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A task-based assessment of parental occupational exposure to organic solvents and other compounds and the risk of childhood leukemia in California

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Abstract

Purpose—Data on parental occupational exposures and risk of childhood leukemia lack specificity. Using 19 task-based job modules, we examined the relationship between occupational exposure to organic solvents and other compounds and the risk of leukemia in children.

Methods—Latino (48%) and non-Latino (52%) children with acute lymphoblastic leukemia (ALL; n=670), acute myeloid leukemia (AML; n=104), and controls (n=1021) were enrolled in a study in California (2000–2008). Logistic regression models were used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs), adjusted for socio-demographic factors.

Results—Among children with non-Latino fathers, none of the exposures evaluated were associated with risks of ALL and AML. In contrast, exposure to any organic solvents in Latino fathers was associated with an increased risk of childhood ALL (OR=1.48; 95% CI: 1.01–2.16); in

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Appendix A. Supporting information: Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2016.06.047.

multivariable analyses, the OR for chlorinated hydrocarbons was 2.28 (95% CI: 0.97–5.37) while the ORs were close to one for aromatic hydrocarbons, glycol ethers, and other hydrocarbon mixtures. We also observed an increased risk of ALL with exposure to combustion exhaust/polycyclic aromatic hydrocarbons (PAHs) (ORs=1.70; 95% CI: 1.16–2.57, and 1.46; 95% CI: 0.94–2.26 with and without adjustment for chlorinated hydrocarbons, respectively). Moderately elevated risks of ALL were seen with exposure to metals, paints, and wood dust, although not statistically significant. An increased risk was reported for asbestos based on small numbers of exposed Latino fathers. No associations were reported between maternal exposures to any exposures and childhood ALL and AML.

Conclusions—Our data support associations between paternal occupational exposures to chlorinated hydrocarbons, combustion exhaust, metals, and possibly asbestos and the risk of ALL in the children of Latino fathers only.

Keywords

Childhood leukemia; Occupational exposure; Chemicals

1. Introduction

Leukemia is the most common cancer in children leading to approximately 12,000 new cases per year in the United States (US) (Howlader et al., 2013). Acute lymphoblastic leukemia (ALL) accounts for about 80% of leukemias, and occurs mainly in children 2–5 years of age. Acute myeloid leukemia (AML) is rare in children (Linabery and Ross, 2008). In the US, the incidence of childhood leukemia has increased by 1% annually since the 1970s, with higher rates reported among Hispanic (or Latino) children (Barrington-Trimis et al., 2015), suggesting that environmental factors specific to ethnic groups are contributing to this trend.

Events occurring at critical times during the fetus' and child's development (i.e., before conception, during pregnancy, and the first years of life) are likely to contribute to early-onset leukemia. A two-hit model of leukemogenesis has been postulated, where both prenatal and postnatal cellular insults are necessary to lead to leukemic clones (Greaves and Wiemels, 2003). Carcinogenic compounds encountered at the parents' workplace may induce leukemia in the offspring via damage to the germ and somatic cells (Colt and Blair, 1998) depending on the timing (i.e., preconception, pregnancy, early life) and mode of exposure (e.g., direct for the parents or via take-home for the child). Previous epidemiologic studies have reported associations between parental occupational exposures to solvents, paints, pigments, pesticides, lead, combustion exhaust and the risk of childhood leukemia (Infante-Rivard et al., 2005; McKinney et al., 2008; Reid et al., 2011; Van Maele-Fabry et al., 2011; Vinson et al., 2011; Wigle et al., 2009). Most studies relied on job titles lacking specificity for type and intensity of exposure, and/or had a small sample size (Colt and Blair, 1998; Van Maele-Fabry et al., 2011; Vinson et al., 2011; Wigle et al., 2009; Keegan et al., 2012; Bailey et al., 2014a, 2014b). Few studies used expert occupational exposure assessment (Infante-Rivard et al., 2005; McKinney et al., 2008; Reid et al., 2011; Monge et al., 2007; Perez-Saldivar et al., 2008; Miligi et al., 2013). Among those examining mothers' work history, increased risks of childhood ALL were reported following preconception

exposure to aliphatic and aromatic hydrocarbons (Miligi et al., 2013), prenatal exposure to combustion exhaust (Reid et al., 2011), and pre- and postnatal exposure to solvents (McKinney et al., 2008), alkanes and aromatic hydrocarbons (Infante-Rivard et al., 2005). Studies of paternal occupations reported increased risks of childhood ALL with pre-and postnatal exposures to metals (Miligi et al., 2013) and combustion exhaust (Reid et al., 2011; Miligi et al., 2013). Studies of parental occupational exposures and risk of childhood AML are sparse. Previous studies have been mainly conducted in Caucasian populations (Van Maele-Fabry et al., 2011; Vinson et al., 2011; Wigle et al., 2009), and little is known about leukemia risk associated with parental occupational exposures in other ethnic groups (Monge et al., 2007; Perez-Saldivar et al., 2008; Shu et al., 1988; Kishi et al., 1993; Ferreira et al., 2013) that have different work experiences (Bureau of Labor Statistics, 2016).

Using detailed task-based job modules (JMs) and expert exposure rating, we evaluated whether paternal and maternal exposures to organic solvents and other compounds increase the risk of childhood ALL and AML, overall and separately in Latinos and non-Latinos, the two major ethnic groups participating in a case-control study in California.

2. Methods

2.1. Study population

The present analysis includes cases and controls enrolled in the California Childhood Leukemia Study (CCLS) and for which detailed occupational exposures were collected from 2000 to 2008. The CCLS is a population-based case-control study conducted in 35 counties in Northern and Central California, as previously described (Metayer et al., 2013; Bartley et al., 2010). Cases were identified within 72 hours after diagnosis at 9 hospitals and were eligible for participation if they were younger than 15 years of age at diagnosis, had an English or Spanish speaking parent, lived in one of the 35 counties that comprised the population base at the time of diagnosis, and had never been previously diagnosed with cancer. Children of all racial and ethnic backgrounds were eligible. Comparison of case ascertainment in the 35-county study area to the California Cancer Registry showed that the CCLS ascertained 93% of cases diagnosed from the participating hospitals. When considering both participating and non-participating hospitals within the 35 study counties, 76% of all diagnosed cases in California were ascertained in the CCLS. Of these, 86% of cases were eligible and consented to participate.

