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Original article

Epidemiology of non-Hodgkin's lymphoma: Recent findings regarding an emerging epidemic

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Summary

Between 1973 and 1989, the incidence of non-Hodgkin's lymphoma (NHL) increased by nearly 60% in the United States, one of the largest increases of any cancer. In 1993, approximately 43 000 new cases of NHL will be diagnosed and over 20 000 deaths due to NHL will occur. The annual incidence rate of NHL per 100 000 persons in the US has risen from 5.9 in 1950 to 13.7 in 1989. This increase has occurred in both males and females, blacks and whites, and in all age groups except the very young. The largest increase has occurred in the elderly, and rates have increased more rapidly in rural areas. Most of the increase cannot be attributed to acquired immunodeficiency syndrome. Similar findings have been reported from other developed countries. Epidemiologic studies indicate that environmental factors may play an important role in the etiology of NHL. In this paper, current knowledge concerning the epidemiology of NHL is summarized, with special emphasis on environmental factors of possible etiologic importance, such as drugs, pesticides, solvents and other chemicals, dusts and particles, hair dyes, smoking, *Helicobacter pylori* infection, and diet. Many different environmental factors of low risk acting on large segments of the population could account for much of the increase in NHL.

Key words: diet, epidemiology, *Helicobacter pylori*, non-Hodgkin's lymphoma, pesticides, solvents

Introduction

In the United States, approximately 43 000 new cases of non-Hodgkin's lymphoma will be diagnosed in 1993 and over 20 000 deaths will be attributed to this cancer [1]. A recent epidemiologic survey [2] has characterized this rapid increase in incidence of NHL in recent years, which was exceeded only by lung cancer among women and malignant melanoma. In contrast, the incidence rates of Hodgkin's disease and leukemia have declined, and multiple myeloma has increased only slightly [2]. Concern about this emerging epidemic of NHL led to an interdisciplinary workshop sponsored by the National Cancer Institute (NCI) in October of 1991, the results of which have recently been published [3]. In this paper, I will summarize the current state of knowledge concerning the epidemiology of NHL with a special emphasis on recent studies of environmental factors of possible etiologic importance.

The Epidemic

Incidence

The annual incidence of NHL per 100 000 persons in the US rose from 5.9 in 1950 to 9.3 in 1975, and to 13.7 in 1989 (Fig. 1) [2]. Since the early 1970s, based on data from the NCI-sponsored Surveillance, Epidemiology, and End Results (SEER) program, the incidence rate has increased by almost 60% and has been increasing at a rate of 3.3% per year (Table 1). The increase has occurred in both males and females, and in blacks and whites (Table 1), with age groups under and over 65 years showing significant increases (Table 2). The largest increases have occurred in the elderly (Fig. 2). For example, the incidence among white men aged 75 years and older increased 300–400% during this time [4]. Incidence rates have been increasing more

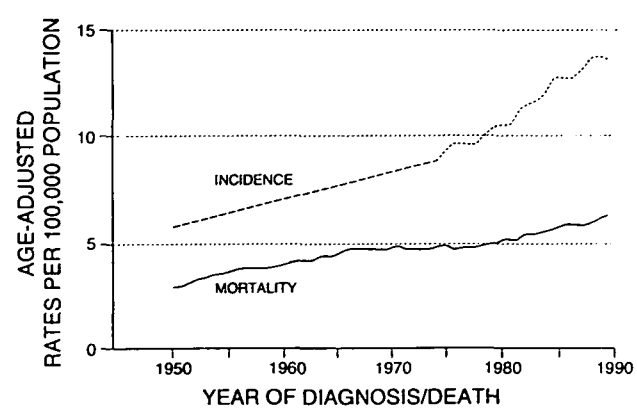

Fig. 1. Age-adjusted incidence and mortality rates of non-Hodgkin's lymphoma in the US estimated from rates in four survey areas (Atlanta, Connecticut, Detroit, San Francisco–Oakland) and the SEER Cancer Registry areas, 1950–89 [2, 7].

