Environment International 100 (2017) 139–147

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Maternal exposure to ambient air pollution and risk of early childhood cancers: A population-based study in Ontario, Canada

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ARTICLE INFO

Article history:
Received 14 July 2016
Received in revised form 15 December 2016
Accepted 6 January 2017
Available online 17 January 2017

Keywords:
Prenatal
Air pollution
Childhood cancer
Maternal

ABSTRACT

Background: There are increasing concerns regarding the role of exposure to ambient air pollution during pregnancy in the development of early childhood cancers.
Objective: This population based study examined whether prenatal and early life (<1 year of age) exposures to ambient air pollutants, including nitrogen dioxide (NO_2) and particulate matter with aerodynamic diameters ≤2.5 μm ($PM_{2.5}$), were associated with selected common early childhood cancers in Canada.
Methods: 2,350,898 singleton live births occurring between 1988 and 2012 were identified in the province of Ontario, Canada. We assigned temporally varying satellite-derived estimates of $PM_{2.5}$ and land-use regression model estimates of NO_2 to maternal residences during pregnancy. Incident cases of 13 subtypes of pediatric cancers among children up to age 6 until 2013 were ascertained through administrative health data linkages. Associations of trimester-specific, overall pregnancy and first year of life exposures were evaluated using Cox proportional hazards models, adjusting for potential confounders.
Results: A total of 2044 childhood cancers were identified. Exposure to $PM_{2.5}$, per interquartile range increase, over the entire pregnancy, and during the first trimester was associated with an increased risk of astrocytoma (hazard ratio (HR) per 3.9 μg/m3 = 1.38 (95% CI: 1.01, 1.88) and, HR per 4.0 $\mu g/m^3$ = 1.40 (95% CI: 1.05–1.86), respectively). We also found a positive association between first trimester NO_2 and acute lymphoblastic leukemia (ALL) (HR = 1.20 (95% CI: 1.02–1.41) per IQR (13.3 ppb)).
Conclusions: In this population-based study in the largest province of Canada, results suggest an association

Abbreviations: HR, hazard ratio; CI, confidence interval; $PM_{2.5}$, particulate matter with a mean aerodynamic diameter <2.5 μm; NO_2, nitrogen dioxide; ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; NHL, non-Hodgkin lymphoma.

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http://dx.doi.org/10.1016/j.envint.2017.01.004

between exposure to ambient air pollution during pregnancy, especially in the first trimester and an increased risk of astrocytoma and ALL. Further studies are required to replicate the findings of this study with adjustment for important individual-level confounders.

1. Introduction

Cancer is one of the leading causes of non-traumatic mortality among children in industrialized countries (Kaatsch, 2010; National Center for Injury Prevention and Control, 2016). A growing body of literature on traffic-related air pollution and childhood cancer has emerged in the past decades and epidemiologic studies suggest that exposure to ambient air pollution during pregnancy and early life may play a role in etiology of early childhood cancer (Heck et al., 2013a; Ghosh et al., 2013; Raaschou-Nielsen and Reynolds, 2006; Boothe et al., 2014; Filippini et al., 2015; Carlos-Wallace et al., 2016; Janitz et al., 2016). However, the evidence remains scarce given variations across studies in exposure assessment methods, pollutants evaluated, and periods of exposure under investigation.

Earlier studies have relied mostly on simple proxy measures such as traffic density or counts, or residential proximity to point-sources and have examined exposures over the entire childhood (Boothe et al., 2014; Sun et al., 2014). More recent investigations have evaluated prenatal or early life exposure to specific pollutants in association with childhood cancers based on measurements from ground based monitors (Heck et al., 2014; Heck et al., 2013b; Heck et al., 2013c; Shrestha et al., 2014; von Ehrenstein et al., 2015) or using more highly spatially resolved air pollution modeling approaches (Heck et al., 2013a; Ghosh et al., 2013; Houot et al., 2015; Danysh et al., 2015). Only two studies have evaluated the impact of exposure to NO_2 on childhood cancer. One study found an association between modeled exposure to NO_2 during childhood and risk of acute lymphoblastic leukemia (ALL) up to age 14 (Amigou et al., 2011) while another study found that exposure to NO_2 during the entire pregnancy increased the risk of ALL before 6 years of age (Ghosh et al., 2013). As well, only one study examined the association between exposure to $PM_{2.5}$ during pregnancy and childhood cancer, but did not find any associations (Heck et al., 2013a). In addition, no single pollutant has been conclusively associated with specific childhood cancers. The most common form of childhood cancer linked to air pollution is ALL (Filippini et al., 2015; Carlos-Wallace et al., 2016), but little is known regarding other rarer cancer types. Given that there is biological plausibility (Gruzieva et al., 2016) and some epidemiological evidence supporting the hypothesis of in utero initiation and first year of life exposure of early childhood cancers (Heck et al., 2013a; von Ehrenstein et al., 2015; Rossig and Juergens, 2008), it is important to address the shortcomings of earlier studies.

