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CHRONIC LYMPHOCYTIC LEUKEMIA IN RELATION TO CHEMICAL EXPOSURES

KATHLEEN E. MALONE,[1,2] THOMAS D. KOEPSELL,[3] JANET R. DALING,[1,3]
NOEL S. WEISS,[1,2] PETER D. MORRIS,[4] JOHN W. TAYLOR,[5]
G. MARIE SWANSON,[5] AND J. LYNN LYON[6]

Malone, K. E. (Fred Hutchinson Cancer Research Center, Seattle, WA 98104), T. D. Koepsell, J. R. Daling, N. S. Weiss, P. D. Morris, J. W. Taylor, G. M. Swanson, and J. L. Lyon. Chronic lymphocytic leukemia in relation to chemical exposures. *Am J Epidemiol* 1989;130:1152–8.

As part of a population-based case-control study carried out in four areas of the United States, 427 cases of chronic lymphocytic leukemia diagnosed between July 1, 1977, and December 31, 1981, and 1,683 controls were interviewed regarding their history of chemical exposure. Respondents were asked if they had ever been "highly exposed" at home, at work, or elsewhere to one or more of a list of chemicals or to any other such substances not on the list. These chemicals were categorized into 20 exposure groups based on chemical composition. Odds ratios were calculated adjusting for age, sex, race, education level, and geographic location by means of unconditional logistic regression. Increased risks were associated with reported past exposure to acid-containing chemicals, "other caustic substances," aliphatic hydrocarbons, and chlorinated hydrocarbons. Because of the large number of exposures investigated in this study, and because of the relatively imprecise means the authors had to assess exposure, further research is needed to verify these findings.

environmental exposure; leukemia, lymphocytic; occupational diseases

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Little is currently known regarding the etiology of chronic lymphocytic leukemia. Most studies that have investigated the possible association of leukemia with chemical exposures have evaluated all types of leukemia combined and have failed to identify risk factors that act to produce this leukemia alone (1–7). Reports of a cluster of cases within a family from which mo members worked in the dry cleaning indu try (8, 9), of a large number of cases amon benzene-exposed workers (3, 10), and o increased risk within the rubber industr (11–13) suggest an association of chron lymphocytic leukemia with certain chem cals. The purpose of this analysis was

evaluate the associatio cytic leukemia with a ical exposures.

MATERIALS AI

This analysis is ba population-based, ca chronic lymphocytic focus of the study was lation of the immune risk factor for multip chronic lymphocytic le formation about other including chemical ex tained. The study wa areas of the United St western Washington s northern Utah, three prise metropolitan De five counties that co Atlanta, Georgia. All by cancer registries wh Surveillance, Epidemi sults (SEER) program cer Institute.

We sought to conc men and women age who were newly dia lymphocytic leukemia and December 31, 198 one of the study areas nosis. Information w percent of cases who r the 430 case interview cent were proxy interv because of death or se were telephone inter and 76 percent were with the case. Of th cases, 41 percent refu not contacted due to p 30 percent were dece available. Three inte information about ch were excluded from ar Controls were ran the general populatio four geographic areas tocols tailored to the Details about the met

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Abbreviations: CI, confidence interval; OR, odds ratio; SEER program, Surveillance, Epidemiology, and End Results program.

Department of Epidemiology, University of Washington, Seattle, WA.

Fred Hutchinson Cancer Research Center, Seattle, WA.

[3] North Carolina Department of Human Resources, Division of Health Services, Raleigh, NC.

[4] Formerly with the Department of Epidemiology, University of Washington, now in private practice.

[5] Division of Epidemiology, Michigan Cancer Foun dation, Detroit, MI.

[6] Division of Epidemiology, Department of Fam and Community Medicine, University of Utah Medic Center, Salt Lake City, UT.

Reprint requests to Kathleen E. Malone, Fr Hutchinson Cancer Research Center, 1124 Colum Street #MP-381, Seattle, WA 98104.

