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A Case–Control Study of Hematopoietic and Lymphoid Neoplasms: The Role of Work in the Chemical Industry

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The present case-control study was conducted in an effort to determine f work in the chemical industry is related to excesses of certain hematopoietic and lymphoid neoplasms. Cases who died from non-Hodgkin's lymphoma, multiple myeloma, and leukemia were matched by race, gender, age, year of death, and county of residence to controls who died from cardiovascular disease. A total of 618 (309 matched pairs) white male residents of Kanawha County, WV, aged 23–96, who had died between 1965 and I990 were identijied. Conditional logistic regression was conducted and Fielded an associution between chemical industry work and death due to non-Hodgkin's lymphoma, multiple myeloma, and lymphoid leukemia among subjects who died at age <65. These results are consistent with the findings of previous studies linking work in chemical manufacturing to hematopoietic and lymphoid neoplasms, and indicate that the excesses may be related to the occupational exposures in men who died ut younger ages. Am. J. Ind. Med. 31:21–27 © 1997 Wiley-Liss, Inc.

KEY WORDS: ***chemical industry; leukemia; malignant lymphoma; mortality; multiple myeloma, occupational diseases***

INTRODUCTION

Concerns about cancer risk to residents living near chemical manufacturing facilities in Kanawha County, West Virginia spawned an epidemiologic study of trends in cancer mortality in that area [Talbott et al., 1992; Day et al., 1992]. Kanawha County death rates were compared to WV state death rates, and to a control county with little chemical manufacturing. There were no significant differences by county for cancer death rates except for leukemia/aleukemia (OR = 1.27, 95% CI = 1.03–1.60) and lymphoreticulosarcoma (OR = 1.66, 95% CI = 1.24–2.07) among white males. The age-adjusted cancer death rates by period were higher for Kanawha County residents for **all** cancers and lung cancer when compared to West Virginia as a whole. The authors noted four limitations of the study. It was ecologic in nature and lacked diagnostic confirmation on the death certificate, as well as specificity. There was also no occupational or environmental information available to link to disease endpoints except for county of last residence.

The present study was undertaken to examine the relationship between occupation in the chemical manufacturing industry and certain hematopoietic and lymphoid neoplasms in Kanawha County, WV. This study addressed two of the previous ecologic study limitations by utilizing individual rather than aggregate data for selected diseases, and by using occupational data as reported on the death certificate. In addition, specific diseases were examined as opposed to broad classes. The population-based methodology allowed for an increased sample size and an evaluation of individuals who may have worked at any number of chemical manufacturing facilities in Kanawha County. To determine

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TABLE I. Disease Analysis Groups Used in the Kanawha County Case–Control Study, 1965–1990, by ICD-9'

Disease analysis group	No.	ICD-9 cause of death
Non-Hodgkin's lymphoma	140	200.0, 200.1, 200.8, 202.0, 202.3. 202.8, 202.9
Multiple myeloma	83	203.0
Acute leukemia	69	204.0, 205.0, 205.2, 206.0, 207.0. 208.0
Acute nonlymphocytic leukemia	45	205.0, 205.2, 206.0, 207.0
Chronic lymphoid leukemia	61	202.4, 204.1
Chronic myeloid leukemia	24	205.1
Lymphoid leukemia	85	202.4, 204.0, 204.1, 204.8, 204.9
Nonlymphoid leukemia	81	205.0, 205.1, 205.2, 205.9, 206.0, 206.1, 206.9, 207.0
Non-Hodgkin's lymphoma, multiple myeloma, and lymphoid leukemia'	309	200.0, 200.1, 200.8, 202.0, 202.3, 202.4, 202.8, 202.9, 203.0, 203.8, 204.0, 204.1, 204.8, 204.9

'ICD-9, International Classification of Diseases 9th Revision.
'One case of an other immunoproliferative neoplasm, ICO-9 203.8, has been included in this overall group, but was not included in the multiple myeloma group above.

if work in the chemical industry was related to hematopoietic and lymphoid neoplasms (ICD-9 200, 202–208), deaths among white males due to the selected neoplasms were identified. Controls were chosen from a pool of eligible deaths due to cardiovascular disease (ICD-9 410–429) and were matched to the neoplasm deaths on age, race, sex, and year of death.

MATERIALS AND METHODS

The case group consisted of all deceased white male residents of Kanawha County whose underlying cause of death was listed as hematopoietic or lymphatic neoplasms (ICD-9 200, 202–208), and who died in-state between 1965 and 1990. Death certificates for the cases were obtained from the State of West Virginia Department of Health and Human Resources Vital Registration Office. A total of 469 death certificates were identified as potential cases.

