Occupational Risk Factors for Subgroups of Non-Hodgkin's Lymphoma

Lilith Tatham,[1] Paige *Tolbert*,[2] and Carl *Kjeldsberg*[3]

The non-Hodgkin's lymphomas (NHL) are a diverse group of neoplasms of the lymphatic system whose incidence has been increasing in recent years. The Centers for Disease Control Selected Cancers Study, a population-based case-control study of several cancers, included a large number of cases of NHL and a pathology review, providing a rare opportunity to study risk factors for groups of NHL subtypes. We examined the relation between occupational exposures and three subgroups of NHL: small cell diffuse lymphomas (N = 185), follicular lymphomas (N = 268), and large cell diffuse lymphomas (N = 526). There were 1,659 controls available for comparison. After controlling for demographic variable, and previously identified risk factors for NHL, we observed two interesting associations, one between solvent exposure and small cell diffuse lymphomas [odds ratio (OR) = 1.60; 95% confidence interval (CI) = 1.10–2.20], and the other between meat packaging/processing and follicular lymphomas (OR = 1.60; 95% CI = 0.99–2.60). The results of this exploratory analysis are primarily negative. Our lack of positive findings may indicate that the subgroups of NHL used may not be etiologically distinct and that further work needs to be done to develop an NHL classification system that is etiologically informative and useful for epidemiologic studies. (Epidemiology 1997;8: 551–558)

Keywords: non-Hodgkin's lymphoma, case-control study, occupational risk factors, solvents, meat processing.

The non-Hodgkin's lymphomas (NHL) are a diverse group of malignant neoplasms of the lymphatic system. Since the early 1970s, the incidence rate of NHL in the United States has been increasing about 3–4% a year, and the mortality rate of NHL has been increasing about 2% a year.[1] Changes in diagnostic criteria and known risk factors such as familial factors, human immunodeficiency virus, immunosuppressive conditions or drugs, and certain occupations only partially explain these rate increases.[2,3]

Etiologic studies aimed at explaining the increasing incidence typically have studied all NHL combined, because the subtypes of NHL are thought to be related and to arise from a common hematopoietic stem cell.[1] The various NHL subtypes, as defined by the Working Formulation classification system,[1] have also been studied separately owing to likely etiologic heterogeneity among the different types of NHL.[4–7] Studying groups of the Working Formulation subtypes may also be useful,[1] because it results in larger numbers of cases than subtype-specific analysis, and possibly more etiologically homogeneous groups than studying all NHL together. The following groups of NHL Working Formulation subtypes have been proposed[4–7]: small cell diffuse lymphomas (small lymphocytic and diffuse small cleaved cell subtypes), follicular **lymphomas** (follicular small cleaved, follicular mixed small and large cell, and follicular large cell subtypes), **large** cell diffuse lymphomas (diffuse mixed small and large cell, large cell diffuse, and large cell immunohlasric subtypes), follicular center cell lymphomas (follicular lymphomas, diffuse mixed small and large cell, large cell diffuse, and small noncleaved

From the [1]Department of Epidemiology and Surveillance Research, American Cancer Society, Atlanta, GA; [2]Departments of Environmental and Occupational Health and Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA; and [3]Department of Pathology, School of Medicine, University of Utah, Salt Lake City, UT.

Address correspondence to: Lilith Tatham, Epidemiology and Surveillance Research, American Cancer Society, 1599 Clifton Road, NE, Atlanta, GA 30329-4251.

Address reprint requests to: Paige Tolbert, Departments of Environmental and Occupational Health and Epidemiology, The Rollins School of Public Health, Emory University, 1518 Clifton Road, NE, Atlanta, GA 30322.

The Selected Cancers Study Cooperative Research Group consists of the Centers for Disease Control and Prevention, Atlanta, GA, eight tumor registries/epidemiologic research groups, and four pathology review panels. Members and major contributors are as follows. *Centers for Disease Control and Prevention*: Principal Investigator: Edward A. Brann. Project Manager: Anthony S. Fowler. Epidemiologists: David S. Freedman, Judith R. Qualters, W. Dana Flanders, Coleen A. Boyle, and Marion R. Nadel. Statisticians: Marcie-Jo Kresnow and Andrew L. Baughman. *Tumor Registries/Epidemiologic Research Groups*: Emory University, Atlanta, GA: Principal Investigator: Raymond S. Greenberg. Co-Principal Investigator: Ralph J. Coates. Yale University, New Haven, CT: Principal Investigator: W. Douglas Thompson. University of Iowa, Iowa City, IA: Principal Investigator: Leon F. Burmeister. University of Kansas, Kansas City, KS: Principal Investigator: Frederick F. Holmes. University of Miami, Miami, FL: Principal Investigator: Marianna K. Baum. California Public Health Foundation, San Francisco, CA: Principal Investigator: Donald F. Austin. Co-Principal Investigator: Peggy Boyd. Michigan Cancer Foundation, Detroit, MI: Principal Investigator: William A. Satariano. Fred Hutchinson Cancer Research Center, Seattle, WA: Principal Investigator: Thomas L. Vaughn. *Lymphoma Pathology Review Panel*: Principal Investigator: Carl R. Kjeldsberg, University of Utah, Salt Lake City, UT. Members: Thomas V. Colby and Ronald L. Weiss.

