. In *Cancer epidemiology and prevention*. Edited by Schottfeld D, Fraumeni JF. New York: Oxford University Press, 1996: 893-919.
- 156 Levine P: Hodgkin's disease. In *Cancer rates and risks*. Edited by HARRAS A, Edwards BK, Blot WJ, Reis LAG. Bethesda: National Institutes of Health, U.S. Department of Health and Human Services, Public Health Services, 1996: 140-143.
- 157 Lyons SF, Liebowitz DN: The roles of human viruses in the pathogenesis of lymphoma. *Sem Oncol* 1998, 25:461-475.
- 158 Enblad G, Sandvej K, Sundstrom C, et al.: Epstein-Barr virus distribution in Hodgkin's disease in an unselected Swedish population. *Acta Oncologica* 1999, 38:425-429.
- 159 Cavdar AO, Pamir A, Gozdasoglu S, et al.: Hodgkin disease in children: Clinicopathologic and viral (Epstein-Barr virus) analyses. *Medical Pediatr Oncol* 1999, 32:18-24.
- 160 Armstrong AA, Alexander FE, Cartwright R, et al.: Epstein-Barr virus and Hodgkin's disease: Further evidence for the three disease hypothesis. *Leukemia* 1998, 12:1272-1276.
- 161 Jarrett RF, MacKenzie J: Epstein-Barr virus and other candidate viruses in the pathogenesis of Hodgkin's disease. *Sem Hematol* 1999, 36:260-269.
- 162 Paydas S, Kilic B, Sahin B, et al.: Prevalence of hepatitis C virus infection in patients with lymphoproliferative disorders in Southern Turkey. *Br J Cancer* 1999, 80:1303-1305.
- 163 Gilman EA, McNally RJQ, Cartwright RA: Space-time clustering of Hodgkin's disease in parts of the UK, 1984-1993. *Leuk Lymphoma* 1999, 36:85-100.
- 164 Dockerty JD, Sharples KJ, Borman B: An assessment of spatial clustering of leukaemias and lymphomas among young people in New Zealand. *J Epidemiol Community Health* 1999, 53:154-158.
- 165 Rowlings PA, Curtis RE, Passweg JR, et al.: Increased incidence of Hodgkin's disease after allogeneic bone marrow transplantation. *Journal Of Clinical Oncology* 1999, 17:3122-3127.
- 166 Petruckevitch A, Del Amo J, Phillips AN, et al.: Risk of cancer in patients with HIV disease. *Int J STD AIDS* 1999, 10:38-42.
- 167 Chokunonga E, Levy LM, Bassett MT, et al.: Aids and cancer in Africa: the evolving epidemic in Zimbabwe. *AIDS* 1999, 13:2583-2588.
- 168 Taylor GM, Gokhale DA, Crowther D, et al.: Further investigation of the role of HLA-DPB1 in adult Hodgkin's disease (HD) suggests an influence on susceptibility to different HD subtypes. *Br J Cancer* 1999, 80:1405-1411.
- 169 Paavolainen P, Pukkala E, Pulkkinen P, et al.: Cancer incidence after total knee arthroplasty: a nationwide Finnish cohort from 1980 to 1996 involving 944 patients. *Acta Orthoped Scand* 1999, 70:609-617.
- 170 McCunney RJ: Hodgkin's disease, work, and the environment: a review. *J Occup Environ Med* 1999, 41:36-46.
- 171 Khuder SA, Mutgi AB, Schaub EA, et al.: Meta-analysis of Hodgkin's disease among farmers. *Scand J Work Environ Health* 1999, 25:436-441.