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Traffic-related air pollution and childhood acute leukemia in Oklahoma

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ABSTRACT

Background: While many studies have evaluated the association between acute childhood leukemia and environmental factors, knowledge is limited. Ambient air pollution has been classified as a Group 1 carcinogen, but studies have not established whether traffic-related air pollution is associated with leukemia. The goal of our study was to determine if children with acute leukemia had higher odds of exposure to traffic-related air pollution at birth compared to controls.
Methods: We conducted a case-control study using the Oklahoma Central Cancer Registry to identify cases of acute leukemia in children diagnosed before 20 years of age between 1997 and 2012 (n=307). Controls were selected from birth certificates and matched to cases on week of birth (n=1013). Using a novel satellite-based land-use regression model of nitrogen dioxide (NO_2) and estimating road density based on the 2010 US Census, we evaluated the association between traffic-related air pollution and childhood leukemia using conditional logistic regression.
Results: The odds of exposure to the fourth quartile of NO_2 (11.19–19.89 ppb) were similar in cases compared to controls after adjustment for maternal education (OR: 1.08, 95% CI: 0.75, 1.55). These estimates were stronger among children with acute myeloid leukemia (AML) than acute lymphoid leukemia, with a positive association observed among urban children with AML (4th quartile odds ratio: 5.25, 95% confidence interval: 1.09, 25.26). While we observed no significant association with road density, male cases had an elevated odds of exposure to roads at 500 m from the birth residence compared to controls (OR: 1.39, 95% CI: 0.93, 2.10), which was slightly attenuated at 750 m.
Conclusions: Although we observed no association overall between NO_2 or road density, this was the first study to observe an elevated odds of exposure to NO_2 among children with AML compared to controls suggesting further exploration of traffic-related air pollution and AML is warranted.

1. Introduction

Acute leukemia is the most common type of childhood cancer, accounting for approximately 26% of all childhood cancers (United States Department of Health and Human Services et al., 2016). Many studies have evaluated the association between acute childhood leukemia and various environmental factors, with conflicting results (Belson et al., 2007; Smith et al., 1999). One environmental exposure of interest is air pollution, a component of which is motor vehicle emissions. According to the International Agency for Research on Cancer, ambient air pollution has been classified as a Group 1 carcinogen (International Agency for Research on Cancer, 2013).

Although studies have used different methodologies to measure nitrogen dioxide (NO_2) at different time points of exposure, several have detected a positive association between NO_2 and childhood leukemia (Amigou et al., 2011; Badaloni et al., 2013; Feychting et al., 1998; Ghosh et al., 2013; Raaschou-Nielsen et al., 2001; Weng et al., 2008). Studies occurred in varying regions of the world, with associations observed at different levels of NO_2 exposure ranging from 6.5 parts per billion (ppb) to 42.6 ppb

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoid leukemia; CI, confidence interval; EPA, Environmental Protection Agency; GIS, Geographic Information System; HC, Highway Contract; LOESS, locally weighted scatterplot smoothing; LUR, land-use regression; m, meters; NO_2, nitrogen dioxide; OCCR, Oklahoma Central Cancer Registry; OMI, Ozone Monitoring Instrument; OR, odds ratio; PO, Post Office; PPB, parts per billion

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(Amigou et al., 2011; Ghosh et al., 2013; Weng et al., 2008). In addition to NO_2, investigators have also evaluated other traffic-related measures to assess the relationship with leukemia and any childhood cancer with mixed results (Abdul Rahman et al., 2008; Amigou et al., 2011; Badaloni et al., 2013; Crosignani et al., 2004; Harrison et al., 1999; Heck et al., 2013; Langholz et al., 2002; Nordlinder and Jarvholm, 1997; Pearson et al., 2000; Raaschou-Nielsen et al., 2001; Reynolds et al., 2001, 2002, 2004; Savitz and Feingold, 1989; Spycher et al., 2015; Steffen et al., 2004; Von Behren et al., 2008). Of the seven studies that measured exposure to main roads or gas stations within 50 meters (m) to 500 m of the residence, five observed positive associations with leukemia (Abdul Rahman et al., 2008; Amigou et al., 2011; Harrison et al., 1999; Spycher et al., 2015; Steffen et al., 2004), while Badaloni et al. (2013) and Houot et al. (2015) observed no association.

Studies have not established whether a specific pollutant, such as benzene, or the combination of pollutants from traffic is carcinogenic. Therefore, it is important to evaluate exposure to traffic as a source of complex chemical mixtures in relation to childhood leukemia in addition to specific pollutants. NO_2 is considered a good indicator of traffic exposure and is commonly used to measure traffic density (Beckerman et al., 2008). As one of the six criteria pollutants established by the Clean Air Act, the Environmental Protection Agency (EPA) set the National Ambient Air Quality Standard of NO_2 at a one-hour limit of 100 ppb and an annual average limit of 53 ppb (United States Environmental Protection Agency, 2011). Although many dispersion models exist to estimate NO_2, Novotny et al. (2011) developed a novel method of estimating NO_2 using satellite-based estimates in combination with ground-level estimates in a land-use regression (LUR) model for the entire United States, resulting in spatially precise estimates. This model accounts for NO_2 from multiple sources, although variables in the LUR model are specifically related to traffic.