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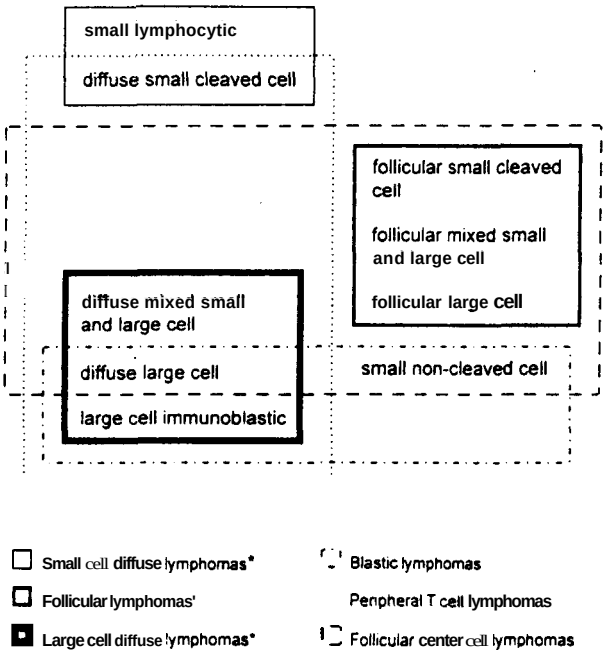

FIGURE 1. Subgroups of non-Hodgkin's lymphoma. * = subgroups used in analyses, selected on the basis of similarity of cell type, likely cell of origin, and behavior as well as their exclusivity.

subtypes), blastic lymphomas (large cell diffuse, large cell immunoblastic, and small noncleaved subtypes), and peripheral T-cell lymphomas (diffuse mixed small and large cell, large cell diffuse, large cell immunoblastic, and diffuse small cleaved cell subtypes) (Figure 1).

Many risk factors for all NHL combined have been identified previously. and the evidence has been reviewed.[9–12] Risks inherent to the individual include a family history of NHL or other cancer and inherited immunodeficiencies. Identified exogenous risk factors include radiation at very high doses, viral infections and related diseases such as AIDS, and phenytoin usage. Occupations that have been associated with excess risk include farmers. pesticide applicators, grain millers, wood and forestry workers, chemists, cosmetologists, machinists, printers. and workers in the petroleum. rubber, plastics and synthetics industries. Cigarette smoking has been found *to* he a risk factor for NHL in most,[13–16] but not all,[17] studies of this association.

In this study, we used the Centers for Disease Control Selected Cancers Study database to identify occupational risk factors for three subgroups of NHL: small cell diffuse lymphomas, follicular lymphomas. and large cell diffuse lymphomas, as defined above.

Methods

Researchers at the Centers for Disease Control initiated the Selected Cancers Study, a population-based case-control study, in 1983 to investigate certain forms of cancer that had been linked to phenoxy herbicide or chlorophenol exposure, in response to concerns about possible health effects of exposure to Agent Orange during the Vietnam War. This study has been described in detail elsewhere.[18,19]

In brief, investigators drew cases from eight population-based cancer registries in the following locations: Atlanta, Connecticut, Iowa, Kansas, Miami, San Francisco, Detroit, and Seattle. **All** males born between 1929 and 1953, and hence of military service age during the Vietnam War, and diagnosed with lymphoma, sarcoma, or nasal. nasopharyngeal. or liver cancer between December 1, 1984, and November 317, 1988, were eligible for inclusion in the Selected Cancers Study. If a case subject died betore participating, next-of-kin or another proxy respondent was identified. Investigators frequency matched controls **on** registry and date of birth in 5-year categories to the expected distribution of all lymphoma cases, identifying controls through random digit dialing. Deceased cases and controls were not used in the present analysis.

