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Non-Hodgkin's Lymphoma and Occupational Exposure'

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Abstract

A case-control study was conducted to assess the effect of occupational exposures on the risk of non-Hodgkin's lymphoma. Interviews were conducted with 303 persons with non-Hodgkin's lymphoma newly diagnosed from January 1, 1980, to May 31, 1982, among residents of the Boston, MA, metropolitan area and 303 age and gender matched controls. The study found an increased risk of disease among persons employed in the agriculture, forestry, and fishing industry [relative risk (RR) = 3.03; the construction industry [RR = 211; and the leather industry [RR = 211. The particular job groupings at increased risk were plant fanners and gardeners (RR unbounded); painters and plasterers (RR = 6.0); and carpenters, brick and stone masons, plumbers, and roofers (RR = 12.0). Although other exposures may have led to these increased risks, the findings in this study are consistent with an increased risk of non-Hodgkin's lymphoma for workers who may be exposed to chlorophenolsor phenoxyacetic acids.

The identification of statistical associations between occupations and the occurrence of cancer can be used to identify particular agents which may lead to the development of cancer. For lymphomas, most of the increased risk in occupational exposures appears to be related to chemical exposures. Li et *al.* (1) reviewed the causes of death of members of the American Chemical Society from 1948 to 1967 and found an observed:expected ratio of 1.8 for lymphoma. Similar results were found in a study of British chemists and pathologists (2, 3). Studies of workers exposed to benzene, vinyl chloride, styrene. and its polymers suggest increased risk of lymphoma (4–7). Goldsmith and Guidotti (8) reported the occupations recorded on death certificates for males who died of lymphosarcoma in California and Washington. Increased rates were found for people working in some types of farming, food processing, delivery services, pulp and paper work, electrical work, some building trades, and some types of clerical work. Relative risks of 2.5 (slight exposure) and 9.3 (heavy exposure) were found for workers exposed to chlorophenols or phenoxy acids containing dibenzodioxins and dibenzofurans as impurities. Workers exposed to these chemicals were employed in farming, forestry, building, and painting (7, 9–11). Several studies of farming and mortality from non-Hodgkin's lymphoma found odds ratios ranging from 1.2 to 1.3 for all ages and higher odds ratios among the elderly (12–14). Cantor *et al.* (15) reported elevated risk among farmers using the pesticides dichlorodiphenyltrichloroethane (RR[4] = 1.5), carbofuran (RR = 1.6), and chloramben (RR = 2.2). In a case-control study, Hoar et *al.* (16) found an odds ratio of 1.6 for farmers who used herbicides, with frequent users having an odds ratio of *8.0.* A case-control study in eastern Nebraska (17) found an odds ratio of 2.4 for those who used 2,4-dichlorophenoxyacetic acid more than 20 days/year and an odds ratio of 2.4 for users of organophosphate insecticides. Leather workers and female textile workers were reported at increased risk of non-Hodgkin's lymphoma due to chemical exposures although no associations with specific chemicals were determined (18, 19). Ross et *al.* (20) found an excess of male patients with large cell lymphomas of the gastrointestinal tract and oral cavity associated with occupational exposure to asbestos. We have conducted a case-control study to identify occupations and exposures that *are* associated with increased risk of all non-Hodgkin's lymphomas or of specific histological subtypes of non-Hodgkin's lymphoma.

Methods

We attempted to identify all *cases* of non-Hodgkin's lymphoma newly diagnosed from January 1, 1980, through May 31,1982, among residents of the Boston Standard Metropolitan Statistical Area who were treated in any one of nine participating hospitals. Three hundred seventy-nine cases of all ages were identified in the participating hospitals. With the approval of his or her physician. each living *case* or next of kin for a deceased case was asked to participate in an interview. Parents or guardians were interviewed for cases ages 17 years or less. Interviews were completed with 202 cases, 94 proxies, and 7 guardians giving an overall participation rate of 80% (303 of 379). Refusals to participate were given by 40 cases, 18 physicians for *case* interviews, 10 proxies, and 8 physicians for proxy interviews.

A pathology review of the cases was done to confirm the diagnosis of non-Hodgkin's lymphoma and to subclassify the type of lymphoma. Each *case* was classified according to the Modified Rappaport Classification (21), the Working Formulation (22), nodular or diffuse pattern, and the probable cell type (B-cell, T-cell).