Eligibility criteria for leukemia-free controls were similar to those for cases. Controls were randomly selected using birth certificates obtained through the California Office of Vital Records, and one or two controls were matched to each case on child's date of birth, sex, Hispanic ethnicity defined as either one or both parents being Hispanic as indicated on the birth certificate record (also referred to as Latino in the text), and maternal race as indicated on the birth certificate record. Among those contacted and eligible during this study period, approximately 90% agreed to participate in the study.

2.2. Data collection

General information on socio-demographic characteristics, home use of chemicals, residential characteristics, mother's and child's medical histories and diets, lifestyle, smoking, social contacts, and family history of cancer, was collected through home-based, in-person interviews, mainly with the biological mother (97%). During this initial interview, a complete occupational history (i.e., job title and duties, company name and type, dates of employment) was gathered separately for each parent for any full and part time jobs reported for more than one month (paid or volunteered) from one year before the child's birth until the child's third birthday or diagnosis date (or reference date in control children), whichever came first. The mother provided information on her job history, as well as the father's job history if the father was not available. When available, the father (55%) provided information on his job history either by phone or in a home-based, in-person interview.

In order to capture detailed parental occupational exposures, a team of scientists in the fields of industrial hygiene, environmental epidemiology, occupational medicine, and toxicology developed 19 additional JMs (Table 1) that were adapted from those designed by the National Cancer Institute (US) (Stewart et al., 1996, 1998). Detailed methods are provided elsewhere (Reinier et al., 2004). In brief, the JMs were designed to test *a priori* hypotheses for the development of leukemia in children, and to capture critical periods of parental occupational exposures, i.e., prenatally (the three months before conception, during pregnancy including 1st, 2nd, and 3rd trimesters) and postnatally (1st, 2nd, and 3rd year after birth or diagnosis/reference date, whichever came first). The JMs included questions about tasks likely to involve exposures of interest such as chemicals and agents identified as possible leukemogens or carcinogens (as described in the introduction), and other products commonly used like disinfectants. Information on the use of protective equipment was also collected. For certain occupations with high certainty of exposure to chemicals (e.g., dry cleaners and exposure to perchlorethylene) or mixtures of chemicals (e.g., parking attendants and exposure to vehicle exhaust), JMs were not developed and relevant exposures were assigned directly (Supplementary Fig. 1). Following the initial interview, trained interviewers assigned JMs based on the parent's job title, industry and a brief job description. No more than two JMs were assigned per family. In the event a family was eligible for more than two JMs (5%), the following selection criteria were applied. The first criterion was the timing of the occupation (i.e., any job held by the mother during pregnancy was selected first, and then any job held by the father during the three months before conception). If, after applying this first criterion, more than two JMs were possible candidates, an additional criterion was used to retain a maximum of two JMs, based on prioritization of exposures of interest (i.e., the order of JMs from first to last priority was Farmer, Gardener, Packer, Pesticide Handler and Applicator, Mechanic, Airplane, Painter, Construction Worker, Manufacturing Worker, Welder, Engineer, Electrician, Cleaner, Artist, Laboratory Worker, Photographer, Teacher, Medical Worker, Dentist). Each parent completed his/her own JM either by phone or in-person (no surrogate respondents were used). All interviews and study materials were available in English and Spanish. Translation was done by a professional, and back translation performed by an independent Spanish speaker. All JM assignments were independently reviewed by research staff (GS, JC) for

quality control, and in few instances (2%), households were re-contacted to administer a JM interview deemed necessary after the review was completed.

Based on empirical knowledge and literature, an industrial hygienist expert (PQ) and occupational epidemiologist (KH) developed a question-by-question exposure coding scheme for each JM to determine exposure to a class (e.g., hydrocarbons), sub-class (e.g., aromatic hydrocarbon), and specific type of chemical (e.g., benzene, toluene), and exposure to non-chemical agents. Exposure assessment took into consideration the type and frequency of each task performed by a parent, as well as the product, material, piece of equipment, and procedure involved for each task. For each question, the expert developed a scheme to code the likelihood of exposure (possible vs. probable) and the intensity of exposure (high vs. low). Intensity was modified if the parent answered affirmatively about wearing protective equipment or provided details about how the task was performed (e.g., exposure may be less intense if parent wore a respirator while applying paint). Expert assessment was done *a priori*, independently of data collection. For about 10% of randomly selected JMs, quality control was conducted (GS and PQ) blinded to case-control status to assess consistency between original data from both the initial and JM interviews, and final exposure assessment. In this subset, the exposure classification matched reported job-tasks, suggesting that systematic errors during data entry, coding, and programming were unlikely in the entire dataset. Our analyses focused on exposures to organic solvents (classified as aromatic hydrocarbons including benzene, chlorinated hydrocarbons, glycol ethers, and other hydrocarbon mixtures), other organic compounds, combustion exhaust including gasoline diesel exhaust and emissions, and polyaromatic hydrocarbons (PAHs), paints, disinfectants, metals/welding fumes, asbestos, and wood dust (Table 1). Exposure to radiation was rare (1%) and not reported in this analysis.

2.3. Sample size

During the initial interview, about 98% of participating households (1767 out of 1795) reported having at least one parent in the workforce. A total of 1120 children had working parent(s) who were eligible and selected for at least one of the 19 JMs (975 for fathers and 596 mothers), and of these, 702 fathers (72%) and 562 mothers (94%) completed one or two JM interviews. For 121 children (~11%), only one of two required JMs was completed providing partial information (Supplementary Fig. 1). Eligible parents who did not complete the JMs were more likely to have lower education and income, compared to those parents who did. This observation was true separately for cases, controls, and non-Latino children but not for Latinos (data not shown). A total of 667 ALL cases, 103 AML cases, and 1020 controls were included in the analyses on paternal exposures, and 670 ALL cases, 104 AML cases, and 1021 controls were included in the analyses on maternal exposures. Approximately 41% of fathers and 43% of mothers were of Latino descent.