Investigators conducted telephone interviews for all cases and controls. The questionnaire covered background characteristics, medical history, **work** history (including detailed questions about specific jobs and exposures to specific dusts and chemicals such as pesticides, herbicides, solvents, and wood preservatives), military history, and life-style.

In an attempt to confirm the pathologic diagnosis of all cases, an expert pathology panel reviewed slides of tissue or tissue blocks. The three pathologists on the lymphoma panel independently reviewed the material and made a diagnosis, and then the group reached a consensus diagnosis.

Investigators identified 2,354 men as lymphoma cases (NHL, Hodgkin's disease. or lymphoma not otherwise specified) and 2,299 men as potential controls and interviewed 2,073 lymphoma cases and 1,910 potential controls. Microscope slides or tissue blocks were obtained for 2,004 of rhe lymphoma cases interviewed, and a lymphoma diagnosis was confirmed for 1,511 cases as NHL. NHL cases were classified according to the Working Formulation. To achieve comparability with the original analyses, we excluded control and case subjects if at least one of the following applied: unknown military service in Vietnam (5 NHL cases. 7 controls); in Vietnam or off rhe coast of Vietnam but not stationed there (13 NHL cases, 27 controls); presence of AIDS or an AIDS-related illness (289 NHL cases, 1 control); or not a U.S. resident betore 1969 (47 NHL cases, 99 controls). We excluded those with missing information regarding education (1 NHL case, 1 control). We also excluded men with the following medical conditions or medical historiss: systemic lupus erythematosus, non-AIDS-related immunodeficiency, rheumatoid arthritis, immunosuppressive drug use, chemotherapy, or medical radiation (108 SHL cases, 116 controls). The final number of cases available for analysis was 1,848, and the final number of controls available was 1.659.

Creation of NHL Subgroups

We examined small cell diffuse lymphomas, follicular lymphomas, and large cell diffuse lymphomas in this

study.[4,8] We chose these three subgroups for several reasons. First, they are mutually exclusive (Figure 1). Second, small cell diffuse lymphomas are of A-cell origin solely,[20–22] as are follicular lymphomas,[20,22,23] and both groups involve subtypes that behave similarly. Large cell diffuse lymphomas, although a mixture of B- (80%) and T-cell lymphomas, are related by their diffuse, large cell nature, aggressive behavior, and their possible origin in activated peripheral lymphoid cells.[22,24] The remaining subgroups—follicular center cell lymphomas, blastic lymphomas, and peripheral T-cell lymphomas—are more heterogeneous groupings phenotypically and behaviorally, and they overlap wich the other selected subgroups and each other.[4,8]

OCCUPATIONAL EXPOSURE ASSESSMENT

The job history portion of the interview first asked participants the following questions regarding all full- or part-time jobs held for at least 1 year: job title, main duties, type of business or industry, year started the job, and year ended rhc job. Participants were then asked about specific jobs (such as meat packaging/processing), and if this job had not been previously mentioned, the questions listed above were asked. The third part of the job history included questions about jobs that may involve the use of herbicides or pesticides and the names of specific pesticides and herbicides, but questions concerning year of contact referred to all of the pesticides or herbicides together rather than specific pesticides or herbicides. The final part of the job history involved questions about specific materials participants may have worked with or around on a job (such as formaldehyde). If the associated job had not been previously mentioned, the questions listed above were asked.

We created a variable describing time since first exposure fur all jobs or exposures for which year srarted the job had been asked. This variable could not be created for specific pesticides or herbicides. We divided time since first exposure into exposure within 10 years and more than 10 years before case diagnosis or control selection. We calculated total years exposed if year started and year ended the job were known, and we used the median of the non-zero values of total years exposed for the case subjects as a cutpoint in creating Juration of exposure variables.

ANALYSIS

We created NHL subgroups by combining various Working Formulation subtypes. The small cell diffuse lymphoma subgroup (N = 185) included small lymphocytic (N = 124) and diffuse small cleaved (N = 61) lymphomas. The follicular lymphoma subgroup (N = 268) encompassed the follicular small cleaved cell (N = 179), follicular mixed small and large cell (N = 56), and follicular large cell (N = 33) lymphomas. The large cell diffuse lymphoma subgroup (N = 526) included immunoblastic (N = 132), diffuse small and large cell (N = 95), diffuse large cleaved (N = 10) and noncleaved (N = 87) cell, and large cell diffuse lymphomas (N = 202).