For purposes of analysis, we grouped the malignant lymphomas according to several larger categories. Using the modified Rappaport Classification, we analyzed all cases of histiocytic lymphoma in one category, whether they were nodular or diffuse. In addition, we defined "lymphocytic" as all malignant lymphomas of well differentiated lymphocytic, intermediate differentiated lymphocytic, poorly differentiated lymphocytic, and lymphocytic not otherwise specified, as well as those cases that were either nodular, nodular and diffuse, or totally diffuse. Malignant lymphomas of probable T-cell origin were defined on morphological grounds exclusively.

Using the Working Formulation, tumors were categorized into three groups. Diffuse large cell included all subclassifications including large cleaved, large noncleaved, and those with sclerosis. The follicular category included all malignant lymphomas classified as follicular with either predominantly small cleaved cells, predominantly large cells, or mixed small cleaved and large cells.

We obtained slides for review for 290 of the 303 cases (96%) and all were reviewed by 2 or more members of a 7-member panel of study pathologists. In this report, the pathology classifications of 286 cases by a single member of the panel (R. S. N.) are used. In a later report, concordancy among panel members will be reported.

For each case, a control of the same sex and age (within 1 year), town, and precinct of residence was selected from town residency lists. By law, each town in Massachusetts must compile lists annually of all residents 17 years of age or older. The list for the town and precinct was entered by a random process and was searched forward to find the first person with the same sex and age as the case. If this potential control subject could not be interviewed, the list was searched forward to identify

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[4] The abbreviation used is: RR, relative risk.

another potential control subject. For cases under 18 years of age, the list was searched matching on the age and sex of one parent or guardian. The potential interviewee was contacted to determine whether he or she had a child of the same age (within 2 years) and sex as the case. This process was continued until a guardian of the required age and sex with a child of the required age and sex was found. Of 423 potential controls, 303 were interviewed, and 120 refused to participate in the study.

Each subject (case or control) was sent an explanatory letter and was contacted by telephone to arrange a home interview. If the subject could not be interviewed at home, a mail questionnaire was used. Home interviews were obtained for 301 cases (99%) and 297 controls (98%). The interview included questions on the demographic characteristics of the subject and on an extensive List of possible risk factors, including occupation. Findings relating to occupation are reported here, and other exposures will be the topic of later reports.

Each subject was asked about his or her current or most recent job, the job held 15 years ago, major occupation, second most major occupation, and up to two occupations in which he or she was exposed to any of the specific agents listed in Table 2. Each occupation was categorized by industry and by occupational title within industry. The industry was coded according to a scheme based on the Standard Industrial Classification Manual of the United States Bureau of the Budget (23.24). The occupational title was coded according to a scheme based on the United States Dictionary of Occupational Titles (23, 25). The first two digits of the occupational code were used, resulting in generally broad and in some instances rather heterogeneous categories. For each occupation. information on the dates of employment and exposure to the specific agents in Table 2 was obtained.

Industry, occupational title, and exposure to specific agents represent three interrelated methods of classifying a work exposure. An increased risk may be experienced by anyone working in a given industry, such as the textile industry, independently of the particular job title held within the industry. Alternatively, an increased risk could be experienced by all workers with the same job title (plumbers, for example) independently of the industry in which the person is employed. In this paper, we will consider each of the three methods of classification separately.

Another goal of the study was to determine whether there was an association between occupation and any of the various histological subtypes of non-Hodgkin's lymphoma. The number of cases of each histological subtype was too small to permit the observation of an association with occupation. Histological subtypes were aggregated into groups with similar histological characteristics in an attempt to form groups sufficiently large for analysis. The data analysis presented here considered the association of occupation with each of five histological groups and with a sixth group that included all cases of non-Hodgkin's lymphoma.

Given the large number of exposure measures and the six possible histological categories, a large number of associations was considered. This led to the problem of distinguishing between true associations and associations that occurred by chance. The approach used was to investigate the pattern of the association within an exposure-histological category as a function of calendar time or of the duration of exposure. Calendar time patterns which showed odds ratios consistently >1 or consistently <1 were considered to favor true associations. Patterns that had a large odds ratio at one point in time and odds ratios near 1 at other times were considered to favor spurious associations. Similarly, if odds ratios for at least 10 and at least 20 years of exposure were both >1, the duration pattern was considered to favor a true association. However, an odds ratio >1 for those with at least 10 years of exposure and <1 for those with at least 20 years of exposure were considered more consistent with a spurious association.

