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Benzene and childhood acute leukemia in Oklahoma

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ABSTRACT

Background: Although childhood cancer is a leading cause of childhood mortality in the US, evidence regarding the etiology is lacking. The goal of this study was to evaluate the association between benzene, a known carcinogen, and childhood acute leukemia.

Methods: We conducted a case-control study including cases diagnosed with acute leukemia between 1997 and 2012 (n = 307) from the Oklahoma Central Cancer Registry and controls matched on week of birth from birth certificates (n = 1013). We used conditional logistic regression to evaluate the association between benzene, measured with the 2005 National-Scale Air Toxics Assessment (NATA) at census tract of the birth residence, and childhood acute leukemia.

Results: We observed no differences in benzene exposure overall between cases and controls. However, when stratified by year of birth, cases born from 2005 to 2010 had a three–fold increased unadjusted odds of elevated exposure compared to controls born in this same time period (4th Quartile OR: 3.53, 95% CI: 1.35, 9.27). Furthermore, the estimates for children with acute myeloid leukemia (AML) were stronger than those with acute lymphoid leukemia, though not statistically significant.

Conclusions: While we did not observe an association between benzene and childhood leukemia overall, our results suggest that acute leukemia is associated with increased benzene exposure among more recent births, and children with AML may have increased benzene exposure at birth. Using the NATA estimates allowed us to assess a specific pollutant at the census tract level, providing an advantage over monitor or point source data. Our study, however, cannot rule out the possibility that benzene may be a marker of other traffic-related exposures and temporal misclassification may explain the lack of an association among earlier births.

1. Introduction

As a leading cause of childhood mortality, childhood cancer is an important health concern in the US (Heron, 2013). However, evidence regarding the etiology is lacking despite numerous studies (Belson et al., 2007; Ries et al., 1999). One environmental risk factor of recent interest is ambient air pollution. According to the International Agency for Research on Cancer (IARC), ambient air pollution has been classified as carcinogenic to humans (International Agency for Research on Cancer, 2013). Furthermore, IARC has classified diesel engine exhaust as carcinogenic and motor vehicle exhaust as possibly carcinogenic (Benbrahim-Tallaa et al., 2012). As the primary pollutant of concern in engine exhaust, benzene has been classified as a known carcinogen in adult acute myeloid leukemia (AML) (International Agency for Research on Cancer, 1982). The minimal risk level established by the Environmental Protection Agency (EPA) for benzene is 0.009 ppm (ppm) (28.71 μg/m^3) for acute exposure lasting less than 15 days and 0.003 ppm (9.57 μg/m^3) for chronic exposure of ≥ 365 days (Department of Health and Human Services, 2007).

Important sources of exposure to benzene are occupational

Abbreviations: ALL, Acute lymphoid leukemia; AML, Acute myeloid leukemia; PM_{10}, Coarse particulate matter; CI, Confidence Interval; EPA, Environmental Protection Agency; HC, Highway Contract Boxes; IARC, International Agency for Research on Cancer; LOESS, Locally weighted scatterplot smoothing; NATA, National-Scale Air Toxics Assessment; OR, Odds ratio; OCCR, Oklahoma Central Cancer Registry; PO, Post Office Boxes; SES, Socioeconomic status; TRI, Toxics Release Inventory

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exposure, gasoline stations, auto-repair shops, traffic, and cigarette smoking (Department of Health and Human Services, 2007). In occupational settings, benzene exposure was higher than that of the general population, with health effects generally observed above 79.8 μg/m^3 (Khalade et al., 2010; Rushton and Romaniuk, 1997). Benzene is also produced through drilling for oil and natural gas, by burning of oil and coal, and by oil and gas refineries (Department of Health and Human Services, 2007; Esswein et al., 2014; McKenzie et al., 2012; United States Environmental Protection Agency, 2015). While Oklahoma is a fairly rural state with an estimated 3.9 million people in 2016 and 34% of the population residing in rural areas, it is the third largest oil and gas producing state in the US (U.S. Energy Information Administration, 2016; United States Census Bureau, 2017a, 2017b).

The biologic mechanism of benzene as a cause of leukemia, the most common form of childhood cancer, is not well understood. However, it is believed to occur through similar mechanisms as chemotherapy-induced AML, which is a result of chromosomal abnormalities and/or translocations secondary to previous chemotherapy treatments (Pedersen-Bjergaard et al., 2008). Benzene is metabolized primarily by the lungs and liver, but secondary metabolism occurs in the bone marrow, where blood cells are formed. Furthermore, benzene-induced chromosomal alterations are similar to those observed in AML cells (Department of Health and Human Services, 2007; McHale et al., 2012).