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evaluate the association of chronic lymphocytic leukemia with a wide range of chemical exposures.

MATERIALS AND METHODS

This analysis is based on data from a population-based, case-control study of chronic lymphocytic leukemia. The main focus of the study was on antigenic stimulation of the immune system as a possible risk factor for multiple myeloma and for chronic lymphocytic leukemia; however, information about other possible risk factors, including chemical exposures, was also obtained. The study was conducted in four areas of the United States: two counties in western Washington state, four counties in northern Utah, three counties that comprise metropolitan Detroit, Michigan, and five counties that comprise metropolitan Atlanta, Georgia. All four areas are served by cancer registries which participate in the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute.

We sought to conduct interviews with men and women aged less than 80 years who were newly diagnosed with chronic lymphocytic leukemia between July 1, 1977, and December 31, 1981, and who resided in one of the study areas at the time of diagnosis. Information was obtained on 82.5 percent of cases who met these criteria. Of the 430 case interviews conducted, 16 percent were proxy interviews with next of kin because of death or severe illness, 9 percent were telephone interviews with the case, and 76 percent were in-person interviews with the case. Of the 81 noninterviewed cases, 41 percent refused, 27 percent were not contacted due to physician refusal, and 30 percent were deceased with no proxy available. Three interviews contained no information about chemical exposure and were excluded from analysis.

Controls were randomly selected from the general population within each of the four geographic areas with the use of protocols tailored to the needs of each site. Details about the methods of control selection have been provided elsewhere (14) but are summarized here. In three areas (Utah, Detroit, and Atlanta), random digit dialing was employed, while in western Washington state, an area sampling method was used. Depending on the joint sex, race, and age distribution of the cases in each area, matching on some or all of these factors was employed in control selection, since these factors are also associated with both the disease and the probability of being exposed to some of the factors of interest. Of the 2,028 eligible controls identified, 83 percent were interviewed. Of the 1,683 control interviews conducted, in-person interviews constituted 81 percent, telephone interviews were used for 18 percent, and less than 1 percent involved proxy interviews.

Trained interviewers administered a standardized questionnaire to each participant which covered a broad range of possible risk factors, including history of chemical exposure. Information on exposure to chemicals was derived principally through the following question: "In your daily life, at home, at work, or elsewhere, was there ever a time when you were highly exposed to products or fumes such as gasoline, turpentine, alcohol (other than liquor), cleaning solvents, benzene, oils, or any others? If yes, what year were you first exposed to this?"

Thirty-one percent of the cases and 23 percent of the controls responded affirmatively to the question of "any others." Without knowledge of case-control status, responses were grouped into 20 categories with the aid of a toxicologist. Responses that involved potential multiple chemical exposure were distributed to all appropriate categories. The list of 20 substance categories and the major constituents of each group, as well as examples of responses which required assignment to multiple categories are available on request from the authors. In addition to the question on chemical exposures, questions were asked concerning employment of six months or more in four specific industries—petroleum, rubber products, dry cleaning, or

meat processing—and concerning participation in five specific hobbies—woodworking, painting, leatherwork, ceramics, and work with engines or motors.

By means of unconditional logistic regression, odds ratios were calculated as estimates of the relative risk for the association of chronic lymphocytic leukemia with exposure to each substance (15). The analysis was repeated after excluding the proxy interview responses to see whether the estimates of effect were altered by the inclusion of a greater proportion of next of kin interviews for cases. Although information on the duration of exposure was not available, the elapsed number of years since first exposure was evaluated with the use of asymptotic tests for trend except where exact tests were needed because of the sparseness of the data (16).

