Is the Decline of the Increasing Incidence of Non-Hodgkin Lymphoma in Sweden and Other Countries a Result of Cancer Preventive Measures?

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Is the decline of the increasing incidence of non-Hodgkin lymphoma (NHL) in Sweden and other countries a result of cancer preventive measures? The yearly age-standardized incidence of NHL increased significantly in Sweden during 1971–1990, for men an average of 3.2% and for women 3.1%. The corresponding figures for 1991–2000 were –0.8% and –0.2%, respectively. A decline of the increasing incidence has also been seen in other countries, such as the United States, Finland, and Denmark. Immunosuppression is one established risk factor for NHL, possibly with interaction with Epstein-Barr virus. Phenoxyacetic acids and chlorophenols, both pesticides, have been associated with NHL. Use of these chemicals was banned in Sweden in 1977 and 1978, respectively. Also, persistent organic pollutants such as polychlorinated biphenyls, hexachlorobenzene, chlordanes, and dioxins have been shown to increase the risk. Exposure of the whole population occurs predominantly through the food chain. Exposure to such chemicals was highest in the 1960s and 1970s. Because of regulation in the 1970s, exposure has declined substantially in the population. The change in incidence of NHL in Sweden and other countries may serve as a good example of how prohibition and limitation of exposure may be reflected in cancer statistics some decades later. *Key words:* incidence, non-Hodgkin lymphoma, persistent organic pollutants, pesticides, prevention. *Environ Health Perspect* 111:1704–1706 (2003). doi:10.1289/ehp.6270 available via *http://dx.doi.org/* [Online 2 July 2003]

Non-Hodgkin lymphoma (NHL) belongs to the types of malignant diseases that have shown the largest increasing incidence in Sweden and in other Western countries during the second half of the 20th century. According to statistics in the National Swedish Cancer Registry, the yearly age-standardized incidence increased significantly for NHL during 1971–1990, an average of 3.2% for men and 3.1% for women (National Board of Health and Welfare 1993). The corresponding figures for 1991–2000 were –0.8% and –0.2%, respectively (National Board of Health and Welfare 2002a). A clear change of the incidence was seen about 1990 (Figure 1).

In the 1990s, the increasing incidence of NHL also leveled off in Denmark (study period 1989–1998; Danish Cancer Registry 2002) and in Finland (study period 1954–2000; Finnish Cancer Registry 2003), but not in Norway (1955–2000; Cancer Registry of Norway 2003) or in the United Kingdom (1971–1997; National Statistics 2001).

The Surveillance, Epidemiology, and End Results (SEER) Program (2003) of the National Cancer Institute is the most authoritative source of information on cancer incidence in the United States. Data have been collected from certain states beginning in 1973; 1999 is currently the last year with available data. The annual percentage change, based on rates that are age adjusted to the 2000 U.S. standard population by 5-year age groups, for all races and both sexes, was +3.6% ($p < 0.05$) during 1973–1990, +1.6% during 1990–1995, and –0.9% during 1995–1999. However, the declining incidence was seen only in men, although a declining mortality was seen in both sexes during 1990–1995. The increasing incidence of NHL since 1973 clearly leveled off during the 1990s (Ries et al. 2002).

Are there any etiologic agents that can be associated with the changing incidence of NHL in Sweden and other countries? The etiology of NHL is only partly known. Immunosuppression, both acquired and hereditary, has been described to increase the risk, for example, of drug-induced immunosuppression after organ transplantation, infection with human immunodeficiency virus (HIV), and certain autoimmune diseases. Also, viruses, especially Epstein-Barr virus (EBV), have been postulated to be of etiologic significance (Evans and Mueller 1990).

These risk factors cannot explain the observed changes of the incidence of NHL, however. The initial large increase of the incidence and later stabilizing or even decreasing incidence might be explained by one or several environmental agents with decreasing exposure of the population (e.g., because of regulation). Because the tumor-induction period in lymphomagenesis, as for other malignant diseases, varies from years to decades, regulation of such risk factors would probably have occurred during the 1970s and 1980s.

In this article, we discuss results from our studies and those of others since the late 1970s about the association between some chemical compounds and the risk for NHL. Our hypothesis is that changes in exposure to these compounds may at least partly explain the observed changes of NHL incidence, with Sweden as one example. Our intention is not to give a complete review of the etiology of NHL (for review, see, e.g., Hardell and Axelson 1998; Hardell et al. 2003). Risk estimates and exposure frequencies in our studies enable calculation of the attributable fraction, that is, the proportion of cases that can be attributed to the particular exposure. This was calculated as the exposed case fraction multiplied by [(OR – 1)/OR], where OR is the odds ratio.

Phenoxyacetic Acids and Chlorophenols

Phenoxyacetic acids were synthesized during World War II and were widely and increasingly used as herbicides (including on hardwood trees) from the early 1950s both in Sweden and in other countries. The chemically related chlorophenols were primarily used as impregnating agents.

