The Role of Agricultural Pesticide Use in the Development of Non-Hodgkin's Lymphoma in Women

SHELIA HOAR ZAHM
Occupational Studies Section
National Cancer Institute
Rockville, Maryland
DENNIS D. WEISENBURGER
Department of Pathology and Microbiology
University of Nebraska Medical Center
Omaha, Nebraska
ROBERT C. SAAL
JIMMIE B. VAUGHT
Westat, Inc.
Rockville, Maryland

PAULA A. BABBITT
Department of Pathology and Microbiology
University of Nebraska Medical Center
Omaha, Nebraska
AARON BLAIR
Occupational Studies Section
National Cancer Institute
Rockville, Maryland

ABSTRACT. Non-Hodgkin's lymphoma has been found to be associated with agricultural pesticide use in men, but little is known about the risk in women. In a recent population-based, case-control study conducted in eastern Nebraska, no increased risk of non-Hodgkin's lymphoma was found in women who had ever lived or worked on a farm (odds ratio [OR] = 1.0). Neither the use of insecticides (OR = 0.8) nor herbicides (OR = 0.7) on the farm was associated with non-Hodgkin's lymphoma; however, the number of women who mixed or applied pesticides was small, particularly in comparison to men on farms. Small nonsignificant associations were observed among the women who personally handled insecticides (OR = 1.3) or herbicides (OR = 1.2). Women who personally handled organophosphate insecticides had a significant 4.5-fold increased risk of non-Hodgkin's lymphoma. Use of chlorinated hydrocarbon insecticides was associated with an OR of 1.6; however, the use on dairy cattle was associated with a 3-fold increased risk. Pesticide-related risks were greater among women with a family history of cancer, particularly a history of lymphatic or hematopoietic cancer among first-degree relatives.

IN NUMEROUS STUDIES conducted throughout the world, risk of non-Hodgkin's lymphoma (NHL) has been found to be increased in agricultural populations.[1] Agricultural exposures associated with excess risk of NHL include the use of phenoxyacetic acid herbicides,[2-9] organophosphate insecticides,[4,10] triazine herbicides,[3,4] fungicides,[3] fuels,[9] and fertilizers.[11] The populations in these published studies have been limited to men. One geographic correlational study in Quebec reported a greater risk for cancers of the lymphatic tissues among rural women in areas with higher pesticide sales than areas with lower sales.[12] It is not known if women who live or work on farms experience excess risk of NHL. This paper presents data on agricultural exposures

among women from a population-based case-control study of NHL in eastern Nebraska. We have reported the results for men previously.[4]

Materials and methods

Detailed methods have been described elsewhere.[4,13] Briefly, cases of NHL, Hodgkin's disease, multiple myeloma, and chronic lymphocytic leukemia among white men and women, aged 21 y or older, residing in the 66 counties of eastern Nebraska and diagnosed between July 1, 1983, and June 30, 1986, were identified through the Nebraska Lymphoma Study Group and area hospitals. Among white women—the subject of this report—there were 206 histologically confirmed cases of NHL.

Controls were selected from residents of the same 66-county area by 3:1 frequency matching by race, sex, vital status, and age (5-y age groups) to the combined age distribution of the four cancer case series. Two-stage random digit dialing[14] was used to select 217 controls for the living cases who were 65 y of age or younger. With regard to living cases who were 65 y or older, 331 female controls were selected from the Health Care Financing Administration (Medicare) records. Female controls (n = 276) for deceased cases were selected from the Nebraska state mortality files, using the additional matching factor of year of death. Persons with an underlying cause of death of NHL, Hodgkin's disease, multiple myeloma, leukemia, malignancy of unknown site, aplastic anemia, suicide, homicide, or legal intervention were excluded as controls. A total of 824 female controls was selected.

Telephone interviews were conducted with 184 NHL cases and 707 controls or with their next-of-kin. The interview response rates were 89% for cases and 86% for controls. The overall control response rate was 84% (a weighted average accounting for the 91% response rate in the household census phase of the random-digit dialing procedure, the 94% response rate of the randomly selected eligible random-digit dialing controls, the 84% response rate of the Health Care Financing Administration controls, and the 82% response rate of the next-of-kin of deceased controls).

The interview included questions on herbicides and insecticides used; the application method used most often; use of protective equipment; duration of time wearing work clothes after handling pesticides; animals raised; and use of fungicides, rodenticides, fumigants, wood preservatives, and fertilizers. Information about each herbicide and insecticide used, i.e., use on crops or animals, years of use, and average annual number of days the pesticides were personally handled, was obtained.