In this study, odds ratios and χ statistics with 1 degree of freedom for matched pairs were calculated by histological group for each of the various industries. occupational titles, and exposures to specific agents for the time periods of 1901–1949, 1950–1959, 1960–1969, and 1970 or later. Both early and late exposures were considered, since there was interest in mechanisms of both tumor induction and tumor promotion. The odds ratios were reviewed to identify odds ratios equal to 2.0 or more or those equal to 0.5 or less. The χ statistics were reviewed for absolute values of 1.73 or greater. If the overall odds ratio or the χ statistic for all time periods together met the above criteria, the odds ratios and χ statistics were reviewed for each of the four time periods. If these data were found to be consistent over the time periods, the association would be included in further analysis. Otherwise, the association was considered to be spurious and would be eliminated from further analysis. Similar analysis was done by duration of exposure for those having specific exposures for at least 10 years, at least 20 years, and at least 30 years.

All of the exposures which showed consistent patterns within histological categories over calendar time or over duration were considered as candidate variables for conditional logistic models, retaining the matching in the original study design. These models were used to determine whether candidate exposures were significant controlling for the effect of other exposures. The candidate exposure could enter the model as an indicator variable for exposure or as an indicator variable for exposure during 1901–1944, 1945–1969, or 1970–1983. For exposures to specific agents, the exposure could be expressed as the number of decades of exposure up to a limit of four decades. No demographic variables or interaction terms were included as candidate variables for the models. However, a series of analyses were done which included religion to control for possible confounding. These models were constructed for each of the six histological groups within each of the three work classifications (industry, occupational title, and occupational agent exposures). Models were constructed which included all subjects; additionally models were used which excluded the proxy responses. Variables were retained in the final model if their coefficients were significant at the 0.05 level. For odds ratios with point estimates of either zero or infinity, a score statistic (26) was used to estimate the level of significance. The boundary of the 95% confidence interval was determined by selecting a mal value for the relative risk and adjusting the value until the score statistic had a probability of 0.05.

Results

A total of 303 cases of non-Hodgkin's lymphoma were interviewed for the study, of whom 152 were males and 151 were females. The median age of cases was 65 years. No statistically significant differences between cases and controls were found for education, marital status, current family income, and highest family income. However, religion did differ between cases and controls. Fewer Protestants and more Jews are among cases as compared to the controls. A matched pair analysis of religion yielded a relative risk of 0.4 ($P < 0.001$) for Protestants as compared to all other religions and a relative risk of 31 ($P < 0.001$) for Jews.

A review of the numbers by pathological classification of the lymphomas showed a scarcity of many histological subtypes, which would provide insufficient cases for analysis by each subtype. In this analysis, we have combined histological subtypes into the groups listed in Table 1. Since the histological groups are formed using more than one system of classification, the groups listed in Table I are not independent of one another. The follicular group in the Working Formulation includes some

Table 1 *Groupings of histological subtypes used in the analysis*

Type	No.
All histologies	303
Modified Rappaport classification	
Histiocytic	99
Lymphocytic	94
Cell type	
T-cell	24
Working formulation	
Follicular	55
Diffuse, large cell	53

cases that are in the lymphocytic group and some in the histiocytic group in the Rappaport Classification. The diffuse, large cell group in the Working Formulation is largely a subgroup of the histiocytic group in the Rappaport Classification. currently, there is no known scheme which would group the various histological subtypes by common etiologies. The groupings used are based on morphological similarity and are studied in this paper to determine whether morphological groups have etiological implications.

Table 2 gives the data for the association between exposures to certain agents and the occurrence of non-Hodgkin's lymphoma. Table 2, Column 2, gives the prevalence of the exposure in the total group of subjects, cases, and controls. This may be thought of as an estimate of the prevalence in the population under the assumption that there is no association between the exposure and disease. The prevalence gives an indication of the probability of observing an association if one exists. In this study, a relative risk of 2 or greater would be observed with an 0.80 probability using a significance level of 0.05 for a prevalence of 4%, with a 0.90 probability for a prevalence of 6%, and with a 0.99 probability for a prevalence of 11%. For a relative risk of 1.5, 0.8 and 0.9 probabilities of observing the association would require prevalences of 15 and 25%, respectively. Table 2 shows an increased risk of non-Hodgkin's lymphoma among those reporting exposure to particles (RR = 1.4) and those reporting exposure to pesticides or insecticides (RR = 1.8). Other agents listed show lower relative risks. although only one is below 1.0. None of these associations reaches statistical significance.