The controls consisted of deaths due to cardiovascular disease (ICD-9 410–429) that most closely matched the case's year of death, county of residence, and age within *5* years. Cases and controis were required to have an occupation or industry that could be identified from the death certificate. In the event that a case had missing data on both the ***kind* of *industry*** and ***usual occupation*** fields, it was dropped. In the event that a control was missing these data, a new control was drawn. In the present study, deceased cardiovascular disease controls were selected because they were a practical choice as opposed to the elusive representative cross section of the population. The choice of this control group should not have introduced serious bias. Wang and Miettinen [1984] discussed the use of cardiovascular controls in occupational cancer studies, and such controls were used in a study of cancer among lens manufacturers [Wang et al., 19831. In a cohort mortality analysis of Kanawha County Union Carbide Corporation chemical workers [Rinsky et al., 19881, the standardized mortality ratio (SMR) for arteriosclerotic heart disease was not statistically differe t from that of the general population (SMR = 96. 95% CI = 93–101). Therefore, no association between nonexposure and death from cardiovascular disease would be expected For many of the younger cases, controls who died of cardiovascular diseases were not available, so accident deaths (ICD-9 E800–E999) were selected as a secondary control group. There is no evidence that the exposures of interest are associated with accidental deaths. All death certificates were coded by a qualified nosologist according to the ICD-9.

The individual four-digit ICD-9 codes were divided into nine groups by the project pathologist (S.H.S.). These groups are based on disease, cell of origin, and. for leukemias, whether they were acute or chronic. The leukemias were grouped based on acute vs. chronic, cell type, and. for the categories without enough cases, a combination of both The neoplasms of lymphoid origin (NHL, MM. and lymphocytic leukemias) were combined and analyzed as one group since the different cell types involved are more closely related to one another than they are to the cells in neoplasms of myeloid origin. Some oncogenic events are more associated with lymphoid neoplasms and others with myeloid neoplasms. Because of the varied criteria used. the nine groups are not mutually exclusive. For example, a case of acute myeloid leukemia would be included in three groups: acute leukemia, acute nonlymphocytic leukemia and nonlymphocytic leukemia. The diseases, sample size. and codes included in each group are shown in Table I.

As the key question to be addressed by the study is occupational exposure of the cases relative to their age-matched controls, a sample of cases and controls were selected from the entire study period (n = 100). Next of kin

... the death certificate were contacted by telephone ... questionnaire was administered to validate residence ... occupation of the decedent. While several attempts ... made to contact the entire sample of 100, due to time ... monetary constraints, only 50 subjects were reached.

... investigator-rated classification system was devised ... assigned a score to each case and control based on their ... occupation and kind of industry. The scoring was ... without knowledge of the status of case or control, and ... performed independently by two observers, and later ... compared. Using this preliminary rating, an agreement of ... was reached. For the remaining subjects, the work ... was reviewed and a consensus was reached. The ... were placed into one of three groups; not exposed. ... exposed, and exposed. The exposed group con... subjects whose occupation or industry data specified ... the chemical industry, or at a known chemical manufacturing facility. The potentially exposed group con... of those whose data did not specify work in a chemical manufacturing facility, but involved exposures to industrial... chemicals such as solvents. clinical laboratory re... in the course of their daily work. The unexposed ... consists of workers not routinely exposed to indus... chemicals during their work. An individual with ... stated or known chemical manufacturer listed as ... their industry, or a chemical worker job title listed in their occupation. was classified as exposed.

The Statistical Package for the Social Sciences–PC (SPSS-PC) and the Epidemiologic Graphics, Estimation and ... Package (EGRET) were used for data analysis. Sta... analysis included chi-square tests for categorical ... For the analysis using conditional logistic regres... odds ratios were determined using two variables, the independent (exposure) and the dependent (the disease categories specified in Table III). Review of the results of the previous study [Day et al., 1990] indicated that the concern might be with men who died at younger ages. To explore whether the increase existed only in younger men as sug... by the previous work. an analysis was performed ... age dichotomization. Therefore, three sets of anal... were performed: one on all subjects; a second on those less than 65 at the time of their death; and a third on those ... or older.