Subjects also reported whether any "blood relatives were ever diagnosed as having leukemia, lymphoma, Hodgkin's disease, multiple myeloma, or any form of cancer"; also provided were the affected relative's relationship to the subject and the type of cancer.

The measure of association was the odds ratio (OR). All risk estimates were adjusted for the effects of age by stratification (21-59, 60-69, 70-79, and greater than 79 y). Maximum likelihood estimates of the overall risk and 95% confidence intervals (CI) were computed by Gart's method.[15] Significance of duration- and frequency-response relationships was assessed by Mantel's one-tailed linear trend test.[16]

Results

A total of 119 women diagnosed with NHL and 471 controls reported ever having lived or worked on a farm (OR = 1.0; CI = 0.7,1.4). Pesticides had been used on the farms of 59 cases and 262 controls, which yielded an OR of 0.8 (CI = 0.5,1.3). Two cases and 1 control had unknown farming status.

In Table 1 is presented the risk of NHL, by class of herbicides used. Use of any herbicide on the farm was associated with a deficit of NHL (OR = 0.7; CI = 0.4,1.2), whereas personal handling any herbicide was associated with a nonsignificant risk of 1.2 (CI = 0.3,4.2). No class of herbicides, whether used on the farm or personally handled, was associated with a significantly increased risk of NHL. Few women, however, reported personally handling herbicides.

Table 1.—Number of Non-Hodgkin's Lymphoma (NHL) Cases and Controls and Odds Ratios, according to Herbicide Use among Women in Eastern Nebraska

Herbicide class	Used on farms				Personally handled			
	NHL	Controls	OR	(CI)*	NHL	Controls	OR	(CI)
Any herbicide	27	149	0.7	(0.4,1.2)	4	13	1.2	(0.3, 4.2)
Phenoxys	14	63	0.9	(0.4,1.7)	2	9	0.9	(0.1, 4.5)
Triazines	12	38	1.2	(0.6,2.6)	1	2	2.2	(0.1, 31.5)
Amides	8	34	0.9	(0.4,2.2)	0	2	—	
Benzoics	4	12	1.2	(0.3,4.4)	0	1	—	
Carbamates	2	14	0.6	(0.1,2.8)	0	2	—	
Trifluralins	3	24	0.5	(0.1,1.7)	0	1	—	
Others	5	28	0.7	(0.2,2.0)	1	4	1.0	(0.04,10.2)
Unknown	10	87	0.4	(0.2,0.9)	3	5	2.5	(0.5, 12.8)

*OR (CI) = odds ratio (95% confidence interval), adjusted for age. The referent category is women who never lived or worked on a farm (63 NHL cases, 235 controls).

Table 2.—Number of Non-Hodgkin's Lymphoma (NHL) Cases and Controls and Odds Ratios, according to Insecticide Use among Women in Eastern Nebraska

Insecticide class	Used on farms				Personally handled			
	NHL	Controls	OR	(CI)*	NHL	Controls	OR	(CI)
Any insecticide	56	245	0.8	(0.5,1.3)	22	69	1.3	(0.7, 2.3)
Chlorinated hydrocarbons	20	46	1.6	(0.8,3.1)	5	12	1.7	(0.5, 5.8)
Carbamates	7	17	1.6	(0.6,4.4)	0	3	—	
Organophosphates	14	43	1.2	(0.6,2.5)	6	5	4.5	(1.1, 17.9)
Metals	3	8	1.6	(0.3,7.5)	0	1	—	
Others	4	17	1.0	(0.3,3.3)	1	4	1.1	(0.04,10.9)
Unknown	40	197	0.8	(0.5,1.2)	15	54	1.1	(0.5, 2.2)

*OR (CI) = odds ratio (95% confidence interval), adjusted for age. The referent category is women who never lived or worked on a farm (63 NHL cases, 235 controls).

The two most commonly reported herbicide classes were phenoxyacetic acids and triazines. Within the phenoxyacetic acid herbicide class, 13 NHL cases and 62 controls reported use of 2,4-dichlorophenoxyacetic acid (2,4-D) on the farm (OR = 0.8; CI = 0.4,1.6); 2 cases and 8 controls reported personal handling of 2,4-D (OR = 1.0; CI = 0.1,5.2). Use of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) was reported by 3 cases and 2 controls (OR = 1.7; CI = 0.3,7.8), and only 1 case and 1 control reported personal handling of 2,4,5-T (OR = 4.2; CI = 0.1,159.5). Use on the farm and personal handling of atrazine were associated with ORs of 1.4 (CI = 0.6,3.0; 11 cases, 31 controls) and 2.2 (CI = 0.1,31.5; 1 case, 2 controls), respectively. Four cases and 12 controls reported use of cyanazine (OR = 1.3; CI = 0.3,4.5). Too few subjects were exposed to these individual herbicides to allow for analysis by duration, frequency, or other characteristics of use.