2.4. Leukemia classification

Clinical and laboratory data relevant to histologic and immunophenotypic classification were abstracted from children's medical records, and reviewed for accuracy by a clinical oncologist. Immunophenotype was determined for ALL cases (600 B-cell ALL and 61 T-cell

ALL) according to the World Health Organization classification using flow cytometry profiles provided in the pathology report.

2.5. Statistical analysis

Descriptive analyses were conducted to compare the distribution of socio-demographic characteristics between cases and controls (Table 2) and to identify potential confounders (socioeconomic status, tobacco smoking, home exposure to paints and solvents). Correlation among specific organic compounds or mixtures was assessed using Pearson coefficients. Analyses were conducted separately for ALL and AML Analyses examining the relationship between paternal exposures and childhood ALL were conducted separately for Latino and non-Latino fathers, due to evidence that Latino ethnicity modified the associations observed with most compounds (p-value for interaction <0.20); data for AML and those for maternal exposures were too sparse to conduct stratified analyses. Unconditional multivariable logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). To maintain the maximum number of observations in the analyses, missing values for exposures of interest (~ 11 to 17% of cases vs. 5 to 18% of controls) were retained in the models as a dummy variable, so that the sample size remained constant for all analyses. Household income differed significantly by case-control status (Table 2) and was included in all models. Household use of paints and solvents, home and occupational exposure to pesticides, and parental education and smoking were not included in the final models because they did not change the OR of interest by more than 10% (data not shown). The final models were adjusted for the original matching factors (child's age at diagnosis/reference date, sex, and Latino ethnicity, maternal race [i.e., black, white, and other]), and household annual income. Overall, results based on unconditional logistic regression (adjusted for matching factors) and conditional logistic regression led to similar conclusions, although the risk estimates from unconditional logistic regression tended to be more precise, especially for analyses among Latinos and/or for rare exposures.

Because approximately 75% of fathers and mothers were classified as being exposed to the same chemical(s) or agent(s) of interest before and after the child's birth, we present the overall risk estimates for pre- and postnatal exposures combined. Each occupational agent (e.g., benzene) and class (e.g., organic compounds) was analyzed separately with three different exposure classifications comparing 1) any exposure vs. none, 2) intensity of exposure: none, low, and high, and 3) likelihood of exposure: none, possible, and probable.

3. Results

No associations were found between most occupational exposures evaluated among non-Latino fathers and childhood ALL in single exposure models (Table 3). Analyses by intensity of exposure did not reveal apparent dose-response relationships for all compounds, except possibly for disinfectants based on small numbers (p for trend <0.05; Supplementary Table 1). In contrast among Latino fathers, several exposures were associated with an increased risk of childhood ALL in single exposure (ever/never) models, including chlorinated hydrocarbons (OR=2.5; 95% CI: 1.4–4.7), benzene (OR=2.0; 95% CI: 1.1–3.7), glycol ethers (OR=1.70; 95% CI: 1.03–2.81), combustion exhaust/PAHs (OR=1.70; 95% CI:

1.16–2.57), metals (OR=2.1; 95% CI: 1.2–3.8), and asbestos although based on small numbers (OR=4.65; 95% CI: 1.26–17.16) (Table 3). Non statistically-significant increased risks of ALL were also observed with paternal exposure to paints and wood dusts (Table 3). We ran two models with different exposure groups (Table 4) in order to assess the independent contribution of individual chemicals. In Model 1, the OR for paternal exposure to chlorinated hydrocarbons was 2.28 (95% CI: 0.97–5.37), while the ORs were close to one for the other organic solvents. In Model 2 including chlorinated hydrocarbons, combustion exhaust/PAHs, and metals, the magnitude of the associations with each exposure was attenuated and of borderline significance for chlorinated hydrocarbons (OR=1.93; 95% CI: 0.98–3.81) and combustion exhaust/PAHs (OR=1.46; 95% CI: 0.94–2.26) (Table 4; Model 2). Exposure to chlorinated hydrocarbons was mainly found among workers in mechanics (29%), construction (29%), and manufacturing (13%). The most common sources of exposure and/or tasks included using a cleaning product to degrease hands (mechanics), thinning paint (construction), cleaning brakes (mechanics), and using spray cans with internal propellants (construction). The majority of exposed fathers had a high-level of exposure to chlorinated hydrocarbons (75%) and a low-level of exposure to combustion exhaust/PAHs (84%) (Supplemental Table 1), limiting our ability to conduct meaningful dose–response analyses. For other compounds, there were no consistent patterns for associations of larger magnitude in workers exposed to high-level chemicals vs. low-level (Supplemental Table 1). Similar to non-Latino fathers, however, we reported a statistically significant dose-response relationship for disinfectants only (p for trend <0.05). All associations reported in Table 3 remained present when limiting the analyses to exposures with probable level of certainty (Supplementary Table 2). There was little difference in the ORs when the analyses were restricted to B-cell immunophenotype; however, there were few ALL with T-cell precursors (results not shown).

Results for all paternal occupational exposures under investigation and the risk of AML, a rare subtype of leukemia in children, were mostly inconclusive, apart from an increased risk with exposure to asbestos based on small numbers (OR=5.51; 95% CI: 2.12–14.37) (Table 5). Except for disinfectants, the prevalence of exposures to any agents at the workplace was fairly low (<10%) in mothers, and no statistically significant associations were observed for maternal exposures and the risk of childhood ALL overall (Table 6). Analyses stratified by maternal Latino ethnicity were not conducted due to limited numbers.

4. Discussion

Our study indicates that children of Latino fathers occupationally exposed to chlorinated hydrocarbons, combustion exhaust/PAHs, metal/welding fumes, and asbestos were at increased risk of ALL, whereas no associations were observed for children of non-Latino fathers. These findings are based on expert-rating of occupational exposures and on the largest number of Latino households to date. Maternal exposures to chemicals and non-chemical agents were generally infrequent, and no associations with childhood ALL were detected overall.