There have been few studies focusing specifically on benzene and childhood leukemia. However, studies to date have reported conflicting results for childhood leukemia overall (Crosignani et al., 2004; Garcia-Perez et al., 2015; Raaschou-Nielsen et al., 2001; Vinceti et al., 2012; Whitworth et al., 2008). Garcia-Perez et al. (2015) observed an association between residence ≤ 2.5 km of an industrial facility releasing benzene and childhood leukemia in Spain (OR: 1.5, 95% CI: 1.1, 2.1). In a study using the EPA's National-Scale Air Toxics Assessment (NATA) estimates to measure benzene, Whitworth et al. (2008) reported an increased rate of leukemia among census tracts with benzene levels > 2.36 μg/m^3 compared to < 1.28 μg/m^3 in their ecologic study (Rate Ratio: 1.4, 95% Confidence Interval [CI]: 1.1, 1.8). Crosignani et al. (2004) reported a relative risk of 3.9 (95% CI: 1.4, 11.3) among those exposed to air concentrations of benzene > 10 μg/m^3 compared to < 0.1 μg/m^3. Among children less than 5 years of age, Vinceti et al. (2012) reported a 2.7 times higher income-adjusted odds of leukemia for each 10-fold increase in exposure to benzene when measured continuously in μg/m^3 (95% CI: 1.1, 6.9). However, Raaschou-Nielsen et al. (2001) observed no association between benzene and leukemia in their case-control study, with rate ratio estimates near unity. In addition, previous studies suggest a stronger relationship between benzene and AML, with limited evidence of a relationship with acute lymphoid leukemia (ALL) (Heck et al., 2014; Houot et al., 2015; Symanski et al., 2016; Vinceti et al., 2012; Whitworth et al., 2008).

While dispersion models were used in previous studies of benzene and childhood acute leukemia, they primarily estimated benzene and other air pollutants along roadways (Crosignani et al., 2004; Raaschou-Nielsen et al., 2001; Vinceti et al., 2012). Our study aims to improve upon previous exposure assessments by using the NATA estimates, which take multiple sources of benzene exposure into account in addition to traffic, applying estimates to all census tracts. The NATA estimates also incorporated activity and microenvironment data to estimate exposures in addition to ambient concentration of benzene. The goal of this study was to determine if children in Oklahoma with acute leukemia had a higher odds of exposure to benzene than children without acute leukemia.

2. Materials and methods

2.1. Study design and data sources

We conducted a case-control study to compare children with acute leukemia from the Oklahoma Central Cancer Registry (OCCR) (n = 360) with controls identified through birth certificate records matched on week of birth to cases (n = 1440). We linked the OCCR to birth certificates using Registry Plus™ Link Plus software v. 2.0 (CDC, Atlanta, GA), with 72% of leukemia cases linking to a birth certificate record. Details of the study design were published previously in an analysis of traffic-related air pollution and childhood leukemia and will be presented in brief (Janitz et al., 2016). Cases were diagnosed with leukemia prior to age 20 and during the years 1997–2012. Because we were unable to geocode all birth residences, our dataset available for analysis included 307 cases and 1013 controls. We obtained data on cases related to their cancer diagnosis from OCCR and data on covariates related to birth, including residence, from birth certificates for all children included in the study. We used the 2014 TIGER/Line files (based on the 2010 U.S. Census) in ArcGIS (ESRI ®, Redlands, CA), using the North American Datum of 1983 as the geographic coordinate system, to geocode cases and controls. For those with rural routes or addresses unable to be geocoded in ArcGIS, we used the Melissa Data® service. We were unable to geocode children with Highway Contract (HC) Boxes or Post Office (PO) Boxes as no physical address was available. Institutional Review Board approval was obtained from both the University of Oklahoma Health Sciences Center and the Oklahoma State Department of Health.

We obtained data on benzene from the EPA's 2005 NATA, which estimated the average concentration of air toxics for the US at the census tract level to provide State/Local/Tribal agencies' directions for prioritization and research in order to better understand the health effects of pollution (United States Environmental Protection Agency, 2013). NATA models were based on data from various sources including state and local air toxics inventories, existing databases related to the EPA air toxics regulatory programs, and the TRI. Estimates from mobile sources, including motor vehicles, non-road engines, and equipment, were also incorporated into the models. Activity, fuel, and vehicle data were obtained from local, state, and federal agencies. Emissions estimates were obtained using emission factors of pollutants and sources of emissions included point (i.e., factory, ship, smokestack), and non-point (i.e., area pollution from small or ubiquitous sources such as dry cleaners) stationary sources, on-road (i.e., cars, trucks, buses) and non-road (i.e., airplanes, trains, lawnmowers) mobile sources, derived background from natural sources, and secondary formation and decay of air toxics from the Community Multiscale Air Quality Model from 2005 (ICF International, 2011).

More specifically, the 2005 NATA used the Assessment System for Population Exposure Nationwide (ASPEN) model and the Human Exposure Model-3 (HEM) American Meteorological Society – U.S. EPA Regulatory Model (AERMOD) Version to determine benzene estimates (ICF International, 2011; United States Environmental Protection Agency, 2011). ASPEN was used to model non-point sources at the census tract level using data from 2005 and census data from 2000. HEM was used to model point, on-road mobile, and non-road mobile emissions sources at the census block level along with dispersion and human exposure, using population data from both the 2000 and 2010 US Census.

To determine population exposure to benzene at the census tract level, the EPA used the Hazardous Air Pollutant Exposure Model (HAPEM). The estimates were calculated using ambient concentrations of air toxics, population data from the 2000 U.S. Census, population activity data, and microenvironmental data. Activity data were obtained from the Consolidated Human Activity Database (CHAD), where a sample of the population was surveyed in order to track activity levels in indoor and outdoor microenvironments.

These model-based assessments were conducted approximately every three to six years beginning in 1990. We used the assessment from 2005 as it incorporated the most advanced models available at the time this study was conducted. The EPA does not recommend combining assessments due to differing methodologies (United States Environmental Protection Agency, 2011).