Analyses similar to those reported in Table 2 were done for each of the histological groups listed in Table 1. The analyses were repeated with the elimination of all responses given by proxies. Tests for trends with increasing duration of exposure were done. Any association which was significant at the 0.1 level was considered to identify a candidate variable for the conditional logistic models. Variables were retained in the final model if their coefficients were significant at $P = 0.05$. The results of these analyses are given in Table 3.

Table 3 shows the significant associations between non-Hodgkin's lymphoma and exposures to the specific agents. Only the conditional logistic model for all cases of non-Hodgkin's lymphoma included a significant term for trend with duration of exposure to particles, expressed in decades of exposure. No other exposures were statistically significant when added to this model. No exposures were significantly related to all cases of non-Hodgkin's lymphoma when proxy responses were excluded from the analysis. The model for cases of histiocytic lymphoma showed an association with exposure to pesticides and insecticides only when the exposure occurred between 1945 and 1969. Those with diffuse, large cell lymphoma (Working Formulation) also showed an association with pesticides and insecticides. However, all the discordant pairs with the case exposed that led to the association with diffuse large cell lymphomas were the same pairs that led to the association observed for the histiocytic lymphomas. When proxy responses were excluded, the model for diffuse, large cell lymphoma showed an association with exposure to particles. None of the models for the other histological groups, with or without proxies had any terms which reached statistical significance. The time dependencies for the associations reported above were selected on the basis of having the largest level of statistical significance. Some of these associations were significant at other time periods or after other durations, but at lower levels of statistical significance.

Table 2 *Associations between even being exposed to specific agents and non-Hodgkin's lymphoma. all cases*

Agents	Prevalence in population (%)	Relative risk	95% confidence interval
Gasoline or kerosene	17	1.0	0.6–1.7
Benzene	4	1.2	0.5–2.6
Chlorinated solvents	24	1.2	0.8–1.8
Fumes or gases	26	0.6	0.6–1.2
Particles (dust. sawdust. fibers)	39	1.4	0.9–1.8
Tar	5	13	0.6–2.8
Radioactivity or X-rays	4	1.3	0.6–2.8
Fertilizers	11	1.1	0.5–2.3
Pesticides or insecticides	7	1.8	0.9–3.7
Heavy metals (lead, mercury)	7	1.2	0.7–2.3

Table 3 also shows the effect of controlling for religion, a demographic characteristic that differed between cases and controls in this study. This table as well as subsequent tables shows that controlling for religion usually results in small shifts in the relative risks and the confidence intervals. In general, controlling for religion does not alter the conclusions of this study.

Associations between employment in specific industries and all non-Hodgkin's lymphomas are given in Table 4. Each occupation entered on the questionnaire was assigned to one of the industries listed in the table; no occupations were excluded from the table. As in Table 2, the prevalence of employment in an industry *can* be used as a guideline in deciding whether the lack of an association reflects the low prevalence in the population or supports the hypothesis that there is no association. Increased relative risks were found for the agriculture, forestry, and fishing industries (RR = 3.0); the construction industry (RR = 2.1): the paper and wood industry (RR = 1.7); and the leather industry (RR = 2.1). The relative risks were statistically significant at the 0.05 level for the agriculture, forestry, and fishing industries and for the construction industry. A statistically significantly decreased risk was found for those employed in the chemicals, drugs, and paints industries (RR = 0.3). Table 5 lists the associations between employment in industries and histological subgroups which closely approached or achieved statistical significance. To be consistent among industries, Table 5 reports the associations for those who were ever employed in the industry. Ever employment had higher statistical significance than employment in a particular time period for all histological categories except for follicular lymphoma, ,where employment in the construction industry between 1945 and 1969 was more statistically significant (RR unbounded; lower 95% confidence interval, 1.0). Table 5 shows that those employed in the construction industry are at increased risk of the lymphocytic (Rappaport) or the follicular (Working Formulation) lymphoma. Those in the agriculture, forestry, and fishing industries were found to be at increased risk for diffuse, large cell lymphoma (Working Formulation). Table 5 also shows the significant associations identified in a conditional logistic model involving multiple industrial exposure terms as related to the total group of all lymphomas. Both the agriculture and leather industries have significant associations after controlling for other industrial exposures.