RESULTS

The original sample of cases consisted of 469 deaths ... hematopoietic or lymphoid neoplasms. Of these, 24 ... among West Virginia residents who died out of state. ... were therefore excluded. This reduced the study population to 445 cases. After the death certificates were coded ... the ninth revision, 10 additional cases were excluded because the underlying cause of death was no longer considered to be a hematopoietic and lymphoid neoplasm (ICD-9 200, 202–208), leaving a total of 435 cases. The results presented in this paper are restricted to the 309 matched pairs where the case died of non-Hodgkin's lymphoma, myeloma, or lymphoid leukemia.

The majority of controls (94%) died of heart disease (ICD-9 410–429), but for 6% of the younger deaths it was necessary to select from among the accident deaths. After coding underlying cause of death in ICD-9, the cause of death for seven of the original controls was not classified as heart disease in ICD-9 (410–429). These controls were not replaced because it was felt that no material difference in calculated risk would result. In no instance did a control have a hematopoietic or lymphoid neoplasm listed as a contributing or other cause of death.

Cases and controls were compared on the basis of demographic characteristics, and found to be similar. Slightly more cases were married at the time of their death. Controls were more likely to have died somewhere other than the hospital, reflecting the nature of their disease, and were therefore slightly less likely to have had an autopsy performed. The median age at time of death for both cases and controls (matched on age) was 69, with a range of 23–96 for cases and 23–92 for controls. There were differences in age by hematopoietic and lymphoid disease group, however, with a median age of NHL cases of 66; MM cases of 71; and LL cases of 72.

The industry category as defined by the Census Bureau system [Bureau of the Census, 1980] is shown for the study population in Table II. The proportion of cases and controls within each major group appears similar. The largest single proportion of both cases and controls is employed in the manufacturing of nondurable goods, of which chemical manufacturing accounts for the majority.

The hypothesis testing was conducted using conditional (matched) logistic regression. Table III shows the results for non-Hodgkin's lymphoma, multiple myeloma, and lymphoid leukemia in the total group and using the age-stratified groupings. Analysis of the potentially exposed group combined with the chemical workers or combined with the not exposed group made no material difference in the results. The analyses presented here compare the chemical workers to the baseline, or not exposed, group. Therefore. pairs where either member was potentially exposed were excluded from the analysis.

A statistically significantly elevated odds ratio was found for chemical workers who died of non-Hodgkin's lymphoma and who were less than 65 years of age at death (OR = 3.11, p = 0.003), while no association was noted in the unstratified data (OR = 1.52, p = 0.168). Among those who died of multiple myeloma, a statistically significant effect is seen with chemical industry work for both age groups combined (OR = 2.39, p = 0.039). No statistically significant associations were seen in those who died of lymphoid leukemia; however, those who died under age 65 had

TABLE II. Industry Classification System for Kanawha County Case–Control Study, 1965–1990: Major Groups by Case–Control Status

	Cases (no. = 309)		Controls (no. = 309)	
Industry category"	No.	%	No.	%
Agriculture, forestry, and fisheries	4	1.3	6	1.9
Mining	28	9.1	39	12.6
Construction	24	7.8	27	8.7
Manufacturing—nondurable	90	29.1	70	22.7
(Chemical manufacturing)	(81)	(26.2)	(58)	(18.8)
Manufacturing-durable	26	8.4	20	6.3
Transportation, communication, and other public utilities	28	9.1	39	12.6
Wholesale—durable	2	0.6	5	1.6
Wholesale—nondurable	7	2.3	9	2.9
Retail trade	24	7.8	30	9.7
Finance, insurance, and real estate	15	4.9	6	1.9
Business and repair services	4	1.3	5	1.6
Personal services	4	1.3	3	1.0
Entertainment and recreation services	1	0.3	2	0.6
Professional and related services	24	7.8	13	4.2
Public administration	10	3.2	13	4.2
Armed forces	0	—	1	0.3
Industry not reported	30	9.7	21	6.8

'Based on Classified Index of Industries and Occupations. US. Bureau of the Census.

odds ninefold higher for chemical exposure (OR = 9.13, p = 0.09). The most statistically significant association is seen in the combined non-Hodgkin's lymphoma, multiple myeloma, arid lymphoid leukemia group, where those who died under age 65 are over three times as likely to have worked in the chemical industry (OR = 3.31, p = 0.001).

A total of 50 interviews with next of kin were completed in order to evaluate the validity of death certificate industry and occupation data. Agreement was defined as both sources indicating the exact same rating of the three exposure classes for a subject. The result was a 95.9% agreement between the two sources, with a kappa statistic of 0.92. There was very little movement from one exposure group to another, and in no case did an individual change from an exposed to a nonexposed group.

