Geospatial Distribution of Age-adjusted Incidence of the Three Major Types of Pediatric Cancers and Waterborne Agrichemicals in Nebraska

Balkissa Ouattara[1], Jagadeesh Puvvula[1], Azar Abadi[1], Siddhi Munde[1], Alan Kolok[2], Shannon Bartelt-Hunt[3], Jesse Bell[4], Christopher Wichman[1], and Eleanor Rogan[1]

[1]University of Nebraska Medical Center
[2]Idaho Water Resources Research Institute
[3]University of Nebraska Lincoln
[4]Univ. Nebraska Medical College

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Abstract

This study was conducted to examine, at the county level, the relationship between pediatric cancers incidence rate and atrazine and nitrate mean concentrations in surface and groundwater. A negative binomial regression analysis was performed to investigate the association between central nervous system (CNS) tumors, leukemia, lymphoma, and atrazine and nitrate mean concentrations in surface and groundwater. The age-adjusted brain and other CNS cancers incidence was higher than the national average in 63% of the Nebraska counties. After controlling for nitrate concentrations in surface and groundwater, counties with atrazine concentrations between 0.95 - 2.82 µg/L in both surface and groundwater had a higher incidence rate for pediatric cancers (brain and other CNS, leukemia, and lymphoma) compared to counties with surface and groundwater atrazine concentrations in the reference group (0.00 - 0.13 µg/L). Additionally, compared to counties with groundwater nitrate concentrations between 0 and 2 mg/L (reference group), counties with groundwater nitrate concentrations between 2.1 and 5 mg/L (group 2) had a higher incidence rate for pediatric brain and other CNS cancers (IRR=13.25; 95% CI: 13.00-13.50), leukemia (IRR=6.13; 95% CI: 6.02-6.26), and lymphoma (IRR=11.53; 95% CI: 11.32-11.75) after adjusting for all covariates in the model. While these findings do not indicate a causal relationship, they suggest that atrazine and nitrate may pose a significant risk relative to the genesis of pediatric brain and CNS cancers, leukemia, and lymphoma.

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[1] Department of Environmental, Agricultural and Occupational Health, College of Public Health, University of Nebraska Medical Center.
[2]Department of Civil and Environmental Engineering, College of Engineering, University of Nebraska-Lincoln.
[3]Idaho Water Resources Research Institute, University of Idaho.
[4]Department of Biostatistics, College of Public Health, University of Nebraska Medical Center.

Corresponding author: Balkissa S. Ouattara (balkissa.ouattara@unmc.edu)

Key Points: Pediatric cancer, atrazine, nitrate

Abstract

This study was conducted to examine, at the county level, the relationship between pediatric cancers incidence rate and atrazine and nitrate mean concentrations in surface and groundwater. A negative binomial regression analysis was performed to investigate the association between central nervous system (CNS) tumors, leukemia, lymphoma, and atrazine and nitrate mean concentrations in surface and groundwater. The age-adjusted brain and other CNS cancers incidence was higher than the national average in 63% of the Nebraska counties. After controlling for nitrate concentrations in surface and groundwater, counties with atrazine concentrations between 0.95 - 2.82 µg/L in both surface and groundwater had a higher incidence rate for pediatric cancers (brain and other CNS, leukemia, and lymphoma) compared to counties with surface and groundwater atrazine concentrations in the reference group (0.00 - 0.13 µg/L). Additionally, compared to counties with groundwater nitrate concentrations between 0 and 2 mg/L (reference group), counties with groundwater nitrate concentrations between 2.1 and 5 mg/L (group 2) had a higher incidence rate for pediatric brain and other CNS cancers (IRR=13.25; 95% CI: 13.00-13.50), leukemia (IRR=6.13; 95% CI: 6.02-6.26), and lymphoma (IRR=11.53; 95% CI: 11.32-11.75) after adjusting for all covariates in the model. While these findings do not indicate a causal relationship, they suggest that atrazine and nitrate may pose a significant risk relative to the genesis of pediatric brain and CNS cancers, leukemia, and lymphoma.

Plain Language Summary

The rate of pediatric cancers in Nebraska is currently among the five highest in the United States. Ninety-two percent (92%) of Nebraska state's total land area is used for agriculture (farming and ranching). It is challenging to establish childhood cancer causes because only 1 in 20 cases are related to heredity. Statistical tools were used to investigate the relationship between the exposure to nitrate and atrazine in surface and groundwater and childhood cancers in Nebraska. Nebraska counties where atrazine or nitrate levels were elevated reported more childhood cancers than counties with lower levels of these chemicals. These results suggest that different agricultural activities across the state might present a risk for developing certain pediatric cancers.

