Risk of Non-Hodgkin's Lymphoma and Prediagnostic Serum Organochlorines: β-Hexachlorocyclohexane, Chlordane/Heptachlor-Related Compounds, Dieldrin, and Hexachlorobenzene

Kenneth P. Cantor,[1] Paul T. Strickland,[2] John W. Brock,[3] David Bush,[4] Kathy Helzlsouer,[4] Larry L. Needham,[3] Shelia Hoar Zahm,[1] George W. Comstock,[4] and Nathaniel Rothman[1]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, USA; [2]Department of Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; [3]National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia, USA; [4]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

Increases in non-Hodgkin's lymphoma (NHL) incidence and mortality rates during the past few decades remain largely unexplained. Studies suggest that organochlorine pesticides may contribute to an increased risk of NHL. In 1974, serum samples were obtained from 25,802 participants in the Campaign Against Cancer and Stroke in Washington County, Maryland (USA), and cryopreserved for future study. We measured prediagnostic levels of chlordane, lindane (γ-hexachlorocyclohexane), β-hexachlorocyclohexane, transnonachlor, heptachlor, heptachlor epoxide, oxychlordane, dieldrin, and hexachlorobenzene in serum samples of 74 cases of NHL and 147 matched controls. Previously, we found an association between NHL and serum levels of total PCBs (polychlorinated biphenyls), but not DDT (dichlorodiphenyltrichloroethane) and related compounds. In this instance, there was no evidence of an association between NHL risk and serum levels of any of the individual lipid- and recovery-corrected organochlorines that we evaluated, nor of the summed chlordane-related compounds (transnonachlor, heptachlor, heptachlor epoxide, oxychlordane). These findings do not support the hypothesis that the organochlorine compounds included in this study are strongly linked to the development of NHL. The possibility of a weak association cannot be excluded by these data. *Key words:* **chlordane, dieldrin, heptachlor, hexachlorobenzene, hexachlorocyclohexane, lindane, non-Hodgkin's lymphoma, organochlorine.** *Environ Health Perspect* **111:179–183 (2003). [Online 15 November 2002]**
doi:10.1289/ehp.4347 available via *http://dx.doi.org/*

Observed rates of non-Hodgkin's lymphoma (NHL) incidence and mortality have increased markedly in the United States and other countries in the last three to four decades (*1*). The increase has been ascribed, in part, to changing diagnostic patterns, the use of immunosuppressive drugs, and increasing rates of HIV infection. However, a substantial fraction of the excess remains unexplained (*2,3*). Widespread exposures to organic solvents, pesticides, hair dyes, and other common chemicals have been suggested, and several of these factors have been linked with elevated NHL risk in case–control and other studies (*4–6*). In a hospital-based case–control study, Hardell et al. (*7*) found NHL risk to be associated with serum chlordane and related compounds. Population-based case–control studies have observed associations of NHL risk with self-reported agricultural exposure to specific organochlorine pesticides (*8–10*).

In this study, we measured prediagnostic concentrations of several organochlorine compounds in stored serum samples from patients with NHL and matched controls identified from a population-based prospective cohort established in 1974 in Washington County, Maryland (USA). We examined the association between risk of NHL and lipid-corrected serum concentrations of these compounds. An evaluation of the risk of NHL with serum levels of polychlorinated biphenyls (PCBs) and dichlorodiphenyltrichloroethane (DDT)-related compounds was previously reported (*11*).

Methods

Detailed methods are reported elsewhere (*11*). In brief, cases and controls were identified from a population of 25,802 adults in Washington County, Maryland (USA), who enrolled in 1974 in the Campaign Against Cancer and Stroke (CLUE I), sponsored by the Johns Hopkins University School of Hygiene and Public Health (now the Bloomberg School of Public Health). A 15-mL blood sample and responses to a brief questionnaire were obtained at enrollment. Serum was stored at –73°C. In 1989, a second blood-collection survey was conducted (CLUE II); approximately 25% of individuals enrolled in CLUE I also participated in CLUE II.

Cases. All incident cases of NHL were identified from the Washington County Cancer Registry. Cases were eligible for this study if they were a CLUE I participant with NHL [*International Classification of Diseases, 8th Revision* (ICD-8) code 200 or 202] (*12*) first diagnosed between 1 January 1975 and 31 May 1994, without a history of cancer, except for nonmelanoma skin cancer, before the diagnosis of NHL. Persons who had migrated out of Washington County before diagnosis were not eligible.

We identified 87 eligible cases, among whom 76 had serum samples available for analysis in our study. Of these, 51 had slides available for pathology. On review, two cases were judged not to be NHL (one Hodgkin's disease and one hairy-cell leukemia). Thus, 74 cases were included in the study.

Controls. Two controls were matched to each case. Eligible controls were alive and without a history of cancer at the time of case diagnosis (except possibly nonmelanomic skin cancer). Matching criteria included race, sex, date of birth within 1 year, participation in CLUE (CLUE I only or CLUE I and CLUE II), date of blood-sample donation within 15 days, participation in private censuses conducted by the Johns Hopkins University Training Center for Public Health Research in 1963 and 1975, and location of stored serum (Hagerstown or Baltimore, MD, USA). If an adequate volume of serum was not available for a control (< 3%), another individual was selected, using the same criteria. We matched cases and controls according to participation in the respective CLUE cohorts to enable comparison, in other settings, of samples from individuals who provided blood samples in both studies.

Organochlorine analysis. Serum samples were grouped in sets of one case and two matched controls, in random order. Samples were thawed, aliquoted into 1.5-mL volumes, and immediately refrozen on dry ice. Nine quality-control sets of three samples each were prepared by staff at Johns Hopkins University. The first sample in each set was a replicate of pooled serum samples collected during the

Address correspondence to K.P. Cantor, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd, EPS-8106, Bethesda, MD 20892-7240 USA. Telephone: (301) 435-4718. Fax: (301) 402-1819. E-mail: cantork@nih.gov

We thank B. Ellis (Batelle-SRA Inc.), R. Mann (Johns Hopkins University), S. Hoffman and J. Hoffman-Bolton (Johns Hopkins University), and E. Gunter (Centers for Disease Control and Prevention).

This research was supported in part by Department of Health and Human Services grants CA60754 and ES03819 and Research Career Award HL21670 (G.W.C.).

Received 24 May 2000; accepted 24 June 2002.