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Resolving uncertainty in the spatial relationships between passive benzene exposure and risk of non-Hodgkin lymphoma

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ABSTRACT

Background: Benzene is a known occupational carcinogen associated with increased risk of hematologic cancers, but the relationships between quantity of passive benzene exposure through residential proximity to toxic release sites, duration of exposure, lag time from exposure to cancer development, and lymphoma risk remain unclear.

Methods: We collected release data through the Environmental Protection Agency's Toxics Release Inventory (TRI) from 1989 to 2003, which included location of benzene release sites, years when release occurred, and amount of release. We also collected data on incident cases of non-Hodgkin lymphoma (NHL) from the Georgia Comprehensive Cancer Registry (GCCR) for the years 1999–2008. We constructed distance-decay surrogate exposure metrics and Poisson and negative binomial regression models of NHL incidence to quantify associations between passive exposure to benzene and NHL risk and examined the impact of amount, duration of exposure, and lag time on cancer development. Akaike's information criteria (AIC) were used to determine the scaling factors for benzene dispersion and exposure periods that best predicted NHL risk.

Results: Using a range of scaling factors and exposure periods, we found that increased levels of passive benzene exposure were associated with higher risk of NHL. The best fitting model, with a scaling factor of 4 kilometers (km) and exposure period of 1989–1993, showed that higher exposure levels were associated with increased NHL risk (Level 4 (1.1–160 kilograms (kg)) vs. Level 1: risk ratio 1.56 [1.44–1.68], Level 5 (>160 kg) vs. Level 1: 1.60 [1.48–1.74]).

Conclusions: Higher levels of passive benzene exposure are associated with increased NHL risk across various lag periods. Additional epidemiological studies are needed to refine these models and better quantify the expected total passive benzene exposure in areas surrounding release sites.

1. Introduction

Benzene, toluene, ethylbenzene, and xylene (BTEX) are volatile organic compounds (VOC) that are typically found in petroleum products, coal tar and various chemical product formulations, and have been associated with increased cancer risk [1]. Among these, benzene is a VOC that has been consistently linked to hematologic cancers such as leukemia and lymphoma through occupational exposure [2–6]. Benzene is a widely used chemical that ranks in the top 20 chemicals for production volume and is used in the production of some types of rubbers, dyes, pesticides, lubricants, and detergents [7]. Studies have shown that subjects in occupations exposed to low levels of airborne benzene exhibit increased incidence of DNA methylation alterations common in acute myelogenous leukemia and other cancer tissues [8], in addition to lower levels of white blood cell and platelet counts [9].

The US Environmental Protection Agency (EPA) estimates that the main routes of benzene exposure occur through the air, via cigarette smoking and exposures from consumer products, car emissions, traffic exhaust fumes, and gas stations [10]. In addition,

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air around some toxic release sites may contain higher levels of benzene than other areas and thus contribute to the amount of passive benzene to which individuals are exposed [7].

The relationship between passive benzene exposure and hematologic cancers is less certain than for occupational exposure. Among hematologic malignancies, NHL is the most common. In 2015, an estimated 71,850 people in the US will be diagnosed with NHL, and 19,790 will die from this cancer [11]. For reasons that remain unclear, NHL incidence rates increased over the last half of the 20th century and only recently stabilized. Although the descriptive epidemiology of NHL has been well characterized using population-based cancer registry data over the last several decades, the etiology of NHL and its specific subtypes is less well understood [12]. To address this problem, InterLymph engaged in a worldwide project to pool case-control studies and perform pooled analyses to maximize the statistical power for identifying risk factors across NHL subtypes. A recent series of publications identified environmental, lifestyle, and clinical risk factors for several NHL subtypes [13–16] and recent genome-wide association studies (GWAS) identified single nucleotide variants associated with increased risk of diffuse large B cell lymphoma [17–23], the most common NHL subtype. Despite these recent seminal advances, relatively little is known about the spatial epidemiology of NHL. Although some studies support links between toxic exposures and NHL incidence, others do not, and thus considerable controversy remains [24–26]. The series of InterLymph studies previously mentioned also identified etiologic commonality across NHL subtypes and highlighted occupational history as linked to NHL [15].

To improve our understanding of the relationship between lymphoma risk and passive exposure through proximity to release sites, we previously collected data from the EPA's TRI and modeled the number of lymphoma cases as a function of indirect exposure to benzene using mean distance to benzene release sites in the state of Georgia [27]. This research identified passive benzene exposure as being associated with increased risk of NHL, but failed to clarify its impact on NHL risk in terms of quantity of exposure, lag time from exposure to cancer development, and duration of exposure.

