Occupation and Risk of Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia

Tongzhang Zheng, ScD
Aaron Blair, PhD
Yawei Zhang, MD
Dennis D. Weisenburger, MD
Shelia H. Zahm, ScD

To investigate the association between occupation and the risk of non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia (CLL), and to test whether the associations may vary by histological type of NHL, we analyzed data from two population-based, case-control studies of NHL performed in Kansas and Nebraska. A total of 555 incident NHL cases, 56 CLL cases, and 2380 population-based controls were included in the analysis. Information on occupation and other confounding factors was collected through telephone interviews. Study pathologists reviewed slides of tumor tissues in all cases. In men, we found an increased risk of NHL and CLL for those working in agricultural, forestry, and logging industries (odds ratio [OR], 1.6; 95% confidence interval [CI], 1.2 to 2.1). The OR was 1.9 (95% CI, 1.4 to 2.6) for those producing crops. An increased risk was also observed for industries involving metalworking machinery and equipment (OR, 8.4; 95% CI, 1.4 to 50.6), motor vehicles and motor vehicle equipment (OR, 4.2; 95% CI, 1.3 to 13.9), and telephone communications (OR, 3.1; 95% CI, 1.2 to 8.0), and for teachers (OR, 2.5; 95% CI, 1.0 to 6.5), farmers (OR, 2.0; 95% CI, 1.5 to 2.8), and welders and solderers (OR, 2.9; 95% CI, 1.2 to 6.9). The risks for these associations increased by duration of employment and seem to vary by histological type. Work in the printing and publishing industry was also associated with an increased risk of NHL among women. These data suggest that the workers employed in these industries or occupations experienced an increased risk of NHL and CLL, and the risks associated with these industries or occupations may vary by histological type of NHL. (J Occup Environ Med. *2002;44:469–474*)

The incidence of non-Hodgkin's lymphoma (NHL) has been increasing in many parts of the world, particularly in developed countries.[1] The risk factors responsible for the increasing incidence are largely unknown. Radiation exposure and lifestyle factors such as smoking, diet, and physical activity are not considered to be strongly associated with a risk of NHL.[2–5] Genetic and acquired immunodeficiencies (including AIDS), although related to NHL, do not explain the increase, especially the more recent increase among older Americans.[6]

The marked international variations in incidence and mortality, and the continuing increase over time, suggest that environmental and occupational exposures may be responsible, at least in part, for the observed increase in NHL. Indeed, epidemiological studies have linked several industries and occupations to the risk of NHL, including employment in agriculture,[7–10] metal production industries,[11] and the food industry.[11,12] An increased risk of NHL has also been observed among pesticide applicators,[13] painters and printers,[11,14] funeral directors and embalmers,[11,15] plumbers,[14] dry cleaners,[11] engineers, mechanics, leather workers, sales and clerical workers, and construction workers.[11,12]

Many of the reported associations between NHL and occupation or industry have not been studied extensively, and few have evaluated the risks by histological type of NHL. Recent epidemiological studies,

From the Division of Environmental Health Science, Yale University School of Public Health (Dr Zheng, Dr Zhang); the Occupational Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute (Dr Blair, Dr Zahm); and the Department of Pathology and Microbiology, University of Nebraska Medical Center (Dr Weisenburger).

Address correspondence to: Dr Tongzhang Zheng, 129 Church Street, Suite 700, New Haven, CT 06510; tongzhang.zheng@yale.edu.

however, suggest that risk of NHL associated with occupation and industry exposures may vary by histological type.[11,16] To further investigate the role of occupational and industrial exposures and the development of NHL, and to further explore associations by histological type, we combined and analyzed data from two population-based, case-control studies of NHL, with similar study designs conducted in Kansas and Nebraska.

Patients and Methods

The study populations and methods for the two population-based, case-control studies have been reported previously.[17,18] Briefly, in the Kansas study, NHL patients aged 21 years and over were identified from the statewide cancer registry in 1979 to 1981. A random sample of 170 men was drawn from the 297 NHL cases diagnosed in Kansas during the eligible time period. The Nebraska study included white men and women, aged 21 years or older, residing in the 66 counties of eastern Nebraska and diagnosed with NHL between July 1, 1983, and June 30, 1986. A total of 385 histologically confirmed NHL cases (201 men, 184 women) were identified through the Nebraska Lymphoma Study Group and area hospitals. Because of the substantial biological similarity between small lymphocytic lymphoma (SLL) and chronic lymphocytic leukemia (CLL),[19] we included the 56 CLL cases (37 men, 19 women) recruited from the Nebraska study in this analysis. Study pathologists reviewed slides of tumor tissues in all cases and classified the NHL cases according to the Working Formulation.[20] Cases were further grouped into four histological types (follicular, diffuse, SLL/CLL, and all other types).