We computed crude odds ratios to compare each NHL subgroup with the control subjects with respect to potential confounders, including life-style and demographic variables. We used the SAS PHREG procedure:' to run conditional logistic regression models to assess the relation between each NHL subgroup and the following exposures: pesticides, herbicides (farming and nonfarming exposure treated separately), wood/saw dust, solvents, shoe/leather dust, meat packaging or processing, metal plating, cutting oils, formaldehyde, chlorophenols, heterocyclic nitrogens, carbamates, organophosphates,. phenoxy herbicides, chlorinated hydrocarbons, and pyrethroids (not considered for small cell diffuse lymphomas owing to absence of exposure among cases). We considered each exposure separately in models chat were stratified on the matching variables registry and date of birth (40 strata), and we controlled for the following potential confounders: age at diagnosis/case selection (5-year age groups), education, ethnicity, year entered the study (year of case diagnosis or control notification of enrollment), being Jewish, having never married, AIDS risk behaviors including intravenous drug use and sex with a male, use of seizure drugs, service in Vietnam, and cigarette smoking. If an occupational exposure variable appeared to be a potential risk factor for an NHL subgroup, we evaluated the impact of duration and time since first esposure.

Results

DESCRIPTIVE ANALYSIS

We present crude associations between NHL subgroups and various potential risk factors in Table 1. High levels of cigarette smoking increased the observed risk tor all subgroups. Hispanic ethnicity and higher education were associated with decreased risk tor all NHL, and a status of never having been married and reported AIDS risk behavior increased the estimated risk for all NHL. For follicular lymphomas, we observed decreased risk for black and Hispanic ethnicity. Never having been married and AIDS risk behavior were associated with increased risk tor large cell diffuse lymphomas, and higher education and low levels of smoking were associated with a reduced risk. Table 2 presents the frequencies of occupational exposures for study subjects.

MODELING RESULTS

Table 3 presents rhe results of models assessing the association between occupational exposures and NHL subgroups. For all NHL combined and for large cell diffuse lymphomas, the risk among the exposed and unexposed appeared similar after controlling for the various covariates. For this reason, we did not perform duration or latency analyses.

Men exposed to solvents appeared to be at increased risk of small cell diffuse lymphomas [odds ratio (OR) = 1.60; 95% confidence interval (CI) = 1.10–2.20]. The results of analyses of duration and time since first expo-

TABLE 1. Distribution of Cases and Controls According to Selected Characteristics, with Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for All Types of Non-Hodgkin's Lymphoma Combined and for Subgroups of Non-Hodgkin's Lymphoma