Table 1. Age-adjusted SEER incidence rates for non-Hodgkin's lymphoma, 1973–89.

	Rate 1989	Average rate 1973–74	Average rate 1985–89	Percent-age of change	EAPC
Total	13.7	8.7	13.5	58.9	3.3*
White males	17.8	10.5	17.3	69.9	3.8*
Black males	11.0	8.3	10.8	43.2	3.0*
White females	11.4	7.7	11.5	51.5	2.8*
Black females	7.9	4.9	7.4	50.9	3.9*

EAPC = estimated annual percent change; * EAPC is significantly different from zero ($p < 0.05$).

Table 2. Age-adjusted SEER incidence rates for non-Hodgkin's lymphoma by age group.

	1985–89 rate <65 yrs.	1985–89 rate 65+ yrs.	1973–89 EAPC <65 yrs.	1973–89 EAPC 65+ yrs.
Total	7.8	65.7	3.3*	3.3*
White males	10.3	81.3	4.1*	3.5*
Black males	7.5	40.3	4.6*	1.2
White females	6.1	60.4	2.2*	3.4*
Black females	4.1	36.8	3.9*	4.2*

EAPC = estimated annual percent change; * EAPC is significantly different from zero ($p < 0.05$); yrs. = years of age.

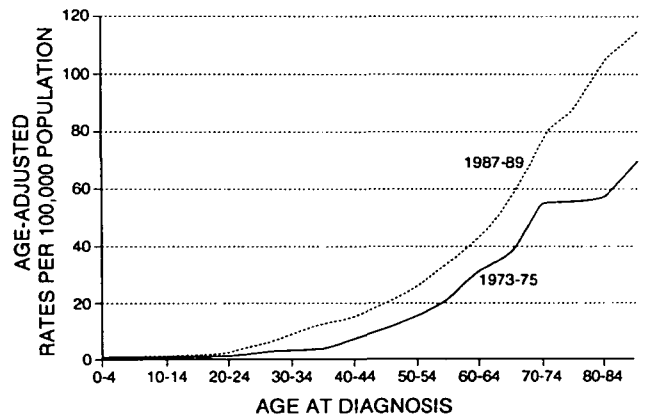

Fig. 2. Age-adjusted incidence rates of non-Hodgkin's lymphoma in US males of all races by age, 1973–75 and 1987–89 [2].

rapidly in rural areas than urban areas, resulting in a decrease in the urban to rural ratio from 1.4 to 1.15 [4]. However, factors associated with socioeconomic status do not appear to be playing a major role in the development of NHL in recent years [4]. White males in the US have the highest rate in the world, although incidence appears to be increasing across virtually all cancer registries in other developed countries [4].

Although much attention has been devoted to NHL arising in persons with acquired immunodeficiency syndrome (AIDS), most of the recent increase in NHL cannot be attributed to AIDS [2]. AIDS-associated NHL was not noted until the mid-1980s and has occurred largely in young, single males. For example, the incidence rate for males aged 20–54 years in San Francisco increased ninefold between 1980 and 1989. However, the current epidemic of NHL began in the 1950s and has occurred primarily in older persons, both males and females. The relative risk of NHL in patients with AIDS is increased over a hundred-fold [5], and it appears that AIDS will be a major cause of NHL in the future, accounting for approximately 10–15% of all new cases of NHL [6].

Mortality

In the US, mortality rates due to NHL are increasing almost 2% per year (Fig. 1) [2]. Survival rates are higher for whites than blacks, and females survive better than males. These differences are most pronounced in those less than 65 years old (Table 3). Survival rates increased significantly for whites between 1974–76 and 1983–88, but the survival for blacks has not changed significantly [2]. Also, the median age at the time of diagnosis of NHL is earlier for blacks than whites (Table 3). These differences are largely unexplained and further research is needed in order to separate socioeconomic and environmental factors from race.