A total of 2380 population-based controls (1673 men, 707 women) were recruited from the same geographical areas as the cases. The controls were frequency matched to the cases by sex, age (±5 years), race, vital status, and state of residence using approximately a 4:1 matching ratio. For living patients aged <65 years, controls were selected by the two-stage random digit dialing methods as described by Waksberg.[21] For living patients aged 65 years and over, controls were selected from the records of the Health Care Financing Administration. For deceased persons, controls were selected from the mortality files in each state with additional matching for year of death.

Telephone interviews were conducted with patients and controls, or their next-of-kin. The participation rate among histologically confirmed NHL cases or proxies was 91% in Nebraska and 96% in Kansas. For CLL cases, the response rate was 81%. For controls, the overall response rate, which took into account the initial response to the random digit dialing component, was 85% in Nebraska and 90% in Kansas. Respondents were asked if the subjects ever worked or lived on a farm and about other part-time or full-time jobs they might have held. They were also asked to report the usual occupation they held during most of their adult life, year begun, year ended, activities or duties, and the products that were produced by the industry. Job titles and industries were coded according to the Standard Occupational Classification (SOC) Manual,[22] and the Standard Industry Classification (SIC) scheme.[23] Information on demographic factors, residence, smoking, past medical history, and first-degree family history of lymphatic or hemopoietic tumors was also collected through the telephone interviews.

Unconditional logistic regression models were used to estimate the association between occupational variables and the risk of NHL and CLL. Separate analyses were performed for each major histological type of NHL (follicular, diffuse, small lymphocytic, and other) and CLL by two-digit or three-digit SIC and SOC codes for those occupations and industries with five or more exposed cases, or for those showing a significant excess for all NHL combined. Cases of NHL and CLL were first analyzed together and then separated by histological type, as done by Amadori et al.[24] Duration of employment was used to assess exposure-response relationship. The referent category for each analysis was subjects not employed in the particular occupation or industry under evaluation. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using SAS™ software (SAS Institute, Cary, NC).[25] ORs were adjusted for age at diagnosis (<45, 45 to 64, ≥65 years), type of respondent (proxy or subject), state of residence, and first-degree family history of lymphatic or hemopoietic tumor (yes/no). Adjustment of several other potential confounders, including hair dye use, smoking, and education, did not materially change the risk estimates, so these variables were not included in the final model.

Results

Table 1 presents industries or occupations by two-digit or three-digit SIC and SOC codes with statistically significant ORs for NHL and CLL for men. An increased risk was observed among those working in agricultural crop production and among farmers. An increased risk was also observed for industries involving metalworking machinery and equipment, motor vehicles and motor vehicle equipment, communication, and business services. Teachers (except college and university level) and welders and solderers also experienced an increased risk of NHL/CLL.

Several industries and occupations had three or more exposed subjects and showed an increased risk, although insignificant (data not shown). These associations included industries producing meat products (OR, 1.8; 95% CI, 0.8 to 4.2), grain mill products (OR, 3.8; 95% CI, 0.8 to 17.7), publishing and painting (OR, 1.6; 95% CI, 0.4 to 4.9), petro-

TABLE 1
Statistically Significant or Marginally Significant Associations Between NHL and CLL and Employment by Industry or Occupation Among Men in Kansas and Nebraska*

Industry/Occupation	Cases/Controls	OR†	95% CI
Industry (SIC code)			
Agricultural production, crops (01)	133/277	1.9	1.4–2.6
Metalworking machinery and equipment (354)	4/2	8.4	1.4–50.6
Motor vehicles and motor vehicle equipment (371)	5/7	4.2	1.3–13.9
Communication (48)	8/16	2.3	1.0–5.7
Telephone communication (wire or radio) (481)	8/11	3.1	1.2–8.0
Business services (73)	9/9	4.8	1.8–12.5
Miscellaneous business services (739)	6/4	7.8	2.0–29.6
Occupation (SOC code)			
Teachers, except college and university (23)	7/15	2.5	1.0–6.5
Farm operators and managers (55)	166/425	1.6	1.2–2.1
Farmers (551)	126/247	2.0	1.5–2.8
Welders and solderers (771)	9/16	2.9	1.2–6.9

* NHL, non-Hodgkin's lymphoma; CLL, chronic lymphocytic leukemia; OR, odds ratio; CI, confidence interval; SIC, Standard Industry Classification; SOC, Standard Occupational Classification.