Variable	Controls (N = 1,659) N	All Non-Hodgkin's Lymphoma (N = 1,048) N	OR* (95% CI)	Small Cell Diffuse Lymphomas (N = 185) N	OR* (95% CI)	Follicular Lymphomas (N = 268) N	OR* (95% CI)	Large Cell Diffuse Lymphomas (N = 526) N	OR* (95% CI)
Ethnicity									
White†	1,400	918	1.00	158	1.00	251	1.00	453	1.00
Black	132	79	0.91 (0.67–1.20)	21	1.30 (0.77–2.20)	9	0.42 (0.21–0.86)	42	0.96 (0.66–1.40)
Asian	30	12	0.74 (0.37–1.50)	0		3	0.89 (0.26–3.10)	5	0.54 (0.20–1.40)
Hispanic	93	34	0.61 (0.40–0.95)	5	0.54 (0.20–1.50)	4	0.29 (0.10–0.84)	23	0.87 (0.52–1.50)
Other/unknown	4	5	2.10 (0.55–8.00)	1	2.40 (0.24–23.00)	1	1.50 (0.16–14.00)	3	2.20 (0.47–10.00)
Age (years) at study entry‡									
31–33	134	60	1.00	5	1.00	15	1.00	32	1.00
36–40	317	148	3.91 (0.59–1.40)	14	1.00 (0.31–3.50)	50	1.10 (0.52–2.30)	73	0.89 (0.51–1.60)
41–45	Hi	187	0.79 (0.45–1.40)	31	1.90 (0.43–8.80)	50	0.59 (0.22–1.50)	98	0.82 (0.39–1.70)
4650	318	214	0.73 (0.37–1.40)	34	1.60 (0.29–8.60)	59	0.50 (0.16–1.50)	112	0.79 (0.33–1.90)
51–55	333	281	0.66 (0.31–1.40)	56	1.50 (0.25–9.30)	61	0.42 (0.12–1.50)	144	0.72 (0.28–1.90)
56–60	210	158	0.50 (0.22–1.10)	45	1.50 (0.22–9.50)	33	0.34 (0.09–1.30)	67	0.47 (0.17–1.30)
Education									
< High school†	180	155	1.00	32	1.00	36	1.00	76	1.00
High school, tech	498	352	0.88 (0.68–1.10)	59	0.86 (0.53–1.40)	97	0.90 (0.58–1.40)	178	0.87 (0.62–1.20)
1–3 years college	341	113	0.85 (0.64–1.10)	38	2.97 (0.57–1.60)	53	0.90 (0.56–1.40)	111	0.82 (0.57–1.20)
≥4 years college	642	328	0.71 (0.55–0.93)	56	0.77 (0.47–1.30)	90	0.70 (0.45–1.10)	161	0.65 (0.47–0.91)
Year of study entry									
1984, 1985†	205	227	1.00	35	1.00	66	1.00	109	1.00
1986, 1987	1,006	581	0.50 (0.40–0.63)	103	0.61 (0.39–0.94)	152	0.47 (0.34–0.66)	289	0.50 (0.38–0.66)
1988, 1989	448	240	0.46 (0.35–0.59)	47	0.55 (0.34–0.90)	50	0.35 (0.23–0.54)	128	0.50 (0.36–0.68)
Cigarette smoking (pack-years)									
Nonsmoker†	560	309	1.00	49	1.00	69	1.00	170	1.00
>0 to <15	367	175	0.87 (0.69–1.10)	31	0.96 (0.60–1.50)	52	1.10 (0.78–1.70)	118	0.69 (0.51–0.94)
15 to <30	338	202	1.10 (0.84–1.30)	34	1.00 (0.66–1.70)	57	1.40 (0.96–2.10)	98	0.92 (0.69–1.20)
30 to <45	207	151	1.10 (0.88–1.50)	31	1.20 (0.76–2.00)	42	1.50 (0.97–2.30)	70	1.00 (0.72–1.40)
≥45	189	199	1.60 (1.30–2.10)	36	1.40 (0.89–2.30)	47	1.90 (1.20–2.90)	103	1.60 (1.20–2.20)
Unknown pack-years	4	12	5.00 (1.60–16.00)	4	9.40 (2.10–42.00)	1	3.00 (0.31–28.00)	7	5.40 (1.50–19.00)
Jewish									
No†	1,610	1,010	1.00	177	1.00	260	1.00	509	1.00
Yes	49	38	1.50 (0.93–2.30)	8	2.00 (0.55–4.40)	8	1.40 (0.65–3.10)	17	1.30 (0.73–2.30)
Never married									
No†	1,537	955	1.00	176	1.00	256	1.00	470	1.00
Yes	122	93	1.50 (1.10–2.00)	9	0.93 (0.46–1.90)	12	0.76 (0.41–1.40)	56	1.70 (1.20–2.40)
Stationed in/off coast of Vietnam									
No†	1,535	956	1.00	172	1.00	240	1.00	479	1.00
Yes	124	92	1.50 (1.10–2.00)	13	1.40 (0.76–2.70)	28	1.60 (1.00–2.60)	47	1.50 (1.00–2.20)
Used seizure drugs									
No†	1,644	1,032	1.00	181	1.00	265	1.00	520	1.00
Yes	15	16	1.60 (0.76–3.20)	4	2.70 (0.86–8.60)	3	1.10 (0.30–3.80)	6	1.20 (0.47–3.20)
AIDS risk behavior									
No†	1,608	1,008	1.00	183	1.00	261	1.00	502	1.00
Yes	51	40	1.70 (1.10–2.70)	2	0.56 (0.13–2.40)	7	1.20 (0.52–2.80)	24	1.90 (1.10–3.20)

* Odds ratios are from conditional logistic models stratified on the matching variables but not adjusted for other covariates.
† Referent category.
‡ Age at case diagnosis or control notification of entry into the study.

sure are presented in Table 4. There was little evidence of a positive duration-response relation between solvent exposure and small cell diffuse lymphomas. First exposure within 10 years was more strongly associated with risk of small cell diffuse lymphomas than first exposure more than 10 years before enrollment in the study.

Only those exposed to meat work appeared to be at increased risk of developing follicular lymphomas (OR = 1.60; 95% CI = 0.99–2.60). We found some evidence of a duration-response relation for meat work, and first exposure within 10 years betore enrollment was more strongly associared with risk of follicular lymphoma than first exposure more than 10 years before enrollment (Table 4).