1 Introduction

Nebraska is primarily an agricultural state, with 92% of the total land area used for farming and ranching (Nebraska Department of Agriculture and USDA NASS, Nebraska Field Office, 2020). The widespread use of agrichemicals such as atrazine and nitrate is common across many Midwestern states, including Nebraska. Atrazine, a triazine herbicide, is the second most used pesticide in Nebraska for leafy weed control (Wieben, 2019), and in 2017, more than 3357 tons of atrazine were applied to Nebraska cornfields (Wieben, 2019). Nitrate is used as fertilizer to enhance crop growth. In 2018, 165 pounds of nitrogen-containing fertilizers were used per acre of Nebraska cornfield (USDA ERS, 2019).

These agrichemicals can contaminate surface water and groundwater, the latter being an essential drinking water source for more than 85% of all Nebraskans (Nebraska Department of Environmental Quality, 2018). Indeed, in Nebraska, surface and groundwater concentrations of nitrate and atrazine have been found in some locations to exceed the United States (US) Environmental Protection Agency (EPA) maximum contaminant limits (MCL) of 10 mg/L for nitrate as nitrogen and three (3) µg/L for atrazine (Nebraska Department of Environmental Quality, 2018; EPA, 2020).

While research involving atrazine has been controversial, some studies have identified an association between atrazine exposure and adverse health outcomes in humans. For example, maternal atrazine exposure was associated with birth defects such as male genital malformations and gastroschisis (Agopian et al., 2013; Waller et al., 2010). Moreover, atrazine exposure has been associated with cancers such as pediatric leukemia and reproductive cancers (Booth et al., 2015; Carozza et al., 2008; Fan et al., 2007; Freeman et al., 2011; Malagoli et al., 2016). Despite these results, the International Agency for Research on Cancer (IARC) lists atrazine in Group 3: not classifiable about its carcinogenicity to humans due to conflicting experimental results. Likewise, the EPA has concluded that human and animal evidence was not sufficient to consider atrazine carcinogenic (Boffetta et al., 2013).

In contrast to atrazine, the association between relatively high nitrate concentration in water and adverse health impacts is well established. For example, in 1945, infant methemoglobinemia was associated with elevated nitrate concentrations in drinking water (Du et al., 2007; Monti et al., 2019). Since then, relatively high nitrate concentrations in drinking water have been associated with many adverse health outcomes, including hypothyroidism (Aschebrook-Kilfoy et al., 2012), congenital anomalies (Brender & Weyer, 2016; Holtby et al., 2014), and malignant tumors such as colorectal, bladder and kidney cancer (Fathmawati et al., 2017; Jones et al., 2016; Jones et al., 2017). Relative to carcinogenicity, ingested nitrate is reduced to nitrite, which interacts with amides or amines to form N-nitroso compounds that are established carcinogens and teratogens (Mensinga et al., 2003; Ward et al., 2018). Although the EPA has not yet classified nitrates as carcinogenic (EPA, 2007), IARC (2010), in its 94th volume monograph, stated that "ingested nitrate or nitrite under conditions that result in endogenous nitrosation is probably carcinogenic to humans (Group 2A)."

The incidence of pediatric cancer has been high in Nebraska (Corley et al., 2018) and above the national average (National Cancer Institute, 2017)**.** Since only about 5% of all childhood cancers are hereditary, this suggests that other factors such as environmental exposure to carcinogenic chemicals may play a prominent role in their etiology (NIH, 2020; Robin & Farmer, 2017). This study was conducted to examine, at the county level, the relationship between pediatric cancers incidence rate and atrazine and nitrate mean concentrations in surface and groundwater; the authors hypothesized that relatively higher concentrations of nitrate and atrazine in surface and groundwater in Nebraska are positively associated with higher pediatric cancers incidence rate.

2 Materials and Methods

2.1 Case definition, study population, and data sources

Cases were defined as all children aged 0-19 years of age and diagnosed with brain and other CNS (Central Nervous System) cancers, leukemia, and lymphoma recorded in the Nebraska Cancer Registry between January 01, 1987 and December 31, 2016. Based on the case definition, the at-risk population encompasses all the children (0-19 years of age) who lived in Nebraska from 1987 to 2016.

