Short Communication

Risk of Childhood Leukemia and Parental Self-reported Occupational Exposure to Chemicals, Dusts, and Fumes: Results from Pooled Analyses of German Population-based Case-Control Studies[1]

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Abstract

A recent large-scale United States study reported an association between parental exposure to hydrocarbons at work and the risk of childhood leukemia. Parental occupational exposure to different chemicals and industrial dusts or fumes also was assessed in three German case-control studies that were conducted from 1992–1997. The design and methods of exposure assessment were similar for these studies; therefore, they were pooled for this analysis. In total, these three studies involved 1138 cases of acute lymphocytic leukemia (ALL) and 2962 controls. We found that maternal exposure to paints or lacquers during the preconception period (odds ratio, 1.6; 95% confidence interval, 1.1–2.4) and during the index pregnancy (odds ratio, 2.0; 95% confidence interval, 1.2–3.3) was related to an increased risk of childhood ALL. Whereas our findings for exposure to paints or lacquers confirmed observations from the United States study, we failed to confirm associations between risk of ALL and maternal exposure to solvents and parental exposure to plastic materials. Our studies provide some evidence that parental occupational exposure to certain substances may be associated with cancer risk in offspring; however, more specific studies are needed to identify such substances and the doses that may be hazardous.

Introduction

In a recent issue of *Cancer Epidemiology, Biomarkers & Prevention*, Shu *et al.* (1) reported results from a large-scale United States case-control study evaluating the association of parental occupational exposure to hydrocarbons with risk of ALL[3] in offspring. Their major findings were increased risks of ALL in offspring after maternal exposure to solvents and paints or thinners during the preconception period and pregnancy and after maternal exposure to plastic materials during the postnatal period.

From 1992–1997, three large-scale population-based case-control studies were conducted in Germany based on data from the nationwide German Childhood Cancer Registry. Data were collected using a self-administered questionnaire and subsequent telephone interviews with both parents. The interview was based on a structured questionnaire developed by the United States Children's Cancer Group (2) but modified to assess country-specific issues. We provided a list of potential occupational exposures to certain chemicals, industrial dusts, and fumes to all parents.

Here we present results of analyses based on 1138 cases of ALL and 2962 controls that have been conducted to confirm or refute the findings of the United States report (1). The strength of the findings of Shu *et al.* (1) would be considerably greater if the results of two comprehensive investigations featuring similar methodology but with different settings and independent populations were consistent.

Materials and Methods

Details of the German case-control studies have been published elsewhere (3–12). Briefly, this pooled analysis comprises three study parts: (*a*) a case-control study on childhood cancer in the Northwestern part of Germany (LSP); (*b*) a case-control study on childhood leukemia and childhood lymphoma embedded in an ecological study in the vicinity of German nuclear installations and selected control regions (NIP); and (*c*) a case-control study on childhood cancer covering the entire region of West Germany (WGP). All studies were based on childhood cancer cases diagnosed before the age of 15 years who were registered with the German Childhood Cancer Registry. All controls were drawn from population registration files. The methods of exposure assessment were identical in all three study parts and were performed by the same personnel.

The LSP started at the end of 1992 and was completed in 1996 (3–6). The following diagnostic groups were considered: (*a*) acute leukemia; (*b*) lymphoma; (*c*) tumor of the central nervous system; (*d*) neuroblastoma; (*e*) nephroblastoma; (*f*) bone tumor; and (*g*) soft tissue sarcoma. Cases were eligible if they were newly diagnosed between July 1988 and June 1993 and if they lived within the boundaries of Lower Saxony at the date of diagnosis. We sampled two controls for each child with leukemia: (*a*) one control from the community where the diseased child lived; and (*b*) another control selected from a randomly selected community in Lower Saxony by a population-weighted sampling procedure. Additional matching criteria were gender and date of birth within 1 year. No controls were drawn for the group of cases with solid tumors.

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[3] The abbreviations used are: ALL, acute lymphocytic leukemia; OR, odds ratio; CI, confidence interval; LSP, study part conducted in Lower Saxony; NIP; study part conducted in the vicinity of nuclear installations; WGP; study part conducted in West Germany.

The NIP study population consisted of children born after July 1, 1975 diagnosed with childhood acute leukemia or lymphoma between January 1980 and September 1994 who lived no more than 15 km (approximately 10 miles) from a German nuclear installation or in a matched control region at the date of diagnosis (7). For all cases, one corresponding control matched for gender, date of birth within 1 year, and community was randomly selected from the respective population registration file.