RESULTS

Five characteristics of each respondent were treated as confounding factors in the analysis. Age, sex, and race were included because they are known risk factors for the disease and were matching factors in at least one study center. The cases had a greater proportion of whites (86.2 percent of cases and 77.6 percent of controls were white), fewer females (63.0 percent of cases and 55.5 percent of controls were male), and a higher mean age than the controls. Level of education was considered to be a confounder because there was a difference in risk by educational level (28.3 percent of cases and 23.9 percent of controls never attended high school) and because the probability of exposure to chemicals may vary by socioeconomic status, for which education was the only available indicator. Finally, area of residence was included as a covariate because the ratio of cases to controls varied among the four areas (Washington, 112/139; Utah, 60/280; Atlanta, 41/130; and Detroit, 217/1,134), thereby introducing an association between residence and disease status.

Due to the statistical instability of odds ratio estimates based on small numbers of exposed individuals in some exposure categories, results are reported only for those exposures to which a minimum of 10 cases were exposed. The categories for which results will not be presented are: aldehydes, chemical asphyxiants, asbestos, esters, ethers, fertilizers, inks and dyes, and organic polymers.

Four exposure categories were suspected of being related to chronic lymphocytic leukemia on the basis of previous reports (table 1). Increased risk among persons exposed to pesticides was suggested by a relative risk estimate of 1.5 (95 percent confidence interval (CI) 0.7–3.1), but the confidence limits included 1.0. Exposure to aromatic hydrocarbons appeared to be only weakly related to the occurrence of chronic lymphocytic leukemia, with an adjusted relative risk estimate of 1.2 (95 percent CI 0.8–2.0). This category includes toluene, benzene, xylene, and creosote. Specific examination of reported exposure to benzene, which has long been suspected of being related to chronic lymphocytic leukemia, revealed a relative risk estimate of 1.1 (95 percent CI 0.6–2.0). A 1.5-fold increase in risk was associated with exposure to aliphatic hydrocarbons (95 percent CI 1.1–2.0). Included in this category are gasoline, diesel fuel, propane, kerosene, butane, and other petroleum products. The final category suspected a priori of posing an increased risk comprised chlorinated hydrocarbons, for which a 1.5-fold increase in risk was observed (95 percent CI 1.1–1.9). This exposure category includes carbon tetrachloride and cleaning solvents as well as dry cleaning solvents, although only one case actually reported exposure to dry cleaning chemicals. Persons who reported exposure to cleaning solvents had a 40 percent increase in risk relative to persons who were not so exposed (95 percent CI 1.04–1.9).

There was an increased risk associated with exposure to acids (odds ratio (OR)=1.8, 95 percent CI 1.0–3.1). Included in this category are all kinds of acids, and no particular acid appeared to account for this

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Exposure
Previously reported or hyp
chemical exposures
Aliphatic hydrocarbons
Aromatic hydrocarbons
Chlorinated hydrocarbon
Pesticides
Chemical exposures not pre
reported
Acids
Alkalies
Carbon monoxide
Other caustics
Dust
Metals
Oils
Paints
Employment in selected ind
Dry cleaning industry
Meat processing
Petroleum industry
Rubber industry
Selected hobbies
Painting
Woodworking
Work on engines or motor

* Adjusted for race, age (1
† CI, confidence interval.

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TABLE 1

Risk of chronic lymphocytic leukemia associated with chemical, occupational, and recreational exposures in four areas of the United States served by cancer registries that *participate* in the SEER program (chronic lymphocytic leukemia cases diagnosed between July *1,* 1977. and December 31, *1981)*

