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nvironmental Epidemiology of Non-Hodgkin's mphoma in Eastern Nebraska

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The incidence of non-Hodgkin's lymphoma (NHL) is increased in many counties in eastern Nebraska. Histologic analysis has revealed a twofold increase in the clinically aggressive, diffuse large cell subtype of NHL. To investigate the possible association between NHL and agricultural exposures, a population-based case-control study was conducted in eastern Nebraska in 1985. Telephone interviews were conducted with 201 men having histologically confirmed NHL and 725 controls. Among men, the use of the herbicide 2,4-D was associated with a 50% increased risk of NHL (OR 1.5, 95% CI 0.9, 2.4). Personal exposure to 2,4-D more than 20 days per year increased the risk threefold (OR 3.3, 95% CI 0.5, 22.1). Several classes of insecticides were also associated with increased risk: organophosphates (OR 1.9, 95% CI 1.1, 3.1), carbamates (OR 1.8, 95% CI 1.0, 3.2), and chlorinated hydrocarbons (OR 1.4, 95% CI 0.8, 2.3). As a result of intense agrichemical use, extensive contamination of shallow groundwater by nitrate and atrazine has also occurred in eastern Nebraska. A twofold increased incidence of NHL is present in counties with greater than 20% of the wells contaminated by nitrate (>10 ppm) and in counties with intense fertilizer use. These findings suggest that NHL in eastern Nebraska may be related to the use of pesticides and nitrogen fertilizers.

ds: pesticides, herbicides, 2,4-D, nitrate, atrazine, farm exposures, drinking water contamination

UCTION

ern Nebraska is an area characterized by intensive agricultural activity, the extensive use of pesticides, nitrogen fertilizers, and irrigation. In 30 million pounds of pesticides and two million tons of nitrogen fertilizers in Nebraska, amounting to an annual expenditure for agrichemicals of tely 700 million dollars. In 1978, a study of Nebraska farmers and com-sticide applicators who used organophosphate and carbamate insecticides gnificant reductions in serum cholinesterase activity in 30% of the indi-d 22% had symptoms of acute insecticide poisoning [Spigiel et al., 1981]. he potential for acute and chronic health effects arising from the use of cals is great in Nebraska.

cer mortality studies during the period of 1950–1979 revealed an excess due to leukemia and lymphoma in Nebraska [Weisenburger, 1985]. In a

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cluster of counties in the central Platte River Valley during this time, the incidence of leukemia and lymphoma was twofold greater than the national average [Caldwell et al., 1973]. During this period, a death certificate study of Nebraska farmers also revealed an elevated risk of leukemia (OR 1.25), with the greatest risk occurring among young farmers (OR 1.83) [Blair and Thomas, 1979]. For some leukemia subtypes, the increased risk was localized to counties with high corn production and high pesticide and fertilizer use [Blair and White, 1985]. These and other studies provided the basis for our hypothesis that the excess of leukemia and lymphoma in Nebraska is due to certain agricultural practices [Weisenburger, 1985; Hoar et al., 1986].

In early 1985, we embarked on a study to determine the incidence of non-Hodgkin's lymphoma (NHL) in eastern Nebraska. The incidence of NHL in persons older than age 21 years in the 66 counties of eastern Nebraska was found to be 17.6/100,000 persons (expected 15.7/100,000) for 1984. The incidence of NHL was greater than expected in 35 counties and greater than 21/100,000 persons in 23 counties [Weisenburger et al., 1987b]. Histologic analysis of NHL in Nebraska has revealed a twofold excess of the clinically aggressive, diffuse large cell subtype of NHL [Weisenburger et al., 1987b; Harrington et al., 1987]. An excess of this particular subtype of NHL in young farmers (OR 2.7) has previously been associated with residence in counties with high agricultural activity and insecticide use [Cantor, 1982].

To investigate further the possible association of NHL and certain agricultural practices, we began a large population-based, case-control study in the 66 counties of eastern Nebraska in late 1985. All white individuals with NHL, Hodgkin's disease, multiple myeloma, or chronic lymphocytic leukemia diagnosed between July 1, 1983, and June 30, 1986, aged 21 years or older, were identified through the University of Nebraska Lymphoma Study Group Registry and area hospitals and physicians. Controls were selected from residents of the 66 county area (three controls per case), matching on age (plus or minus 2 years), sex, race, and vital status. All cases underwent pathology review.

A preliminary report of some of our findings for men with NHL has recently been presented [Zahm et al., 1988]. Telephone interviews were conducted with 201 men having histologically confirmed NHL and 725 controls. There was no overall excess of NHL among men who had ever lived or worked on a farm. However, use of the herbicide 2,4-D was associated with a 50% increased risk of NHL (OR 1.5, 95% CI 0.9, 2.4). Personal exposure to 2,4-D more than 20 days per year increased the risk of NHL threefold (OR 3.3, 95% CI 0.5, 22.1). Our findings regarding the association of 2,4-D exposure with NHL are similar to those of the Kansas study [Hoar et al., 1986], although the risks are lower. An elevated risk for NHL was also associated with atrazine use (OR 1.4, 95% CI 0.8, 2.2) and increased with duration, with odds ratios of 0.9, 0.8, 2.0, and 2.0 for use 1–5, 6–15, 16–20, and 21+ years, respectively. Several classes of insecticides were also associated with increased risk: organophosphates (OR 1.9, 95% CI 1.1, 3.1), carbamates (OR 1.8, 95% CI 1.0, 3.2), and chlorinated hydrocarbons (OR 1.4, 95% CI 0.8, 2.3). Further analysis of these data as well as data on other agricultural and non-agricultural factors evaluated in the study are forthcoming.

DISCUSSION

As a result of intense agrichemical use and irrigation, extensive contamination of shallow groundwater by nitrate and atrazine has occurred in eastern Nebraska. A

variety of pesticides have also recently been detected in the Platte River of eastern Nebraska, a source of drinking water for several communities. In a preliminary ecologic study [Weisenburger et al., 1987b], we found a twofold increased incidence of NHL in counties with greater than 20% of the wells contaminated by nitrate (>10 ppm nitrate-nitrogen) and in counties with intense fertilizer use. These findings suggest that the increased incidence of NHL in some Nebraska counties may be related to the intense use of nitrogen fertilizers and resultant groundwater contamination. Alternatively, elevated nitrate levels in groundwater may just be a marker for pesticide contamination. Further information from the case-control study with regard to fertilizer use and nitrate intake in drinking water and the diet remains to be evaluated.

In the laboratory, we have synthesized N-nitrosoatrazine (NNAT) and found it to be readily formed from atrazine and nitrite at acid pH [Weisenburger et al., 1987a]. NNAT is a weak mutagen in the Ames test; however, it is a strong mutagen in the Chinese hamster V-79 assay, producing revertants 3.4 times the dimethylnitrosamine control [Weisenburger et al., 1988]. We have not found atrazine to be mutagenic in either system [Weisenburger et al., 1988], although it has been reported to induce breast tumors in laboratory animals (Ciba-Geigy, personal communication, 1986). Carcinogenesis tests of atrazine and NNAT have not shown an increased number of tumors in our laboratory, however [Weisenburger et al., 1990].

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