Discussion

The large number of lymphoma cases in the Centers for Disease Control Selected Cancers Study and the pathology review performed for the study presented an impor-

TABLE 2. Frequencies of Occupational Exposures for Controls and Cases, According to Subgroups of Non-Hodgkin's Lymphoma

Exposure	Numher (%)				
	Controls (N = 1.659)	All Non-Hodgkin's Lymphoma (N = 1,048)	Small Cell Diffuse Lymphomas (N = 185)	Follicular Lymphomas (N = 268)	Large Cell Diffuse Lymphomas (N = 526)
Farming exposure to herhicides					
Yes	281 (16.9)	171 (16.3)	26 (14.0)	57 (21.3)	81 (15.4)
No	1,378 (83.1)	877 (83.7)	159 (86.0)	211 (78.7)	445 (84.6)
Farming exposure co pesticides					
Yes	384 (23.1)	236 (22.5)	34 (18.4)	83 (31.0)	108 (20.5)
NO	1,275 (i6.9)	812 (77.5)	51 (81.6)	185 (69.0)	418 (79.5)
Sonfarming exposure to herhicides					
Yes	191 (11.5)	120 (11.4)	15 (18.1)	37 (13.8)	55 (10.5)
NO	1.468 (88.5)	928 (88.6)	70 (91.9)	231 (86.2)	471 (89.5)
Chlorinnred hydrocarbons					
Yes	82 (4.9)	49 (4.7)	9 (4.9)	15 (5.6)	22 (4.2)
NO	1.577 (95.1)	999 (95.3)	76 (95.1)	253 (94.4)	504 (95.8)
Hererocvclic nitrogens					
Yes	67 (4.2)	40 (3.8)	4 (2.2)	11 (4.1)	21 (4.0)
NO	1,592 (96.0)	1,008 (96.2)	181 (97.8)	257 (95.9)	505 (96.0)
Chlorophenoxy herhicides					
Yes	98 (5.9)	53 (5.1)	6 (3.2)	19 (7.1)	26 (4.9)
NO	1.561 (94.1)	995 (94.9)	179 (96.8)	249 (92.9)	500 (95.1)
Carbamates					
Yes	47 (2.8)	27 (2.6)	3 (1.6)	11 (4.1)	I? (2.3)
NO	1,612 (97.2)	1,021 (97.4)	182 (98.4)	257 (95.9)	514 (97.7)
Organophosphates					
Yes	83 (5.0)	37 (3.5)	4 (2.2)	10 (3.7)	22 (4.2)
No	1,576 (95.0)	1,011 (96.5)	181 (97.8)	258 (96.3)	504 (35.8)
Pyrethroids					
Yes	IC (0.6)	3 (0.3)	0 (0.0)	2 (0.8)	1 (0.2)
NO	1,649 (99.4)	1,045 (99.7)	185 (100.0)	266 (99.2)	525 (99.3)
Chlorophenols					
Yes	182 (11.0)	132 (12.6)	28 (15.1)	44 (16.4)	52 (9.9)
NU	1,477 (89.0)	916 (87.4)	157 (84.9)	224 (83.6)	474 (90.1)
Metal plating					
Yes	54 (3.2)	30 (2.9)	4 (2.2)	7 (2.6)	15 (2.9)
No	1.605 (96.3)	1,018 (97.1)	181 (97.8)	261 (97.4)	511 (97.2)
Meat packaging/processing					
Yes	96 (5.8)	72 (6.9)	16 (8.7)	29 (10.8)	22 (4.2)
No	1,563 (94.2)	976 (93.1)	169 (91.3)	239 (89.2)	504 (95.8)
Chemical solvents					
Yes	679 (40.9)	451 (43.0)	96 (51.9)	114 (42.5)	213 (40.5)
No	980 (59.1)	597 (57.0)	89 (48.1)	154 (57.5)	313 (59.5)
Formaldehyde					
Yes	13Q(7.8)	93 (8.9)	21 (11.3)	17 (6.3)	46 (8.8)
NO	1,529 (92.2)	955 (91.1)	164 (88.7)	251 (93.7)	480 (91.2)
Wood/saw dust					
Yes	441 (26.6)	281 (26.8)	57 (30.8)	72 (26.9)	139 (26.4)
No	1,218 (73.4)	767 (73.2)	128 (69.2)	196 (73.1)	387 (73.6)
Shoe/leather dust					
Yes	22 (1.3)	15 (1.4)	2 (1.1)	7 (2.6)	5 (1.2)
No	1,637 (98.7)	1,033 (98.6)	183 (98.9)	261 (97.4)	521 (99.3)
Cutting oils					
Yes	340 (20.5)	215 (20.5)	47 (25.4)	49 (18.1)	105 (20.0)
No	1,319 (79.5)	833 (79.5)	138 (74.6)	219 (81.7)	421 (80.0)

TABLE 3. Associations between Occupational Exposures and Subgroups of Non-Hodgkin's Lymphoma*