Our study incorporated a novel method of estimating NO_2 for the contiguous United States using a satellite-based LUR model at the census block level, which we compared with a standard individual-level measure of road density. Only one other study has incorporated satellite-based methods to estimate NO_2 in Italy (Badaloni et al., 2013). While the authors observed no association with childhood leukemia, others have detected a positive association with NO_2 estimated from traffic or monitoring stations, indicating the importance of further evaluating this methodology in the US. The goal of our study was to determine if children with acute leukemia had higher odds of exposure to traffic-related air pollution, measured through NO_2 and road density, compared to controls.

2. Methods

2.1. Study design and data sources

To evaluate the association between traffic-related air pollution and acute leukemia, we conducted a case-control study using the Oklahoma Central Cancer Registry (OCCR) as our source for acute leukemia cases (n=360) diagnosed between 1997 and 2012 prior to the age of 20 years. Controls were selected from birth certificate records and matched to cases on week of birth (n=1440). We initially matched controls to cases in a 4:1 ratio, but because some addresses failed to geocode, 307 cases and 1013 controls were available for analysis resulting in a ratio of approximately 3.3:1. Data on covariates, including address, were obtained from the birth certificate records for all children and data related to the leukemia diagnosis were obtained from OCCR. To determine urbanization of the child's residence, we used the 2000 US Census, which classified census blocks as urban or rural. We obtained IRB approval from the University of Oklahoma Health Sciences Center and the Oklahoma State Department of Health.

2.2. Measurement of the outcome

We included children diagnosed with acute leukemia under 20 years of age between the years of 1997 and 2012 in Oklahoma. To define acute leukemia, we included children with International Classification of Diseases of Oncology, Third Edition histology codes for both acute lymphoid leukemia (ALL) (9820, 9823, 9826, 9827, 9831–9837, 9940, 9948) and acute myeloid leukemia (AML) (9840, 9861, 9866, 9867, 9870–9874, 9891, 9895–9897, 9910, 9920, 9931) as classified by the International Classification of Childhood Cancers, Third edition (Steliarova-Foucher et al., 2005). We linked acute leukemia cases to birth certificates using Registry Plus™ Link Plus software v. 2.0 (CDC, Atlanta, GA). To link the databases we used name and date of birth since a unique identifier was not available, resulting in 72% of leukemia cases linking to birth records. Because we matched controls to cases on week of birth, all children born in the same week who were at risk of developing leukemia at the time the index case was diagnosed were eligible to be selected as a control.

2.3. Geocoding

After standardizing all addresses with the United States Postal Service (United States Postal Service, 2014), we used ArcGIS (ESRI®, Redlands, CA) to geocode residence at birth using 2014 TIGER/Line files. Because ArcGIS can only geocode complete street addresses, we used Melissa Data® to geocode rural routes and any addresses that did not geocode in ArcGIS (Melissa Data, 2014). This allowed us to geocode 25% of children with rural route addresses. However, we were unable to geocode Highway Contract (HC) Boxes or post office (PO) Boxes since a physical address was not available from birth certificate records. We obtained 2000 US census blocks from the US Census TIGER/Line files (United States Census Bureau, 2014).

2.4. Satellite measurement of NO_2

To evaluate NO_2, we used the satellite-based LUR model developed by Novotny et al. (2011). The authors used a linear regression model to predict NO_2 for the contiguous United States for 2006, which included data from NO_2 monitors, land-use characteristics from geographic information systems (GIS), and data on satellite-based NO_2 from the Ozone Monitoring Instrument (OMI).

Monitored ground-level annual-mean NO_2 levels were obtained from 369 of the EPA's 423 monitors in the contiguous United States. Monitors missing $>25\%$ of hourly measurements were excluded per the EPA's reliability criteria. The final LUR model was determined using stepwise linear regression (Novotny et al., 2011). Variables included in the final annual mean model were impervious surface, annual OMI NO_2, tree canopy, major roads, minor roads, elevation, and distance to the coast, in addition to the monitoring station parameters (distance to major road, annual NO_2, latitude, and longitude). The authors applied the final model to all census blocks within the contiguous United States using the 2000 US Census. While the LUR model included all sources of NO_2, including industry, airports, and harbors, the model estimated traffic-related NO_2 better than industrial sources. In validating the LUR model, the authors observed high correlation between the data used to build the model (90%) and the model-testing data (10%) ($R^2=0.78$ for model-building data, $R^2=0.76$ for model-testing data).