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Polycyclic aromatic hydrocarbons in residential dust and risk of childhood acute lymphoblastic leukemia ☆

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ABSTRACT

Several polycyclic aromatic hydrocarbons (PAHs) are known or probable human carcinogens. We evaluated the relationship between PAH exposure and risk of childhood acute lymphoblastic leukemia (ALL) using concentrations in residential dust as an exposure indicator. We conducted a population-based case-control study (251 ALL cases, 306 birth-certificate controls) in Northern and Central California from 2001 to 2007. We collected residential dust using a high volume small surface sampler (HVS3) ($n=185$ cases, 212 controls) or by sampling from participants' household vacuum cleaners ($n=66$ cases, 94 controls). We evaluated log-transformed concentrations of 9 individual PAHs, the summed PAHs, and the summed PAHs weighted by their carcinogenic potency (the toxic equivalence). We calculated odds ratios (ORs) and 95% confidence intervals (CI) using logistic regression adjusting for demographic characteristics and duration between diagnosis/reference date and dust collection. Among participants with HVS3 dust, risk of ALL was not associated with increasing concentration of any PAHs based on OR per ln (ng/g). Among participants with vacuum dust, we observed positive associations between ALL risk and increasing concentrations of benzo[*a*]pyrene (OR per ln [ng/g]=1.42, 95% CI=0.95, 2.12), dibenzo[*a*,*h*]anthracene (OR=1.98, 95% CI=1.11, 3.55), benzo[*k*]fluoranthene (OR=1.71, 95% CI=0.91, 3.22), indeno[1,2,3-*cd*]pyrene (OR=1.81, 95% CI=1.04, 3.16), and the toxic equivalence (OR=2.35, 95% CI=1.18, 4.69). The increased ALL risk among participants with vacuum dust suggests that PAH exposure may increase the risk of childhood ALL; however, reasons for the different results based on HVS3 dust samples deserve further study.

1. Introduction

Leukemia is the most common childhood cancer, accounting for approximately one third of incident cases in U.S. children under age 15 years. Acute lymphoblastic leukemia (ALL) constitutes approximately 80% of childhood leukemia cases in most Western countries (Ross and Spector, 2006). The incidence rates in industrialized countries are approximately four times higher than non-industrialized countries (Parkin et al., 1998), suggesting that the etiology of this disease is related to lifestyle factors or environmental exposures, though few specific risk factors have been identified (Buffler et al., 2005; Chang, 2009). The early peak in age of diagnosis (ages 2–5 years) suggests that the preconception, prenatal, and early childhood time periods may be etiologically relevant exposure windows.

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous byproducts of incomplete combustion. Sources of PAHs in air include

Abbreviations: ALL, acute lymphoblastic leukemia; PAHs, polycyclic aromatic hydrocarbons; HVS3, high volume small surface sampler; TEQ, toxic equivalence; OR, odds ratio; 95% CI, 95% confidence interval

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domestic wood-burning, motor vehicles, industrial facilities such as power plants, forest fires, tobacco smoke, gas-burning appliances, and cooking smoke (ATSDR, 1995; Bostrom et al., 2002; IARC, 2010). PAHs can also be found in foods grown in areas with polluted air or soil and those that are charred or cooked over an open flame (Phillips, 1999). Several PAHs are classified as known or probable human carcinogens or mutagens based on epidemiologic studies of occupational groups and animal carcinogenicity studies (IARC, 2010). To our knowledge, no previous epidemiologic study of leukemia has measured levels of PAHs in environmental media. However, some studies have suggested that exposure to certain sources of PAHs are associated with the risk of childhood leukemia, including parental occupational exposure to vehicle exhaust (Castro-Jimenez and Orozco-Vargas, 2011; Colt and Blair, 1998; McKinney et al., 2003), paternal smoking (Chang, 2009; Milne et al., 2012), and proximity to traffic (Pearson et al., 2000; Visser et al., 2004), though results have been inconsistent, particularly for parental occupational exposures and residential proximity to traffic.