This study makes use of a large population-based sample to examine the associations of prenatal and early life (<1 year of age) exposures to nitrogen dioxide (NO_2) as a marker of traffic related air pollution and particulate matter with aerodynamic diameters ≤2.5 μm ($PM_{2.5}$) as a marker of the complex mixture of outdoor air pollution, with common childhood cancers among approximately 2.4 million singleton live births in the province of Ontario, Canada from 1988 to 2012.

2. Material and methods

2.1. Study population and design

Our study population included a retrospective cohort of pregnant women giving birth to live born singleton infants in the province of Ontario, Canada between April 1st 1988 and March 31st 2012. The province of Ontario is the largest province of Canada with a population of about 12 million individuals in 2006. Mother-infant pair data for this time period were obtained from the Mother-Baby Linked database (MOMBABY), an administrative database linking the hospital admission records of delivering mothers and their newborns across Ontario. We also captured information on maternal smoking status during pregnancy (i.e. yes or no) from the Better Outcomes Registry & Network (BORN) Ontario database (http://www.bornontario.ca) for the time period April 1st 2006 to March 31st 2012. In fact, maternal smoking during pregnancy is suspected to be associated with certain types of childhood cancers (Heck et al., 2016). The BORN database captures more extensive information on maternal health, obstetric, intrapartum, and neonatal information in and around the perinatal period of pregnancy than the MOMBABY database (Dunn et al., 2011). At the time this study was conducted, only the time period from 2006 to 2012 was available from BORN for linkage purposes. We linked mother-infant pair data from the MOMBABY database with the BORN database using encrypted unique identifiers. The encrypted unique identifier (also referred to the IKN) is a common identifier that is used to link health administrative data within the Institute for Clinical Evaluative Sciences (ICES) in Ontario, Canada. Gestational age was determined from the mother's last menstrual period. The first trimester of pregnancy was defined as gestational week 1 through week 12, the second trimester as week 13 to week 27 and the third trimester of pregnancy from week 28 to birth.

We also linked the mother-infant pair data with the Registered Persons Database (RPDB) to identify each mother's postal code of residence during pregnancy and to assess the child's vital status throughout the follow-up period. This database also records postal code changes which have been reported to the Ministry of Health for all Ontario residents who have ever had a health insurance number. It contains the postal code, a start and end date defining the period during which the postal code applied to the subscriber. For each year, using July 1st as a reference point, the best known postal code address is captured using the latest postal code reported across health administrative databases in the 1st half of each year or else the earliest one identified in the 2nd half of each year. Therefore, this database can capture to some extent postal code changes during pregnancy and therefore assign exposures accordingly. Information on maternal residential location(s) based on residential postal code(s) was geo-coded using the Postal Code Conversion File Plus (PCCF+) to obtain Statistics Canada's standard geographic identifiers and dissemination area (DA) information (Wilkins and Peters, 2012). In urban areas, the 6-digit postal code generally represents one side of a city block or a large apartment complex while it usually represents a larger area in rural areas. Pregnancies with postal codes of residence outside Ontario (i.e. <1% of all pregnancies) were excluded from the analysis. We excluded 11.4% of subjects (302,824 out of 2,656,356 eligible subjects) with missing date of birth, sex, 6-digit postal code value and/or exposure estimates.

2.2. Childhood cancers

We identified incident childhood cancer cases from the Pediatric Oncology Group of Ontario Networked Information System (POGONIS) for the time period April 1st 1988 to March 31st 2013. This population-based registry prospectively captures all cases of pediatric cancer diagnosed and treated at one of the five tertiary pediatric oncology centres in Ontario. Approximately 98% of Ontario children aged 0–14 with cancer, as identified by the Ontario Cancer Registry (OCR), are captured in POGONIS (Greenberg et al., 2003). Infants identified from the birth databases were linked deterministically with POGONIS using encrypted