Our first study on risk factors for NHL in men, which was initiated by a clinical observation (Hardell 1979), was published in 1981. We found a significant association between exposure to phenoxyacetic acids and chlorophenols and malignant lymphoma, both NHL and Hodgkin disease (Hardell et al. 1981). The results for NHL were also published separately (Hardell et al. 1994) and have been replicated by other research groups both in Sweden (Persson et al. 1989) and in other countries (Zahm et al. 1990; for updated review, see Hardell et al. 2003).

Our first investigation on NHL included patients diagnosed during 1974–1978 and mainly assessed exposures from the late 1940s and later (Hardell et al. 1981, 1994). The phenoxyacetic acids 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) constituted Hormoslyr (Gullvik, Sweden), one of the most widely used pesticides in Sweden during that period. 2,4,5-T was contaminated with dioxins during the production. Most hazardous among these dioxins was 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), one of the most toxic chemicals in the world and now classified as a group I human carcinogen

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by the International Agency for Research on Cancer (IARC 1997a). Agent Orange, as used during the Vietnam War, contained the same phenoxyacetic acids as Hormoslyr, and thus the same contaminations. In 2,4-D, lower chlorinated dioxins occurred.

The use of Hormoslyr was prohibited in Sweden in 1977, and chlorophenols were prohibited in January 1978. In our first study (Hardell et al. 1981, 1994), the attributable fraction for Hormoslyr was 13% and that for chlorophenols was 26%. A substantially lower attributable fraction of 3.0% for phenoxyacetic acids was calculated in a study on men and women in central Sweden (Persson et al. 1989), but a small number of subjects in the study had been exposed to chlorophenols.

Our next epidemiologic study on NHL (Hardell and Eriksson 1999) encompassed 1987–1990 and was further analyzed in combination with a study on hairy cell leukemia, a subgroup of NHL, for 1987–1992 (Hardell et al. 2002). Only men were included in these studies. Lower ORs for exposure to 2,4-D and 2,4,5-T (Hormoslyr) were obtained. The risk was highest with a latency period of 10–20 years and decreased with longer tumor induction periods (Hardell et al. 2002). The attributable fraction calculated for Hormoslyr was 3.0%, and that for chlorophenols was 3.5%.

In a study from Kansas (USA), the attributable fraction for the phenoxyacetic acids was calculated to be 7.7% (Hoar et al. 1986), and for 2,4-D in eastern Nebraska (USA), it was 7.1% (Hoar Zahm et al. 1990).

Organic Solvents

In our first study, the attributable fraction for NHL was calculated to be 25% for organic solvents (Hardell et al. 1981, 1994). In our next study (Hardell and Eriksson 1999), no significantly increased risk was found. One explanation might be that newer organic solvents are chemically different from earlier ones and are handled under better hygienic conditions than before (Axelson and Hogstedt 1994). In another Swedish study with exposures during the same period (Persson et al. 1989), the attributable fraction was calculated to be 16%.

Persistent Organic Environmental Pollutants

In a number of studies, we have measured concentrations of certain persistent organic pollutants in patients with NHL, both males and females, and compared these with concentrations from population controls (Hardell et al. 1996, 2001a). These results have been corroborated in other studies (Rothman et al. 1997). We found an interaction between polychlorinated biphenyls (PCBs), and EBV antigen, with an attributable fraction of 25%. The attributable fraction was of the same magnitude for hexachlorobenzene and chlordanes. Also, for dioxins calculated as toxic equivalents, we found a similar attributable fraction (Hardell et al. 2001b). All samples (blood or adipose tissue) in our studies were taken before patients received any treatment for the disease. It should also be pointed out that the concentrations of these persistent organic pollutants have substantially declined in the environment and population in Sweden since the 1980s (Bernes and Naylor 1998; Norén and Merionyté 2000).

Certainly, the interaction between EBV and chemical exposures in the etiology of NHL is still hypothetical. However, polyclonal B-cell proliferation is often seen among organ transplantation recipients. Immunosuppression in these patients may lead to loss of cell-mediated immune control of reactivated EBV as part of this process, and clonal EBV has been found in posttransplantation EBV (Patton et al. 1990). A Finnish cohort of subjects with elevated EBV antibodies was found to have an increased risk for malignant lymphoma (Lehtinen et al. 1993). EBV has been classified by IARC as a group I (sufficient evidence) human carcinogen (IARC 1997b).