Pathology

The majority of NHLs arise in lymph nodes, but primary extranodal disease accounts for 20–30% of all cases. Whereas the absolute increase in nodal disease exceeded that of extranodal disease between 1974 and 1988, proportional increases have been greater for extranodal NHL [4]. Incidence rates increased 1.7–2.5% per year for nodal cases compared to 3.0–6.9% for extranodal cases, with the highest increases occurring in blacks (5.0–6.9% per year). The most frequent extranodal sites were the stomach, intestines, and skin, with increases of 49%, 56–60%, and 67%, respectively. However, the largest proportional increases occurred in the brain and other areas of the nervous system (244%) and the eye (140%). With regard to histology, increases occurred in almost all Working Formulation categories, with the largest increases occurring in the diffuse subtypes of NHL, particularly the diffuse large-cell and immunoblastic subtypes (110%) [2, 4].

Table 3. Median ages of onset and five-year SEER survival rates for non-Hodgkin's lymphoma.

	Median age (yrs.)	1983–88 survival (yrs.) All ages	<65 yrs.	65+ yrs.
Total	65	51.3	58.0	42.9
White males	63	50.3	54.9	42.6
Black males	52	41.3	41.3	37.7
White females	69	53.8	64.7	44.2
Black females	64	44.4	54.9	31.5

Yrs. = years of age.

Etiology

A variety of predisposing and causal factors for NHL are well known, and include congenital and acquired immunodeficiencies of various types, autoimmune disorders (rheumatoid arthritis, Sjögrens syndrome, celiac disease), familial factors, and various viral infections [3, 5–7]. Recent epidemiologic studies have suggested that environmental factors may also play an important role in the etiology of NHL. Occupational studies have found that persons with certain types of jobs have an increased risk of NHL, including farmers, pesticide applicators, grain millers, wood and forestry workers, chemists, cosmetologists, machinists, printers, and workers in the petroleum, rubber, plastics, and synthetics industries [7, 8]. Thus, environmental exposures of various types may be etiologic for NHL. The rest of this paper will deal primarily with recent findings concerning this subject.

Drugs

The prototype for induction of NHL by carcinogenic agents is the use of alkylating agents and/or radiotherapy for the treatment of various malignancies. Recent studies have shown a three- to ninefold increased risk of NHL in such patients [9–11]. The latency period for the development of NHL following such high-dose exposures is about 5 to 6 years [9–12], similar to that of secondary acute leukemia. The latency period for NHL in such cases may be as short as 2 years, but may also be as long as 15 or more years. An idealized graph showing latency curves for NHL due to short-term, high-dose (curve A) and long-term, low-dose (curve B) carcinogenic exposures is shown in Figure 3. Short-term, high-dose exposures would be expected to result in a short latency period, whereas long-term, low-dose exposures would be expected to result in a long latency period. The implications of these findings for the design and interpretation of epidemiologic studies has been discussed [12]. No other medications have been clearly linked to the induction of NHL, with the exception of immunosuppressive drugs [3, 7]. Recent surveys of a large number of epileptic patients have failed to confirm an excess risk for those using phenytoin [13].

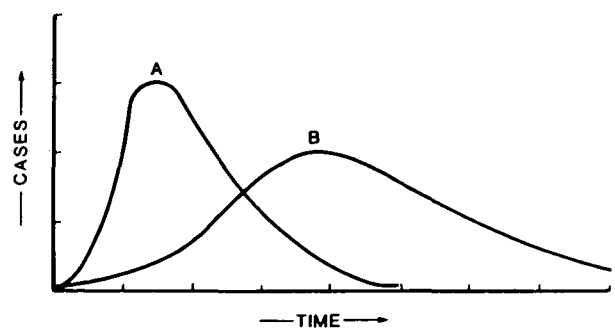

Fig. 3. Idealized latency curves for non-Hodgkin's lymphoma associated with short-term, high-dose (A) and long-term, low-dose (B) carcinogenic exposures [12].