Pediatric cancer data were obtained from the Nebraska Department of Health and Human Services Cancer Registry. Atrazine and nitrate data were retrieved from the water quality portal (National Water Quality Monitoring Council, 2020) and Nebraska Quality-Assessed Agrichemical Contaminant Database (University of Nebraska-Lincoln, 2000). Moreover, the Nebraska state and county boundary shapefiles were extracted from the United States Census Bureau (2019). The 2010 US decennial census data and Nebraska county populations were obtained from the National Historical Geographic Information System database (IPUMS NHGIS, 2020).

2.2 Data analysis

The Age-adjusted incidence for each Nebraska county and the state as a whole were determined by first calculating the crude incidence according to the equation:

$$\text{Crude incidence} = [\text{New cases}_{\text{county}} / (\text{Population at risk}_{\text{county}} * \text{Time of analysis})] * 100000$$

The crude incidence was then used to determine the age-adjusted incidence according to the equation:

$$\text{Age-adjusted incidence} = \sum \text{crude incidence}_{\text{county}} * \text{Age distribution of standard population}_{\text{Age group}}.$$

The age distribution of the standard population was obtained by dividing the population in any specific age group by the total U.S. 2010 standard population.

The ages were categorized into four groups: 0-4, 5-9, 10-14, and 15-19 years.

Although a percent change in the county population ranged between - 48% and 37% , for the Nebraska pediatric (0-19 years old) population during the study period (1987-2016), the 2010 census population was used as it best represented the study population. Counties with a total pediatric population of fewer than 200 people were excluded from the analysis.

Additionally, using ArcGIS Pro version 2.4 (ESRI, 2019), the spatial distribution of the age-adjusted incidence of pediatric brain and other CNS cancers, leukemia, and lymphoma in Nebraska was compared to the national average.

Both univariable and multivariable negative binomial regression analyses were conducted in SPSS (Statistical Package for the Social Sciences) (IBM Corp, 2019), to identify predictors of the three most common pediatric cancers counts (brain and other CNS cancers, leukemia, and lymphoma) with offset for the county level pediatric population size. The independent variables were the growing season mean nitrate and atrazine concentrations in groundwater and surface water. The growing season (months of April to October) was emphasized, as atrazine and nitrate are applied during growing season, and their concentration in the water is expected to be higher.

The independent variables were classified into four groups (Table 1) using the quantile classification in ArcGIS to determine automatic groups for atrazine concentrations in surface and groundwater. For nitrate concentrations in surface and groundwater, the function "manual intervals" in ArcGIS was used to set specific concentration ranges (ESRI, 2020).

Table 1. Classification of mean atrazine and nitrate concentrations in categories

	Atrazine (μg/L)		Nitrate (mg/L)	
Categories	**SW[1]**	**GW[2]**	**SW**	**GW**
Group 1	0.0000 - 0.1313	0.0000 - 0.0002	0.0000-2.0000	0.0000-2.0000
Group 2	0.1314 - 0.9473	0.0003 - 0.0213	2.1000 -5.0000	2.1000 -5.0000
Group 3	0.9474 - 2.8187	0.0214 - 0.0995	5.0100-10.0000	5.0100-10.0000
Group 4	2.8188 - 18.5750	0.0996 - 2.5118	10.0100-15.1500	10.0100-12.4200

[1]SW= surface water [2]GW=groundwater

4 Results

4.1 Descriptive Statistics

4.1.1. Pediatric cancers

Among the 2559 pediatric cancer cases reported in the Nebraska cancer registry from 1987 to 2016, thirteen (13) types of cancer were identified. Brain and other CNS cancers were the most represented with 26% (665/2559) of all cases, followed by leukemia, 24.4% (625/2559), and lymphoma, 16% (405/2559). Table 2 compares the most predominant pediatric cancer types in Nebraska and the U.S. (ACCO, 2014).

Table 2. Most common pediatric cancers types in Nebraska (1987-2016) and the US

Cancer type	Frequency in Nebraska (%)	Frequency in the U.S. (%)
Brain and other CNS	26	18
Leukemia	24	26
Lymphoma	16	14
Other types	34	42

4.1.2. Nitrate and atrazine concentration

Growing seasons groundwater (GW) and surface water (SW) mean atrazine concentrations (Table 3) during the study period were below the EPA maximum contaminant limit of 3 µg/L. In contrast, 16% of all groundwater nitrate measurements were above the MCL of 10 mg/L.

