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Solvent exposure and non-Hodgkin Lymphoma: no risk in a population-based study in the San Francisco Bay Area

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Abstract

The literature on environmental exposures and risk of non-Hodgkin Lymphoma(NHL) is inconsistent and no occupational exposures have been conclusively identified as causal factors. We used job exposure matrices to assess the association between occupational exposure to solvents in a population-based case-control study of NHL (N=1591 cases,N=2515 controls) in the San Francisco Bay Area between 1988 and 1995. Occupational histories were collected during in-person interviews and were coded according to the 1980 U.S. Department of Commerce Alphabetic Index of Industries and Occupations. Odds ratios (ORs) and 95% confidence intervals (CI) were adjusted for potential confounders. Our results have provided no support for an association between NHL and occupational exposure to solvents.

Keywords

lymphoma, non-Hodgkin; case-control; occupational exposure; solvents

Introduction

In 2009 in the United States approximately 66,000 newly diagnosed cases and 19,500 deaths from NHL are expected(1). Few risk factors for NHL have been identified to explain the increase in NHL incidence since the 1970s(2-7). The literature on risk of NHL and environmental exposures, including viral, chemical, lifestyle and occupational, has identified few etiologic factors(2,8) with no occupational exposures, including solvents, have been (9-17) conclusively established as causal factors(2,8,18-20). To address these inconsistent results in previous studies, we used job-exposure-matrices to estimate the effect of occupational solvent exposure on NHL risk in our large population-based case-control study of NHL in the San Francisco Bay Area.

Materials and Methods

Detailed methods of patient recruitment previously have been reported(21-25). Briefly, a rapid case-finding system was used to identify NHL patients within approximately one month of diagnosis in hospitals in six San Francisco Bay Area counties. Eligible patients were diagnosed between 1987 and 1993, were between 21 and 74 years of age and resided in six Bay Area counties at the time of diagnosis. Diagnostic pathology materials were re-reviewed and

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classified using the Working Formulation by the expert study pathologist. Results are presented for all NHL and common subtypes reflecting recent WHO classifications(26): diffuse large-cell and immunoblastic large-cell(DLCL); follicular lymphomas(FL); chronic lymphocytic leukemia/small-lymphocytic lymphoma(CLL/SLL); and "other" NHL. A total of 1591(72%) eligible NHL patients completed interviews. Control participants were identified using random-digit dial(27,28) and were frequency matched to the cases by sex, county of residence and age in 5-year groups. Eligibility criteria were the same as for cases with the exception of NHL diagnosis. A total of 2515(78%) eligible control participants completed interviews.

The UCSF Committee on Human Research approved study protocols and procedures and all participants provided written informed consent prior to interview. Structured interviews were conducted in-person by trained interviewers. No proxy interviews were conducted. Detailed questions were asked regarding history of occupational and other exposures and lifestyle factors. Occupational history included jobs held for ≥6 months when ≥18 years old. Most questions pertained to incidence of exposures or activities up until one year before diagnosis (cases) or interview(controls).

The 1980 U.S. Department of Commerce Alphabetical Index of Industries and Occupations was used to code 231 industries and 509 occupations(29). Exposure to any organic solvent and to benzene and formaldehyde was assessed by linking the coded occupation and industry data with job-exposure matrices(JEMs) developed by Dosemeci et al.(30,31) and as described by Wang et al.(14). Each occupation and industry was assigned an estimate of exposure intensity (I) and probability(P) (0=none, 1=low, 2=medium, and 3=high exposure). Exposure I and P were estimated on the expected exposure level for a worker in that industry or occupation. If the exposure depended upon occupation *or* industry only, then the exposure score was the square of the exposure estimation for that occupation or industry ($I=I^2$ and $P=P^2$). If the exposure depended upon occupation *and* industry, then the exposure score was the product of the occupational and industrial exposure estimation ($I=I_{occupation}*I_{industry}$ and $P=P_{occupation}*P_{industry}$). For each study participant, this information was combined with job duration in years(D) to estimate average exposure intensity, $\sum[(I_{job}*D_{job})/D_{exposure}]$, and probability, $\sum[(P_{job}*D_{job})/D_{exposure}]$. Average exposure intensity and probability were summarized over multiple jobs and categorized as never exposed(0), low(<3), medium(3–5), and high intensity/probability(≥6).

Unconditional logistic regression was used to obtain ORs as estimates of relative risk(hereafter called risk) and 95% CIs in SAS(v. 9.1; SAS Institute,Cary,NC). All statistical tests were two-sided. All models were adjusted for age in 5-year groups, sex, race/ethnicity(Hispanic white, non-Hispanic white, African-American, Asian, other) and education level(≤12 years, >12 years). Analyses were restricted to HIV-negative participants(N=1262 cases, N=2094 controls).