The risk of NHL, according to class of insecticides, is presented in Table 2. Chlorinated hydrocarbon (OR = 1.6), carbamate (OR = 1.6), organophosphate (OR = 1.2), or metal (OR = 1.6) insecticide use on the farm was associated with nonsignificant increased risks of NHL. No individual insecticide was associated with a significant risk of NHL among women, but nonsignificant increases were seen for several insecticides. Odds ratios of 1.3 or greater, based on at least 3 exposed cases, were observed for aldrin (OR = 1.3; 3 cases, 9 controls); DDT (OR = 1.7; 16 cases, 36 controls); diazinon (OR = 1.9; 7 cases, 16 controls); fonofos (OR = 2.5; 7 cases, 11 controls); heptachlor (OR = 2.0; 4 cases, 8 controls); lindane (OR = 1.8; 5 cases, 11 controls); malathion (OR = 1.9; 9 cases, 18 controls); Paris Green (OR = 1.6; 3 cases, 8 controls); and sevin (OR = 2.6; 5 cases, 8 controls). Women who had personally handled organophosphate insecticides had a 4.5-fold (CI = 1.1,17.9) increased risk of NHL. Study subjects reported handling seven specific organophosphate insecticides: chlorpyrifos (1 case); diazinon (2 cases, 2 controls; OR = 4.1; CI = 0.4,43.2); dichlorvos (1 case); famphur (1 control); fonofos (1 case); malathion (3 cases, 3 controls; OR = 3.6; CI = 0.5,23.9); and terbufos (3 controls).

There was little variation in risk, by insecticide use on dairy cattle, other livestock, crops, or buildings and lots, although risk appeared greater (OR = 1.8) for personal handling of insecticides for farm buildings or lots (Table 3). Examination by insecticide class and type of use was hampered by the inability of most female subjects to identify specific insecticides. The risk of NHL was elevated among those who used chlorinated hydrocarbon insecticides on dairy cattle (OR = 3.0; CI = 0.9,9.3; 7 cases, 10 controls). Other nonsignificant associations of interest were for the use of chlorinated hydrocarbon insecticides on other livestock (OR = 1.9) and on farm buildings and lots (OR = 1.6), the use of carbamates on crops (OR = 1.9), the use of organophosphates on livestock other than dairy cattle (OR = 2.1) and on buildings and lots (OR = 4.1), and use of "other" insecticides on livestock other than dairy cattle (OR = 6.6).

Risk of NHL varied by pesticide application method and precautions taken to reduce exposures. A nonsignificant excess of NHL was observed among women who most often used handheld sprayers to apply crop insecticides (OR = 2.6; CI = 0.8,8.4; 6 cases, 9 controls) or who poured on animal insecticides (OR = 1.8; CI = 0.3,8.6; 3 cases, 6 controls). Other application methods showed no excess risk or had less than 3 exposed cases. Few women reported use of protective equipment when handling insecticides or herbicides (2 cases, 8 controls), but they appeared to have a lower risk of NHL (OR = 1.1) than nonusers (OR = 1.4; CI = 0.7,2.6; 21 cases, 62 controls). Women who reported that they changed to clean work clothes immediately after handling pesticides had a lower risk of NHL (OR = 1.1; CI = 0.3,3.3; 5 cases, 19 controls) than women who changed at the end of the day (OR = 1.4; CI = 0.7,2.9; 15 cases, 42 controls), although the confidence intervals overlap. Only 1 case and 4 controls (OR = 1.0) reported delaying the change to clean work clothes to the following day or later.

There was no association between NHL and the use of fungicides (OR = 0.6), rodenticides (OR = 0.9), fumigants (OR = 0.7), or nitrogen fertilizers on corn on the farm (OR = 0.8), or with handling chemically treated wood or fence posts (OR = 0.9).