Pesticides

The cancer mortality time-trends map for NHL during 1950–80 shows a significant increase in the central part of the US, a predominantly agricultural area [14]. This finding led to a number of studies which confirmed the suspicion of Hardell and colleagues [15] that certain pesticide exposures may cause NHL [16, 17]. The most extensive data regarding pesticides and NHL implicates the phenoxy herbicides, particularly 2,4-D. Case-control studies in Kansas [18] and Nebraska [19] have demonstrated an increased risk of NHL (odds ratios, 1.3–2.2) among male farmers using 2,4-D, with the risk increasing significantly to three- to sevenfold among those resporting use for 21 or more days per year. The risk was higher among farmers who did not regularly use protective equipment when applying pesticides [18], and among those who wore their application work clothes for long periods of time [19]. These findings concerning the phenoxy herbicides have recently been confirmed by others [20–23].

In Nebraska, we also found a 2.4-fold increased risk of NHL for male farmers who used organophosphate insecticides, independent of the effects of 2,4-D, with the risk increasing to over threefold for those using such insecticides 21 or more days per year [19]. Recent studies have also shown that farm women may be at increased risk for NHL [24, 25], particularly those who personally handle organophosphate insecticides (odds ratio, 4.5) [25]. No increased risk has been associated with the herbicide atrazine [26], although fungicides were associated with NHL in Kansas [18]. Flour millers are exposed to fungicides and fumigant pesticides and have an over fourfold increased risk of NHL, with the risk rising to over ninefold with long follow-up [27]. Recent studies of pesticide applicators have demonstrated a significant increase in chromosomal rearrangements associated with application, some of which have also been observed in NHL cells [28–30]. Studies of the histologic types of NHL occurring in pesticide applicators have revealed increased risks for all of the various NHL subtypes with the highest risk being for intermediate-grade NHL, particularly the large-cell subtypes [31, 32]. The rapidly increasing use of pesticides since the mid-1940s and their widespread use today also suggest an important role for certain pesticides in the current epidemic of NHL [17].

Solvents and other chemicals

Early studies [7, 8, 15, 33] suggesting an etiologic link between solvent and other chemical exposures and NHL have recently been confirmed [20, 34–38]. Some of the specific chemicals implicated in the various studies include benzene, styrene, 1,3-butadiene, trichlorethylene, perchlorethylene, creosote, lead ar-

senate, formaldehyde, paint thinners, and oils and greases. Olson and Brandt [34] found an over threefold increased risk of NHL for workers exposed to solvents, with a significantly increasing risk with increasing duration of exposure (odds ratio of 6.0 for 30 years). Blair and colleagues [38] found that both follicular and diffuse NHL were associated with benzene, whereas diffuse NHL was linked to other solvents and formaldehyde, and follicular NHL was excessive among workers exposed to oils and greases. Chromosomal studies of NHLs from patients exposed to solvents have shown a high proportion of cases with complex clonal aberrations, including frequent translocations involving chromosome 14 at band q32 [39].

Dusts and particles

Small increases in risk for NHL (odds ratios, 1.2–1.9) have recently been associated with occupational exposures to dusts and particles [32, 40, 41]. Specific dusts implicated have been wood dust and cotton dust. Scherr and colleagues [32] found an eightfold increased risk for diffuse large-cell lymphoma in workers exposed to dusts and particles. Additional studies are needed to confirm these findings and to separate the potentially confounding effects of wood preservatives, such as creosote and pesticides (chlorophenols, phenoxy acids), from the effects of the dusts themselves.