The NIP and the WGP were conducted simultaneously between 1993 and 1997. The WGP consisted of the same diagnostic groups as the LSP (8–12). Cases were included if the disease was diagnosed between October 1992 and September 1994 and if the child lived in West Germany at the date of diagnosis. Again, controls were drawn from the population registration file of the same community as the corresponding case and were matched for gender and date of birth within 1 year. Unlike the LSP, individual controls were chosen in the WGP for all cases, irrespective of their diagnosis.

The self-administered questionnaire used in all study parts listed a number of chemicals to which parents might have been occupationally exposed. This list contained four groups of chemicals and three groups of industrial dusts or fumes. The groups of chemicals were as follows: (*a*) solvents; (*b*) paints, thinners, colorants, or lacquers (referred to as paints or lacquers throughout this study); (*c*) oil products; and (*d*) pesticides. The groups of industrial dusts or fumes were as follows: (*a*) fumes from plastic or resin processing; (*b*) industrial dusts (*e.g.*, from the coal or wood industry); and (*c*) fumes or dusts from metal melting. Mothers and fathers were asked the same questions for three different time of exposure windows: (a) during the year before conception; (*b*) during pregnancy; and (*c*) after birth.

The statistical approach for calculating pooled risk estimates for all study parts was to break matching status and use all available cases and controls. ORs and 95% CIs were then obtained by logistic regression models involving a posterior stratification for gender, age, and year of birth, with additional adjustments for degree of urbanization (urban, mixed, or rural) and socioeconomic status (high or other) (13). Socioeconomic status was estimated by family net income and parental education. We also calculated ORs based on the original 1:1 matching by conditional logistic regression analysis. Both models were used to obtain ORs for the three individual study parts. In this report, we present the results for the first statistical approach. Results from the 1:1 matched analyses and study-specific results will be discussed if they reveal differences from the favored model that cannot be explained by random variability. All exposures were analyzed by time of exposure windows.

Results

In total, response rates were 81% among cases and 67% among controls. There were only small differences between the study parts, with the WGP having the highest response rates. The major reason for nonresponse was parental refusal. Participation details have been described previously (3, 7, 8). A telephone interview was conducted with 95.1% of all families. We conducted 88.8% of the telephone interviews with both parents (parents of ALL cases, 87.9%; parents of controls, 89.2%), 9.0% of the telephone interviews with the mother only (mothers of cases, 9.4%; mothers of controls, 8.8%), and 2.2% of the telephone interviews with the father only (fathers of cases, 2.7%; fathers of controls, 2.0%).

Table 1 presents demographic characteristics of ALL cases and total controls. Controls were more likely to come from a family with a higher socioeconomic status. Table 1 also shows that the WGP contributed about one-half of all study cases and almost two-thirds of all study controls to the analysis, whereas the LSP had the smallest study population. Differences in the age distributions are due to controls who were individual matches for cases with diagnoses other than ALL (*i.e.*, solid tumors) who, on average, were older than ALL patients at the date of diagnosis. Because individual controls for children with a solid tumor were sampled only in the WGP, this study accounts for the entire difference in the age distribution of the pooled study population.

Table 1 Demographic characteristics of ALL cases and controls

	Cases (n = 1138)	Controls (n = 2962)	P
Gender			
Male	671 (59.0%)	1700 (57.4%)	
Female	467 (41.0%)	1262 (42.6%)	0.36
Age (yrs)			
<1	42 (3.7%)	252 (8.5%)	
1–4	649 (57.0%)	1304 (44.0%)	
5–9	318 (27.9%)	893 (30.1%)	
10+	129 (11.3%)	513 (17.3%)	<0.01
Degree of urbanization			
Urban	398 (35.0%)	1065 (36.0%)	
Mixed	412 (36.2%)	1032 (34.8%)	
Rural	328 (28.8%)	865 (29.2%)	0.71
Socioeconomic status			
Other	855 (75.1%)	2112 (71.3%)	
High	283 (24.9%)	850 (28.7%)	0.01
Study part[a]			
LSP	144	433	
NIP	481	688	
WGP	650	2057	

[a] Because some subjects fulfilled the eligibility criteria of more than one study part, the sum of participants for the individual studies is larger than the total when all study parts are combined.

Table 2 presents the association of parental occupational exposures to certain chemicals, industrial dusts, and fumes with childhood ALL risk. No major differences between cases and controls were found for any paternal occupational exposure to chemicals, plastic or resin fumes, and metal melting. More case fathers reported being exposed to industrial dusts; however, with ORs ranging between 1.2 and 1.3, the association was rather weak. The highest risks of ALL were found to be associated with maternal exposure to paints or lacquers during the preconception period (OR, 1.6; 95% CI, 1.1–2.4) and during the index pregnancy (OR, 2.0; 95% CI, 1.2–3.3). During the postnatal period, the ALL risk was close to unity. Elevated ORs between 1.2 and 1.3 were observed for maternal exposure to solvents during the preconception period and index pregnancy. ORs for the preconception period and gestation were also somewhat higher for exposure to oil products, plastic or resin fumes, and industrial dusts; however, due to the smaller number of subjects, the risk estimates were less precise, and the CIs were wide.

Risk estimates were relatively consistent across the study parts, particularly for maternal exposure to paints or lacquers. The largest difference occurred with regard to paternal exposure to plastic or resin fumes at any time, which was associated with ALL risk in the LSP [OR, 2.0; 95% CI, 1.0–4.1; reported by Kaatsch *et al.* (3)] but not in either the WGP (OR, 1.2; 95% CI, 0.8–1.8) or NIP (OR, 0.7; 95% CI, 0.4–1.4). On the basis

Table 2 Association of childhood ALL with paternal and maternal occupational exposure to chemicals, dusts, and fumes[a]

	Any time		Preconception		During pregnancy		Postnatal	
	Case/control	OR (95% CI)	Case/control	OR (95% CI)	Case/control	OR (95% CI)	Case/control	OR (95% CI)
Paternal exposure to								
Solvents	151/382	1.0 (0.8–1.3)	138/359	1.0 (0.8–1.2)	113/292	1.0 (0.8–1.3)	111/303	1.0 (0.8–1.2)
Paints or lacquers	157/369	1.1 (0.9–1.4)	147/345	1.1 (0.9–1.4)	129/298	1.1 (0.9–1.4)	115/296	1.0 (0.8–1.3)
Oil products	180/412	1.1 (0.9–1.3)	167/384	1.1 (0.9–1.3)	151/325	1.2 (0.9–1.5)	137/332	1.0 (0.8–1.3)
Plastic or resin fumes	60/132	1.1 (0.8–1.5)	54/116	1.1 (0.8–1.6)	43/96	1.1 (0.7–1.6)	41/101	1.0 (0.7–1.4)
Industrial dusts	160/353	1.3 (1.0–1.6)	143/321	1.3 (1.0–1.6)	123/281	1.2 (1.0–1.6)	119/282	1.2 (0.9–1.5)
Metal melting	109/286	0.9 (0.7–1.2)	99/262	0.9 (0.7–1.2)	81/207	1.0 (0.8–1.3)	77/215	0.9 (0.7–1.2)
Maternal exposure to								
Solvents	66/147	1.1 (0.8–1.6)	62/123	1.2 (0.9–1.7)	36/73	1.3 (0.8–1.9)	22/59	1.1 (0.6–1.8)
Paints or lacquers	54/77	1.8 (1.2–2.6)	45/71	1.6 (1.1–2.4)	32/42	2.0 (1.2–3.3)	18/44	1.0 (0.6–1.8)
Oil products	25/50	1.3 (0.8–2.2)	25/44	1.5 (0.9–2.5)	18/31	1.6 (0.8–2.9)	9/25	1.1 (0.5–2.4)
Plastic or resin fumes	16/29	1.3 (0.7–2.5)	14/22	1.5 (0.7–3.0)	10/16	1.5 (0.6–3.5)	4/15	0.8 (0.3–2.5)
Industrial dusts	24/53	1.3 (0.8–2.2)	20/41	1.4 (0.8–2.5)	15/33	1.3 (0.7–2.4)	11/30	1.1 (0.5–2.2)
Metal melting	26/77	0.9 (0.6–1.5)	23/63	1.0 (0.6–1.7)	14/43	0.9 (0.5–1.7)	9/29	0.9 (0.4–2.0)

[a] ORs and respective 95% CIs derived from logistic regression analysis stratified for gender, age, and year of birth and adjusted for socioeconomic status (high or other) and degree of urbanization (urban, mixed, or rural).

of the 1:1 matched analytical approach, the association between ALL and maternal exposure to solvents during the preconception period became somewhat stronger, with the respective OR being 1.6 (95% CI, 1.0–2.4). However, this was due to a considerably lower prevalence of exposure among control mothers of the NIP, whereas the prevalence of exposure for mothers of ALL cases and mothers of controls in the other two study parts was similar.

The latter observation led us to examine the time pattern of prevalences of exposures. Whereas the interviews were conducted between 1992 and 1997, the dates of diagnosis ranged from 1980 to 1994 (however, for only 24.5% of all subjects, the date of diagnosis was before 1992). Therefore, it might have been difficult for the parents to remember substances that they were exposed to during the year before conception or during pregnancy. It might have been even more difficult for parents of controls to recall past occupational exposures, whereas parents of cases had probably already spent some time thinking about possible causes for the disease in their child. In fact, we observed a decline in prevalence of exposure for some of our potential risk factors with longer time periods between the date of the interview and the date of birth, but there were no differences between case and control groups. For maternal exposure to paints or lacquers, the prevalences of exposure for the shortest to the longest time lag between interview and birth (in steps of 3 years) were 4.4%, 5.5%, 4.6%, and 4.4% among ALL cases and 2.2%, 3.8%, 2.1%, and 2.0% among controls, respectively.

Discussion

The major strength of the German study is that it was population-based because cases were identified from an almost complete nationwide cancer registry (14), and controls were drawn randomly from complete population registration files. However, the study also has serious limitations: (*a*) nonparticipation bias cannot be completely ruled out; (*b*) due to the large number of comparisons, some results might be chance findings; (*c*) we used broad categories to assess occupational exposures, therefore the risk estimates might have been biased towards unity if only some substances in an exposure group were carcinogenic and others within the same group were not carcinogenic; and (*d*) because we obtained no information on the intensity of exposure, subjects with low levels of exposure were grouped with subjects with high levels of exposure, which could also lead to an underestimation of potential risk.

Differential bias, on the other hand, could result in bias of the OR away from unity. This might occur if parents of children with cancer were more sensitive to the perception of exposure. We already discussed the possibility of recall bias when we found childhood leukemia to be associated with self-reported parental occupational exposure to pesticides (12). Therefore, we examined whether the time lag between the time of exposure windows and the interview date was associated with the prevalence of exposure and whether this association was different for cases and controls. There was no difference, particularly with regard to maternal exposure to paints or lacquers. Furthermore, we examined the job titles of mothers who claimed an occupational exposure to paints or lacquers: (*a*) for 46.7% of mothers of ALL cases, an exposure seemed plausible; (*b*) for 49.3% of mothers of ALL cases, exposure did not clearly correspond to the job title but was not implausible; and (*c*) for 4% of mothers of ALL cases, an occupational exposure was not very likely. The respective percentages for mothers of control children were 50.5%, 47.7%, and 1.8%. However, the benefit of job titles as an instrument of validation is limited. As shown in Table 2, we found considerably more ORs > 1 than ORs < 1. It must also be noted that among case families, the number of subjects exposed to chemicals, dusts, and fumes during pregnancy was consistently higher than the number of subjects exposed to chemicals, dusts, and fumes during the postnatal period, whereas this was not true among controls. Differential recall remains a concern, and a more comprehensive exposure assessment, *e.g.*, based on exposure information from company records, is recommended.

However, the primary intention of this analysis was to compare the results of our study with those of the recent United States case-control study (1). A moderately elevated risk of ALL with maternal exposure to paints or lacquers during the preconception period and during pregnancy was confirmed by our study. The biological plausibility of this finding has already been discussed in detail by Shu *et al.* (1). With regard to the association between risk of ALL and maternal exposure to solvents, we observed the same tendency as seen in the United States study, but the associations in our study were weaker. Whereas Shu *et al.* (1) reported ORs between 1.6 and 1.8 for exposure during pregnancy and the preconception period, the

respective ORs from our study were 1.2 and 1.3, and both studies observed no association during the postnatal period. A general pattern observed in both studies was that risk estimates were higher with regard to maternal occupational exposures as compared with paternal occupational exposures and that parental occupational exposures before birth were more relevant than exposures after birth. An additional finding was that the risk of ALL was not related to parental exposure to plastic and resin fumes, thus we failed to confirm an observation from the first study part that had been reported by Kaatsch *et al.* (3).

In summary, this study suggests that maternal occupational exposure to paints or lacquers before birth is associated with an increased risk of childhood ALL. A small increase in ALL risk with paternal exposure to industrial dusts and maternal exposure to solvents should be investigated again in additional studies. However, this study also demonstrates the limitations of a commonly used interview-based method for assessing occupational exposure and indicates that future studies investigating the effects of past parental occupational exposure to certain substances need more specific exposure information and a validation of this exposure information.

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