Some Aspects of the Etiology of Non-Hodgkin’s Lymphoma

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In epidemiologic studies, non-Hodgkin’s lymphoma (NHL) has been associated with exposure to chemicals such as phenoxyacetic acids; chlorophenols; dioxins; organic solvents including benzene, polychlorinated biphenyls, chlordane; and immunosuppressive drugs. Experimental evidence and clinical observations indicate that these chemicals may impair the immune system. The risk is increased for NHL in persons with acquired and congenital immune deficiency as well as autoimmune disorders. Also, certain viruses have been suggested to be of etiologic significance for NHL. In some cases of NHL the common mechanism for all these agents and conditions may be immunosuppression, possibly in combination with viruses. — Environ Health Perspect 106(Suppl 2):679–681 (1998). http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-2/679-681/hardellabstract.html

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During the last two decades, non-Hodgkin’s lymphoma (NHL) has been one of the most rapidly increasing malignant diseases in the developed countries (1). The etiology of NHL is not well understood although the knowledge in this respect has accumulated during the past decades.

In this paper etiologic aspects are discussed with some emphasis on results of Swedish studies. The aim is not to give a thorough review on the epidemiology of NHL; this is found in other papers. Some hypotheses on etiology are discussed at the end of the paper.

A number of NHL patients with exposure to phenoxyacetic acid herbicides and to chlorophenol impregnating agents were first reported in 1979 (2). Subsequent studies on malignant lymphoma including both Hodgkin’s disease and NHL showed increased odds ratios for exposure to phenoxyacetic acids, chlorophenols, or organic solvents including benzene (3–8).

Whether impurities such as dioxins and dibenzofurans in chlorophenols and certain phenoxyacetic acids are of etiologic significance has been discussed. In that context it is of interest that the levels of some dioxin and dibenzofuran congeners were significantly higher in the adipose tissue of 7 patients with malignant lymphoproliferative disease than in 12 surgical controls without malignant disease (9). Also, the 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) toxic equivalent factor was significantly higher in these 7 patients; 64.7 pg/g wet basis (19.9–187) compared to 29.7 (12.9–53.4), p = 0.04 (Wilcoxon’s two-tailed test). Six cases reported potential occupational exposure to dioxins and dibenzofurans. One case was a high consumer of fish from the Baltic sea. Similarly, the higher chlorinated congeners of polychlorinated biphenyls (PCBs) were significantly elevated in 27 NHL patients compared with 17 surgical controls without malignancy (10). The mean sum of PCBs was 1614 ng/g lipid (637–4705) in the cases compared to 1213 (366–2282) in the controls with a Wilcoxon’s two-tailed p value of 0.06 (Figure 1). Also, for the insecticide chlordanes, significantly higher concentrations were found in NHL cases than in controls in the same study (11). The sum of chlordanes in the 27 NHL patients was 180 ng/g lipid (48.3–678) compared to 92.8 (37.0–164) in the 17 surgical controls, p = 0.002 (Figure 2). No significant differences were found between cases and controls for dioxins, dibenzofurans, hexachlorobenzene, or p,p’-DDE. The results reflect exposure, mainly through the food chain, to environmental concentrations of these organochlorines (12,13). It should be noted that on the basis of occupational exposure to the studied chemicals the case group was not included. Exposure to PCBs and increased risk of NHL appear to be corroborated in a recent study from the United States (14).

Both PCBs and chlordanes are immunotoxic substances (15,16). Immunotoxic effects also have been reported for other chemicals such as dioxins (17–19), chlorophenols (20,21), and organic solvents (22,23), which have been associated with increased risk for NHL. Recent evidence shows immunologic changes among farmers exposed to phenoxy herbicides (24). The incidence of NHL increases with age and an age-related decline in the protective immune response has been reported and may be added to the list of immunosuppressive factors (25).

Figure 1. Box plot of the sum of PCBs expressed as nanogram per gram of lipid for cases and controls where 50% of the subjects have values within the box; median value, 25th, and 75th percentiles are shown. Smallest and largest values that are not outliers as shown by bars. o, outlier more than 1.5 box length from 75th percentile; *, extreme more than 3 box lengths from the 75th percentile. n, numbers of cases and controls.
immune deficiency (27) or autoimmune diseases such as rheumatoid arthritis (28,29), Sjögren’s syndrome (30), and systemic lupus erythematosus (31). It is also well known that immunosuppressive therapy increases the risk for NHL (32,33). NHL has also been reported to be a late complication of certain chemotherapy and radiotherapy regimens in patients with Hodgkin’s disease (34).

Ultraviolet (UV) irradiation may cause immunosuppression (35). However, studies that have especially evaluated the possible role of UV light in NHL have not shown an increased risk for outdoor occupations (5,36) or exposure to sunlight (37).

Epstein-Barr virus (EBV), a herpes virus, has been associated with Burkitt lymphoma (38). EBV is persistent in over 95% of adults in nasopharyngeal epithelium and B cells (39). Normally, EBV production is held back by active cellular and humoral immune mechanisms. In immunodeficiency states, this balance may be disrupted, and EBV-infected B cells begin to proliferate (40).

The retrovirus human immunodeficiency virus-I is endemic in parts of the world and has been demonstrated to cause adult T-cell leukemia/lymphoma (41). Other retroviruses such as human immunodeficiency viruses are associated with acquired immune deficiency syndrome and an increased incidence of NHL (42).

Finally, a working group at the International Agency for Research on Cancer recently classified TCDD as a Group 1 human carcinogen (43). It was concluded that based on epidemiologic evidence exposure to TCDD increases the risk for all cancers combined, but with higher relative risks for NHL and soft-tissue sarcoma.

It is postulated that exposures or conditions that affect the immune system increase the risk for NHL. Virus proliferation is under immunologic surveillance and impairment of the immune system may cause B-cell lymphomas (40) and also T-cell lymphoma (44). Studies of the interaction between immune response, viruses, and various agents, therefore, would be of great interest.

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