Table 3. Groundwater (GW) and surface water (SW) mean atrazine and nitrate concentrations in the growing season

	Atrazine GW concentration (µg/L)	Atrazine SW concentration (µg/L)	Nitrate GW concentration (mg/L)	Nitrate SW concentration (mg/L)
Number of records	86	77	86	66
Mean	0.13	1.86	6.66	1.71
Median	0.02	0.95	6.04	1.09
Standard deviation	0.35	2.67	3.38	2.35
Minimum	0.00	0.01	0.58	0.00
Maximum	2.51	18.58	15.15	12.42

4.2 Age-adjusted incidence of pediatric cancers in Nebraska and the national average

The age-adjusted incidence for pediatric brain and other CNS cancers in Nebraska was 4.42 per 100,000 population between 1987 and 2016 (Table 4). This incidence was higher than the national average age-adjusted incidence for pediatric brain and other CNS cancers reported to be 3.16 per 100,000 population in average between 1999 and 2016 (U.S. Cancer Statistics Working Group, 2020). The incidence of leukemia (3.67 per 100,000 persons) and lymphoma (2.72 per 100,000 persons) were lower in Nebraska than the national average.

Table 4. Age-adjusted incidence of pediatric cancers in Nebraska and the U.S.

Cancer type	Nebraska age-adjusted incidence (per 100,000)	National age-adjusted incidence (per 100,000)
Brain and other CNS cancers	4.42	3.16
Leukemia	3.67	4.66
Lymphoma	2.72	2.65

4.3 Geospatial analysis

The incidence of the three major types of pediatric cancer is shown on a map of Nebraska with counties delineated (Figure 1A-C). The four colors on the map represent pediatric cancer incidence in quartiles with the first quartile incidence below the national average. Counties excluded from the analysis are left blank.

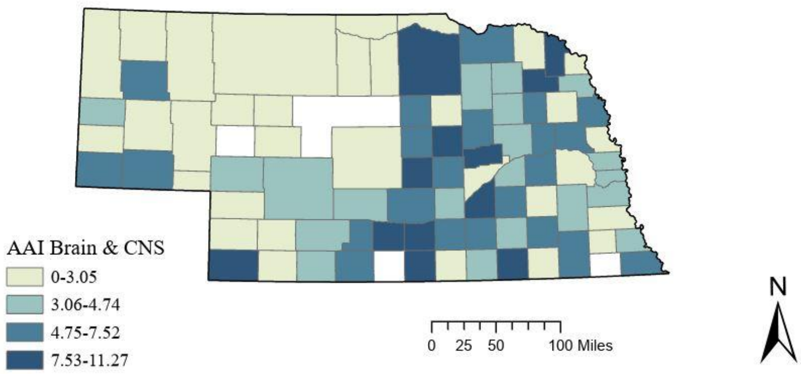

Fig 1A. Age-adjusted incidence (AAI) of pediatric brain and other CNS cancers per county in Nebraska from 1987-2016

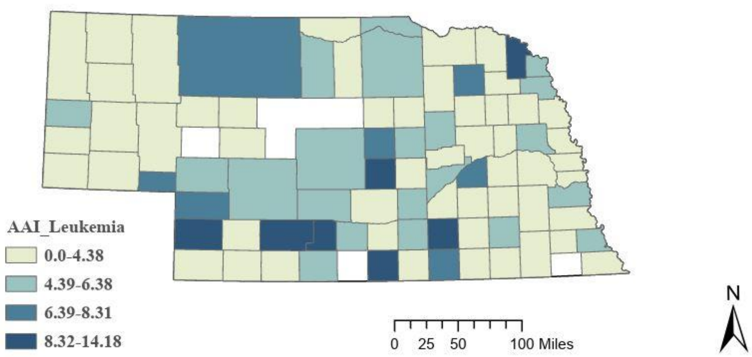

Fig 1B. Age-adjusted incidence (AAI) of pediatric leukemia per county in Nebraska from 1987-2016