Table 6 gives associations between employment in an occupation and all non-Hodgkin's lymphomas. Table 6 does not include all occupations, since the prevalence of employment in some occupations was quite low. Only occupations with a prevalence of at least 3% or a relative risk significant at the 0.1 level

Table 3 *Associations between exposure to specific agents and histological groups of non-Hodgkin's lymphoma*

Histology	time dependency	Exposures	Relative risk	95% confidence interval	Controlling for religion: Relative risk	Controlling for religion: 95% confidence interval
All	Decades of exposure[a]	Particles (dust, sawdust, fibers)	1.2[a]	1.0–1.3	1.1	1.0–1.3
Histiocytic	Exposed 1945–1969	Pesticides and insecticides	Inf	1.3–Inf	Inf	1.2–Inf
Diffuse large cell	Ever exposed	Pesticides and insecticides	Inf[b]	1.3–Inf	Inf	1.5–Inf
Diffuse[c] large cell	Ever exposed	Particles (dust, sawdust, fibers)	8.0	1.3–49	8.2	0.8–79

[a] The average relative increase in relative risk for any step in the progression of 0 years, 1–9 years, 10–19 years, 20–29 years, and 30 or more years of exposure.
[b] Inf, infinite
[c] Excluding proxies.

Table 4 *Associations between employment in specific industries and non-Hodgkin's lymphoma. all c a w*

Industry	Prevalence in population (%)	Relative risk	95% confidence interval
Agriculture, forestry, fishing	3	*3.0*	1.0–8.8
Construction	5	2.1	1.0–4.6
Paper and wood	3	1.7	0.7–4.2
Metal	4	1.2	0.6–2.5
Machinery	*9*	*0.8*	0.4–1.4
Shipbuilding, auto	10	1.0	0.6–1.7
Food and tobacco	16	*0.9*	0.6–1.3
Textiles	*9*	1.1	0.6–1.9
Chemicals. drugs, paints	3	0.3	*0.1–0.9*
Leather	4	2.1	0.9–4.8
Medicine and science	10	*0.9*	0.5–1.5
Entertainment and recreation	4	*0.8*	0.4–1.6
Art	3	0.6	0.3–1.4
Job with few exposures	*19*	0.7	*0.5–1.1*

were included in Table 6. Increased relative risks were found for plant farmers and gardeners (RR unbounded); painters, plasterers, and housepainters (RR = 6.0); and carpenters, brick and stone masons, plumbers, and roofers (RR = 12.0). A further analysis which considered separately each of the building trades that make up the latter two high risk groups showed that workers in each of the building trades were at increased risk although the number of individuals employed in each trade was not large enough to reach statistical significance Decreased relative risks were found for mathematicians and programmers (RR = 0.2) and for those employed in the sewerage, water treatment, and utilities production industries (RR = 0.0).

Associations with specific histological subtypes and occupation are reported in Table 7. The associations were reported for those who were ever employed in the occupation, since these associations were more statistically significant than employment in a particular time period. For histiocytic lymphoma (Rappaport), those employed as carpenters, brick and stone masons, plumbers. and roofers were found to have elevated relative risks (RR unbounded); while those employed as students and educators were at decreased risk (RR = 0.1). Carpenters, brick and stone masons, plumbers, and roofers also had elevated relative risks (RR unbounded) for follicular lymphoma (Working Formulation). Those who were students or educators were at decreased risk (RR = 0.0) for diffuse, large cell lymphoma (Working Formulation). Table 7 also gives the results of the conditional logistic model for all histologies of non-Hodgkin's lymphoma. Carpenters, brick and stone masons, plumbers, and roofers were at increased risk of non-Hodgkin's lymphoma while mathematicians and programmers were at decreased risk. A model that controlled for religion showed an increased risk for carpenters, brick and stone masons, plumbers, roofers, and plant farmers. The association with mathematicians and programmers, however, was not statistically significant.