4.1. Paternal occupational exposures

Chlorinated hydrocarbons are organic solvents widely used in industrial degreasers for metal parts and textiles, and also in domestic cleaning products and pesticides. Their use has declined since 1970, and remains concentrated in chemical production plants. Trichloroethylene (TCE), a volatile chlorinated hydrocarbon, has been classified as a known human carcinogen (System IRI, 2013; Guha et al., 2012). Other chlorinated hydrocarbons are classified as possible or probable human carcinogens based on animal studies (Guha et al., 2012). TCE-exposed workers are at risk of developing cancer of the kidney, and possibly liver, lung, cervix and non-Hodgkin lymphoma (Guha et al., 2012; Purdue, 2013; Karami et al., 2013; Vlaanderen et al., 2013). Metabolites of TCE are genotoxic, and TCE is also known to impair DNA synthesis in vitro and immune function in humans (System IRI, 2013; Bassig et al., 2013; Scott and Cogliano, 2000).

The JMs in our study were not designed to assess the type of chlorinated hydrocarbons, and we cannot directly infer whether fathers were exposed to TCE or other chlorinated hydrocarbons. Our null findings related to chlorinated hydrocarbons among non-Latino fathers are consistent with recent studies based upon expert review of occupational exposures (Reid et al., 2011; Miligi et al., 2013) and self-reports (Shu et al., 1999). These childhood leukemia studies were conducted in Caucasian populations in the 1990s and reported no associations between paternal exposure to chlorinated hydrocarbons, (Reid et al., 2011; Miligi et al., 2013; Shu et al., 1999) including TCE (Miligi et al., 2013), and ALL. However, earlier studies conducted prior to the 1990s in the United Kingdom (1974–1988) (McKinney et al., 1991) and US (1980–1984) (Lowengart et al., 1987) suggested a 2- to 3-fold increased risk of childhood leukemia (and non-Hodgkin lymphomas) (McKinney et al., 1991) following self-reported exposures to TCE. Interestingly, the previous US study (Lowengart et al., 1987) was conducted in Los Angeles County where Latinos represented ~30% of the population during the study period (Lopez, 2002), but analyses stratified by race/ethnicity were not conducted. Studies in Caucasian populations consistently support associations between childhood leukemia and exposure to mixtures of carcinogens from vehicle and/or combustion exhaust (Colt and Blair, 1998; Reid et al., 2011; Miligi et al., 2013), but not with paints, welding fumes, and wood dust (Colt and Blair, 1998; Reid et al., 2011; Miligi et al., 2013). Our data showed associations with some of those compounds only for Latino fathers, and not for non-Latinos. A study conducted in Mexico also reported an increased risk of childhood leukemia when fathers were exposed to carcinogens, using a validated occupational index that takes into account industry type, task, protective equipment, self-reported exposure to known carcinogenic agents, and frequency and intensity of exposure (Perez-Saldivar et al., 2008).

The lack of consistency of our findings for non-Latinos with some European studies may be partly explained by differences in working conditions/exposures over time and across countries. In addition in our study, the risk differences by ethnic group may reflect differences in the type and level of exposure to chemicals, as well as differences in access and proper use of protective equipment. Per the US Bureau of Labor Statistics (Bureau of Labor Statistics, 2016), Latinos represent 25–50% of the workforce in industries related to food preparation, cleaning/maintenance, construction, manufacturing, and agriculture, likely

leading to disproportionate exposure to a wide array of chemicals. Similarly, working conditions are also found more dangerous in immigrants compared to US-born workers (Orrenius and Zavodny, 2009; Loh and Richardson, 2004). In our study, Latino fathers were more likely to be classified as being exposed to high levels of organic solvents, combustion exhaust/PAHs, and metals/welding fumes, compared to non-Latino fathers, but this was limited to fathers of children diagnosed with leukemia. Similarly, Latino "case" fathers were more likely to be classified into probable level of exposure, than possible. About 55% of Latino fathers spoke Spanish and 45% English, and in general, the distribution of exposed fathers by case-control status was similar in both groups (data not shown). This suggested that English and Spanish speaking fathers had somewhat similar working experience, despite various levels of acculturation.

Whether our observations reflect true exposures or are the result of differential recall biases (Latinos vs. non-Latinos and/or cases vs. controls) remains unclear. Alternatively, underlying differences of variants for genes involved in the metabolism of many chemicals such as cytochrome P450 oxidation and gluthathione conjugation may also contribute to differential risk (Lash et al., 2000). We previously showed that risk of childhood leukemia associated with variants in *CYP1A2, CYP1B1, CYP2B6*, and *GSTM1* deletion varied between Latino and non-Latino children (Chokkalingam et al., 2012).

Our finding of a 4-fold increased risk of childhood ALL associated with paternal exposure to asbestos should be interpreted with caution due to the small sample size. Asbestos is known to cause solid cancers but its effect on tumors of the hematopoietic system is not well characterized (Straif et al., 2009). A cohort of 2500 men and women living close to asbestos-contaminated areas during childhood reported 2- to 4-fold excess risks of developing adult leukemia (Reid et al., 2013). However, little is known for risk of childhood leukemia.

4.2. Maternal occupational exposures

Two studies suggested that maternal exposure to combustion exhaust increased the risk of childhood ALL (Reid et al., 2011; Miligi et al., 2013), but we did not replicate these observations. With the exception of one study in Italy (Miligi et al., 2013), most previous investigations with expert rating (Infante-Rivard et al., 2005; McKinney et al., 2008; Reid et al., 2011) indicated that maternal occupational exposure to solvents does not appear to contribute to large numbers of ALL in the offspring, because of no (or low magnitude) associations and low frequency of exposures, which is consistent with our findings.

4.3. Route and period of exposure to carcinogens

Dermal absorption and inhalation are the main routes of exposure to volatile organic chemicals (Brown et al., 1984; Mumtaz and George, 1995; Heinrich-Ramm et al., 2000). Although volatile compounds like TCE are present in exhaled air of exposed workers (Pleil et al., 1998; Wallace et al., 1984), the half-life is short and second-hand exposure to the mother or child at home is not well characterized. As a result, the critical period of paternal exposure to volatile organic compounds may occur prior to conception, via damage to the sperm. While animal studies have reported changes in sperm morphology as a possible result of genetic changes following exposure to TCE (Land et al., 1981; Kan et al., 2007), studies

in humans are inconclusive (Chia et al., 1996; Rasmussen et al., 1988). The routes of exposure to semi-volatile organic chemicals (like PAHs contained in combustion exhaust) include inhalation, ingestion, and skin contact (Mumtaz and George, 1995). Semi-volatile compounds can also be deposited on common surfaces in homes (Weschler and Nazaroff, 2012) and clothing, and tracked into house dust (Curl et al., 2002). As a result, relevant periods of exposure to semi-volatile compounds can be both pre- and postnatal. Mixtures of volatile and non-volatile chemicals that are found in combustion exhaust are similar to those found in tobacco smoke and ambient air pollution, which have been shown to be germ-cell mutagens to animals and humans (DeMarini, 2004). In our study, time-specific analyses were not feasible because parental exposures before and after birth were highly correlated.

