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Risk of leukemia in relation to exposure to ambient air toxics in pregnancy and early childhood

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ABSTRACT

There are few established causes of leukemia, the most common type of cancer in children. Studies in adults suggest a role for specific environmental agents, but little is known about any effect from exposures in pregnancy to toxics in ambient air. In our case–control study, we ascertained 69 cases of acute lymphoblastic leukemia (ALL) and 46 cases of acute myeloid leukemia (AML) from California Cancer Registry records of children <age 6, and 19,209 controls from California birth records within 2 km (1.3 miles) (ALL) and 6 km (3.8 miles) (AML) of an air toxics monitoring station between 1990 and 2007. Information on air toxics exposures was taken from community air monitors. We used logistic regression to estimate the risk of leukemia associated with one interquartile range increase in air toxic exposure. Risk of ALL was elevated with 3rd trimester exposure to polycyclic aromatic hydrocarbons (OR = 1.16, 95% CI 1.04, 1.29), arsenic (OR = 1.33, 95% CI 1.02, 1.73), benzene (OR = 1.50, 95% CI 1.08, 2.09), and three other toxics related to fuel combustion. Risk of AML was increased with 3rd trimester exposure to chloroform (OR = 1.30, 95% CI 1.00, 1.69), benzene (1.75, 95% CI 1.04, 2.93), and two other traffic-related toxics. During the child's first year, exposure to butadiene, ortho-xylene, and toluene increased risk for AML and exposure to selenium increased risk for ALL. Benzene is an established cause of leukemia in adults; this study supports that ambient exposures to this and other chemicals in pregnancy and early life may also increase leukemia risk in children.

Introduction

Leukemia is the most common cancer type in children, with 5000 new cases expected in the US in 2012 (Howlader et al., 2012). The most common type of childhood leukemia is acute lymphoblastic leukemia (ALL), which accounts for 78% of cases in childhood, followed by acute myeloid leukemia (AML) which makes up 16% of childhood leukemias (Ries et al., 1999). Established causes of childhood leukemia including genetic predisposition, ionizing radiation, and chemotherapeutic agents are estimated to explain <10% of cases, leaving the majority of cases with an unresolved etiology (IARC, 2012a, 2012d; Strahm and Malkin, 2006).

In adults, occupational exposure to benzene, 1,3 butadiene, and formaldehyde, as well as employment in certain industries such as rubber manufacturing, are established causes of hematopoietic cancers (IARC, 2012c). Although there are many fewer studies of children, researchers have observed excess risk for leukemias with maternal employment in machinery production and the textile industry and with maternal occupational exposure to vehicle exhaust, paints, pigments, lacquers, toluene, carbon tetrachloride, wood dust, and benzene (Magnani et al., 1990; McKinney et al., 1991; Reid et al., 2011; Schuz et al., 2000; Shu et al., 1988, 1999; Vianna et al., 1984).

Less is known about whether exposure to the lower levels of chemicals that pregnant mothers and children are exposed to in everyday life ("ambient exposures") increase risk for leukemia. Recently, two studies by our group observed increases in ALL in children with greater exposure to traffic-related pollution during the mother's pregnancy period (Ghosh et al., 2013; Heck et al., 2013d). Of the other studies on this topic with high quality exposure assessment, a majority have found similar results (Amigou et al., 2011; Crosignani et al., 2004; Feychting et al., 1998; Raaschou-Nielsen et al., 2001; Vinceti et al., 2012; Weng et al., 2008).

The initiating steps of carcinogenesis of some types of leukemia have been previously demonstrated in studies that identified hallmark chromosome translocations in the bloodspots of newborns (Wiemels et al., 1999, 2002). Due to the fetus' greater vulnerability to toxins (Selevan et al., 2000), environmental exposures occurring

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during the perinatal period may be of most relevance to leukemia risk. Using a population-based sample, the purpose of the present study was to further examine possible traffic-related and other pollution effects by investigating the influence of specific air toxics on leukemia risk.

Materials and methods

The Air Pollution and Childhood Cancer Study (APCC) is a large population-based study, which is described in detail elsewhere (Heck et al., 2013a). In brief, cases were selected from children younger than age 6 who were listed in the California Cancer Registry between 1990 and 2007. We chose to restrict to this young age because our primary hypothesis was that exposures during the perinatal period would be of the most etiologic relevance. Using first name, last name, date of birth, and social security number when available, we matched cases to California birth certificates (89% matching rate). The majority of cases that were not matched to a birth certificate were likely born out of state (Urayama et al., 2009). Controls, frequency-matched by year of birth to all childhood cancer cases in the parent APCC study, were selected at random from California birth certificates for the same time period (20:1 matching). After linkage with California death records, we excluded 1550 controls who died of other causes in childhood (<age 6). There were 9234 children lacking information on gestational age on their birth certificates that were excluded from the present study. We additionally excluded 71 likely non-viable births among controls (<500 g birth weight or <20 weeks gestational age) and 494 children whose home address was listed as being outside of California.