Among farm and nonfarm women, neither use of

Table 3.—Number of Female Non-Hodgkin's Lymphoma (NHL) Cases and Controls and Odds Ratios in Eas Nebraska, according to Insecticides Used on Dairy Cattle, Other Livestock, Crops, and Buildings and Lots

Insecticide use	Dairy cattle				Other livestock			
	NHL	CO*	OR	(CI)†	NHL	CO	OR	(CI
Ever used on farm	31	114	1.1	(0.6, 1.8)	32	105	1.1	(0.7,
Personally handled	12	49	1.0	(0.4, 2.1)	9	29	1.2	(0.5,
Insecticide class used on farms:								
Chlorinated hydrocarbons	7	10	3.0	(0.9, 9.3)	9	18	1.9	(0.7,
Carbamates	1	0	—		2	1	8.6	(0.6,
Organophosphates	1	2	2.0	(0.1, 32.5)	5	9	2.1	(0.6,
Metals	0	0	—		0	1	—	
Others	1	1	4.6	(0.1, 183.7)	3	2	6.6	(0.8,
Unknown	24	104	0.9	(0.5, 1.6)	24	87	1.0	(0.6,

*CO = controls.
OR (CI) = odds ratio (95% confidence interval), adjusted for age. The referent category is women who never li worked on a farm (63 NHL cases, 235 controls).

herbicides (OR = 0.9; CI = 0.6,1.3) nor insecticides (OR = 1.2; CI = 0.8,1.8) around the home, family garden, or yard was significantly associated with NHL. Risk increased, however, with the number of days per year that women handled herbicides around the home, garden, or yard (1 d/y: OR = 0.6; 2 d/y: OR = 1.2; 6+ d/y: OR = 1.6), but the trend was not significant.

Family history of cancer was associated with an increased risk of NHL (OR = 1.8, CI = 1.2,2.6) and enhanced the effect of farm exposures (Table 4). Risks of NHL associated with ever living or working on a farm and with insecticide use increased progressively with a family history of cancer, a family history of lymphatic and hematopoietic cancer, and a history of those cancers among first-degree relatives. Four- to 5-fold risks were observed for women with first-degree relatives with lymphatic or hematopoietic cancers, who personally handled insecticides or who used insecticides on milk cows, other livestock, or farm buildings or lots.

Discussion

The incidence of NHL has increased more than 50% during the past 15 y in the United States,[17] and it is one of the most rapidly increasing malignancies in the United States and in other developed countries.[18] AIDS-related lymphoma and changes in diagnostic practices explain some, but not all, of the recent increase.[19] It has been suggested that pesticide use may also be responsible for some of the increase.[1,20] Agricultural use of herbicides and home and garden use of both insecticides and herbicides have increased dramatically preceding and during the time period in which the incidence of NHL has increased.[20] Given that the incidence of NHL has increased in both men and women, it is important to evaluate if NHL is associated with pesticide exposure in women.

It was difficult to assess the effects of "direct" exposure to pesticides among women in this study because few women reported personally handling pesticides. Among controls who had ever lived or worked on farms, the percentages of men[4] and women who reported insecticide (men: 60%; women: 52%) or herbicide (men: 38%; women: 32%) use on the farm were similar. Personal handling of insecticides (men: 45%; women: 15%) or herbicides (men: 29%; women: 3%), however, was much less frequent among the women. Although farm women live in an environment in which pesticides are used, it appears that only a small proportion are directly engaged in pesticide mixing and application. No significant excesses of NHLs were observed for any class of insecticide or herbicide used on the farm, although nonsignificant excesses were associated with the use of chlorinated hydrocarbon, carbamate, and metal insecticides. Risks tended to be greater among the few women who personally handled pesticides. Among women who personally handled organophosphate insecticides, a significant 4.5-fold increased risk of NHL was observed. This finding is consistent with reports for men in Nebraska[4] and Iowa and Minnesota.[10] Newcombe has proposed that organophosphates may play a role in the development of lymphoma through their inhibition of serine esterases, which are critical components in the cytolytic activities of T lymphocytes and natural killer cells.[21]

With respect to other pesticide classes, it is difficult to determine if the women had an excess risk of NHL associated with exposure, because the numbers of exposed women were too small to be very informative. For example, the herbicide 2,4-D, which has been associated with 2- to 8-fold increased risks of NHL among frequent male users,[3,4,9] was personally handled by only 2 female cases and 8 controls (OR = 1.0).