DISCUSSION

Chemical manufacturing in the Kanawha Valley began prior to World War II, around the Kanawha river which served as both a water supply and a source of transportation [Talbott et al., 1992]. The initial processes made use of abundant natural gas supplies in the area. During the war, and shortly thereafter, the industry began a rapid growth phase, **as** natural rubber sources were cut off [Rinsky et al., 19881, and the need for varied chemical products expanded. In a 1986 report, the National Institute for Chemical Studies reported that the Kanawha Valley chemical complex ranked fifth in the U.S. in terms of its size and overall complexity. Over the past 20 years, the plants have become more specialized, and some have limited their production to a few specific end products.

Several studies of health effects among chemical workers have included Kanawha County chemical workers in their populations. The mortality experience of a cohort of 29,139 male chemical workers employed at any of three Union Carbide Corporation facilities in the Kanawha Valley was assessed by Rinsky [1988]. With 19.9% of the cohort deceased, a statistically significant excess of deaths was noted for lympho- and reticulosarcoma. Elevations of the lymphatic tissue cancers were noted across most employment duration categories and latency strata, but no duration–response trends were seen.

A nested case–control study was conducted on 52 cases of non-Hodgkin's lymphoma (NHL) (International Classification of Diseases 9th Edition [DHEW, 19771 ICD-9 200, 202), 20 cases of multiple myeloma (MM) (ICD-9 203), 30 cases of nonlymphoid leukemia (NLL) (ICD-9 205, 206), and 18 cases of lymphoid leukemia (LL) (ICD-9 **204)** from the cohort study [Ott et al., 19891. Controls consisted of workers randomly selected from the total employee population. Elevated odds ratios were seen for NHL in the em-

TABLE III. Summary of Regression Results for Kanawha County Case–Control Study, 1965–1990: Chemical Workers vs. Not Exposed

Disease group	Matched pairs	Odds ratio	p value	95% CI[a]
Non-Hodgkin's lymphoma	106	1.52	0.168	0.84–2.76
<65	50	3.11	0.033	1.10–8.82
265	56	0.97	0.938	0.45–2.08
Myeloma	63	2.39	0.039	1.04–5.48
<65	27	2.50	0.121	0.078–7.97
≥65	36	2.14	0.211	0.65–7.01
Acute leukemia	51	0.69	0.412	0.28–1.69
<65	28	0.69	0.500	0.23–2.03
265	23	0.62	0.590	0.11–3.52
Acute nonlymphoid leukemia	36	1.09	0.865	0.40–2.96
<65	22	1.00	1.00	0.32–3.18
≥65	14	1.26	0.824	0.16–9.66
Chronic lymphoid leukemia	45	1.79	0.258	0.65–4.93
<65	9	b		
≥65	36	1.18	0.777	0.39–3.58
Chronic myeloid leukemia	19	b		
<65	8	b		
≥65	11	b		
Lymphoid leukemia	60	1.10	0.821	0.48-2.51
<65	14	9.13	0.092	0.70–119.40
≥65	46	0.68	0.433	0.26-1.77
Nonlymphoid leukemia	64	0.82	0.606	0.38–1.76
<65	35	1.27	0.628	0.49–3.30
≥65	29	0.29	0.117	0.06-1.37
Non-Hodgkin's lymphoma, myeloma, & lymphoid leukemia	230	1.58	0.030	1.05–2.38
<65	91	3.31	0.001	1.58–6.91
≥65	139	1.02	0.948	0.61–1.71

[a]CI, confidence interval
[b]Did not converge—model not fit.

anol unit, among foremen, and among instrument men in the maintenance and construction work area. When latency was considered, the relationship grew stronger among the instrument men. No apparent association with duration of employment was seen in the ethanol unit. Several significantly positive associations were found for suspect chemical groups, including alkyl sulfates, and metal salts of high toxicity.

Another large-scale cohort study was conducted on 29,289 Union Carbide Corporation workers, which included workers in the Kanawha Valley, as well as elsewhere [Teta et al., 1990]. A significant excess of deaths due to lympho- and reticulosarcoma was noted among hourly employees. Examination of specific locations led to the discovery of a cluster of cases at the South Charleston Chemicals and Plastics location in Kanawha County. No other locations appeared to have an excess of these cancers.