This study has some major strengths including ultra-rapid ascertainment of children diagnosed with incident leukemia, use of detailed task-based interviews adapted from validated JMs (Stewart et al., 1996, 1998), and the conduct of JM interviews with the index parents. Expert rating was conducted by an industrial hygienist and occupational epidemiologists to estimate the type and level of exposure to various agents based on historical knowledge of working practices in the study area and period. In addition, quality control procedures were implemented to assess the accuracy of all JM assignments and exposure ratings. However, although detailed characterization of occupational exposures was obtained, misclassification bias may have occurred in part due to the use of self-reported job-tasks, long interval between prenatal exposure and interview for older children, variability of exposures over time, uncertainties in correct use of protective equipment, and inability to assess the intensity of exposure with a finer gradient. Also, the low exposure prevalence among mothers reduced the ability to detect associations. Case families had lower socio-economic status than controls, regardless of Latino ethnicity. Although selection bias cannot be ruled out, it may not fully explain the observed difference in risk by Latino ethnicity. The participation rate of households in the main interview was slightly lower in cases than controls, whereas participation in the JM interviews was fairly similar between cases and controls. Also, fathers were less likely to participate than mothers (in both the initial interview and follow-up JM). Among Latinos, participating fathers and non-participating fathers had similar socio-economic characteristics, reducing the potential to introduce systematic biases. It is unlikely that unmeasured confounders could explain the large ethnic difference in risk associated with paternal exposures. By design, all leukemia cases diagnosed at the participating hospitals were enrolled (and of those approximately 92% were born in California), whereas only controls born in California participated in the study. As a result, the exclusion of children born outside California such as immigrants may limit the generalizability of our findings for Latinos. While grouping all non-Latino fathers introduces some heterogeneity, the analyses limited to non-Latino white fathers did not differ from those including all non-Latino fathers (data not shown). Lastly, although we tested *a priori* hypotheses, multiple comparisons may have led to false positive findings.

In conclusion, based on the largest study of Latino children and expert occupational exposure rating, our findings support the associations between paternal occupational exposures to chlorinated hydrocarbons, combustion exhaust/PAHs, metals, and possibly asbestos and the risk of ALL in the children of Latino fathers. In contrast, no associations

were observed for non-Latino fathers, raising questions about possible differences in levels of exposures, methodological issues and underlying biological mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
CCLS	California Childhood Leukemia Study
JM	Task-based job-specific module
PAHs	Polycyclic aromatic hydrocarbons
TCE	Trichloroethylene
US	United States

Table 1

Nineteen task-based job-specific module questionnaires developed for occupational exposure assessment in the California Childhood Leukemia Study, and selected agents of interest assessed in each job-specific module (broad categories only).

Job types included in each module[a]	Number of completed job modules included in analyses			Agents of interest							
	Father		Mother	Organic solvents[b]	Other organic compounds[c]	Combustion exhaust/PAHs[d]	Paints[e]	Metals[f]	Asbestos	Wooddust	Disinfectants[g]
	Latino	Non-Latino									
Airplane mechanic **worker**	**1**	**4**	**0**	x	x	x	x	x	x	x	
Artist or art teacher	**0**	**1**	**11**	x	x	x	x	x		x	
Cleaner or janitor	**28**	**17**	**110**	x	x	x	x	x	x	x	x
Construction worker or carpenter	**75**	**76**	**2**	x	x	x	x	x	x	x	x
Dentist or dental worker	**1**	**3**	**18**	x	x			x			x
Electrician, lineman, or cable puller	**8**	**27**	**1**	x	x	x	x	x	x	x	
Engineer or environmental scientist	**3**	**29**	**6**	x	x	x		x			x
Farmer or ranch worker	**106**	**13**	**42**	x	x	x	x	x		x	x
Gardener, groundskeeper, landscaper or nursery worker	**46**	**10**	**9**	x	x	x	x	x	x	x	x
Laboratory worker or lab science teacher	**5**	**18**	**18**	x	x			x	x		x
Manufacturing worker, assembly, industrial operations or product repair	**39**	**45**	**42**	x	x	x	x	x	x	x	x
Auto, truck or bus **mechanic**	**26**	**23**	**0**	x	x	x	x	x	x	x	x
Physician, nurse or **medical** technician	**6**	**22**	**116**	x	x	x	x				x
Agricultural **packer**	**15**	**2**	**62**	x	x	x			x	x	
Painter or wallpaperer	**11**	**7**	**1**	x	x	x	x	x		x	x
Pesticide handler or applicator	**1**	**7**	**0**	x	x	x	x			x	
Photographer or framer or photography teacher	**1**	**5**	**6**	x	x		x				x
Teacher of preschool to grade 5	**2**	**5**	**118**	x	x	x	x	x	x		x
Welder or joiner	**8**	**6**	**0**	x	x	x	x	x			
Total	**382**	**320**	**562**								

[b] Organic solvents included aromatic solvents, chlorinated solvents, glycol ethers, and other hydrocarbon mixtures.

[c] Other organic compounds included coal tars, asphalt, and creosote.

[d] Combustion exhaust included gasoline and diesel exhaust and emissions, and polyaromatic hydrocarbons (PAHs).

[e] Paints included water-borne paints (e.g. acrylics, vinyls, styrene-based resins, water color, tempera), oil-based paints (e.g. alkyd or modified alkyd resins and varnish, lacquers, stains), and spray paints

[f] Metals included welding fumes and metal dusts.

[g] Disinfectants included chlorinated and phenolic disinfectants, ethylene oxide, formaldehyde, isopropanol, and other disinfectants.

[a] Abbreviated titles for job-modules are in bold.

Table 2

Socio-demographic characteristics of children with leukemia and controls recruited in the California Childhood Leukemia Study, 2000–2008.