Exposure	Odds Ratio (95% Confidence Interval)			
	All Non-Hodgkin's Lymphoma	Small Cell Diffuse Lymphomas	Follicular Lymphomas	Large Cell Diffuse Lymphomas
Farming exposure to herbicides	0.87 (0.69–1.10)	0.73 (0.46–1.20)	1.10 (0.76–1.50)	0.84 (0.62–1.10)
Farming exposure to pesticides	0.91 (0.75–1.10)	0.67 (0.44–1.00)	1.30 (0.96–1.80)	0.81 (0.62–1.00)
Nonfarming exposure to herbicides	1.30 (0.80–1.30)	3.73 (0.41–1.30)	1.32 (0.84–1.90)	0.92 (0.66–1.30)
Chlorinated hydrocarbons	0.91 (0.62–1.30)	0.78 (0.37–1.60)	1.10 (0.60–2.00)	0.80 (0.49–1.30)
Heterocyclic nitrogens	0.81 (0.53–1.30)	0.49 (0.17–1.40)	0.61 (0.30–1.20)	0.97 (0.56–1.70)
Chlorophenoxy herbicides	0.76 (0.52–1.10)	0.45 (0.19–1.10)	1.00 (0.58–1.80)	17.76 (0.47–1.20)
Carbamates	0.93 (0.56–1.50)	0.64 (0.19–2.20)	1.10 (0.55–2.30)	0.87 (0.44–1.70)
Organophosphates	0.66 (0.43–1.00)	0.44 (0.15–1.30)	0.54 (0.27–1.10)	0.86 (0.52–1.40)
Pyrethroids	0.52 (0.14–1.90)	—†	0.98 (0.20–4.70)	3.41 (0.05–3.30)
Chlorophenols	1.10 (0.86–1.40)	1.317 (0.85–2.10)	1.40 (0.94–2.00)	0.84 (0.60–1.20)
Metal plating	0.83 (0.52–1.30)	0.69 (0.24–2.00)	2.80 (0.35–1.80)	0.79 (0.43–1.50)
Meat packaging/processing	1.00 (0.72–1.40)	1.20 (0.66–2.10)	1.60 (0.99–2.60)	0.59 (0.36–0.96)
Chemical solvents	1.10 (0.90–1.30)	1.60 (1.10–2.20)	1.00 (0.79–1.40)	3.97 (0.79–1.20)
Formaldehyde	1.20 (0.86–1.50)	1.40 (0.87–2.40)	0.71 (0.41–1.20)	1.10 (0.79–1.70)
Wood/saw dust	1.00 (0.84–1.20)	1.30 (0.93–1.90)	0.88 (0.64–1.20)	1.00 (0.80–1.30)
Shoe/leather dust	1.10 (0.53–2.10)	0.93 (0.21–4.20)	1.62 (0.64–4.20)	3.71 (0.26–1.90)
Cutting oils	0.92 (0.75–1.10)	1.20 (0.84–1.80)	0.72 (0.51–1.00)	3.91 (0.70–1.20)

* Conditional logistic regression involved stratifying on matching variables registry and date of birth and controlling for age at diagnosis, year entered the study, ethnicity, education, Jewish religion, never having married, AIDS risk behaviors, use of seizure medication, service in or off the coast of Vietnam, and smoking status.
† Not considered because of absence of exposure among cases.

tant opportunity to perform robust analyses of occupational risk factors for NHL subgroups considered possibly less etiologically heterogeneous than all NHL combined. The few previous studies reporting subgroup-specific results have been small, and risk estimates have generally been unstahle. In these studies, risk factors associated with follicular lymphomas have included the occupations embalmer/funeral director,[26] carpenter/plumber and construction worker,'; residing near a stone, clay, or glass industrial facility,[28] and exposure to benzene, oils, and greases.[29] Farming and the use of natural product insecticides and organophosphates on livestock were associated with small lymphocytic lymphomas.'@ Exposure to pesticides and insecticides and to dust, sawdust, and fiber particles was associated with large cell diffuse lymphomas in one study.[27] Based on these scant findings, there is little prior evidence to form the basis of testable hypotheses, and rather, the present analyses should be viewed as hypothesis generating. Although primarily a negative study, the two associations observed in this exploratory analysis provide leads to be investigated in future studies.