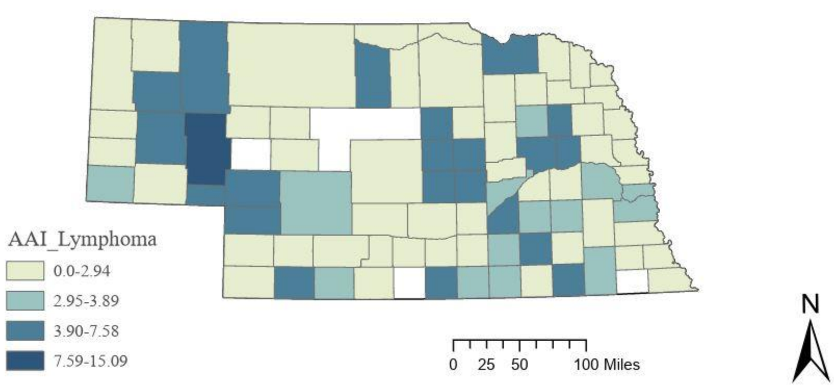

Fig 1C. Age-adjusted incidence (AAI) of pediatric lymphoma per county in Nebraska from 1987-2016

Relative to the national average, the age-adjusted incidence of pediatric brain and other CNS cancers (Figure 1A) is higher in 63% (54/86) of the Nebraska counties. In 41% (35/86) and

43% (38/86) of Nebraska counties; the incidence of pediatric cancers is higher than the national average, respectively, for leukemia (Figure 1B) and lymphoma (Figure 1C).

4.4. Analysis of the relation between the incidence of the pediatric cancers (brain and other CNS, leukemia, and lymphoma) and agrichemicals in water (nitrate and atrazine)

The results of the negative binomial regression univariable (crude model) and multivariable (full model) analyses are presented in Table 5. The univariable analysis did not yield any positive association between surface water nitrate concentration and pediatric brain and other CNS cancers, leukemia, or lymphoma; thus, surface water nitrate concentration was not included in the multivariable analysis.

Table 5. Negative binomial regression analysis of the association between pediatric cancers (Brain and other CNS, leukemia, and lymphoma) and agrichemicals in water (atrazine and nitrate)

Variables	Brain and other CNS		Leukemia		Lymphoma	
	Crude IRRc* (95% CI)	**Full model** IRR_a* (95% CI)	**Crude** IRRc* (95% CI)	**Full model** IRR_a* (95% CI)	**Crude** IRRc* (95% CI)	**Full model** IRR_a* (95% CI)
Atrazine SW[1]						
Group 2	0.93 (0.92-0.94)	3.04 (2.99-3.09)	0.87 (0.86-0.89)	2.96 (2.91-3.00)	1.04 (1.02-1.05)	3.42 (3.37-3.48)
Group 3	17.32 (17.13-17.32)	4.67 (4.61-4.73)	13.38 (13.24-13.53)	4.19 (4.13-4.24)	15.75 (15.57-15.93)	6.53 (6.44-6.62)
Group 4	6.39 (6.31-6.46)	3.95 (3.89-4.01)	5.79 (5.73-5.86)	5.58 (5.49-5.67)	6.64 (6.56-6.72)	4.75 (4.68-4.83)
Group 1	Reference	Reference	Reference	Reference	Reference	Reference
Atrazine GW[2]						
Group 2	10.54 (10.42-10.66)	1.11 (1.09-1.14)	9.50 (9.39-9.61)	0.89 (0.87-0.91)	7.99 (7.89-8.08)	1.00 (0.99-1.02)
Group 3	28.03 (27.73-28.34)	2.39 (2.35-2.44)	22.64 (22.40-22.89)	2.73 (2.69-2.78)	17.96 (17.77-18.17)	1.58 (1.55-1.60)
Group 4	6.27 (6.20-6.34)	1.33 (1.31-1.36)	3.99 (3.3.95-4.04)	1.12 (1.09-1.13)	4.95 (4.89-5.01)	0.91 (0.90-0.93)
Group 1	Reference	Reference	Reference	Reference	Reference	Reference
Nitrate SW[1]						
Group 2	0.49 (0.48-0.50)	-	0.57 (0.56-0.58)	-	0.54 (0.54-0.55)	-
Group 3	0.08 (0.08-0.09)	-	0.79 (0.78-0.80)	-	0.14 (0.14-0.15)	-
Group 4	0.03 (0.03-0.04)	-	0.01 (0.01-0.02)	-	0.01 (0.01-0.02)	-
Group 1	Reference		Reference		Reference	
Nitrate GW[2]						
Group 2	32.43 (31.92-32.95)	13.25 (13.00-13.50)	18.73 (18.44-19.01)	6.13 (6.02-6.26)	20.96 (20.62-21.30)	11.53 (11.32-11.75)
Group 3	2.22 (2.18-2.25)	1.69 (1.66-1.72)	1.51 (1.49-1.54)	0.89 (0.87-0.91)	1.65 (1.63-1.68)	1.77 (1.74-1.81)
Group 4	2.58 (2.53-2.63)	1.79 (1.76-1.83)	1.23 (1.21-1.25)	0.88 (0.86-0.89)	1.85 (1.82-1.89)	1.51 (1.48-1.55)
Group 1	Reference	Reference	Reference	Reference	Reference	Reference