Hair dyes

Because of some limited data that suggested that cosmetologists may have an increased risk of hematopoietic cancer, and a study of Iowa men that showed a twofold increased risk of NHL associated with the use of hair dyes [42], we included questions concerning hair dye use in our case-control study of NHL in Nebraska [43]. In our study, we found an increased risk of NHL (odds ratio, 1.5) in women who used hair dyes, particularly permanent and dark-colored dyes (odds ratios, 2.0–4.1). Long duration of use and early age at first use tended to increase the risk. Increased risks were also found for Hodgkin's disease (odds ratio, 1.7) and multiple myeloma (odds ratio, 1.8). In Iowa men, increased risks were also found for leukemia (odds ratio, 1.8) and multiple myeloma (odds ratio, 1.9) [41, 44], and in myeloma the risk increased with frequent use (odds ratio, 4.3) [44]. These findings are not surprising given the numerous mutagenic and carcinogenic compounds in hair dyes [43]. The percentage of US women who have used hair dyes ranges from 20% to 40%. If the results of our study represent a causal association, use of hair-coloring products would account for 35% of NHL cases in exposed women and 20% of cases in all women [43]. Thus, hair dyes may be an important etiologic factor in the current epidemic of NHL. Bernard and associates [33] also found that the use of hair sprays was associated with an increased risk of NHL in younger women (odds ratio, 4.7). Further studies of hair care and other beauty products are clearly needed to better characterize the risks of individual products and their components.

Smoking

Three recent studies have suggested an increased risk (odds ratios, 1.4–3.8) for NHL associated with smoking and tobacco use [45–47]. In one study the risk increased with the amount of consumption [47], and in another, the risk was highest for high-grade NHL (odds ratios, 2.5–4.8) [46]. Also, two recent studies of childhood NHL [48, 49] have suggested a role for passive exposure to parental smoke as a possible cause. Additional studies are clearly needed to confirm these findings.

Helicobacter pylori infection

Recent studies showing an association between gastric carcinoma and *H. pylori* infection also suggest an association of *H. pylori* infection and NHL [50–52]. A study from northern Italy [53] recently reported a remarkably high incidence of primary gastric NHL in an area where the rate of gastric carcinoma is also high, and *H. pylori* infection was demonstrated in 87% of the gastric biopsies taken from patients in the area during a one-year period. Also, Wotherspoon and colleagues [54] found *H. pylori* infection in 92% of their cases of primary gastric NHL and suggested that the infection-induced gastritis provides the background lymphoid tissue in which the NHL develops. Rodriguez and associates [55] recently reported an over sixfold increased risk of primary gastric NHL in persons with *H. pylori* infection. Thus, *H. pylori* appears to be an important predisposing factor for the development of gastric NHL.

Diet

Increased rates of NHL have recently been found in areas where nitrate contamination of groundwater by agriculture is a problem [56]. Although nitrate per se does not appear to present a cancer risk, it is the precursor to nitrite, which reacts with nitrosatable dietary substrates in the stomach to produce N-nitroso compounds, which are potent carcinogens in experimental animals. Further studies are needed to better understand the role of N-nitroso compounds in the etiology of gastric NHL and other types of NHL.

Recent dietary studies have suggested that high consumption of milk, butter, liver, polyunsaturated oils, and methylxanthine-containing beverages (coffee, tea, cola) increase the risk of NHL, whereas high consumption of whole-grain breads and pasta, and green vegetables and carrots, appears to have a protective effect [57, 58]. In a recent report from Nebraska [59], we did not find an increased risk of NHL associated with the consumption of milk or other animal protein, or coffee

or tea, but we did find protective effects for high consumption of citrus fruits, green vegetables, and carrots. These findings suggest that vitamin C and carotene may be important chemopreventive agents for NHL, as has been shown for many other cancers.

Conclusions

An epidemic of NHL is clearly upon us and some of the etiologic factors are beginning to be elucidated. In this paper, I have emphasized environmental factors of possible etiologic importance. Many different environmental factors of low risk acting on large segments of the population could account for much of the recent increase in NHL. For example, two studies have suggested that industrial contamination of communities by chemicals led to increased rates of NHL [60, 61]. Further epidemiologic studies of NHL are clearly needed to better identify and quantify risk factors so that preventive measures can be taken in the future.

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