Women were much more likely to have personally handled insecticides used on animals than on crops. In this study, we observed a 3-fold increased risk of NHL associated with the use of chlorinated hydrocarbon in-

Crops				Farm buildings, lots			
NHL	CO	OR	(CI)	NHL	CO	OR	(CI)
26	122	0.8	(0.5,1.3)	15	52	1.1	(0.6, 2.3)
5	16	1.3	(0.4,4.1)	6	13	1.8	(0.6, 5.6)
7	23	1.2	(0.4,3.2)	7	19	1.6	(0.5, 4.3)
6	12	1.9	(0.6,5.8)	0	1	—	
9	35	1.0	(0.4,2.3)	4	4	4.1	(0.8, 21.6)
2	6	1.4	(0.2,8.6)	1	0	—	
0	3	—		1	12	0.3	(0.02, 2.5)
14	77	0.7	(0.3,1.3)	9	25	1.4	(0.6, 3.3)

secticides on dairy cattle and an almost 2-fold risk for use on other livestock. Organophosphate use on animals was also associated with a 2-fold increased risk of NHL. Associations between use of insecticides on animals and the risk of soft tissue sarcoma[22] and leukemia,[23] but not for NHL,[10] have been observed previously in studies of male farmers. There may be a greater potential for inhalation and dermal exposures during the application of insecticides on animals. Also, animals are typically sprayed more frequently than crops, and often by hand. For example, in the past, it was not unusual for dairy cattle to be sprayed twice daily by hand prior to milking.

Many women also reported exposure to insecticides used on farm buildings and lots, which probably included the family home. The increased risk of NHL associated with the use of organophosphate and chlorinated hydrocarbon insecticides on buildings and lots was greater than for use on crops. This risk difference may reflect the different levels and frequencies of exposure.

There are many activities through which farm women may have been exposed to pesticides that were not assessed in this study. The Nebraska study questionnaire did not include questions concerning laundering pesticide-contaminated clothing, location of the home in relation to field where pesticide spraying occurred, participation in purchasing and transporting pesticides, and other activities that might have resulted in "indirect" or secondary exposure to pesticides. It might also have been useful to inquire where pesticides were stored. One Canadian survey reported that 30% of farmers who stored pesticides in the winter kept them in the basement of their homes.[24] Risks associated with these various activities and modes of exposure may have been missed in this study and deserve evaluation in future investigations.

Risks associated with agricultural exposures were greater among women with a family history of cancer, particularly lymphatic or hematopoietic cancer among first-degree relatives. Familial cancer risk may reflect shared environmental exposures or be a crude indicator of greater genetic susceptibility to the carcinogenic effects of agricultural exposures. Alternatively, NHL cases with first-degree relatives with lymphatic and he-

Table 4.—Odds Ratio for Non-Hodgkin's Lymphoma, according to Pesticide Use and Family History of Cancer among Women in Eastern Nebraska

Pesticide use	No family history of cancer	Any family history of cancer	History of lymphatic or hematopoietic cancer	First-degree history of lymphatic or hematopoietic cancer
Never lived/worked on farm	1.0	1.2	1.3	2.0
Lived/worked on farm	0.7	1.4	1.7	2.5†
Herbicides: used on farm	0.6	0.8	0.5	0.6
Insecticides				
Used on farm	0.6	1.2	1.5	2.3
No personal handling	0.5	0.9	0.6	0.9
Personally handled	0.6	2.0	4.1	5.8†
Used on crops	0.8	0.8	0.9	1.5
Used on milk cows	0.6	1.7	2.8†	4.2†
Used on other livestock	0.9	1.5	2.8	5.3†
Used on farm buildings or lots	1.8	1.6	1.9	5.3

*Odds ratio, adjusted for age. The reference category is women who never lived or worked on a farm and who had no family history of cancer (27 NHL cases, 114 controls).
†$p < .05$.

matopoietic cancers may be more prone to case-response bias than other cases. There was no independent verification of the self-reported family cancer histories or agricultural exposure histories. Increased agricultural-related risks in subjects with family histories of cancer were also observed in case-control studies of lymphoma in Tasmania[25] and leukemia and NHL in Iowa and Minnesota.[26]

Overall, this study suggests that the risk of NHL from pesticide exposures among women who live or work on farms, if real, is smaller than for men. This may reflect lower levels of exposure, unstable risk estimates that result from the small number of exposed women, or failure to collect information on the activities most likely to result in exposure of women. When exposure was reported by women, such as exposure to organophosphates or chlorinated hydrocarbons used on animals or buildings and lots, excess risks of NHL were seen. Research on farm family members should utilize questionnaires that are carefully tailored to capture all possible modes of exposure and attempt to identify high risk subgroups, such as people with a family history of cancer.

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Requests for reprints should be sent to: Shelia Hoar Zahm, Sc.D., Occupational Studies Section, National Cancer Institute, Executive Plaza North, Room 418, Rockville, MD 20892.

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