We geocoded home addresses, as listed on birth certificates, with a manual resolution process for unmatched addresses, as previously described (Goldberg et al., 2008). Full addresses (number and street) were available on electronic birth certificates starting in 1998. Prior to that date, electronic records only included zip code, thus we geocoded everyone to the zip code centroid. We conducted sensitivity analyses to determine whether the use of zip code centroid instead of addresses changed estimates in models.

The state of California has conducted community-based environmental monitoring of air toxics since 1985, with data available from 1990. Air monitors collect 24-h samples every 12 days. While air monitors are located across the state, most are sited near heavy industry, busy freeways, or in agriculturally intense rural regions (for map, see Cox et al., 2008). Across the study period, monitors were located at 39 different sites. The number of air toxics that are collected has changed over time (ranging between ~60 and 189), and not every air toxic was collected at every monitor, with many collected only in certain years or at specific monitors. Of the available toxics, we selected 42 for the present study because they had been listed as established or suspected carcinogens by the International Agency for Research on Cancer (IARC, 2011). We additionally created a new variable, total polycyclic aromatic hydrocarbons (PAHs), which consisted of the sum of all PAH values [benzo(b)fluoranthene, benzo(k)fluoranthene, indeno(1,2,3-cd)pyrene, dibenz(a,h)anthracene, benzo(g,h,i)perylene, and benzo(a)pyrene].

We ascertained the gestational age of each child from birth certificates, and calculated the start and end date of each trimester (estimating the trimesters as days 1–90, 91–181, and 181+ of the pregnancy). Time-specific exposure averages were calculated based upon the gestational age and date of birth of each child, with estimates generated for each trimester, the entire pregnancy period, and the child's first year of life. In calculating first year of life exposures, we excluded children diagnosed with leukemia prior to age 1. For each pollutant, we included children in the analysis who had at least one reading for each full month of the pregnancy, and because the last month of pregnancy rarely is exactly one month in length, with at least one reading within the last 30 days of pregnancy. Only children who lived within a specific radius around a monitor were included in analyses, and we examined different radii around the monitors to evaluate consistency in effect estimates across distances. Our goal was to choose the smallest radii that allowed for adequate sample size for estimating effects for most pollutants. Here, we report results for 2 km (~1.3 miles) (ALL) and 6 km (~3.8 miles) (AML) buffer areas. This excluded 2584 cases (ALL), 394 cases (AML) and 142,188 controls from the original study that lived outside the 2 K and 6 K radii. In the interest of having adequate sample sizes, we report only upon the air toxics for which a minimum of 20 cases had values assigned at the respective distance.

Because air toxics frequently arise from the same sources, pollutant measurements are sometimes correlated with one another. Correlations between the pollutants in this study have been previously reported (Heck et al., 2013c). To address this issue, we conducted factor analysis with varimax rotation in order to group highly correlated toxics together. The air toxics loaded to four main factors (eigenvalues >1) with the remaining air toxics not loading to any factor. Results are presented with correlated toxics loading on each factor grouped together.

We used unconditional logistic regression adjusted for the matching variable, birth year, to compare demographic and other characteristics of cases and controls. We then used unconditional logistic regression to estimate the risk of leukemia from each interquartile range increase in air toxic exposure, for each pollutant separately. Interquartile ranges for these pollutants have been previously published (Heck et al., 2013b). Models adjusted for birth year, maternal race/ethnicity (White non-Hispanic/Hispanic/Other), mother's birth place (US/foreign), parity (0/1+ prior pregnancies), and neighborhood socioeconomic index. Neighborhood socioeconomic index was created by principal components analysis as a single, 5-level measure based on seven census-level indicators of socioeconomic status (education, median household income, percent living 200% below poverty, percent blue-collar workers, percent older than 16 years without employment, median rent, and median house value) (Heck et al., 2012; Yost et al., 2001). These characteristics have been associated with ALL, AML, and/or exposure to air pollution (Abdullaev et al., 2000; Altieri et al., 2006; Howe et al., 2006; Johnson et al., 2008; Pastor et al., 2004). We also examined adjustment for maternal race/ethnicity using a 4-level variable (White non-Hispanic/Black non-Hispanic/Hispanic/Other), but results were nearly identical to those seen with the 3-level race/ethnicity level variable. We considered additional adjustment for child's sex, rural/urban area of residence, and maternal age, but as these did not change effect estimates by >5%, they were left out of final models (Greenland, 1989).

Although it has not been established that socioeconomic status is independently associated with childhood leukemia (Adam et al., 2008; Carozza et al., 2010; Poole et al., 2006), we conducted sensitivity analyses to examine the effect of adjustment for two other socioeconomic measures, maternal educational attainment and the type of health insurance used to pay for prenatal care (private insurance vs. Medi-Cal, other governmental sources or self-pay). The inclusion of these variables in regressions did not change point estimates by more than 5%.

Results

Analyses of ALL included 69 cases and 2994 controls who lived within 2 km of an air pollution monitor, and analyses of AML included 46 cases and 19,209 controls living within 6 km of an air monitor. Children excluded from analyses because they were