Children may be exposed to PAHs via inhalation of indoor and outdoor air, dietary ingestion, non-dietary ingestion of dust or soil, dermal absorption (Chuang et al., 1999), breastfeeding (Kim et al., 2008) and placental transfer (Perera et al., 2004). Non-dietary ingestion of residential dust represents an important PAH exposure pathway in children due to their high proportion of time spent on the floor and propensity to engage in hand-to-mouth activity. Non-dietary ingestion of residential dust and soil has been estimated to constitute approximately 24% of total PAH exposure for low-income children aged 2–4 years (Chuang et al., 1999). PAH concentrations in residential dust were associated with outdoor PAH concentrations, gas heating, older residence age, and household smoking practices within the current study population (Whitehead et al., 2011, 2013). Because PAHs accumulate in carpets, measured levels in residential dust may also be indicative of children's early life exposures (Butte and Heinzow, 2002; Roberts et al., 2009; Whitehead et al., 2013). In a reproducibility study of a subset of the current study population (Whitehead et al., 2013), concentrations of PAH were moderately correlated between two dust sampling rounds separated by 3–8 years (range of $r_{Spearman}$: 0.44–0.54). Because the rank order of PAH dust levels remained relatively consistent across this study population for a period of five years, a single measurement made shortly after diagnosis could be a useful representation of PAH exposures that occurred during the etiologically relevant time period for ALL (Whitehead et al., 2013).

The Northern California Childhood Leukemia Study is a population-based case-control study of childhood leukemia in Northern and Central California. In the current analysis, we evaluated whether exposure to PAHs, as determined by concentrations in residential dust, is associated with risk of ALL in children in the Northern California Childhood Leukemia Study.

2. Methods

2.1. Study population

As previously described (Bartley et al., 2010; Metayer et al., 2013), we rapidly ascertained leukemia cases (usually within 72 h of diagnosis) from nine of the ten major pediatric clinical centers in 35 counties in the San Francisco Bay Area and the Central Valley (University of California Davis Medical Center, University of California San Francisco, Children's Hospital of Central California, Lucile Packard Children's Hospital, Children's Hospital Oakland, Kaiser Permanente Roseville, Kaiser Permanente Santa Clara, Kaiser Permanente San Francisco, and Kaiser Permanente Oakland). Only one hospital (Sutter Hospital) declined to participate. Children eligible for inclusion in the study were <15 years of age at the time of enrollment, had no prior cancer diagnosis, were resident in one of the 35 counties at the time of diagnosis, and had an available English- or Spanish-speaking parent. All pathological reports available in the medical chart were reviewed by an independent pediatric oncologist to confirm diagnosis. Comparison of case ascertainment in the 35-county study area with the California Cancer Registry (1997–2003) showed that approximately 95% of children diagnosed with leukemia in the participating study hospitals were included in the study, which corresponded to 76% of all cases diagnosed in any (participating and non-participating) hospital within the 35 study counties. We selected controls randomly from California birth certificate files maintained by the Center for Health Statistics in the California Department of Public Health and individually matched them to cases on child's sex, age, and Hispanic ethnicity and mother's race. A total of 997 children with leukemia and 1226 cancer-free controls were enrolled.