The most striking finding of this study is the association between work in the chemical industry and non-Hodgkin's lymphoma in the men who died at less than 65 years of age. An association was also seen for myeloma and work in the chemical industry, although statistical significance was achieved for myeloma only with the increased sample size of the overall group. Lymphoid leukemia, largely composed of cases of chronic lymphoid leukemia, was strongly associated with chemical industry work in men who died under age 65, although not statistically significant. A grouping of the three diseases, non-Hodgkin's lymphoma, myeloma, and lymphoid leukemia, showed the strongest association, with a tripling of the risk in the younger age group. In the overall group, the association was statistically significant, although no effect was observed in the older age group alone. A reanalysis of the data using the true median age at death as a cutpoint revealed no appreciable differences in the results.

There are several possible reasons why the increased risk of these diseases was noted only in men who died under the age of 65. The first is that chemical workers of all ages have an increased risk of these diseases, but the increased **risk** could only be demonstrated in the younger age group. The incidence and prevalence of these diseases increase dramatically at older ages. and it is likely that these diseases are multicausal. Controlling for specific risk factors in future studies could provide much more information about the true risk to older men. A second explanation might be that the disease is occurring more in the younger age group because the chemical industry exposure is either causing more disease in younger men, or shortening the latency of a disease that would have normally occurred at older ages. An examination of the type, grade, and duration of lymphomas would provide more information about this. If lymphomas that typically occur at older ages were found in younger men, this would support the shortened latency theory. Thirdly, since the cases were selected based on the underlying cause of death, there could have been hematopoietic and lymphoid neoplasms that were not included because they were listed as a contributing cause, or as another significant condition. Lastly, occupation and industry data as recorded on the death certificate may be more accurate for individuals dying at a younger age, as they are more likely to be employed at the time of their death.

Several limitations of this study are worthy of mention. **A** shortcoming of this study was the loss of power due to resmcting the study population to those with appropriate underlying causes of death. Also, the measure of exposure is indirect and uses secondary data sources. **A** validity study was conducted and showed death certificate and interview occupation and industry data were in agreement. Other **ex**posure characterizations that would be useful include the duration of exposure. the time since exposure, specific agents and processes involved, and any exposures aside from work, including hobbies, and the environment.

The measures of disease were not highly specific. As with any mortality study. the type, grade, and stage of the non-Hodgkin' s lymphoma or multiple myeloma and the criteria used for classification of the acute leukemias were unknown. The accuracy of cause of death coding for hematopoietic and lymphoid neoplasms appears to be relatively high, with 98.1% agreement in coding of MM, **88.4%** of NHL, and a range of **34.3–86.3% of** various types of leukemia [Percy et al.. 19811. Overall, the hematopoietic and lymphoid neoplasms were found to have specific concordance between 60.8 and 64.8% of the time [Gobbato et al., 1992]. Most coding errors involved assigning the code for another cancer within the hematopoietic and lymphoid neoplasms grouping (ICD-9 200, 202–208). Although the literature indicates that death certificates appear to be relatively accurate for these types of cancer, the review of histologic and other material would reduce the misclassification of disease. It is possible that an even stronger association would have been found if, for example, the non-Hodgkin's lymphomas could be differentiated as to those of low vs. intermediate and high grade.

With regard to selection bias, it is theoretically possible that the WV residents who died out of state were in some way different from those who died in-state: however. this number was small and was spread across all disease groups. Observation bias was also not likely to have played a role in this study because any exposure ratings were done in a blinded fashion. One limitation of this study was the fact that potential confounders such as previous occupational exposures and smoking could not be controlled for.

The results of this study were consistent with the findings of previous ecologic research in detecting excesses of NHL, MM, and possibly LL in Kanawha County white males using a population-based case-control methodology. It is also consistent with the studies carried out by the National Institute for Occupational Safety and Health. and the chemical manufacturing industry. This methodology allowed for complete ascertainment of deaths due to the selected cancers through 1990, and an increased sample size compared to the cohort studies and the case-control studies at Union Carbide Corporation. In addition. the chemical worker population was not limited to Union Carbide Corporation employees, but included all residents of Kanawha County employed in chemical manufacturing. Future studies of hematopoietic and lymphoid neoplasms should include an examination of age at death or preferably age at exposure, as the present study showed an effect only in those who died under age 65. Had the data not been stratified on age at death. only a weakly positive effect would have been detected in the overall group.

Further research efforts in this area should include an independent review of the diagnostic material and medical records if at all possible. This could provide more reliable and detailed information about the type, grade. and duration of the hematopoietic and lymphoid neoplasms. which might offer clues to the etiology. In addition, it would be useful to review employment records of the major chemical manufacturers in the region. to determine if a cluster exists in any single or group of plants.

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