			Acute lymphoblastic leukemia		Acute myeloid leukemia	
	Controls		Cases		Cases	
	N	(%)	N	(%)	N	(%)
Characteristics	1021		670		104	
Child's sex						
Male	585	(57)	376	(56)	56	(54)
Female	436	(43)	294	(44)	48	(46)
Child's age at diagnosis or reference (years)						
0 – <2	140	(14)	72	(11)	34	(33)
2 – <6	538	(53)	380	(57)	21	(20)
6 – <9	155	(15)	95	(14)	13	(13)
≥9	188	(18)	123	(18)	36	(35)
Mean	6	(SD 4)	6	(SD 4)	6	(SD 4)
Mother's age at diagnosis or reference (years)						
Mean	29	(SD 6)	28	(SD 6)	28	(SD 6)
Father's age at diagnosis or reference (years)						
Mean	32	(SD 7)	31	(SD 7)	30	(SD 7)
Child's ethnicity/race						
Latino	468	(46)	336	(50)	54	(52)
White	*435*	(*93*)	*289*	(*86*)	*46*	(*85*)
African-American	*0*	(*0*)	*1*	(*<1*)	*0*	(*0*)
Other[a]	*33*	(*7*)	*46*	(*14*)	*7*	(*13*)
Unknown race	*0*	(*0*)	*0*	(*0*)	*1*	(*2*)
Non-Latino	553	(54)	334	(50)	50	(48)
White	*391*	(*71*)	*212*	(*63*)	*34*	(*68*)
African-American	*30*	(*5*)	*22*	(*7*)	*4*	(*8*)
Other[a]	*132*	(*24*)	*100*	(*30*)	*12*	(*24*)
Mother's ethnicity/race						

	Controls		Acute lymphoblastic leukemia Cases		Acute myeloid leukemia Cases	
	N	(%)	N	(%)	N	(%)
Latina	416	(41)	311	(46)	48	(46)
White	*415*	(*100*)	*304*	(*98*)	*47*	(*98*)
African-American	*0*	(*0*)	*0*	(*0*)	*0*	(*0*)
Other[a]	*1*	(<1)	*7*	(*2*)	*1*	(*2*)
Non-Latina	605	(59)	359	(54)	56	(54)
White	*457*	(*76*)	*245*	(*68*)	*44*	(*79*)
African-American	*32*	(*5*)	*27*	(*8*)	*4*	(*7*)
Other[a]	*116*	(*19*)	*87*	(*24*)	*8*	(*14*)
Father's ethnicity/race						
Latino	397	(39)	294	(44)	48	(46)
White	*387*	(*97*)	*257*	(*87*)	*43*	(*90*)
African-American	*0*	(*0*)	*1*	(*<1*)	*0*	(*0*)
Other[a]	*10*	(*3*)	*36*	(*12*)	*4*	(*8*)
Unknown race	*0*	(*0*)	*0*	(*0*)	*1*	(*2*)
Non-Latino	623	(61)	373	(56)	55	(53)
White	*481*	(*77*)	*263*	(*70*)	*38*	(*69*)
African-American	*48*	(*8*)	*29*	(*8*)	*6*	(*11*)
Other[a]	*94*	(*15*)	*81*	(*22*)	*11*	(*20*)
Unknown Latino ethnicity	1	(<1)	3	(<1)	1	(1)
Household annual income (USD)						
<15,000	102	(10)	112	(17)	22	(21)
15,000–29,999	134	(13)	114	(17)	21	(20)
30,000–44,999	133	(13)	108	(16)	14	(13)
45,000–59,999	135	(13)	100	(15)	12	(12)
60,000–74,999	101	(10)	37	(6)	7	(7)
≥75,000	416	(41)	199	(30)	28	(27)
Mother's education						
No schooling or elementary school	89	(9)	83	(12)	10	(10)

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	Controls		Acute lymphoblastic leukemia Cases		Acute myeloid leukemia Cases	
	N	(%)	N	(%)	N	(%)
High school or similar	279	(27)	222	(33)	38	(37)
College or similar	306	(30)	180	(27)	28	(27)
Bachelor's degree or higher	346	(34)	184	(27)	28	(27)
Unknown	1	(<1)	1	(<1)	0	(0)
Father's education						
No schooling or elementary school	112	(11)	84	(13)	13	(13)
High school or similar	312	(31)	235	(35)	43	(41)
College or similar	252	(25)	129	(19)	16	(15)
Bachelor's degree or higher	310	(30)	190	(28)	29	(28)
Unknown	35	(3)	32	(5)	3	(3)
Mother's tobacco smoking						
Never	746	(73)	505	(75)	77	(74)
Ever	274	(27)	165	(25)	27	(26)
Unknown	1	(<1)	0	(0)	0	(0)
Father's tobacco smoking						
Never	614	(60)	364	(54)	53	(51)
Ever	394	(39)	291	(44)	50	(48)
Unknown	13	(1)	15	(2)	1	(1)

Abbreviations: SD=standard deviation; USD=United States dollars.

[a]Other races reported on California birth certificates included American Indian, East Asians, Southeast Asians, Asian Pacific Islanders, Eskimo, and others.

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Table 3

Paternal occupational exposures associated with the risk of acute lymphoblastic leukemia by fathers' Latino ethnicity.