Discussion

The analysis of the associations of non-Hodgkin's lymphoma and occupational exposures has considered three aspects of exposure in an attempt to identify risk factors for the disease. The first aspect was an attempt to look at classes of chemicals or agents which might increase the risk of disease. This approach would be the most desirable if information were accurate, since it might lead to the identification of specific causal agents. Accurate data on chemical exposures are difficult to obtain in home interviews, since the employee may have forgotten or never known the specific agents used in the past. The second approach was to classify occupational exposures by industry. This approach would make the best use of the data when all workers in the industry shared a common exposure, although specific etiological interpretations would be more difficult than in the first approach. The third approach was to categorize occupational exposures by specific occupations, such as secretaries and plumbers, so that workers with similar jobs could be aggregated independently of the industry, As with industry as the defining exposure, specific occupation would be best if occupational titles identified common exposures. Although each of these three approaches has its limitations, a number of potentially useful results have been identified.

For occupational exposures categorized by exposure to classes of agents. we found an increased risk of disease for those exposed to particles (dust, sawdust, fibers) and those exposed to pesticides and insecticides. An increased risk of disease with dust exposure has not been generally noted for non-Hodgkin's lymphoma. Increased risk with generalized dust exposure, however, has been reported for Hodgkin's disease (27). For exposure to pesticides and insecticides, we found an increased relative risk of 1.8 for all lymphomas and a large relative risk for the diffuse, large cell lymphomas in particular. An increased risk of 1.9 has been reported for all lymphomas by Everett et *al.* (28). Cantor (13) has reported relative risks ranging from 1.53 to 2.4 for farmers under the age of 65. Cantor also noted (15) an increased risk of small cell lymphocytic lymphoma among users of specific pesticides. Hoar *et al.* (16) observed an odds ratio of 1.5 for pesticide exposure. The odds ratio decreased to 1.1 when controlled for herbicide exposure suggesting that the increased risk observed for pesticide exposure may result from the high correlation between exposure to pesticides and exposure to herbicides.

We did not observe an increased risk for those exposed to benzene. The association between lymphoma and benzene had been reported by Vianna and Polan (4), where they compared the proportional mortality rate for lymphoma among those.?! had worked in an industry that used benzene with the rate for those who worked in all other industries. A review of the article

Table 5 *Association between employment in selected industries and histological types of non-Hodgkin's lymphoma*

Histology	Industry	Relative risk	95% confidence interval	Controlling for religion: Relative risk	Controlling for religion: 95% confidence interval
All[a]	Agriculture	3.4	1.1–10.8	4.4	1.4–14
	Leather	2.4	1.0–5.6	2.2	0.9–5.4
Lymphocytic	Construction	Infinite	1.5–infinite	Infinite	1.3–infinite
Follicular	Construction	6.0	0.9–38	4.1	0.5–40
Diffuse, large cell	Agriculture	Infinite	1.0–infinite	Infinite	1.5–infinite

[a] The results for the total group of all histologies with multiple exposures were obtained using a conditional logistic model.

Table 6 *Association between employment in selected occupations and non-Hodgkin's lymphoma, all cases*

Occupation	Prevalence (%)	Relative risk	95% confidence interval
Mathematician, programmer	2	0.2	0.1–0.9
Physician	3	1.3	0.6–3.0
Student, educator	11	0.7	0.4–1.2
Accountant, auditor	4	1.6	0.7–3.5
Official, manager	10	0.6	0.3–1.0
Manager (am) radio operator, air traffic controller	3	0.6	0.2–1.4
Office work, secretary	11	0.8	0.5–1.4
Clerk (office work)	4	0.8	0.4–1.7
Salesperson	12	0.9	0.5–1.5
Domestic housewife, nurse's aide	25	1.3	0.8–2.2
Waitress, chef, meat cutter	7	1.0	0.5–1.8
Laundering, dry cleaning, leather products fabrication	3	1.6	0.6–4.0
Protective services (policeman, fireman, military)	4	0.7	0.3–1.6
Service occupations (janitor)	4	1.7	0.7–4.2
Plant farmer and gardener	1	Inf[a]	1.3–Inf
Electrical equipment assembler	3	1.1	0.5–2.7
Upholsterer, Sewer, stitcher	4	1.2	0.5–2.6
Painter, plasterer, housepainter	1	6.0	0.9–38
Carpenter, brick and stone mason, plumber, roofer	2	12.0	2.0–72
Truck driver, train conductor	4	1.0	0.4–2.3
Airplane or auto mechanic, gas station attendant	3	1.4	0.6–3.6
Packaging, warehouseman	5	0.9	0.4–1.8
Working in sewerage or water treatment, or utilities	1	0.0	0.0–0.8

[a] Inf. infinite.

showed that the strength of their association was strongly supported by the increased risk of disease presumably due to benzene for woodworkers and farmers. Subsequently, it has &en suggested that the increased risk among woodworkers and farmers may be due to other agents. A later study also found no increased risk with exposure to benzene (29).