Exposure	Exposure frequency		All respondents			Self-respondents only	
	Cases (n = 427) No. (%)	Controls (n = 1,683) No. (%)	Unadjusted odds ratio	Adjusted* odds ratio	95% CI†	Adjusted odds ratio	95% CI†
Previously reported or hypothesized chemical exposures							
Aliphatic hydrocarbons	94 (22.0)	242 (14.4)	1.7	1.5	1.1-2.0	1.6	1.2-2.2
Aromatic hydrocarbons	26 (6.1)	72 (4.3)	1.5	1.2	0.8-2.0	1.1	0.6-2.0
Chlorinated hydrocarbons	89 (20.8)	236 (14.0)	1.6	1.5	1.1-1.9	1.5	1.0-1.9
Pesticides	12 (2.8)	26 (1.5)	1.8	1.5	0.7-3.1	1.5	0.7-3.1
Chemical exposures not previously reported							
Acids	19 (4.4)	42 (2.5)	1.8	1.8	1.0-3.1	1.7	1.0-3.2
Alkalies	10 (2.3)	31 (1.8)	1.3	1.1	0.5-2.3	1.1	0.5-2.4
Carbon monoxide	20 (4.7)	57 (3.4)	1.4	1.4	0.8-2.4	1.3	0.7-2.3
Other caustics	14 (3.3)	31 (1.8)	1.8	1.9	1.0-3.6	2.1	1.1-4.2
Dust	18 (4.2)	59 (3.5)	1.2	1.1	0.7-2.0	1.1	0.6-2.0
Metals	21 (4.9)	73 (4.3)	1.1	1.1	0.7-1.9	1.1	0.7-1.9
Oils	78 (18.3)	284 (16.9)	1.1	1.0	0.7-1.3	1.0	0.7-1.4
Paints	26 (6.1)	81 (4.8)	1.3	1.3	0.8-2.1	1.4	0.8-2.2
Employment in selected industries							
Dry cleaning industry	14 (3.3)	59 (3.5)	0.9	1.1	0.6-2.0	0.9	0.4-1.8
Meat processing	19 (4.4)	52 (3.1)	1.5	1.4	0.8-2.4	1.4	0.8-2.5
Petroleum industry	23 (5.4)	45 (2.7)	2.1	1.6	0.9-2.6	1.9	1.1-3.2
Rubber industry	11 (2.6)	33 (2.0)	1.3	1.3	0.7-2.7	1.4	0.7-3.0
Selected hobbies							
Painting	48 (11.2)	131 (7.8)	1.5	1.2	0.9-1.8	1.4	0.9-2.0
Woodworking	92 (21.6)	289 (17.2)	1.3	1.1	0.8-1.4	1.1	0.8-1.6
Work on engines or motors	58 (13.6)	165 (9.8)	1.4	1.1	0.7-1.5	1.0	0.4-2.4

* Adjusted for race, age (10-year age groups), education, sex, and study site.

† CI, confidence interval.

elevation. For the group of persons exposed to "other caustics," which includes chlorine, sulfur, fluorine, phosgene, and nitrogen, a relative risk of 1.9 was observed (95 percent CI 1.0-3.6). Little or no increase in risk was observed for persons exposed to alkalies, carbon monoxide, dust, metals, oils, and paints.

Exclusion of the proxy respondents from analysis did not substantially alter the odds ratios for any of these exposures (table 1).

For a few exposures, there was some suggestion of a difference in effect based on the amount of time that had elapsed since first reported exposure, although interpretation must be cautious because of very small numbers. Reported exposure to acids that began 20 or more years earlier was associated with a higher risk (20-39 years: OR = 2.1, 95 percent CI 1.0-4.5; ≥40 years: OR = 2.1, 95 percent CI 0.5-8.5) than was exposure that began within the last 19 years (OR = 1.5, 95 percent CI 0.2-9.4). The association with aliphatic hydrocarbons was strongest among subjects who reported first exposure in the more recent past (1-19 years: OR = 2.0, 95 percent CI 1.0-3.8; 20-39 years: OR = 1.5, 95 percent CI 1.0-2.3; ≥40 years: OR = 1.3, 95 percent CI 0.8-2.1). Exposure to chlorinated hydrocarbons that began within the last 39 years was associated with a greater elevation in risk than was such exposure that began 40 or more years earlier (1-19 years: OR = 1.7,

95 percent CI 0.9–3.1; 20–39 years: OR = 1.7, 95 percent CI 1.2–2.5; ≥40 years: OR = 0.9, 95 percent CI 0.5–1.7). No other suggestions of trend related to elapsed time since first exposure were observed.