† Adjusted for age, state of residence, type of respondent, pesticides, and first-degree relative with a lymphatic or hemopoietic cancer.

leum refining (OR, 2.2; 95% CI, 0.8 to 6.4), transportation services (OR, 6.1; 95% CI, 0.9 to 40.0), gas production and distribution (OR, 1.5; 95% CI, 0.5 to 4.7), and auto and home supply stores (OR, 1.5; 95% CI, 0.4 to 5.8).

Analyses by duration of employment (data not shown) suggested an increased risk for those who had worked for 10 or more years as farmers (OR, 2.1; 95% CI, 1.5 to 2.9), electrical and electronic equipment repairers (OR, 2.8; 95% CI, 0.9 to 8.3), fabricators and assemblers (OR, 1.9; 95% CI, 0.9 to 4.1), welders and solderers (OR, 3.5; 95% CI, 1.4 to 8.6), and elementary and secondary schoolteachers (OR, 2.7; 95% CI, 1.1 to 6.9).

Table 2 presents the significant association among men for histological types of NHL by industry and occupation based on two-digit or three-digit SIC and SOC codes. Increased risks of SLL/CLL were observed for workers in agricultural production and for farmers. Employment in the meat product industry was associated with an increased risk of follicular NHL. Employment in the telephone communication industry was associated with all four types of NHL, although stratification by histological type made the associations less stable. Employment in the business services industry was associated with all NHL histological types except for SLL/CLL. Welders and solderers had an increased risk of diffuse NHLs and other types of NHL. Membership organization occupations and supervisory occupations in production industries were associated with an increased risk of follicular NHL. Elementary and secondary schoolteachers also had an increased risk of other types of NHL.

Among women, significant associations were observed only for those working in the printing and publishing industry and for insurance carriers (data not shown). No significant association was observed for any occupation, based on two- or three-digit SOC codes, or by duration of exposures (data not shown).

Risks of follicular NHL among women was significantly associated with working as bookkeepers and in health service occupations (Table 3). Diffuse NHL was associated with working in eating and drinking establishments and for teachers other than in a college and university. Female agricultural crop production workers and farmers had an elevated risk of SLL/CLL. Elementary and secondary teachers were at increased risk for diffuse and other types of NHL.

Discussion

In this analysis, we found a significantly increased risk of NHL and CLL among farmers and those employed in agricultural industries. The association with NHL seems largely attributable to an increase in small lymphocytic NHL and CLL. An association between farming and NHL risk has been noted in several, but not all, previous studies. In a review by Blair and Zahm,[10] 11 of 21 follow-up studies reported excesses of NHL among farmers, with three being statistically significant. Of the 19 case-control and cross-sectional studies, 12 reported excess NHL among farmers, with 8 reporting statistically significant associations. Two more recent meta-analyses of NHL and farming[7,9] suggest that farmers residing in the United States have a slightly elevated risk of contracting NHL. Exposure to pesticides, particularly herbicides, is considered to be responsible for the increased risk of NHL observed among farmers.[13,26–28] However, farmers could also have been exposed to fertilizers, fuels and engine exhausts, and organic and inorganic dusts.[29] The exposures of individual farmers, however, can vary greatly, depending on the types of crops grown, operation size, and other factors. Combining all farmers into one group could dilute risk estimates for subgroups of farmers at higher risk.

A significantly increased risk of NHL was also observed among metalworking machinery and equipment workers, fabricators, assemblers, welders, and solderers. Fabricators, assemblers, and, in particular, welders and solderers had an increased risk of diffuse NHL and "other" types of NHL. An increased risk of NHL has been previously reported for those exposed to metal in various occupations in Italy[30] and in a pop-

TABLE 2
Risk of NHL and CLL by Histologic Type for Selected Industries and Occupations Among Men in Kansas and Nebraska*