	Overall						Latino fathers						Non-Latino fathers					
	Cases		Controls		OR[a]	95% CI	Cases		Controls		OR[a]	95% CI	Cases		Controls		OR[a]	95% CI
Exposures	**667**	**(%)**	**1020**	**(%)**			**294**	**(%)**	**397**	**(%)**			**373**	**(%)**	**623**	**(%)**		
Any organic compounds																		
No	395	(59)	656	(64)	1.00	–	141	(48)	231	(58)	1.00	–	254	(68)	425	(68)	1.00	–
Yes	196	(29)	250	(25)	1.25	(0.99–1.57)[‡]	107	(36)	102	(26)	1.72	(1.22–2.44)	89	(24)	148	(24)	0.95	(0.70–1.31)
Organic solvents																		
No	425	(64)	669	(66)	1.00	–	165	(56)	236	(59)	1.00	–	260	(70)	433	(70)	1.00	–
Yes	151	(23)	194	(19)	1.18	(0.92–1.51)[‡]	78	(27)	75	(19)	1.48	(1.01–2.16)	73	(20)	119	(19)	0.98	(0.70–1.38)
Aromatic hydrocarbons																		
No	452	(68)	718	(70)	1.00	–	174	(59)	209	(53)	1.00	–	278	(75)	383	(61)	1.00	–
Yes	102	(15)	122	(12)	1.23	(0.92–1.66)	54	(18)	37	(9)	1.68	(1.08–2.61)	48	(13)	65	(10)	0.95	(0.64–1.43)
Benzene																		
No	519	(78)	807	(79)	1.00	–	207	(70)	289	(73)	1.00	–	312	(84)	518	(83)	1.00	–
Yes	48	(7)	50	(5)	1.38	(0.91–2.11)	30	(10)	20	(5)	2.03	(1.11–3.70)	18	(5)	30	(5)	0.92	(0.50–1.71)
Chlorinated hydrocarbons																		
No	503	(75)	775	(76)	1.00	–	197	(67)	286	(72)	1.00	–	306	(82)	489	(78)	1.00	–
Yes	52	(8)	67	(7)	1.14	(0.76–1.68)[*]	31	(11)	17	(4)	2.53	(1.36–4.71)	21	(6)	50	(8)	0.63	(0.36–1.08)
Glycol ethers																		
No	489	(73)	754	(74)	1.00	–	190	(65)	266	(67)	1.00	–	299	(80)	488	(78)	1.00	–
Yes	67	(10)	82	(8)	1.10	(0.77–1.56)[†]	41	(14)	32	(8)	1.70	(1.03–2.81)	26	(7)	50	(8)	0.70	(0.42–1.18)
Other hydrocarbon mixtures																		
No	419	(63)	671	(66)	1.00	–	158	(54)	234	(59)	1.00	–	261	(70)	437	(70)	1.00	–
Yes	133	(20)	171	(17)	1.19	(0.91–1.55)	68	(23)	66	(17)	1.50	(1.01–2.23)	65	(17)	105	(17)	0.98	(0.69–1.41)
Other organic compounds																		
No	535	(80)	838	(82)	1.00	–	216	(73)	306	(77)	1.00	–	316	(85)	532	(85)	1.00	–
Yes	41	(6)	39	(4)	1.66	(1.05–2.63)	22	(7)	13	(3)	2.40	(1.18–4.89)	19	(5)	26	(4)	1.21	(0.65–2.25)
Paints																		

	Overall						Latino fathers						Non-Latino fathers					
	Cases		Controls		OR[a]	95% CI	Cases		Controls		OR[a]	95% CI	Cases		Controls		OR[a]	95% CI
Exposures	**667**	**(%)**	**1020**	**(%)**			**294**	**(%)**	**397**	**(%)**			**373**	**(%)**	**623**	**(%)**		
No	524	(79)	799	(78)	1.00	–	213	(72)	287	(72)	1.00	–	311	(83)	512	(82)	1.00	–
Yes	50	(7)	64	(6)	1.08	(0.73–1.61)	27	(9)	25	(6)	1.37	(0.77–2.44)	23	(6)	39	(6)	0.88	(0.51–1.52)
Combustion exhaust/PAHs																		
No	473	(71)	746	(73)	1.00	–	176	(60)	256	(64)	1.00	–	297	(80)	490	(79)	1.00	–
Yes	102	(15)	121	(12)	1.24	(0.92–1.67)	64	(22)	56	(14)	1.70	(1.16–2.57)	38	(10)	65	(10)	0.88	(0.57–1.37)
Disinfectants																		
No	593	(89)	916	(90)	1.00	–	253	(86)	344	(87)	1.00	–	340	(91)	572	(92)	1.00	–
Yes	32	(5)	46	(5)	1.10	(0.67–1.76)	15	(5)	19	(5)	1.16	(0.57–2.34)	17	(5)	27	(4)	1.04	(0.55–1.97)
Metals																		
No	496	(74)	764	(75)	1.00	–	201	(68)	284	(72)	1.00	–	295	(79)	480	(77)	1.00	–
Yes	71	(11)	89	(9)	1.29	(0.92–1.80)[≠]	35	(12)	23	(6)	2.14	(1.22–3.75)	36	(10)	66	(11)	0.93	(0.60–1.45)
Welding fumes																		
No	542	(81)	824	(81)	1.00	–	221	(75)	300	(76)	1.00	–	321	(86)	524	(84)	1.00	–
Yes	29	(4)	36	(4)	1.29	(0.77–2.15)	16	(5)	9	(2)	2.44	(1.05–5.66)	13	(3)	27	(4)	0.82	(0.41–1.63)
Asbestos																		
No	589	(88)	917	(90)	1.00	–	249	(85)	246	(62)	1.00	–	340	(91)	571	(92)	1.00	–
Yes	16	(2)	14	(1)	1.75	(0.84–3.66)	10	(3)	3	(1)	4.65	(1.26–17.16)	6	(2)	11	(2)	0.92	(0.33–2.54)
Woodust																		
No	563	(84)	889	(87)	1.00	–	237	(81)	333	(84)	1.00	–	326	(87)	556	(89)	1.00	–
Yes	45	(7)	49	(5)	1.41	(0.92–2.16)	24	(8)	19	(5)	1.72	(0.92–3.22)	21	(6)	30	(5)	1.17	(0.65–2.11)

Abbreviations: OR=odds ratio; CI=confidence interval; PAHs=polycyclic aromatic hydrocarbons.

Missing values for exposures of interest were retained in the models as a dummy variable to maintain the maximum number of observations. Corresponding risk estimates are not shown.

[*] p for interaction (between exposure and Latino ethnicity) =0.01.

[†] p for interaction (between exposure and Latino ethnicity) < 0.10.

[≠] p for interaction (between exposure and Latino ethnicity) < 0.20.

[a] OR adjusted for child's age at diagnosis/reference date, sex, and Latino ethnicity, maternal race, and household annual income.

Table 4

Multiple paternal occupational exposures associated with the risk of acute lymphoblastic leukemia among Latino fathers.