As shown in table 1, little elevation in risk was observed for employment in the rubber industry (OR = 1.3, 95 percent CI 0.7–2.7) or in the dry cleaning industry (OR = 1.1, 95 percent CI 0.6–2.0). Employment in the petroleum industry was associated with a 1.6-fold increase in risk (95 percent CI 0.9–2.6).

Only slight or no increases in risk were observed for exposure to the hobbies of woodworking, painting, leatherwork, ceramics, or working on engines or motors.

Discussion

The nature of the question asked of study subjects which yielded most of the data utilized in this analysis raises concern about the possibility of recall bias. With an open-ended question, there is a risk that cases or their next of kin may overreport or selectively volunteer more information about such exposures. While more case than control interviewees gave an affirmative response to this question, it was reassuring that positive associations were not observed for every exposure category. In particular, only very weak associations were observed for benzene and for aromatic hydrocarbons as a whole, which, after ionizing radiation, are the most well-known leukemogenic agents.

Another limitation concerns the possibility of misclassification of responses. A large proportion of responses to the "any other chemical" part of the question required judgments about the exposure classifications into which such a response should be distributed. It is possible that some of these assignments were incorrect, in that a person may not have been exposed to all of the substances attributed to the particular response. However, since the exposures of both cases and controls were classified without knowledge of their disease status, any misclassification of this nature would be expected to bias the results toward the finding of no association. It is also possible that some individuals were exposed to chemicals of which they were unaware, and which increased their risk, and that some of these were correlated with one of the reported exposures. This would produce a spuriously high risk associated with the latter type of exposure.

A third limitation is the scarcity of information on the "dose" of exposure, such as frequency, intensity, or duration of exposure. This omission was largely because the primary focus of the study was on a different set of risk factors. The only variable related to "dose" was the year of first exposure to each substance. Examination of this variable was conducted cautiously since at best any trend detected would be a crude indicator of some relation with time. Lastly, because 20 exposures were examined, there remains the likelihood that some positive findings may be attributable to chance.

The observation of a suggestive increase in risk associated with pesticide exposure supported the findings of several prior studies which examined farming as a risk factor for leukemia, although none of these studies examined chronic lymphocytic leukemia specifically and none ascertained specific chemical exposures (17–19). In a mortality study based on Iowa death certificates (20), there was an almost twofold increase in the incidence of chronic lymphocytic leukemia among farmers in counties with high herbicide use (OR = 1.9, 95 percent CI 1.2–3.1). At least one case-control study of chronic lymphocytic leukemia that examined farming found a small negative association (21). Among studies of pesticide manufacturers and/or applicators, there has been no suggestion of any association with leukemia (22–28). Many of these studies suffer from sample size constraints. To some extent, this was true in our study, because each of our four study centers is urban and thus a relatively small fraction of subjects reported that they had been exposed to pesticides.

The finding of no association for exposure to aromatic hydrocarbons was unex-

pected since chemicals long been suspected of occurrence of leukemia lymphocytic leukemia. of employment in th McMichael et al. (12, exposure to be commor associated with an elev lymphocytic leukemia. matic solvents were pr until the early 1940s, the most common sol by the 1950s, petroleu major source of aroma 30). Several studies ha sistent results (12, 13, separately the risks r based solvents and pe vents, using either date surrogates or industrial of solvents used. Thert gestion of an associati coal-based solvents, an that we found little ass a lack of exposure to coa within the study popula young enough to have e posure to coal tar-based At least two other st elevated risks for leuke bined) associated with leum or other aliphati 32, 33). Two studies w risk for chronic lymph sociated with employme industry found no ass Petroleum-based solven aliphatic in structure, di dominate in industry u 1950. As is true for som aliphatic hydrocarbons contamination by subst benzene impurities (34) evaluation of time sinc aliphatic hydrocarbons higher risk for those fi 20-year period preceding study is needed to deter is related to qualitative natu re of recent exposur Past reports of chroni