	Follicular			Diffuse			SLL/CLL			Other		
Industry/Occupation	Ca/Co	OR†	95% CI	Ca/Co	OR†	95% CI	Ca/Co	OR†	95% CI	Ca/Co	OR†	95% CI
Industry (SIC code)												
Agricultural production, crops (1)	25/277	1.4	0.7–2.5	45/277	1.3	0.8–2.1	44/277	*8.9*	*4.5–17.3*	18/277	1.2	0.6–2.3
Meat products (201)	4/19	*4.6*	*1.5–15*	1/19	0.5	0.1–3.9	1/19	1.4	0.2–11.0	2/19	2.1	0.5–9.5
Telephone communication (481)	2/11	2.8	0.6–14	3/11	2.9	0.8–11	2/11	*5.2*	*1.0–25.9*	1/11	2.1	0.3–17
Business services (73)	3/9	*4.8*	*1.2–19*	4/9	*5.6*	*1.7–19*	0/9			2/9	*6.2*	*1.3–30*
Elementary and secondary schools (821)	2/19	1.8	0.4–8.3	2/19	1.2	0.3–5.3	1/19	2.2	0.3–17.5	3/19	*4.1*	*1.1–15*
Membership organizations (86)	5/13	*5.5*	*1.8–17*	0/13			1/13	1.6	0.2–13.8	1/13	2.2	0.3–18
Occupation (SOC code)												
Insurance, securities, real estate (42)	3/26	*3.5*	*1.0–12*	1/26	0.5	0.1–3.5	1/26	2.3	0.3–18.4	3/26	2.7	0.8–9.3
Farm operators and managers (55)	30/425	1.2	0.7–2.1	67/425	*1.5*	*1.0–2.2*	45/425	*5.7*	*3.1–10.7*	23/425	0.8	0.5–1.5
Farmers (551)	25/247	1.5	0.8–2.9	40/247	1.2	0.7–2.0	43/247	*11.6*	*5.3–25.8*	17/247	1.2	0.6–2.6
Supervisors, production occupations (71)	5/38	*2.6*	*1.0–7.0*	3/38	0.8	0.2–2.7	0/38			1/38	0.6	0.1–4.3
Supervisors, production occupation (711)	5/17	*5.0*	*1.7–15*	2/17	1.1	0.2–4.8	0/17			1/17	1.3	0.2–10
Welders and solderers (771)	0/16			5/16	*3.4*	*1.2–9.8*	1/16	3.0	0.4–25.2	3/16	*3.6*	*1.0–13*

* Data in italics indicate significantly significant or marginally significant associations. NHL, non-Hodgkin's lymphoma; CLL, chronic lymphocytic leukemia; Ca/Co, case/control; OR, odds ratio; CI, confidence interval; SIC, Standard Industry Classification; SOC, Standard Occupational Classification.

† Adjusted for age, state of residence, type of respondent, pesticides, and first-degree relative with a lymphatic or hemopoietic cancer.

TABLE 3
Risk of NHL and CLL by Histologic Type for Selected Industries and Occupations Among Women in Nebraska*

	Follicular			Diffuse			SLL/CLL			Other		
Industry/Occupation	Ca/Co	OR†	95% CI	Ca/Co	OR†	95% CI	Ca/Co	OR†	95% CI	Ca/Co	OR†	95% CI
Industry (SIC code)												
Agricultural production, crops (1)	22/283	1.1	0.6–2.0	29/283	1.1	0.7–1.9	17/283	*2.2*	*1.0–4.9*	18/283	0.8	0.4–1.4
Telephone communication (481)	2/15	1.8	0.4–8.6	2/15	1.4	0.3–6.4	0/15			1/15	0.9	0.1–7.3
Eating and drinking places (581)	1/22	0.7	0.1–5.6	6/22	*2.9*	*1.1–7.6*	0/22			0/22		
Hospitals (806)	5/30	2.1	0.8–5.9	0/30			0/30			0/30		
Educational services (82)	2/51	0.4	0.1–1.9	8/51	1.8	0.8–4.0	1/51	0.5	0.1–3.6	9/51	*2.8*	*1.3–6.0*
Elementary and secondary schools (821)	1/38	0.3	0.0–2.0	7/38	2.0	0.8–4.6	1/38	0.6	0.1–4.5	7/38	*2.8*	*1.2–6.7*
Occupation (SOC code)												
Teachers, except college and university (23)	0/31			7/31	*2.4*	*1.0–5.8*	1/31	0.7	0.1–5.4	6/31	*2.9*	*1.1–7.3*
Secondary schoolteachers (233)	0/6			2/6	3.2	0.6–16.4	1/6	4.0	0.5–35.7	2/6	4.3	0.8–22.5
Sales occupations, commodities (41)	3/26	1.5	0.4–5.3	2/26	0.8	0.2–3.6	3/26	3.3	0.9–11.9	2/26	1.0	0.2–4.5
Other sales occupations (416)	2/21	1.2	0.3–5.4	1/21	0.5	0.1–3.6	2/21	2.4	0.5–11.0	1/21	0.6	0.1–4.7
Bookkeepers, billings, etc (471)	5/16	*4.7*	*1.6–14.3*	2/16	1.3	0.3–5.7	0/16			2/16	1.8	0.4–8.0
Service occupation, except private (52)	8/63	1.8	0.8–4.1	8/63	1.4	0.6–3.1	1/63	0.4	0.1–3.1	6/63	1.3	0.5–3.1
Food and beverage preparation (521)	2/35	0.8	0.2–3.6	7/35	2.2	0.9–5.2	0/35			2/35	0.7	0.2–3.1
Health service occupations (523)	4/8	*6.6*	*1.8–24.3*	0/8			1/8	3.8	0.4–32.2	0/8		
Farmers (551)	22/282	1.1	0.6–2.0	29/282	1.1	0.7–1.9	17/282	*2.3*	*1.0–5.0*	18/282	0.8	0.4–1.5