Our prior model simplified estimation of residential exposure patterns by determining the average distance from all benzene releasing sites for a given location. While this approach identified associations between benzene exposure and increased lymphoma risk, mean distance from release sites remains a crude measure that does not take into account the magnitude of passive exposure. An individual's personal exposure to VOCs is related to indoor and outdoor sources, including points of release such as TRI facilities and non-point releases such as on-road, secondary, and background. Although the contribution of point sources to the outdoor concentration of a VOC and to an individual's total exposure may be small, differences in VOC release amount and proximity may result in distinct levels of risk for populations with varying degrees of exposure. We sought to examine the collective impact on the relationships between residential benzene exposure and NHL risk as influenced by distance from TRI release sites, amount of benzene released per site, and lag time from the period of release.

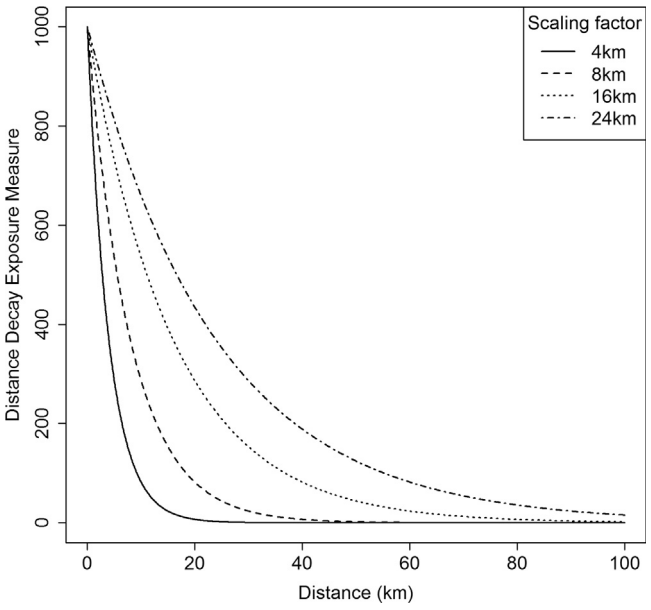

Fig. 1. Effect of scaling factor on the measure of distance decay exposure over increasing distances. Exposure at the point source (Distance = 0 km) is assumed to be 1000.

2. Data

We collected lymphoma incidence data from the GCCR for patients diagnosed with NHL from 1999 to 2008, benzene release data within Georgia from the EPA's TRI from 1989 to 2003, and state population characteristics from United States Census Bureau data for the year 2000. In the 2000 US census, there were 1618 census tracts within Georgia, of which 1616 had available population and demographic data. Data on sex, age, and race were obtained from Summary File 1 from the Census 2000 Data for the United States [28]. Georgia tract boundaries obtained from the Census Bureau's 2000 TIGER/Line files [29] were utilized for the purposes of allocating GCCR cases to Georgia census tracts. Census data for median year moved into residence (MYMI) were collected in our previous study, but were not found to be associated with NHL risk [27]. As a result, MYMI was not considered for further modeling purposes. Additionally, we collected Summary Files 3 and 4 socioeconomic status (SES) Sample Data, specifically the census tract level estimates for percent of the population older than 25 who are high school graduates and median income, in order to determine whether adjustments for these characteristics altered our findings [28]. All data were aggregated to the census tract level. Data collection was approved by the Emory University Institutional Review Board, the Winship Cancer Institute Clinical and Translational Review Committee, and the Georgia Department of Public Health Institutional Review Board.

2.1. Georgia Comprehensive Cancer Registry Data

From 1999 to 2008, the GCCR identified 12,716 NHL cases among adults $\geq$20 years of age living in Georgia at the time of diagnosis, of which 11,355 were successfully geocoded. Gender, race, and age-specific national NHL rates were obtained using data from SEER*Stat Version 7.05 [30]. Based on the demographic structure of each tract, we estimated the expected number of cases for each tract using these incidence rates. Thirty-two cases (0.28%) without gender, race, or age were excluded from further analysis. Lymphoma subgroups and subtypes were defined using ICD-O-3 codes based on the proposed World Health Organization-based nested classification of malignant lymphoid neoplasms for epidemiologic research from the International Lymphoma Epidemiology Consortium (InterLymph) [31].