Analysis of the data by industry found that workers in the agriculture. forestry, fishing industry; the construction industry : and the paper and wood industry were at increased risk of non-Hodgkin's lymphoma. Increased risks among agricultural workers have been reported in a number of studies (12–17). The increased risk may, in part, be a result of exposure to pesticides (dichlorodiphenyltrichloroethane, carbofuran, and chloramben) and to herbicides (chlorophenols and phenoxyacids) containing dibenzodioxins and dibenzofurans as impurities. The increased risk among workers in the forestry, construction, wood and paper industry may result from exposure to chlorophenols or phenoxyacids being used as herbicides or as wood preservatives. Workers in forestry would be exposed as they applied the herbicides, and workers using the wood would be exposed when they worked with the wood which was treated with these compounds.

In the literature, an increased risk of non-Hodgkin's lymphoma has been reported for workers in the leather and textile industries. In this study, employment in the leather industry had a relative risk of 2.1 for non-Hodgkin's lymphoma. Rather than being limited to any particular occupation or group of occupations, the increased risk was noted among all persons employed in this industry. This *finding* is consistent with the study by Decoufle (18), who first reponed the association in 1979. In that report, Decoufle renewed the various potential carcinogens used in the leather industry but did not single out any *specific* agents. Chlorophenols, a waterproofing agent used in the leather industry (30), would be a candidate for further study. In this study, we found a relative risk of 1.1 (confidence interval. 0.6–1.9) for employment in the textile industries, a value which would be consistent with no increased risk among textile workers. Delzell and Grufferman (19), however, reported a proportional mortality ratio of 1.7 for former female textile industry employees. The 95% confidence interval for this study includes their point estimate.

Analysis of the occupational exposure data by occupation group identified three groups of workers at increased risk of non-Hodgkin'slymphoma. The first of *these* groups is the plant farmers and gardeners. This finding is consistent with our observation of an increased risk for exposure to insecticides and pesticides, exposures that should be highly correlated with plant farmers and gardeners within the same study. Plant farmers and gardeners may also be exposed to herbicides, but this exposure was not investigated as part of this study.

The second and third groups of occupations at increased risk were (a) painters, plasterers, and housepainters and (b) carpenters, brick and stone masons, plumbers and roofers. This result is consistent with the increased risk found for workers exposed to particles such as dust, sawdust. and fibers. Part of the increased risk could be associated with exposure to wood containing chlorophenols. Also, there has been a report of an increased risk of small cell follicular lymphoma among plumbers, presumably resulting from the use of vinyl pipe (31). However, the exposures experienced by workers in these building trades are far too complicated to be attributed to the exposures mentioned above without a more detailed investigation.

It is possible that the results of this study could be biased by the use of proxy interviews which accounted for approximately one-third of all the responses from cases. Proxy interviews were not used for any of the controls. The use of proxies could have had differing effects on the three categorizations of occupational exposure. The influence of proxy responses on dative risks was probably greatest for the exposures to specific agents. Here it is unlikely that the proxy respondent would be familiar with the lifetime history of exposures experienced by the case. Since underreporting of exposures in proxy responses would occur only in the case series. there would be a decrease in the relative risk reported for causal factors and overestimate of effect of any protective factors. In this study, since most of the significant effects observed relate to increased risk, the use of proxy responses would have tended to underestimate the relative risk. Other effects actually present in this series may have

Table 4 *Associations between employment in selected occupations and histological groups of non-Hodgkin's lymphoma*