		Latino fathers					
		Cases		Controls		OR[a]	95% CI
Model	Exposures	294	(%)	397	(%)		
1	Aromatic hydrocarbons	54	(18)	45	(11)	1.08	(0.46–2.55)
	Chlorinated hydrocarbons	31	(11)	17	(4)	2.28	(0.97–5.37)
	Glycol ethers	41	(14)	32	(8)	0.90	(0.44–1.84)
	Other hydrocarbon mixtures	68	(23)	66	(17)	1.19	(0.58–2.48)
2	Chlorinated hydrocarbons	31	(11)	17	(4)	1.93	(0.98–3.81)
	Combustion exhaust/PAHs	64	(22)	56	(14)	1.46	(0.94–2.26)
	Metals	35	(12)	23	(6)	1.47	(0.77–2.80)

Abbreviations: OR=odds ratio; CI=confidence interval; PAHs=polycylic aromatic hydrocarbons.

Missing values for exposures of interest were retained in the models as a dummy variable to maintain the maximum number of observations in the analyses. Corresponding β coefficients are not shown.

[a]OR adjusted for child's age at diagnosis/reference date, sex, and Latino ethnicity, maternal race, and household annual income.

Table 5

Paternal occupational exposures associated with the risk of acute myeloid leukemia.

	Overall					
	Cases		Controls		OR[a]	95% CI
Exposures	**103**	**(%)**	**1020**	**(%)**		
Any organic compounds						
No	61	(59)	656	(64)	1.00	–
Yes	36	(35)	250	(25)	1.45	(0.93–2.27)
Organic solvents						
No	65	(63)	669	(66)	1.00	–
Yes	27	(26)	194	(19)	1.30	(0.80–2.11)
Aromatic hydrocarbons						
No	77	(75)	718	(70)	1.00	–
Yes	14	(14)	122	(12)	0.96	(0.52–1. 76)
Benzene						
No	86	(83)	807	(79)	1.00	–
Yes	6	(6)	50	(5)	0.90	(0.37–2.20)
Chlorinated hydrocarbons						
No	84	(82)	775	(76)	1.00	–
Yes	7	(7)	67	(7)	0.88	(0.39–2.02)
Glycol ethers						
No	84	(82)	754	(74)	1.00	–
Yes	7	(7)	82	(8)	0.62	(0.28–1.41)
Other hydrocarbon mixtures						
No	66	(64)	671	(66)	1.00	–
Yes	23	(22)	171	(17)	1.24	(0.74–2.08)
Other organic compounds						
No	88	(85)	838	(82)	1.00	–
Yes	6	(6)	39	(4)	1.47	(0.60–3.63)
Paints						

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	Overall					
	Cases		Controls		OR[a]	95% CI
Exposures	**103**	**(%)**	**1020**	**(%)**		
No	85	(83)	799	(78)	1.00	–
Yes	7	(7)	64	(6)	0.92	(0.40–2.09)
Combustion exhaust/PAHs						
No	78	(76)	746	(73)	1.00	–
Yes	16	(16)	121	(12)	1.16	(0.65–2.08)
Disinfectants						
No	92	(89)	916	(90)	1.00	–
Yes	6	(6)	46	(5)	1.30	(0.53–3.17)
Metals						
No	80	(78)	764	(75)	1.00	–
Yes	12	(12)	89	(9)	1.31	(0.67–2.54)
Welding fumes						
No	85	(83)	824	(81)	1.00	–
Yes	6	(6)	36	(4)	1.62	(0.65–4.04)
Asbestos						
No	89	(86)	917	(90)	1.00	–
Yes	7	(7)	14	(1)	5.51	(2.12–14.37)
Woodust						
No	88	(85)	889	(87)	1.00	–
Yes	9	(9)	49	(5)	1.77	(0.83–3.78)

Abbreviations: OR=odds ratio; CI=confidence interval, PAHs=polycyclic aromatic hydrocarbons.

Missing values for exposures of interest were retained in the models as a dummy variable to maintain the maximum number of observations in the analyses. Corresponding β coefficients are not shown.

[a]OR adjusted for child's age at diagnosis/reference date, sex, and Latino ethnicity, maternal race, and household annual income.

Table 6

Maternal occupational exposures associated with the risk of acute lymphoblastic leukemia.

	Overall					
	Cases		Controls		OR[a]	95% CI
Exposures[b]	670	(%)	1021	(%)		
Any organic compounds						
No	572	(85)	879	(86)	1.00	–
Yes	93	(14)	137	(13)	1.03	(0.77–1.37)
Organic solvents						
No	579	(86)	885	(87)	1.00	–
Yes	84	(13)	124	(12)	1.02	(0.75–1.37)
Aromatic hydrocarbons						
No	639	(95)	978	(96)	1.00	–
Yes	15	(2)	19	(2)	1.40	(0.70–2.81)
Chlorinated hydrocarbons						
No	649	(97)	979	(96)	1.00	–
Yes	7	(1)	16	(2)	0.71	(0.29–1.75)
Glycol ethers						
No	614	(92)	946	(93)	1.00	–
Yes	39	(6)	48	(5)	1.07	(0.68–1.66)
Other hydrocarbon mixtures						
No	595	(89)	903	(88)	1.00	–
Yes	55	(8)	88	(9)	0.99	(0.69–1.42)
Paints						
No	636	(95)	962	(94)	1.00	–
Yes	23	(3)	48	(5)	0.86	(0.51–1.44)
Combustion exhaust/PAHs						
No	648	(97)	992	(97)	1.00	–
Yes	11	(2)	12	(1)	1.17	(0.51–2.70)
Disinfectants						

	Overall					
	Cases		Controls		OR[a]	95% CI
Exposures[b]	**670**	**(%)**	**1021**	**(%)**		
No	575	(86)	893	(87)	1.00	–
Yes	85	(13)	118	(12)	1.10	(0.81–1.49)
Metals						
No	649	(97)	985	(96)	1.00	–
Yes	8	(1)	20	(2)	0.60	(0.26–1.40)

Abbreviations: OR=odds ratio; CI=confidence interval

Missing values for exposures of interest were retained in the models as a dummy variable to maintain the maximum number of observations in the analyses. Corresponding β coefficients are not shown.

[a]OR adjusted for child's age at diagnosis/reference date, sex, and Latino ethnicity, maternal race, and household annual income.

[b]Results shown when numbers of exposed cases and controls are ≥ 5.