At an initial interview, we collected demographic and exposure information, including residential and parental occupational histories, from the child's caregiver (98% the mother) using a self-administered questionnaire and an in-person interview. Subsequently, children who were <8 years of age at diagnosis (or at reference date for controls) and were still living at the home they occupied at diagnosis/reference were eligible for a second interview (2001–2007) in the home. During the second interview, we collected a residential dust sample and obtained detailed information about the characteristics of the home (e.g., type, year the home was built), smoking habits of household members, and pesticide use in and around the home. We limited the eligibility for the second interview to younger cases and controls and to those who had not moved since diagnosis/reference so the residential dust sample would reflect exposures over a substantial portion of the child's early life. Because eligibility for the second interview was based strictly on residential eligibility criteria, matched case-control sets were not maintained in the study recruitment and in the statistical analysis. The participation rate in the first interview was 86% for both cases and controls. Among the 324 cases and 407 controls eligible for the second interview, 296 leukemia cases (91%), including 269 ALL cases, and 333 controls (82%) participated. The study protocols were reviewed and approved by the internal review boards at University of California Berkeley, the National Cancer Institute, the California Department of Health, and all participating hospitals. Informed consent was obtained from parents of participating children.

2.2. Dust sample collection

As described in detail previously (Colt et al., 2008; Ward et al., 2009), from October 2001 to June 2006, we collected carpet dust samples using a high volume small surface sampler (HVS3) (Cascade Stack Sampling Systems, Bend, OR). We sampled the room where the child had spent the most time while awake (other than the kitchen or the child's bedroom) in the year before the diagnosis/reference date if there was at least 9 ft^2 of carpets or rugs available. Most samples were collected from the living room or family room. We sampled a 6- by 4-foot area; if needed, additional carpeted areas of the room were sampled to collect approximately 10 mL of dust. Because this method was labor-intensive, we conducted a methodologic study to evaluate collection of the dust from the home vacuum cleaner. In 45 homes, including 33 from the current study, we collected dust samples using both methods and compared the concentrations of several chemicals in the pairs of samples from each home (Colt et al., 2008). We found that the correlations in chemical concentrations from the two methods were generally strong ($r_{Spearman}>0.7$). Therefore, between July 2006 and November 2007, we collected the dust samples by removing the used bag from the home vacuum (~65% of participants), or emptying loose dust from bagless vacuums (~35% or participants) into a polyethylene bag. However, Spearman correlation coefficients showed only moderate correlations ($r_{Spearman}<0.7$) between the two sampling methods for concentrations of some PAH compounds ($r_{Spearman}$: benzo[a]pyrene: 0.55, dibenzo[*a*,*h*]anthracene: 0.67, benzo[*a*]anthracene: 0.69, benzo[*b*]fluoranthene: 0.68, benzo[*k*]fluoranthene 0.55, chrysene: 0.78, indeno[1,2,3-*c*,*d*]pyrene: 0.77, coronene: 0.81, dibenzo[*a*,*e*]pyrene: 0.70) (Colt et al., 2008). Therefore, we decided *a priori* to conduct the statistical analyses separately by sample type and combine if results were similar.

2.3. Laboratory analysis

A total of 251 ALL cases and 306 controls had sufficient dust samples for analysis. We analyzed HVS3 dust for 185 ALL cases and 212 controls and vacuum dust was for 66 ALL cases and 94 controls. We used a multi-residue analysis method which covered 65 different analytes from polar and non-polar compound classes, including nine PAHs: benzo[*a*]pyrene, dibenzo[*a*,*h*]anthracene, benzo[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, chrysene, indeno[1,2,3-*c*,*d*]pyrene, coronene, and dibenzo[*a*,*e*]pyrene. Details of the dust sample shipping, processing, and chemical analyses have been described previously (Colt et al., 2008; Whitehead et al., 2011). Briefly, 0.5-g portions of dust were spiked with 250 ng of each of two surrogate recovery standards, $^{13}C_6$-benzo[*k*]fluoranthene and $^{13}C_6$-dibenzo[*a*,*e*]pyrene. Dust samples were extracted by ultrasonification in 1:1 hexane:acetone, solvent exchanged into hexane, purified by solid-phase extraction, and concentrated to 1 ml. Concentrated extracts were spiked with the internal standard d_{12}-benzo[*e*]pyrene and analyzed using gas chromatography-mass spectrometry in the multiple ion detection mode. Quality control samples in each batch included a duplicate of one sample in that batch, an additional aliquot of the