* Data in italics indicate significantly significant or marginally significant association. NHL, non-Hodgkin's lymphoma; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; Ca/Co, case/control; OR, odds ratio; CI, confidence interval; SIC, Standard Industry Classification; SOC, Standard Occupational Classification.

† Adjusted for age, type of respondent, pesticides, and first-degree relative with a lymphatic or hemopoietic tumor.

ulation-based case-control study in Iowa and Minnesota.[11] Contact with metals and various organic solvents may be associated with the development of NHL in these workers.[11]

It is interesting to note that several occupations with potential for exposure to solvents showed an increased risk of NHL, although insignificant, including publishing, painting, petroleum and coal production, petroleum refining, transportation services, gas production and distribution, business services (including window cleaning, disinfecting, and exterminating services), and auto and home supply stores. Workers employed in cleaning and building services (including janitors, cleaners, maids, and pest controllers) also experienced an increased risk of NHL. Earlier epidemiological studies have reported an increased risk of NHL for laundry and garment cleaning workers,[11] dry

cleaners,[31] and aircraft maintenance workers.[32] Workers in these industries or occupations may come into close contact with various solvents. There is sufficient evidence from animal experiments to associate carcinogenicity with various aliphatic chlorinated and aromatic organic solvents, such as benzene, trichloroethylene, tetrachloroethylene, carbon tetrachloride, methylene chloride, and chloroform.[33,34] As recently reviewed by Lynge et al,[35] epidemiological studies have also linked these compounds to the risk of NHL or lymphohematopoietic malignancies.

Our study also found an increased risk for male electrical and electronic equipment repairers who had worked at their job for 10 or more years (OR, 2.8; 95% CI, 0.9 to 8.3) and also among women (OR, 5.6; 95% CI, 0.9 to 34.7). An increased risk of NHL for all major histological types was also observed for telephone communication industry workers, with a significant association for small lymphocytic NHL and CLL. A potential association between exposure to electromagnetic fields and NHL risk has been proposed by several investigators, although the hypothesis continues to be widely debated, as summarized by Villeneuve et al[36] A recent study in Ontario reported an increased risk of NHL among electric utility workers, which the authors suggested may be attributable to electric fields.[36] Burch et al[37] found that magnetic fields induce melatonin suppression in humans. Melatonin has oncostatic, immunological, and antioxidant properties, thus its suppression by electromagnetic fields may represent a biologically plausible mechanism for increased cancer risks.[37]

Several novel associations were also noticed in this analysis. Workers in industries producing meat products and grain mill products had an increased risk of NHL, notably follicular NHL. A recent study by Amadori et al,[24] involving 164 NHL cases and 23 chronic lymphocytic leukemia cases, reported an increased risk of these diseases among those working in agriculture industries associated with animal breeding. The authors suggested that the observed increase in risk could be related to exposure to animal-transmitted diseases, specific chemicals used in animal breeding, or chemicals used in agriculture.

In conclusion, in this combined analysis of case-control data from two studies, we found an increased risk of NHL and CLL among agricultural workers, metalworking machinery workers, fabricators, assemblers, welders, solderers, electrical and electronic equipment repairers, and various other workers with potential solvent exposures. These observations are consistent with the results from earlier epidemiological studies. Our results also suggest that the risks associated with these industries or occupations may vary by histological type of NHL. Although the relatively small numbers of subjects grouped by the histological type limit the interpretation of the results in this study, further investigation of these associations is warranted.

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