pected since chemicals in this category have long been suspected of being related to the occurrence of leukemias, including chronic lymphocytic leukemia. In an examination of employment in the rubber industry, McMichael et al. (12, 13) found solvent exposure to be common to most of the jobs associated with an elevated risk of chronic lymphocytic leukemia. Virtually all aromatic solvents were produced from coal tar until the early 1940s, with benzene being the most common solvent used, whereas, by the 1950s, petroleum had become the major source of aromatic solvents (12, 29, 30). Several studies have tried, with inconsistent results (12, 13, 29, 31), to evaluate separately the risks related to coal tar-based solvents and petroleum-based solvents, using either dates of employment as surrogates or industrial records of the type of solvents used. There is a stronger suggestion of an association with the earlier coal-based solvents, and it is conceivable that we found little association because of a lack of exposure to coal tar-based solvents within the study population, which may be young enough to have avoided massive exposure to coal tar-based solvents.

At least two other studies have reported elevated risks for leukemia (all sites combined) associated with exposure to petroleum or other aliphatic hydrocarbons (7, 32, 33). Two studies which addressed the risk for chronic lymphocytic leukemia associated with employment in the petroleum industry found no association (34, 35). Petroleum-based solvents, which are more aliphatic in structure, did not begin to predominate in industry until approximately 1950. As is true for some other chemicals, aliphatic hydrocarbons have a history of contamination by substantial amounts of benzene impurities (34). In our data, the evaluation of time since first exposed to aliphatic hydrocarbons revealed a slightly higher risk for those first exposed in the 20-year period preceding interview. Further study is needed to determine whether this is related to qualitative differences in the nature of recent exposures.

Past reports of chronic lymphocytic leukemia in a family employed in the .dry cleaning industry have led to speculation about the risk associated with exposure to dry cleaning chemicals. The observation of an elevated risk for exposure to chlorinated hydrocarbons, the category in which dry cleaning chemicals are grouped, would be compatible with such an association. However, only one case reported exposure to dry cleaning chemicals specifically. Included in this category are chemicals such as trichlorethylene and tetrachlorethane, both of which were commonly used in the dry cleaning industry and both of which, at least in the past, were known to be contaminated by benzene impurities (36).

We are aware of no previous findings of a heightened risk associated with exposure to acids or caustic substances. A factor which detracts from the credibility of the elevation associated with caustic substances is the large number of responses which led to a subject being included within this category, such as exposure to mustard gas, tear gas, argon gas, welding fumes, and a number of responses simply designated as "caustic vapor or caustic chemicals."

Participation in any of the five hobbies addressed in the interview was not found to be associated with chronic lymphocytic leukemia. The findings of no association for hobbies involving engines or motors as well as woodwork differ somewhat from a recent report by Flodin et al. (37) in which occupational exposure to each was found to be associated with chronic lymphocytic leukemia (engine exhaust: OR = 2.5, 95 percent CI 1.5-4.0; fresh wood OR = 3.2, 95 percent CI 1.5-6.6). The contrast in their findings from those in this study may be attributable to the possibly large differences between the level of exposure experienced in an occupation compared with that encountered through a recreational source.

The increased risk estimates observed in these data for chlorinated hydrocarbons and aliphatic hydrocarbons support previous reports and warrant further, more specific probing with more detailed exposure and occupational information. The

suggestively increased estimates for exposure to pesticides should be further explored in populations with a higher prevalence of exposure. Last, the elevations in risk associated with exposure to acids and other caustic substances deserve attempts at replication. Given the paucity of current information regarding the etiology of chronic lymphocytic leukemia, further exploration of the possible association of chemical exposures and this disease is warranted.

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in high-risk industri
others) was significa
Alcohol intake and h
that were not statisti

alcohol drinking; b
tract

Environmental factors
suspected of contributing
cancer of the lower urinary
linked the occupational
stuff workers to urinary
1895 (1). Since then, a nu
occupations for this cance
tified, including employm
leather, paint, and chemi
(2–6).

Besides occupation, oth
factors which have been s

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