Results

The mean age for NHL and control participants was 57 and 54 years, respectively after removal of HIV-positive cases. Cases were somewhat less educated and a greater proportion were men. The median lifetime number of jobs for NHL and control participants was four and five, respectively. There was no association between average intensity(Table 1) and probability (Table 2) of solvent, benzene or formaldehyde exposure and NHL risk for all NHL, DLCL, FL, CLL/SLL or "other" NHL. Results did not differ when men and women were analyzed separately and there were few women in the various exposure subgroups(data not shown).

Discussion

This large population-based case-control study provides no support for an association between occupational exposure to solvents and NHL. Several factors may contribute to the inconsistent results across previous studies that have evaluated the relationship between occupational solvent exposure and NHL(8,16,18,32,33). Studies that assume exposures based on job titles lack specific individual-level exposure information. Many occupational settings entail exposure to multiple chemicals that when coupled with exposure levels presumed by specific job titles can lead to substantial measurement error and exposure misclassification. Exposure studies often lack complete job and lifestyle histories that may confound or modify the main occupational effects.

This study has several strengths, including its large sample size, study design diminishing potential selection bias(e.g. random-digit-dial to identify age-, sex- and county-matched controls from the same population from which the cases arose), and rapid case ascertainment to identify all incident NHL cases diagnosed in six Bay Area counties between 1988 and 1993. To diminish interviewer bias, the study hypotheses were not known to the experienced interviewers who conducted in-person interviews with participants. Because specific occupations are not known to be risk factors for NHL there was less likelihood of response bias. The design of this case-control study allowed us to adjust for potential confounders and examine potential risk factors by NHL subtype. With our large sample size, we had 80% power to detect an OR of ≥1.5 for the lowest frequency exposure(5%).

In conclusion, we found no evidence that occupational exposure to solvents was associated with NHL. Examination of other potential risk factors including viral, chemical, lifestyle and occupational exposures is needed to increase our understanding of the etiology of NHL.

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Table 1

Odds Ratios (ORs) and 95% confidence intervals (CIs) for non-Hodgkin lymphoma (NHL) and NHL subtypes associated with average intensity of solvent exposure, San Francisco Bay Area, California.

Total	Controls[a] N=2094 n (%)	Total NHL[a] N=1262 n (%)	OR (95 % CI)[b]	DLCL N=497 n (%)	OR (95 % CI)[b]	FL N=340 n (%)	OR (95 % CI)[b]	CLL/SLL N=148 n (%)	OR (95 % CI)[b]	Other NHL N=277 n (%)	OR (95 % CI)[b]
Solvents											
Never	526 (25)	344 (27)	1.0	140 (28)	1.0	92 (27)	1.0	41 (28)	1.0	71 (26)	1.0
Ever	1568 (75)	918 (73)	0.95 (0.80-1.1)	357 (72)	0.93 (0.74-1.2)	248 (73)	1.1 (0.79-1.4)	107 (72)	0.95 (0.63-1.4)	206 (74)	0.87 (0.64-1.2)
Low	1147 (55)	662 (52)	0.95 (0.79-1.2)	250 (50)	0.89 (0.69-1.1)	181 (53)	1.0 (0.77-1.4)	80 (54)	0.97 (0.63-1.5)	151 (55)	0.87 (0.62-1.2)
Med-High	421 (20)	256 (20)	0.95 (0.78-1.2)	107 (22)	1.1 (0.78-1.4)	67 (20)	1.1 (0.75-1.5)	27 (18)	0.90 (0.53-1.5)	55 (20)	0.88 (0.59-1.3)
Benzene											
Never	726 (35)	479 (38)	1.0	191 (38)	1.0	138 (41)	1.0	57 (39)	1.0	93 (34)	1.0
Ever	1368 (65)	783 (62)	0.93 (0.79-1.1)	306 (62)	0.93 (0.74-1.2)	202 (59)	0.90 (0.69-1.2)	91 (61)	0.90 (0.61-1.3)	184 (66)	0.95 (0.70-1.3)
Low	967 (46)	551 (44)	0.92 (0.77-1.1)	208 (42)	0.89 (0.70-1.1)	142 (42)	0.89 (0.67-1.1)	67 (45)	0.93 (0.61-1.4)	134 (48)	0.97 (0.71-1.3)
Med-High	401 (19)	232 (18)	0.95 (0.77-1.2)	98 (20)	1.0 (0.76-1.4)	60 (18)	0.92 (0.64-1.3)	24 (16)	0.84 (0.50-1.4)	50 (18)	0.89 (0.6-1.3)
Formaldehyde											
Never	839 (40)	505 (40)	1.0	201 (40)	1.0	134 (39)	1.0	58 (39)	1.0	112 (40)	1.0
Ever	1255 (60)	757 (60)	1.0 (0.87-1.2)	296 (60)	1.0 (0.82-1.2)	206 (61)	1.1 (0.85-1.4)	90 (61)	1.0 (0.73-1.5)	165 (60)	0.94 (0.73-1.2)
Low	781 (37)	485 (38)	1.0 (0.88-1.2)	202 (41)	1.1 (0.88-1.4)	123 (36)	1.0 (0.78-1.3)	59 (40)	1.1 (0.73-1.6)	101 (36)	0.92 (0.69-1.2)
Med-High	474 (23)	272 (22)	1.0 (0.81-1.2)	94 (19)	0.85 (0.65-1.1)	83 (24)	1.2 (0.87-1.6)	31 (21)	0.99 (0.63-1.6)	64 (23)	0.99 (0.71-1.4)