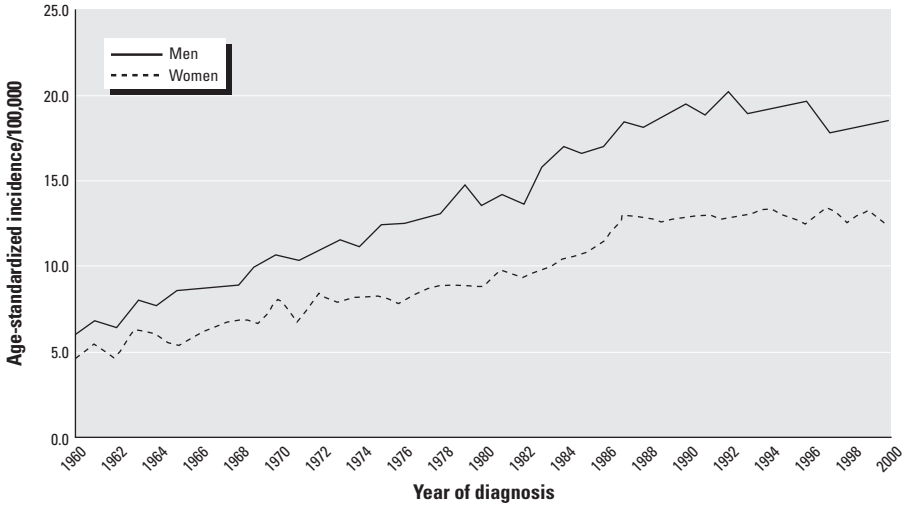

Figure 1. Age-standardized incidence per 100,000 of NHL (ICD-7 code 200) according to the Swedish Cancer Registry for all ages in 2000 (National Board of Health and Welfare 2002a).

Human Immunodeficiency Virus

HIV has been shown to be a risk factor for NHL, and it has been estimated that the probability of developing NHL is 29% after 36 months of antiviral therapy (Pluda et al. 1993). However, in Sweden the prevalence of HIV is low and has been rather stable during the 1990s; 335 cases were reported in 1990, which increased to 390 in 1993 and declined to 277 in 2001 (National Board of Health and Welfare 2002b). Thus, these numbers do not explain the change of NHL incidence during the 1990s in Sweden.

Discussion

Of interest is that the leveling off of the incidence of NHL during the 1990s has also occurred in countries other than Sweden. Data from the United States, Finland, and Denmark show a similar trend. However, for Norway and the United Kingdom, no such clear pattern has yet emerged. These data might reflect changes of common risk factors in different populations. Different chemicals that have been widely used in the Western World might constitute such factors, among them, persistent organic pollutants.

Most of the chemicals discussed in this article were introduced during or shortly after World War II. Exposure of the population increased until restrictions during the 1970s for Hormoslyr, chlorophenols, and PCBs, among others. The highest exposure occurred during the 1970s for persistent organic pollutants such as dioxins, chlorophenols, and PCBs (Bernes and Naylor 1998). After that, the concentrations in the environment and thus also in the food chain have declined, although the rate has leveled off during the 1990s. It should also be emphasized that work practices for herbicides in general have improved over the years with the use of protective equipment. This may also contribute to a lower risk for NHL.

In previous studies organic solvents have been shown to increase the risk for hematopoietic malignancies. Also for these chemicals, improvement in exposure conditions has occurred, such as bans of some organic solvents, cleaner and more water-based products, and better hygienic conditions during handling.

Immunosuppression is an established risk factor for NHL. Most of the chemicals described here have immunotoxic properties, as discussed in the publications cited. After organ transplantation, a very high risk for NHL has been found, and the risk increase is

largest during the first years after transplantation. Interactions between immunosuppression and EBV have been discussed as one explanation (Newstead 1998). Our results showing the highest risk for exposure to phenoxyacetic acids and chlorophenols with a rather short latency period (Hardell et al. 2002) may fit with the findings among organ transplantation patients. The finding of an interaction between chemicals and EBV might be of interest in this context (Hardell et al. 2001a, 2001b; Nordström et al. 1999, 2002).

Exposure to the risk factors discussed here, such as phenoxyacetic acids (e.g., Hormoslyr), chlorophenols, and organic solvents, has mainly been occupational. There are also geographic differences in exposure frequency in Sweden. If the lowest calculated attributable fraction of 3% is used for phenoxyacetic acids, 30 patients out of 1,000 with NHL would have avoided the disease without these herbicides on the market. Similarly, the number of patients in Sweden attributed to exposure to chlorophenols and organic solvents may be calculated.

Regarding persistent organic pollutants, the situation is quite different because the whole population is exposed, mainly thorough the food chain (e.g., fatty fish and dairy products). Probably, these chemicals have been of larger etiologic significance in the whole population than have pesticides and organic solvents. An attributable fraction of 25% contributes to 250 of 1,000 cases diagnosed yearly. However, in Sweden, the incidence of NHL has been higher in men than in women, indicating that occupational risk factors might be of some significance. Furthermore, of interest is the fact that the incidence has declined during the 1990s somewhat more in men than in women and, in the United States, only in men thus far.

Finally, we must emphasize that any single subject may be exposed to several of the agents discussed here, with the potential for interaction in lymphomagenesis. This of course complicates the calculation of the attributable fraction for a single agent. In this article we do not cover all aspects of lymphomagenesis, but we show that the ban of carcinogenic chemicals may be one explanation for the decline in incidence within a rather short time, although the quantitative effect of an individual agent cannot be defined.

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