TABLE 4. Results of Duration and Time since First Exposure Analyses for Occupational Exposures Noted to Be Associated with Small Cell Diffuse and Follicular Lymphomas

Subgroup of Non-Hodgkin's Lymphoma	Exposure	Exposure History	Number of Cases*	Number of Controls' (N = 1,659)	Odds Ratio†	95% Confidence Interval
Small cell diffuse lymphomas (N = 185)	Solvents	Duration of exposure (years)				
		Nor exposed‡	89	980	1.00	
		≤9	47	394	1.50	0.99–2.20
		>9	47	279	1.70	1.10–2.60
		Time since first exposure (years)				
		Not exposed‡	89	980	1.00	
		≤10	16	38	3.00	1.60–5.80
		>10	78	575	1.50	1.00–2.10
Follicular lymphomas (N = 268)	Meat packaging/ processing	Duration of exposure (years)				
		Not exposed‡	239	1,563	1.00	
		≤2	14	6?	1.20	0.63–2.20
		>2	14	33	2.10	1.10–4.20
		Time since first exposure (years)				
		Not exposed‡	239	1,563	1.00	
		≤10	3	1	9.00	0.90–90.00
		>10	25	94	1.40	0.85–2.30

* Numbers do not add to total owing to missing data.
† Conditional logistic regression involved stratifying on the matching variables registry and date of birth and controlling for age at diagnosis, year entered the study, ethnicity, education, Jewish religion, never having married, AIDS risk behaviors, use of seizure medication, service in or off the coast of Vietnam, and smoking status.
‡ Referent category.

In this study, only two associations were noted in the espected direction: exposure to solvents appeared to increase the risk of small cell diffuse lymphomas, and exposure to meat work appeared to increase the risk of follicular lymphomas.

We found little evidence of a duration-response relation for the association between small cell diffuse lymphomas and solvent exposure. The observed association may not De meaningful, or the lumping together of many different chemicals into the category "solvents" may have obscured a dose-response relation in this analysis.. Our finding is supported by most studies of the relation between all NHL and solvent exposure (usually defined as a general exposure to organic solvents or work in an industry where exposure to organic solvents is expected, such as the rubber industry), which did find an association.[13,29,31–40] Fewer studies reported no association.[27,41,42] There are also suggesrions that solvent exposure may be involved in lymphomagenesis by decreasing T-lymphocyte counts[43] or causing clonal aberrations.[44]

Exposure to meat packaging/processing may increase the risk of follicular lymphomas, as is suggested by an elevated odds ratio and positive duration-response relation. Meat work involves many potential exposures, including nitrite, incomplete combustion products, fumes from meat packaging materials (benzene included), preservatives, 2,4,6-trichlorophenol, and viruses that cause cancer in cattle (bovine leukemia virus) and chickens (avian leukosis virus and Marek's disease virus) and are widely present in raw meat.[45–47] Few studies of the relation between meat work and NHL exist. Abattoir workers were found to be at increased risk of NHL,[47] as were workers with potentially similar exposures in the food processing[27] and leather[27] industries. Another study did not find meat workers to be at increased risk of NHL.[46] Veterinarians, a group with potentially similar exposures, were found not to be at increased risk ot NHL in one study.[48]

There are several limitations of the Selected Cancers Study that may have affected our results. Many occupational exposures were rare, resulting in scanty data. As the study involves self-reported exposures, there is a porential for recall bias that could bias the estimates toward or away from the null.[49] La Vecchia et al.[41] however, have suggested that chrre is no reason to assume a differential recall between cases and controls for broad occupational categories similar to ours. The validity of self-reported work history is also an issue. In general, self-reported work history has been shown to be valid,[50–53] although the validity tends to increase with length of time on the job[50,51,53] and decrease with number ot jobs held.[50,51] Overall, we would most suspect in this study nondifferential misclassification due to a lack of precision in self-reported exposure chat would bias our results toward the null.[49] If 10% of the subjects were classified as unexposed when they were actually exposed, the true crude odds ratio for solvents and risk of small cell diffuse lymphomas would be 1.63 (estimated crude OR = 1.56), and that for meat work and follicular lymphomas would be 2.22 (estimated crude OR = 1.98). These calculations indicate little bias to the null.

A general concern with these analyses is that known etiologic subgroups of the non-Hodgkin's lymphomas do not currently exist.[4,54] The subgroups used in these analyses have been proposed by researchers[4,8] and have been used recently to a limited extent,[26–30] but our lack of findings suggests that they may not De etiologically informative. Further classification of NHL for epidemiologic studies may be improved by the inclusion of information such as tumor location, phenotype, and specific genetic changes.

A final concern of this study involves the large number of comparisons. We found two associations in the expected direction and three associations in an unexpected direction (cutting oils and follicular lymphomas, and farming exposure to pesticides and meat packaging/processing and large cell diffuse lymphomas) out of a total of 67 assessed associations. As this is an exploratory analysis, these findings will need to be replicated.

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