Histological group	Occupation	Relative risk[a]	95% confidence interval[a]	Controlling for relrgion: Relative risk[a]	Controlling for relrgion: 95% confidence interval[a]
All histologies	Carpenter, plumber	11.0	1.6–92	13.2	1.7–102
	Mathematics, programmer	0.2	0.0s–1.0		ns[b,c]
	Plant farming	[b]	ns[b]	Inf	1.5–In
Histiocytic	Carpenter, plumber	Inf	1.O–Inf	[b]	ns[b]
	Student, educator	0.1	0.01–0.5	0.1	0.01–0.6
Follicular	Carpenter. plumber	Inf	1.3–Inf	Inf	1.0–In!
Diffuse, large cell	Student, educator	0.0	0.0–0.4	0.0	0.0–0.5

[a] Relative risk estimated from a conditional logistic model.
[b] Variable not included in the model.
[c] ns. not significant; Inf. infmite.

been missed because of the high proportion of proxy respondents. For occupational exposures characterized by industry. the influence of proxy responses is expected to be relatively small. Here, the respondent is expected to know only about the cases' recent occupations and major occupations. For the exposures characterized by specific occupation, there may be a tendency for the respondent to "promote" the deceased to a more prestigious position than the position that was actually held. Such promotions have been observed in studies of occupations reported on death certificates (32). These promotions would tend to remove the case from an occupation of higher exposure to an occupation of lesser exposure, since the exposures identified tend to be associated with less prestigious occupations. This would tend to reduce the estimated magnitude of a "causal" association and thereby reduce the chance of detecting a small true association. For causal associations observed for all three categories of occupational exposures, these considerations would lead one to believe that with the use of proxy responses, the observed relative risk would be lower than would have been found if direct patient responses could have been obtained.

We investigated the proxy effect by analyzing our data using all respondents and, separately, using direct respondents only. In the study of occupational exposure to dust, sawdust, and fibers, a significant association was found using all respondents. but the risk was not significant when direct respondents were considered alone. On the other hand, this exposure was found to be significantly associated with the histological subtype of diffuse, large cell lymphomas when direct respondents were considered, although it did not reach significance when proxies were included. We do not know of a consistent explanation of these findings, although it seems reasonable to propose that the significant relation found using direct respondents and the more homogeneous subtype of diffuse large cell tumors is a true association. In other parts of this study, the inclusion or exclusion of proxy reports did not affect conclusions.

A second factor which could bias the study results is the selection of those histologies which formed the histological groups for analysis. A broad histological group as used here might contain diseases having different etiologies associated with different specific histologies. For example, the poorly differentiated lymphocytic lymphoma may have a different etiology from that of the well differentiated lymphocytic lymphoma, both of which we have included in the category lymphocytic lymphoma. If there were a causal or a protective association between exposure and only one of the types of lymphoma in a group, the magnitude of the association observed for the group would be less than the magnitude of the true association for that particular histology. In general, the formation of these groups might mean that a true association could be missed. Since the number of cases of each specific histological subtype was too small for a meaningful analysis, the only opportunity to observe any association with histological subtype was obtained by forming histological groups.

Such a dilution effect appears to be present in the associatioc of lymphoma with the student-educator occupation in the present data. In Table 6, we showed a weak effect in the direction of risk reduction for the student-educator occupation in relation to all histological types taken together. In Table 7. we found a strong risk reduction for student-educators in relatioc to histiocytic lymphomas (Rappaport) or diffuse large cell tumors (Working Formulation). In fact. the two histological subtypes are associated with student-educator occupation in discordant directions in our data. The subtype of lymphocytic (Rappaport) or follicular (Working Formulation) lymphoma is increased in the student-educator group and tends to obscure the stronger risk reduction effect for histiocytic or diffuse large cell types. A less striking example of such a dilution is seen in the construction industry, where the lymphocytic or follicular subtype is greatly increased (Table 5) although the associarioc of this industry with lymphomas generally is of borderline significance (Table 4).

In conclusion, we have found an increased risk of lymphoma among persons exposed to insecticides, pesticides, and particles such as dust. People employed in the agriculture, forestn. fishing industry; consuuction, paper and wood industry and leather industry were also found to be at increased risk. The specific occupations at increased risk were those of plant farmers. gardeners, and people in the building trades such as painters, plasterers, housepainters, carpenters, brick and stone masons, plumbers, and roofers. In each of the occupations workers had the possibility of exposure to chlorophenols or phenoxyacids. The results of this study suggest the need for a further investigation of the leather and construction industries to identify other agents which may confer increased risk.

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