[a] The number of participants may vary because of missing data

[b] Age, sex, education, race, and ethnicity adjusted values; DLCL, diffuse large-cell and immunoblastic large-cell; FL, follicular lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma.

Table 2

Odds Ratios (ORs) and 95% confidence intervals (CIs) for non-Hodgkin lymphoma (NHL) and NHL subtypes associated with average probability of solvent exposure, San Francisco Bay Area, California.

Total	Controls[a] N=2094 n (%)	Total NHL[a] N=1262 n (%)	OR (95 % CI)[b]	DLCL N=497 n (%)	OR (95 % CI)[b]	FL N=340 n (%)	OR (95 % CI)[b]	CLL/SLL N=148 n (%)	OR (95 % CI)[b]	Other NHL N=277 n (%)	OR (95 % CI)[b]
Solvents											
Never	526 (25)	344 (27)	1.0	140 (28)	1.0	92 (27)	1.0	41 (28)	1.0	71 (26)	1.0
Ever	1568 (75)	918 (73)	0.95 (0.8 - 1.1)	357 (72)	0.93 (0.74 - 1.2)	248 (73)	1.1 (0.79 - 1.4)	107 (72)	0.95 (0.63 - 1.4)	206 (74)	0.87 (0.64 - 1.2)
Low	727 (35)	427 (34)	0.95 (0.79 - 1.2)	168 (34)	0.95 (0.73 - 1.2)	117 (34)	1.1 (0.77 - 1.5)	52 (35)	1.0 (0.64 - 1.6)	90 (32)	0.83 (0.59 - 1.2)
Med-High	841 (40)	491 (39)	0.95 (0.78 - 1.2)	189 (38)	0.92 (0.71 - 1.2)	131 (39)	1.0 (0.76 - 1.4)	55 (37)	0.90 (0.57 - 1.4)	116 (42)	0.90 (0.64 - 1.3)
Benzene											
Never	726 (35)	479 (38)	1.0	191 (38)	1.0	138 (41)	1.0	57 (39)	1.0	93 (34)	1.0
Ever	1368 (65)	783 (62)	0.93 (0.79 - 1.1)	306 (62)	0.93 (0.74 - 1.2)	202 (59)	0.90 (0.69 - 1.2)	91 (61)	0.90 (0.61 - 1.3)	184 (66)	0.95 (0.70 - 1.3)
Low	672 (32)	377 (30)	0.90 (0.75 - 1.1)	148 (30)	0.92 (0.71 - 1.2)	98 (29)	0.88 (0.65 - 1.2)	47 (32)	0.96 (0.61 - 1.5)	84 (30)	0.89 (0.63 - 1.2)
Med-High	696 (33)	406 (32)	0.95 (0.79 - 1.1)	158 (32)	0.94 (0.73 - 1.2)	104 (31)	0.91 (0.67 - 1.2)	44 (30)	0.85 (0.54 - 1.3)	100 (36)	1.0 (0.72 - 1.4)
Formaldehyde											
Never	839 (40)	505 (40)	1.0	201 (40)	1.0	134 (39)	1.0	58 (39)	1.0	112 (40)	1.0
Ever	1255 (60)	757 (60)	1.0 (0.87 - 1.2)	296 (60)	1.0 (0.82 - 1.2)	206 (61)	1.1 (0.85 - 1.4)	90 (61)	1.0 (0.73 - 1.5)	165 (60)	0.94 (0.73 - 1.2)
Low	885 (42)	552 (44)	1.0 (0.89 - 1.2)	232 (47)	1.1 (0.91 - 1.4)	139 (41)	1.0 (0.80 - 1.4)	61 (41)	0.98 (0.67 - 1.4)	120 (43)	0.96 (0.73 - 1.3)
Med-High	370 (18)	205 (16)	0.93 (0.76 - 1.1)	64 (13)	0.73 (0.54 - 1.0)	67 (20)	1.2 (0.85 - 1.6)	29 (20)	1.2 (0.73 - 1.9)	45 (16)	0.91 (0.63 - 1.3)

[a] The number of participants may vary because of missing data

[b] Age, sex, education, race, and ethnicity adjusted values; DLCL, diffuse large-cell and immunoblastic large-cell; FL, follicular lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma.