Parental Occupational Exposure to Hydrocarbons and Risk of Acute Lymphocytic Leukemia in Offspring[1]

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Abstract

Parental exposure to hydrocarbons at work has been suggested to increase the risk of childhood leukemia. Evidence, however, is not entirely consistent. Very few studies have evaluated the potential parental occupational hazards by exposure time windows. The Children's Cancer Group recently completed a large-scale case-control study involving 1842 acute lymphocytic leukemia (ALL) cases and 1986 matched controls. The study examined the association of self-reported occupational exposure to various hydrocarbons among parents with risk of childhood ALL by exposure time window, immunophenotype of ALL, and age at diagnosis. We found that maternal exposure to solvents [odds ratio (OR), 1.8; 95% confidence interval (CI), 1.3–2.5] and paints or thinners (OR, 1.6; 95% CI, 1.2–2.2) during the preconception period (OR, 1.6; 95% CI, 1.1–2.3) and during pregnancy (OR, 1.7; 95% CI, 1.2–2.3) and to plastic materials during the postnatal period (OR, 2.2; 95% CI, 1.0–4.7) were related to an increased risk of childhood ALL. A positive association between ALL and paternal exposure to plastic materials during the preconception period was also found (OR, 1.4; 95% CI, 1.0–1.9). The ALL risk associated with parental exposures to hydrocarbons did not vary greatly with immunophenotype of ALL. These results suggest that the effect of parental occupational exposure to hydrocarbons on offspring may depend on the type of hydrocarbon and the timing of the exposure.

Introduction

In 1974, Fabia and Thuy (1) first reported that paternal employment in hydrocarbon-related occupations was associated with an increased risk of childhood leukemia and other cancers. Subsequently, a number of studies found an association between childhood leukemia and paternal exposure to benzene (2); chlorinated or unspecified solvents (3, 4); paint, methyl ethyl ketone, cutting oils (3), and plastic and resin fumes (5); and maternal exposure to benzene, gasoline, and solvents (6, 7). Excessive leukemia risk was also reported among children whose fathers were employed as automobile, truck, or aircraft mechanics (8) or motor vehicle drivers (9). Other studies, however, have failed to find a positive relation between paternal (6, 7, 10–13) or maternal exposure (3) to hydrocarbons.

Parental exposure to occupational hazards could contribute to the risk of cancer in offspring through a number of mechanisms. These include carcinogenic or mutagenic damage to germ cells of either the mother or father prior to pregnancy, to the developing fetus through transplacental transmission during gestation, and/or directly to children during the postnatal period by contaminated breast milk or environmental contamination from the parents' working clothes or breath. All but a few studies (2, 3, 6), however, failed to evaluate the role of parental occupational exposure by exposure time windows, probably due to small sample sizes (4, 8, 10) and/or limited exposure information, *e.g.*, studies based on death or birth certification or surrogate interview (1, 7, 9, 13). Given the low prevalence rate of most occupational exposures and high correlations between these exposures across preconception, gestation, and postpregnancy periods, a study with a large sample size and a comprehensive occupational history would be needed to assess the effect of parental occupational exposures on the risk of leukemia in their offspring by specific exposure time windows.

The CCG[4] has recently completed a large-scale comprehensive case-control study, including 1842 childhood ALL patients and 1986 matched controls, which provided us with a unique opportunity to conduct an in-depth evaluation of the association between parental occupational exposure and the risk of childhood ALL. We present here the results of parental self-reported occupational exposure to various hydrocarbons and the risk of ALL among offspring.

Subjects and Methods

Details of this case-control study have been elsewhere submitted (14). Briefly, eligible cases in this study consisted of all children under the age of 15 who were newly diagnosed with ALL between January 1, 1989 and June 15, 1993 by a CCG member or affiliated institution (CCG Protocol E-15). Addi-

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[4] The abbreviations used are: CCG, Children's Cancer Group; ALL, acute lymphocytic leukemia; OR, odds ratio; CI, confidence interval.

tional eligibility criteria included the presence of a telephone in the case's residence and the availability of the biological mother, who had to be English speaking, for an interview. During the study period, 2458 ALL cases were diagnosed by CCG institutions, and 2081 were eligible for this study. A telephone interview with the case mother was completed for 1914 cases (92%). Among the 167 nonrespondents, there were 41 (2%) physician refusals, 70 (3.4%) parental refusals, 18 (0.9%) lost to follow-up after first contact, and 38 (1.8%) other reasons.

At the time of diagnosis, a sample of bone marrow was sent to a designated CCG reference laboratory for immunophenotyping. Of the 1842 ALL cases for whom a matched control was available (see paragraph below for details), early pre-B-cell leukemia (48.5%) was the most common subtype, followed by pre-B-cell (12.6%) and T-cell leukemia (9.9%). There were 231 B-cell leukemia cases (12.5%) who had insufficient information to be classified as either early pre-B or pre-B-cell type. Bone marrow slides were unavailable for immunophenotyping for 302 ALL cases (16.4%).

Controls were randomly selected, using a random digit dialing procedure described previously (15), and individually matched to cases on age (within 25% of the case's age at diagnosis for cases under the age of 8 and within or equal to 2 years for cases between the ages of 8–14 years), race (white, black, or other), and telephone area code and exchange. In a few situations where an exact match could not be achieved after dialing 300 random numbers, relaxation of the age- and race-match was implemented. As with the cases, there had to be a telephone in the control's residence and the biological mother had to be available for an interview and speak English. A total of 2597 eligible controls were identified, and the mother's interview was completed for 1987 subjects (76.5%). One control was excluded because the matched case was later determined ineligible for the study. The major reason for nonparticipation of controls was parental refusal ($n = 457$; 17.6%). The remainder were due to loss of follow-up ($n = 17$; 0.7%) and other reasons ($n = 136$; 5.2%). Matched controls were not found for 72 (3.8%) interviewed cases. After exclusion of these nonmatched cases and controls, a total of 1842 case-control pairs (1704 sets of 1:1 match, 132 sets of 1:2 match, and 6 sets of 1:3 match) remained for statistical analyses. During control selection, there were situations where the first eligible control was not immediately available for an interview, necessitating identification of the next eligible control. Some of the "first controls" were subsequently successfully interviewed, thus resulting in multiple matched controls per case.

Data were collected by independent telephone interviews with mothers and, whenever available, fathers of cases and controls using structured questionnaires. The mother's questionnaire included information relating to demographics, maternal history of disease, medication use, occupation, personal habits, household exposure prior to and during the index pregnancy and birth, reproductive and family medical history, as well as history of disease, medication use, and exposure to environmental hazards (*e.g.*, pesticides and insecticides) of the index child. The father's questionnaire focused on medication use, personal habits, household exposures, occupational history, and family medical history. The father's questionnaire was completed for 1801 of the 2081 eligible cases (86.5%) and 1813 of the 2597 eligible controls (69.8%), resulting in 1618 matched sets. Of these matched sets, direct interviews with fathers were obtained for 83.4% of cases and 67.7% of controls. The remaining interviews were completed by mothers as surrogates for the fathers. The major reasons for nonresponse among case fathers were: respondent not available (4.1%), parental refusal (4.3%), physician refusal (2.0%), and other reasons (2.2%). Nonresponse in control fathers was due mainly to parental refusal (19.1%) and other reasons (6.4%).

Detailed information on parental occupation and occupational exposure was collected. A list of exposures was included in the interview guide that was sent to the respondents prior to the interview. Parents were first asked about the job title, industry, duties, starting and stopping date for all jobs held by the father for more than 6 months since he was 18 years of age, and by the mother for all jobs held at least 6 months in the period from 2 years prior to the index pregnancy to date of diagnosis of leukemia cases (or the reference date of the controls). Parents were then asked during the interview about specific exposures, *i.e.*, solvents, degreaser or cleaning agents (*e.g.*, carbon tetrachloride, trichloroethylene, benzene, toluene, xylene, and others), plastic materials (*e.g.*, polyvinyl chloride, polystyrene, polyethylene, polyurethane, and others), paints, pigments or thinners (spray paints, printing inks, lacquers, turpentine, and others), and oil or coal products (*e.g.*, coal, cooling and cutting oils, and others) (see Tables 2 and 4 for other specific chemicals included in the study). If the parents had ever been exposed, cumulative length of exposure during the relevant job was queried. Self-reported exposures that were not on the list were classified into these same exposure categories by an industrial hygienist without knowledge of the case-control status.

Exposure information was then linked to start and stop date of the relevant job to determine the timing of exposure related to specific windows of interest (*e.g.*, preconception, gestation, and postnatal periods). Duration of exposure during each specific time window was estimated. Duration of exposure was categorized using the median exposure time of the control group as the cut point.

Exposures to both individual chemicals and to grouped chemicals were analyzed by exposure time windows, as well as by age at diagnosis and immunophenotype of ALL. ORs, as approximations of relative risk, were used to measure the association between parental occupational exposure and risk of ALL. Conditional (for mother's exposure) and unconditional (for father's exposure) logistic regression models were used in data analyses to obtain ORs and 95% CIs, adjusting for potential confounders. Tests for trends were performed by treating the categorical variables (no exposure, less than the median exposure, and greater than the median exposure) as continuous variables in the logistic model.

Results

As typical for ALL, there were slightly more boys among cases (55.3%), and cases were predominantly between the ages of 2 and 5 years (55.4%; Table 1). Controls were well-matched to cases on gender ($P = 0.50$) and age ($P = 0.07$). In addition, compared with cases, controls were more likely to be white and to come from a family with a higher parental education and family income (Table 1).

Table 2 presents the association of maternal occupational exposures (ever *versus* never) to hydrocarbons with childhood leukemia risk. Mothers of ALL cases were more likely to report having been exposed to any listed solvents and paints or thinners during the preconception period (OR, 1.8; 95% CI, 1.3–2.5 and OR, 1.6; 95% CI, 1.2–2.2, respectively) and during the index pregnancy (OR, 1.6; 95% CI, 1.1–2.3 and OR, 1.7; 95% CI, 1.2–2.3). When specific exposures were examined, paint remover, paint thinner, and nonsprayed paints were associated with a significantly elevated risk of ALL for both periods and

Table 1 Demographic characteristics of cases and controls

	Cases n = 1842	Controls n = 1986	*P*
Sex			
Male	1018 (55.3%)	1076 (54.2%)	0.50
Female	824 (44.7%)	910 (45.8%)	
Age			
<12 months	64 (3.5%)	81 (4.1%)	0.07
12–23 months	138 (7.5%)	189 (9.5%)	
2–5 years	1020 (55.4%)	1038 (52.3%)	
6–10 years	408 (22.2%)	466 (23.5%)	
11+ years	212 (11.5%)	212 (10.7%)	
Race			
White	1492 (81.0%)	1720 (86.6%)	<0.01
Black	109 (5.9%)	94 (4.7%)	
Hispanic	153 (8.3%)	121 (6.1%)	
American Indian/Alaska Native	19 (1.0%)	13 (0.7%)	
Asian/Pacific Islander	56 (3.0%)	32 (1.6%)	
Other or Unknown	13 (0.7%)	6 (0.3%)	
Maternal education			
≤High school	797 (43.3%)	762 (38.4%)	
Some post-high school	592 (32.1%)	701 (35.3%)	<0.01
≥College	453 (24.6%)	523 (26.3%)	
Paternal education[a]			
≤High school	676 (41.8%)	638 (37.1%)	
Some post-high school	480 (29.7%)	510 (29.6%)	<0.01
≥College	462 (28.6%)	574 (33.4%)	
Income ($)			
<10,000	217 (11.8%)	176 (8.9%)	<0.01
10,000–19,999	390 (21.2%)	370 (18.6%)	
20,000–29,999	433 (23.5%)	475 (23.9%)	
30,000–39,999	334 (18.1%)	369 (18.6%)	
40,000–49,999	204 (11.1%)	221 (11.1%)	
50,000+	250 (13.6%)	357 (18.0%)	
Unknown	14 (0.8%)	18 (0.9%)	

[a] Based on 1618 cases and 1722 matched controls who responded to paternal interview.

turpentine during pregnancy only. Exposure to methyl ethyl ketone, benzene, toluene, or naphtha was not positively associated with the risk. Most other individual solvents, except the category of possible organic solvents, were associated with an elevated but not statistically significant risk. Exposure to plastic materials during preconception and index pregnancy was associated with nonstatistically significantly elevated ORs of 2.1 (95% CI, 0.9–4.9) and 2.4 (95% CI, 0.9–6.2).

No major differences between cases and controls were found for maternal exposure to solvents (OR, 1.1; 95% CI, 0.8–1.4) and paints or thinners (OR, 1.1; 95% CI, 0.8–1.5) during the postnatal period. A statistically significant elevated ALL risk, however, was associated with maternal exposure to plastic materials during the postnatal period (OR, 2.2; 95% CI, 1.0–4.7), with individual plastic materials being associated with an elevated but statistically nonsignificant risk. No statistically significant positive association was found between risk of childhood ALL and maternal exposure to oils or other hydrocarbon-related products during any time window.

There was a low correlation between exposure groups within the same time window (correlation coefficients ranged from 0.11 to 0.27). When all of the hydrocarbon classes were included in a regression model, the pattern of association reported above remained unchanged (data not shown). The correlation of the same exposure across different time windows, however, was high (correlation coefficients ranged from 0.82 to 0.92 for preconception and during-pregnancy exposures, 0.49 to 0.68 for preconception and postnatal exposures, and 0.58 to 0.74 for pregnancy and postnatal exposures). This high correlation, particularly for maternal exposure to plastic materials (the correlation coefficient was 0.92 and 0.74, respectively, for pregnancy to preconception and postnatal exposures), compromised our ability to separate the effect of maternal exposure during the different time windows. When exposure during all three time windows (preconception, during pregnancy, and postnatal) was analyzed in a regression model, a statistically significant risk of ALL was found to be associated with maternal exposure to solvents (OR, 1.6; 95% CI, 0.8–3.2) and oil or coal products (OR, 1.9; 95% CI, 0.7–5.3) during the preconception period. Maternal exposure to paints or thinners during pregnancy (OR, 1.6; 95% CI, 0.8–3.2) and to plastic materials (OR, 1.9; 95% CI, 0.7–5.3) during the postnatal period was associated with an elevated but statistically nonsignificant risk.

The associations with the duration of maternal exposure during relevant time windows are shown in Table 3. Median exposure intervals among the control group were used to categorize the exposure duration. No linear dose-response relationship was observed for exposures with the preconception, during-pregnancy, or postnatal periods. The associations between childhood ALL and maternal exposure to solvents, paints, or thinners during the preconception period and index pregnancy, and to plastic materials during the postnatal period, were statistically significant only when the exposure duration was short (equal or below the median). Exposures to those substances for a longer period (more than median) were not associated with a higher and significant risk.

Table 4 presents the association of reported paternal exposure to hydrocarbons and risk of childhood leukemia. Because women may not know what chemicals are used in the workplace of their spouse, subjects with a surrogate interview for paternal questionnaires were excluded from this analysis. An unconditional logistic regression model, instead of a conditional logistic model, was applied in the analyses to maximize the number of subjects being included in the analysis, with adjustment of two major matching variables: age and sex of child. Compared with control fathers, more case fathers reported having exposure to plastic materials during the preconception period (OR, 1.4; 95% CI, 1.0–1.9). All individual materials for this category of exposure were associated with an elevated risk (polyvinylchloride: OR, 1.4; polystyrene: OR, 2.4; polyethylene: OR, 1.7; and polyurethane: OR, 1.4), but only the point estimate for polystyrene reached statistical significance. The association between ALL risk and paternal exposure to plastic materials during pregnancy was similar to that seen in the preconception period (OR, 1.3; 95% CI, 0.9–2.0), but it was not statistically significant. Paternal exposure to solvents, paints or thinners, oil or coal products, and other hydrocarbons for any time window was not associated with an elevated risk of childhood ALL.

When duration of exposure was examined, the effect of paternal exposure to plastic materials during the preconception period on childhood ALL appeared to increase slightly with duration of exposure (test for linear trend, $P = 0.05$; Table 5). No trend was observed for plastic materials exposure during other time windows or for other exposures for any time windows.

To evaluate the possible influence of breaking matching status in these analyses, additional analyses using a conditional logistical model were conducted. The point estimates of the association between paternal exposure to hydrocarbons and risk of childhood ALL generally remained unchanged, although the confidence intervals were much wider due to the decrease of sample sizes by excluding unmatched case and control fathers.

Table 2 Association of childhood ALL with any *versus* no maternal occupational exposure to specific hydrocarbons

	Anytime		Preconception		During pregnancy		Postnatal	
	Case/ Control	OR (95% CI)[a]	Case/ Control	OR (95% CI)[a]	Case/ Control	OR (95% CI)[a]	Case/ Control	OR (95% CI)[a]
Solvents, degreasers, or cleaning agents								
Carbon tetrachloride	12/8	1.6 (0.7–4.1)	7/4	1.9 (0.5–6.8)	4/3	1.4 (0.3–6.8)	5/6	0.8 (0.2–2.7)
Trichloroethylene	15/9	1.8 (0.8–4.1)	9/6	1.8 (0.6–5.2)	6/4	1.8 (0.5–6.4)	9/6	1.4 (0.5–4.1)
Perchlorethylene	4/9	0.4 (0.1–1.4)	3/2	1.4 (0.2–8.6)	3/2	1.3 (0.2–8.4)	4/8	0.4 (0.1–1.5)
Methyl ethyl ketone	18/20	1.0 (0.5–1.9)	9/14	0.8 (0.3–1.9)	5/10	0.6 (0.2–1.8)	10/14	0.7 (0.3–1.7)
Benzene	11/15	0.7 (0.3–1.6)	7/10	0.7 (0.3–1.8)	4/8	0.5 (0.1–1.6)	7/11	0.6 (0.2–1.6)
Toluene	9/15	0.7 (0.3–1.5)	5/11	1.5 (0.6–3.8)	7/7	1.2 (0.4–3.5)	6/7	1.1 (0.4–3.4)
Freon	23/13	2.0 (1.0–4.1)	3/7	1.9 (0.8–5.0)	10/5	1.8 (0.6–5.4)	14/7	2.0 (0.8–5.0)
Naphtha	4/6	0.6 (0.2–2.1)	2/3	0.5 (0.1–3.0)	2/2	0.7 (0.1–5.1)	3/4	0.7 (0.2–3.2)
Chlorinated solvents	5/2	3.5 (0.6–18.9)	2/1	1.8 (0.2–20.8)	2/1	1.8 (0.2–20.8)	2/2	1.5 (0.2–11.6)
Organic, not chlorinated, solvents	30/24	1.4 (0.8–2.4)	22/12	2.0 (1.0–4.2)	13/12	1.1 (0.5–2.5)	18/21	0.9 (0.5–1.6)
Possible organic solvents	60/51	1.3 (0.9–1.9)	39/21	2.0 (1.2–3.5)	29/16	1.9 (1.0–3.6)	38/41	1.0 (0.6–1.6)
Any above	138/114	1.3 (1.0–1.7)	93/58	1.8 (1.3–2.5)	68/46	1.6 (1.1–2.3)	87/87	1.1 (0.8–1.4)
Plastic materials								
Polyvinyl chloride	7/2	3.2 (0.7–15.7)	2/1	1.5 (0.1–17.9)	2/1	1.5 (0.1–17.9)	6/2	2.8 (0.6–14.1)
Polystyrene	3/6	0.6 (0.1–2.4)	2/3	0.7 (0.1–4.8)	2/1	1.9 (0.2–23.4)	3/3	1.1 (0.2–5.8)
Polyethylene	7/6	1.3 (0.4–3.9)	5/3	1.6 (0.4–6.9)	4/2	1.7 (0.3–9.7)	6/5	1.2 (0.4–4.2)
Polyurethane	13/7	2.1 (0.8–5.3)	8/3	2.8 (0.7–10.8)	7/1	7.2 (0.9–60.8)	9/5	1.8 (0.6–5.4)
Other	10/2	5.1 (1.1–24.2)	6/2	3.4 (0.7–17.8)	5/2	2.5 (0.5–13.4)	9/2	4.1 (0.9–19.6)
Any above	31/14	2.3 (1.2–4.4)	18/9	2.1 (0.9–4.9)	15/6	2.4 (0.9–6.2)	24/10	2.2 (1.0–4.7)
Paints or thinners								
Spray paints	53/59	1.0 (0.7–1.5)	27/24	1.3 (0.7–2.3)	27/21	1.4 (0.8–2.6)	38/33	1.2 (0.7–1.9)
Other paints	87/82	1.3 (0.9–1.7)	44/28	1.9 (1.2–3.1)	37/22	2.0 (1.2–3.5)	51/47	1.3 (0.9–2.0)
Printing inks	47/51	1.1 (0.7–1.6)	30/28	1.3 (0.7–2.1)	25/21	1.4 (0.7–2.5)	25/34	0.9 (0.5–1.5)
Lacquers	25/24	1.2 (0.6–2.1)	16/11	1.6 (0.7–3.5)	15/7	2.3 (0.9–5.7)	20/16	1.3 (0.7–2.6)
Turpentine	23/20	1.4 (0.8–2.6)	16/9	1.9 (0.8–4.5)	15/5	3.5 (1.3–10.0)	16/12	1.6 (0.8–3.5)
Paint remover	23/22	1.2 (0.7–2.2)	16/8	2.5 (1.0–5.9)	17/4	5.2 (1.7–15.8)	19/14	1.4 (0.7–2.9)
Paint thinner	41/39	1.1 (0.7–1.7)	28/15	1.9 (1.0–3.7)	27/9	3.3 (1.5–7.1)	28/27	1.1 (0.7–1.9)
Lacquer thinner	11/24	0.5 (0.3–1.2)	5/10	0.6 (0.2–1.8)	6/9	0.7 (0.3–2.2)	11/16	0.8 (0.3–1.7)
Any above	169/167	1.1 (0.9–1.4)	97/70	1.6 (1.2–2.2)	88/59	1.7 (1.2–2.3)	105/103	1.1 (0.8–1.5)
Oil or coal products								
Cooling, cutting oils	60/56	1.1 (0.7–1.6)	33/33	1.0 (0.6–1.7)	25/26	0.9 (0.5–1.7)	42/41	1.0 (0.7–1.6)
Coal	5/5	1.3 (0.4–4.4)	5/1	6.6 (0.8–56.9)	2/1	2.8 (0.2–31.4)	0/5	
Coal tar	8/11	1.0 (0.8–1.4)	5/4	1.8 (0.5–7.1)	3/3	1.9 (0.4–9.4)	2/8	0.4 (0.1–1.7)
Petroleum products	58/53	1.2 (0.8–1.7)	33/31	1.1 (0.7–1.8)	24/27	0.9 (0.5–1.5)	38/37	1.0 (0.6–1.7)
Any above	104/107	1.0 (0.8–1.4)	63/62	1.1 (0.7–1.5)	43/54	0.8 (0.5–1.2)	67/79	0.9 (0.6–1.2)
Other								
Epoxy resins	13/14	1.1 (0.5–2.4)	9/10	1.1 (0.4–2.8)	8/5	1.6 (0.5–5.2)	8/7	1.3 (0.5–3.8)
Formaldehyde	29/41	0.9 (0.5–1.4)	20/25	1.0 (0.6–1.9)	13/20	0.9 (0.4–1.8)	17/32	0.7 (0.4–1.2)
Glues	77/67	1.3 (0.9–1.8)	47/38	1.4 (0.9–2.1)	35/28	1.4 (0.8–2.3)	47/40	1.3 (0.8–2.0)
Exhaust	25/28	1.0 (0.6–1.7)	14/15	1.2 (0.5–2.5)	8/13	0.7 (0.3–1.9)	17/17	1.0 (0.5–2.1)
Fuels	20/11	1.8 (0.9–3.9)	13/7	1.9 (0.8–4.9)	12/6	2.1 (0.8–5.6)	13/8	1.6 (0.7–4.0)
Cooking oils	4/3	1.8 (0.4–8.0)	1/3	0.5 (0.1–5.0)	0/2		3/3	1.4 (0.3–6.9)
Thermal decomposition prods.	9/2	4.3 (0.9–20.6)	3/1	2.4 (0.2–24.7)	4/1	3.5 (0.4–33.3)	7/1	7.0 (0.8–59.2)
Glycols	2/4	0.6 (0.1–3.3)	2/3	0.8 (0.1–4.8)	2/2	1.3 (0.2–9.6)	2/4	0.6 (0.1–3.3)
Ethylene oxide	2/7	0.4 (0.1–2.0)	1/1	2.3 (0.1–37.1)	1/1	2.3 (0.1–37.1)	2/7	0.4 (0.1–2.0)
Polycyclic aromatic hydrocarbons	8/11	1.1 (0.4–2.7)	5/2	3.1 (0.6–17.1)	5/2	2.5 (0.5–13.4)	5/8	0.9 (0.3–2.9)
Alcohol	23/30	0.8 (0.5–1.5)	16/17	1.0 (0.5–2.1)	14/11	1.4 (0.6–3.2)	20/23	0.9 (0.5–1.8)
Any above	184/177	1.2 (0.9–1.5)	118/103	1.3 (1.0–1.7)	90/78	1.3 (1.0–1.8)	127/126	1.1 (0.9–1.5)

[a] ORs were adjusted for maternal education, race, and family income.

Similar to maternal exposures, there was a low correlation between paternal exposure to different types of hydrocarbons within the same exposure window (the correlation coefficient ranged from 0.12 to 0.38) but a high correlation for the same type of hydrocarbon across different exposure windows (the correlation coefficient ranged from 0.51 to 0.81). Further analyses, including either all types of hydrocarbons within an exposure time window or an exposure from all exposure time windows, consistently showed that plastics material exposure during the preconception period was the only paternal exposure associated with an elevated risk of childhood ALL.

The association between risk of ALL and combined parental occupational exposure has been examined. It was observed that, compared to neither parent being exposed, a mother's exposure to solvents and paints or thinners during preconception and pregnancy and to other hydrocarbons during pregnancy alone was associated with an increased risk of childhood ALL (data not shown). We did not observe that having both parents exposed to a substance was related to a higher risk of ALL than having a single parent exposed, with a possible exception of plastics material. For this exposure, no control children had both parents exposed, but seven cases had both parents exposed (four exposed during the preconception, two during pregnancy, and four during postnatal period). It should

Table 3 Association of childhood ALL with maternal occupational exposures to hydrocarbons by duration of time of exposure

	Anytime		Preconception		During pregnancy		Postnatal	
	Case/ Control	OR (95% CI)[a]	Case/ Control	OR (95% CI)[a]	Case/ Control	OR (95% CI)[a]	Case/ Control	OR (95% CI)[a]
Solvents, degreasers, or cleaning agents								
None	1704/1872	1.0	1743/1921	1.0	1768/1933	1.0	1749/1892	1.0
≤Median	88/54	1.8 (1.3–2.6)	56/29	2.1 (1.3–3.4)	37/23	1.9 (1.1–3.2)	58/45	1.4 (1.0–2.1)
>Median	45/53	0.9 (0.6–1.4)	37/29	1.4 (0.8–2.3)	31/23	1.3 (0.7–2.2)	29/42	0.7 (0.4–1.1)
Test for trend (*P*)		0.24		<0.01		0.07		0.63
Plastic materials								
None	1811/1972	1.0	1822/1976	1.0	1825/1979	1.0	1816/1975	1.0
≤Median	14/7	2.3 (0.9–6.2)	7/5	1.6 (0.5–5.4)	4/3	1.5 (0.3–7.0)	17/5	3.0 (1.1–8.2)
>Median	15/6	2.3 (0.9–6.0)	11/4	1.6 (0.8–8.3)	11/3	3.2 (0.9–11.7)	7/5	1.5 (0.5–4.7)
Test for trend (*P*)		0.03		0.09		0.07		0.09
Paints or thinners								
None	1673/1819	1.0	1730/1881	1.0	1739/1892	1.0	1722/1848	1.0
≤Median	74/67	1.3 (0.9–1.8)	54/35	1.8 (1.2–2.9)	45/30	1.8 (1.1–3.0)	53/52	1.2 (0.8–1.8)
>Median	83/67	1.4 (1.0–1.9)	43/35	1.4 (0.9–2.2)	43/29	1.5 (0.9–2.4)	52/51	1.1 (0.7–1.6)
Test for trend (*P*)		0.04		0.02		0.01		0.56
Oils or coal products								
None	1738/1879	1.0	1774/1918	1.0	1794/1926	1.0	1770/1901	1.0
≤Median	57/51	1.2 (0.8–1.8)	32/31	1.1 (0.6–1.7)	24/17	0.9 (0.5–1.6)	33/40	0.9 (0.5–1.4)
>Median	43/50	0.9 (0.6–1.4)	31/31	1.1 (0.6–1.8)	19/27	0.7 (0.4–1.3)	34/39	0.9 (0.6–1.4)
Test for trend (*P*)		0.10		0.77		0.22		0.49
Other								
None	1658/1809	1.0	1718/1875	1.0	1746/1900	1.0	1709/1852	1.0
≤Median	105/86	1.3 (1.0–1.8)	72/52	1.5 (1.0–2.2)	44/39	1.3 (0.9–2.1)	71/63	1.3 (0.9–1.8)
>Median	74/84	1.0 (0.7–1.4)	46/51	1.1 (0.7–1.7)	46/39	1.3 (0.8–2.0)	56/63	1.0 (0.7–1.5)
Test for trend (*P*)		0.40		0.14		0.11		0.54

[a] ORs were adjusted for maternal education, race, and family income.

be noted that the combined analysis was based on very few exposed subjects, due to the low concordance between paternal and maternal occupational exposure (correlation coefficients ranged from 0.02 to 0.06 for solvents, 0.04 to 0.07 for plastic materials, 0.05 to 0.09 for paints, and 0.07 to 0.12 for oil or coal products).

Finally, we analyzed the data by age at diagnosis and immunophenotype of cases. The elevated ALL risk associated with maternal exposure to paints or thinners was restricted largely to children diagnosed under the age of 6; ORs for children <2, 2–5, and >5 years of age were 1.9, 1.8, and 1.2 for preconception exposure and 2.1, 1.9, and 1.2 for exposure during pregnancy. The association of ALL risk with maternal exposure to solvents was more pronounced among children older than 5. ORs for children <2, 2–5, and >5 years of age were 1.3, 1.6, 2.3, and 1.0, 1.3, 2.3, respectively, for exposure to solvents during preconception and pregnancy periods. A similar pattern was observed for maternal exposure to plastic materials during the postnatal period; ORs were 1.4 and 3.1 for children ≤ 5 and >5 years of age. No clear age-specific association pattern was observed for ALL risk and paternal exposures. We did not find that the association between parental occupational exposure to hydrocarbons and childhood ALL risk varied greatly with immunophenotype of ALL.

Discussion

Association between parental occupational exposure and risk of childhood cancers has been a topic of at least four reviews (16–19) since paternal exposure to hydrocarbons was first linked to risk of childhood cancer in 1974. An elevated risk of childhood leukemia associated with paternal exposure to solvents (2–4); paint, methyl ethyl ketone, cutting oils (3); and plastic and resin fumes (5) has been reported, but no paternal hydrocarbon exposure-related risk was evident in other studies (6, 7, 10–13). Maternal occupational exposure has been less well studied. A positive association between childhood leukemia risk and maternal exposure to benzene, gasoline, and solvents during pregnancy was reported (6, 7).

Our study is one of the few epidemiological studies that has collected detailed information on parental exposure in the preconception, pregnancy, and postnatal periods. This, along with the large sample size and the availability of immunophenotype data, provided us with a unique opportunity to evaluate the association between parental occupational exposure and risk of ALL, not only by these time windows, but also by age at diagnosis and immunophenotype of ALL. We found that self-reported paternal exposure to plastic materials during the preconception period was associated with the risk of ALL at all ages. Maternal exposure to solvents and paints or thinners during preconception or during pregnancy, and to plastic materials during the postnatal period, was related to an increased risk of childhood ALL. The elevated risk associated with maternal exposure to paints or thinners was restricted largely to children diagnosed at 5 years of age or younger, and the association with solvents and plastic materials was more pronounced among children older than 5 years at diagnosis. We did not find any major differences when analyses were stratified by immunophenotype.

There is sufficient evidence indicating that chlorinated solvents, *e.g.,* carbon tetrachloride, trichloroethylene, and perchloroethylene, can cause cancers including leukemia and lymphoma in laboratory animals (20, 21). The carcinogenic effect of chlorinated solvents in humans, however, has not been consistently documented (20, 21). An association of paternal exposure to these substances has been linked previously to an increased risk of leukemia (3) and brain tumors (22). In contrast

Table 4 Association of childhood ALL with any *versus* no paternal occupational exposure to specific hydrocarbons

	Anytime		Preconception		During pregnancy		Postnatal	
	Case/ Control	OR (95% CI)[a]	Case/ Control	OR (95% CI)[a]	Case/ Control	OR (95% CI)[a]	Case/ Control	OR (95% CI)[a]
Solvents, degreasers, or cleaning agents								
Carbon tetrachloride	93/73	1.1 (0.8–1.5)	76/59	1.1 (0.8–1.6)	37/29	1.1 (0.6–1.7)	38/32	1.0 (0.6–1.5)
Trichloroethylene	136/104	1.1 (0.8–1.5)	100/18	1.1 (0.8–1.5)	56/52	0.9 (0.6–1.4)	77/66	1.0 (0.7–1.3)
Perchlorethylene	25/23	0.9 (0.5–1.6)	21/22	0.8 (0.5–1.5)	8/14	0.5 (0.2–1.1)	10/15	0.5 (0.2–1.2)
Methyl ethyl ketone	141/116	1.0 (0.8–1.3)	107/28	1.1 (0.8–1.5)	69/43	1.3 (0.9–2.0)	89/63	1.1 (0.8–1.6)
Benzene	97/71	1.2 (0.8–1.6)	74/55	1.2 (0.8–1.2)	28/24	1.0 (0.6–1.7)	40/28	1.2 (0.7–1.9)
Toluene	104/88	1.0 (0.8–1.4)	82/70	1.1 (0.8–1.5)	43/34	1.0 (0.6–1.6)	54/49	0.8 (0.6–1.3)
Xylene	85/64	1.2 (0.8–1.7)	67/51	1.2 (0.8–1.8)	43/23	1.5 (0.9–2.6)	51/29	1.4 (0.9–2.3)
Freon	178/133	1.1 (0.9–1.4)	126/101	1.1 (0.8–1.4)	67/61	0.9 (0.6–1.3)	90/75	0.9 (0.7–1.3)
Naphtha	83/67	1.0 (0.7–1.4)	62/45	1.2 (0.8–1.7)	34/21	1.3 (0.7–2.2)	46/30	1.2 (0.7–1.9)
Chlorinated solvents	14/15	0.8 (0.4–1.6)	9/8	1.0 (0.4–2.5)	4/6	0.5 (0.1–1.7)	7/11	0.5 (0.2–1.2)
Organic, not chlorinated, solvents	89/62	1.2 (0.9–1.7)	61/42	1.3 (0.8–1.9)	25/27	0.8 (0.5–1.4)	46/38	1.0 (0.6–1.6)
Possible organic solvents	222/177	1.0 (0.8–1.3)	183/133	1.1 (0.9–1.4)	94/67	1.1 (0.8–1.5)	113/89	0.9 (0.7–1.3)
Any above	602/481	1.0 (0.9–1.2)	490/375	1.1 (0.9–1.3)	276/221	1.0 (0.8–1.2)	344/283	0.9 (0.8–1.1)
Plastic materials								
Polyvinyl chloride	59/37	1.4 (0.9–2.1)	46/92	1.4 (0.9–2.3)	22/17	1.2 (0.6–2.0)	30/23	1.1 (0.6–1.9)
Polystyrene	35/20	1.5 (0.8–2.6)	30/11	2.4 (1.2–4.8)	12/5	2.1 (0.7–5.9)	16/9	1.5 (0.6–3.3)
Polyethylene	33/17	1.6 (0.9–2.9)	28/14	1.7 (0.9–3.3)	14/9	1.4 (0.6–3.2)	18/12	1.3 (0.6–2.7)
Polyurethane	76/51	1.2 (0.8–1.7)	55/33	1.4 (0.9–2.2)	34/19	1.5 (0.8–2.6)	67/25	1.5 (0.9–2.4)
Other	33/27	1.0 (0.6–1.6)	25/16	1.4 (0.7–2.7)	12/8	1.3 (0.5–3.1)	18/16	0.9 (0.4–1.7)
Any above	152/113	1.1 (0.8–1.4)	119/72	1.4 (1.0–1.9)	63/39	1.3 (0.9–2.0)	87/63	1.1 (0.8–1.5)
Paints or thinners								
Spray paints	364/305	0.9 (0.7–1.1)	272/223	1.0 (0.8–1.2)	157/121	1.0 (0.8–1.3)	208/155	1.0 (0.8–1.2)
Other paints	315/272	0.9 (0.7–1.1)	226/196	0.9 (0.7–1.1)	117/92	1.0 (0.7–1.3)	163/129	0.9 (0.7–1.2)
Printing inks	100/89	0.9 (0.6–1.2)	78/68	0.9 (0.7–1.3)	36/41	0.7 (0.4–1.1)	47/55	0.6 (0.4–1.0)
Lacquers	217/150	1.1 (0.8–1.3)	168/110	1.2 (0.9–1.6)	90/54	1.3 (0.9–1.8)	119/79	1.1 (0.8–1.5)
Turpentine	145/103	1.1 (0.8–1.5)	109/81	1.1 (0.8–1.5)	59/27	1.7 (1.1–2.8)	75/38	1.5 (1.0–2.2)
Paint remover	167/129	0.9 (0.7–1.2)	120/95	1.0 (0.7–1.3)	66/38	1.3 (0.8–1.9)	89/50	1.2 (0.9–1.8)
Paint thinner	193/235	0.9 (0.8–1.1)	226/171	1.0 (0.8–1.3)	128/84	1.2 (0.9–1.5)	167/123	1.0 (0.7–1.2)
Lacquer thinner	171/118	1.1 (0.8–1.3)	132/81	1.3 (0.9–1.7)	80/43	1.4 (0.9–2.0)	99/64	1.1 (0.8–1.8)
Other	8/5	1.2 (0.4–3.9)	5/4	1.0 (0.3–3.9)	1/1	0.6 (0.0–9.4)	2/2	0.6 (0.1–4.1)
Any above	619/115	0.9 (0.8–1.1)	478/388	1.0 (0.8–1.2)	267/216	0.9 (0.8–1.1)	356/290	0.9 (0.7–1.1)
Oil or coal products								
Cooling, cutting oils	599/442	1.1 (0.9–1.3)	507/382	1.1 (0.9–1.3)	303/237	1.0 (0.8–1.2)	388/282	1.1 (0.9–1.3)
Coal	78/56	1.2 (0.8–1.7)	51/34	1.3 (0.8–2.0)	26/21	1.0 (0.6–1.9)	36/37	0.8 (0.5–1.4)
Coal tar	113/87	1.0 (0.8–1.4)	74/68	0.9 (0.6–1.2)	42/35	1.0 (0.6–1.5)	67/43	1.3 (0.8–1.9)
Petroleum products	534/434	1.0 (0.8–1.2)	465/369	1.0 (0.9–1.2)	250/207	0.9 (0.7–1.1)	325/248	1.0 (0.8–1.2)
Greases	17/19	0.7 (0.4–1.4)	14/16	0.7 (0.3–1.5)	9/6	1.2 (0.4–3.3)	11/10	0.8 (0.3–2.0)
Any above	781/600	1.1 (0.9–1.2)	682/529	1.1 (0.9–1.3)	427/335	1.0 (0.8–1.2)	537/395	1.1 (0.9–1.3)
Other								
Epoxy resins	134/115	0.9 (0.7–1.2)	92/76	1.0 (0.8–1.4)	49/41	1.0 (0.6–1.5)	59/61	0.7 (0.5–1.1)
Formaldehyde	73/72	0.8 (0.6–1.2)	52/50	0.9 (0.6–1.4)	31/35	0.7 (0.5–1.2)	43/45	0.8 (0.5–1.2)
Synthetics	14/11	1.0 (0.4–2.2)	13/10	1.1 (0.5–2.4)	8/3	2.0 (0.5–7.5)	8/5	1.2 (0.4–3.6)
Glues	294/213	1.1 (0.9–1.3)	229/152	1.2 (1.0–1.6)	136/92	1.1 (0.9–1.5)	173/134	1.0 (0.7–1.2)
Exhaust	54/61	0.6 (0.4–0.9)	47/50	0.7 (0.5–1.1)	18/24	0.6 (0.3–1.1)	25/30	0.6 (0.3–1.0)
Fuels	61/30	1.5 (1.0–2.4)	41/22	1.5 (0.9–2.6)	14/13	0.7 (0.3–1.6)	33/19	1.2 (0.7–2.2)
Cooking oils	5/8	0.6 (0.2–1.7)	5/6	0.8 (0.3–2.7)	1/1	1.1 (0.1–16.9)	1/3	0.3 (0.0–2.7)
Thermal decomposition products	14/10	1.1 (0.5–2.6)	13/4	2.7 (0.9–8.5)	9/2	3.6 (0.8–17.0)	10/7	1.1 (0.4–3.0)
Glycols	27/29	0.7 (0.4–1.2)	19/23	0.7 (0.4–1.3)	5/10	0.4 (0.1–1.1)	10/13	0.5 (0.2–1.3)
Rubber	8/5	1.2 (0.4–3.8)	7/4	1.5 (0.4–5.2)	1/0		2/1	1.2 (0.1–13.0)
Polycyclic aromatic hydrocarbons	50/49	0.8 (0.5–1.2)	39/33	1.0 (0.6–1.6)	13/17	0.7 (0.3–1.4)	21/25	0.7 (0.4–1.2)
Alcohol	66/75	0.7 (0.5–1.0)	50/53	0.9 (0.6–1.3)	23/34	0.6 (0.3–1.0)	31/44	0.6 (0.3–0.9)
Wax	16/13	1.0 (0.5–2.1)	12/12	0.9 (0.4–1.9)	2/3	0.5 (0.1–3.2)	4/4	0.7 (0.2–2.7)
Any above	534/449	0.9 (0.8–1.1)	439/343	1.0 (0.9–1.3)	254/212	0.9 (0.8–1.2)	322/287	0.8 (0.7–1.0)

[a] ORs were adjusted for paternal education, race, family income, age, and sex of the index child.

to these earlier studies, we did not find that paternal exposure to chlorinated solvents was related to the risk of ALL. Instead, maternal exposure to chlorinated solvents (*e.g.*, carbon tetrachloride, trichloroethylene, and other nonspecified chlorinated solvents, but not perchloroethylene) during the perinatal period was related to an elevated, although not statistically significant, risk of childhood ALL. Maternal exposure to paints and thinners, materials that often contain solvents, had a similar pattern of association with childhood ALL, although some other components in these chemicals may also be carcinogenic to humans (21). We, however, did not find that spray paints, which are likely to result in higher exposures than other types of paints, were associated with higher ORs than nonspray paints. Van Steense-Moll *et al.* (6) also found that maternal exposure to paints during pregnancy was related to an increased risk of childhood ALL. Lowengart *et al.* (3) reported that only paternal

Table 5 Association of childhood ALL with paternal occupational exposures to hydrocarbons by duration of time of exposure

	Anytime		Preconception		During pregnancy		Postnatal	
	Case/ Control	OR (95% CI)[a]	Case/ Control	OR (95% CI)[a]	Case/ Control	OR (95% CI)[a]	Case/ Control	OR (95% CI)[a]
Solvents, degreasers, or cleaning agents								
None	885/733	1.0	957/801	1.0	1171/955	1.0	1103/893	1.0
≤Median	270/224	1.0 (0.8–1.2)	233/188	1.0 (0.8–1.3)	136/112	1.0 (0.8–1.3)	165/142	0.9 (0.7–1.2)
>Median	298/222	1.1 (0.9–1.4)	257/187	1.2 (0.5–1.5)	140/109	1.0 (0.8–1.3)	179/141	1.0 (0.8–1.2)
Test for trend (*P*)		0.42		0.14		1.00		0.66
Plastic materials								
None	1333/1101	1.0	1360/1123	1.0	1416/1156	1.0	1392/1132	1.0
≤Median	73/47	1.2 (0.8–1.8)	59/36	1.3 (0.9–2.1)	37/20	1.5 (0.9–2.7)	52/32	1.3 (0.8–2.0)
>Median	72/47	1.3 (0.9–1.9)	60/36	1.4 (0.9–2.2)	26/19	1.2 (0.6–2.1)	35/31	0.9 (0.6–1.5)
Test for trend (*P*)		0.13		0.05		0.28		0.90
Paints or thinners								
None	868/703	1.0	961/777	1.0	1172/949	1.0	1083/875	1.0
≤Median	286/233	0.9 (0.8–1.2)	236/194	1.0 (0.8–1.2)	135/108	1.0 (0.7–1.3)	185/145	0.9 (0.7–1.2)
>Median	288/230	0.9 (0.8–1.1)	242/194	1.0 (0.8–1.2)	132/108	0.9 (0.7–1.3)	171/145	0.8 (0.6–1.0)
Test for trend (*P*)		0.41		0.80		0.48		0.11
Oils or coal products								
None	703/614	1.0	787/673	1.0	1042/867	1.0	932/807	1.0
≤Median	406/295	1.1 (0.9–1.4)	362/266	1.1 (0.9–1.4)	231/170	1.1 (0.9–1.4)	302/198	1.2 (1.0–1.5)
>Median	358/294	1.0 (0.8–1.2)	320/263	1.0 (0.8–1.2)	196/165	0.9 (0.7–1.1)	235/197	0.9 (0.7–1.2)
Test for trend (*P*)		0.92		0.84		0.58		0.75
Other								
None	953/765	1.0	1025/845	1.0	1210/976	1.0	1142/901	1.0
≤Median	276/212	1.0 (0.8–1.3)	240/172	1.2 (1.0–1.5)	134/160	1.0 (0.8–1.3)	175/145	0.9 (0.7–1.2)
>Median	235/212	0.9 (0.7–1.1)	199/171	1.0 (0.8–1.2)	120/106	0.9 (0.7–1.1)	147/142	0.7 (0.6–1.0)
Test for trend (*P*)		0.23		0.90		0.38		0.02

[a] ORs were adjusted for paternal education, race, family income, age, and sex of the index child.

exposure to paint during pregnancy was related to the risk, but this study included very few working mothers.

It is not clear how the risk of parental occupational exposure is conveyed to the offspring, although mechanisms, such as direct exposure to the parental germ cell and/or transplacental exposure to the fetus, and exposure through breast milk or contaminated clothes have been suggested (17). It is known that solvents are fat soluble, and some chlorinated solvents have been found in breast milk (3). Exposure through breast milk, however, is unlikely to be the mechanism, because breastfeeding was inversely associated with the risk of ALL in our study (23). Additional adjustment for breastfeeding in our study also did not alter the results. A genotoxic effect on the germ cell and/or transplacental carcinogenicity are more likely to be the underlying mechanisms and warrant further study.

Although very little evidence has linked plastic materials to cancer risk, the production of plastic materials is known to involve some human carcinogens, such as vinyl chloride (24). In our study, an elevated ALL risk was found to be associated with maternal exposure (significant only for the postnatal period) and paternal exposure (during the perinatal period) to plastic materials. Both parents of seven ALL cases, but no controls, reported exposure to plastic materials. Examination of job histories of these parents confirmed occupations in plastic manufacturing.

It is noteworthy that most of the risk estimates found in this study were moderate. Some of the findings might be the result of multiple comparisons, given the large amount of information obtained and the large number of statistical analyses conducted in this study. The risk estimation could be underestimated due to some limitations of the study:

(*a*) The information for this study on exposures came primarily from the respondents reviewing a list of specific substances, although the respondents were able to volunteer other exposures. It is not unusual that respondents have no knowledge of or cannot recall specific substances to which they were exposed (25). It has been shown that surveys using broad categories of exposures (*e.g.*, oils) can increase sensitivity, but decrease specificity, whereas using more specific classifications (*e.g.*, benzene) increases specificity but decreases sensitivity (26). We included both broad and individual exposure categories in our survey and analyses and focused our interpretation of the results based on the consistency of the association across specific windows and the related groupings rather than purely on the point estimates and statistical significance.

(*b*) We collected only information on duration of exposure but not on the level or intensity of exposure. Subjects with low, infrequent exposure, therefore, were grouped with high, frequently exposed subjects, which could bias the risk estimates toward the null. The latter may be particularly influential on the risk estimate of long-duration exposure, because subjects exposed to high concentrations of toxic materials at high frequencies might be more likely to quit the job within a short period of time, whereas those holding a job for a longer period might have less exposure. This may explain why the risk of ALL did not increase with the duration of most parental exposures.

(*c*) In some cases, the information on exposures provided by the parents that was not on a prior list was not always specific enough to ensure correct categorization. An exposure was therefore assigned to the likeliest category. The effect of this procedure would be to move the observed risks to the null.

(*d*) Direct paternal interviews were not available for a sizable number of study participants. An earlier study has suggested that the participation rate is positively correlated with the socioeconomic status (27). The potential biases resulting from selective participation, therefore, would be most likely to lead to an underestimation of the risk.

As with all studies using the case-control design, differential recall or reporting bias is always a concern. In a study of parents' occupation and risk of mental retardation in children, however, no difference was found between the exposures reported by case and control parents (28). In our study, the ALL risk associated with parental exposure to hydrocarbons varied with the time window of exposure, and the association appeared to be determined by the nature of the chemicals. For example, maternal exposure to solvents, paints, and thinners (substances that are fat soluble, highly volatile, and likely to be able to cross the placenta) was associated with an increased risk of ALL during the perinatal period, whereas maternal exposure to the same chemicals during the postnatal period was unrelated to the risk. In contrast, maternal exposure to plastic materials, which are less likely to be able to cross the placenta, was not related to the risk of ALL during the perinatal period but was associated with an elevated risk postnatally. These time-specific associations strengthen the validity of our findings and argue against a differential recall bias.

In summary, this study suggested that parental, mainly maternal, occupational exposure to hydrocarbons was associated with an increased risk of childhood ALL. Such an association was determined by the timing of exposure to the particular type of hydrocarbon. It is important to point out that the effect of parental exposure to hydrocarbons, if confirmed, can only explain a small proportion of childhood ALL because of low exposure rate. Nevertheless, pregnant women should be advised to avoid exposure to hydrocarbons as much as possible, given their potential impact on pregnancy outcomes and health of children.

Appendix

Appendix Participating Principal Investigators—Children's Cancer Group

Institution	Investigators	Grant no.
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University of Wisconsin Hospital Madison, Wisconsin	Diane Puccetti, M.D.	CA 05436
Children's Hospital & Med. Ctr. Seattle, Washington	J. Russell Geyer, M.D.	CA 10382
Rainbow Babies & Children's Hosp. Cleveland, Ohio	Susan Shurin, M.D.	CA 20320
Children's National Medical Ctr. Washington, D.C.	Gregory Reaman, M.D.	CA 03888
Children's Hospital of Los Angeles Los Angeles, California	Paul Gaynon, M.D.	CA 02649
Children's Hospital of Columbus Columbus, Ohio	Frederick Ruyman, M.D.	CA 03750
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Appendix Continued

Appendix Participating Principal Investigators—Children's Cancer Group

Institution	Investigators	Grant no.
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University of British Columbia Vancouver, Canada	Christopher Fryer, M.D.	CA 29013
Children's Hospital Medical Center Cincinnati, Ohio	Robert Wells, M.D.	CA 26126
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