*IRR_c/IRR_a=Incidence rate ratio (crude/adjusted)
[1] Atrazine or nitrate concentration in surface water
[2] Atrazine or nitrate concentration in groundwater

4.4.1 Brain and other CNS cancers

While holding all other variables (nitrate concentration in surface and groundwater, atrazine concentration in groundwater) constant in the model, the incidence rate of brain and other CNS cancers in counties with surface water atrazine concentration in group 3 was 4.67 times higher

(95% CI: 4.61-4.73) than the incidence rate for counties in the reference group (group 1). Similarly, the incidence rate of brain and other CNS cancers in counties with surface water atrazine concentration in groups 2 and 3 were respectively 3.04 (95% CI: 2.99-3.09) and 3.95 (95% CI: 3.89-4.01) times higher than the incidence rate for counties in the reference group. Additionally, compared to counties with groundwater atrazine concentration in group 1 (reference group), counties with groundwater atrazine concentration in group 3, 2, and 4 have brain and other CNS cancers incidence rate ratio of 2.39 (95% CI: 2.35-2.44), 1.11(95% CI: 1.09-1.14) and 1.33 (95% CI: 1.31-1.36) respectively.

Regarding nitrate, keeping all other variables (atrazine concentration in surface and groundwater, nitrate concentration in surface water) constant, counties with groundwater nitrate concentration in group 2 have a higher incidence rate of pediatric brain and other CNS cancers than counties with groundwater nitrate concentration in the reference group 1 (IRR=13.25; 95% CI: 13.00-13.50). Additionally, counties with nitrate groundwater concentration in groups 3 and 4 have a higher incidence rate of pediatric brain and other CNS cancers than counties in the reference group, although the relationship is not as strong as between groups 2 and 1.

4.4.2 Leukemia

After adjusting for all covariates (nitrate concentration in surface and groundwater, atrazine concentration in groundwater) in the model, counties with surface water atrazine concentration in group 2, 3, and 4 have leukemia incidence rates of 2.96 (95% CI: 2.91-3.00), 4.19 (95% CI: 4.13-4.24), and 5.58 (95% CI: 5.49-5.67) times higher than leukemia incidence rate for counties with surface water atrazine concentration in the reference group (group1), respectively. Additionally, compared to counties with groundwater atrazine concentration in group 1 (reference group), counties with groundwater atrazine concentration in group 3 and 4 have leukemia incidence rate ratio of 2.73 (95% CI: 2.35-2.44) and 1.12 (95% CI: 1.09-1.13), respectively.

Regarding nitrate, keeping all other variables (atrazine concentration in surface and groundwater, nitrate concentration in surface water) constant, counties with groundwater nitrate concentration in groups 2 have a higher incidence rate of leukemia than counties with groundwater nitrate concentration in group 1 (IRR=6.13; 95% CI: 6.02-6.26).

4.4.3 Lymphoma

Compared to counties with surface water atrazine concentration in group 1 (reference group), counties with surface water atrazine concentrations in group 2, 3, and 4, after adjusting for all covariates in the model, have a lymphoma incidence rate ratio of 3.42 (95% CI: 3.37-3.48), 6.53 (95% CI: 6.44-6.62), and 4.75 (95% CI: 4.68-4.83). Additionally, the incidence rate of lymphoma in counties with groundwater atrazine concentration in group 2 was 1.58 (95% CI: 1.55-1.60) times higher than the incidence rate for the reference group.

Regarding nitrate, keeping all other variables constant, counties with groundwater nitrate concentration in group 2 have a higher incidence rate of leukemia than counties with groundwater nitrate concentration in group 1 (IRR=11.53; 95% CI: 11.32-11.75).

5. Discussion

The age-adjusted incidence was determined for pediatric brain and other CNS cancers, leukemia, and lymphoma across Nebraska counties, along with the mean concentrations of nitrate and atrazine in each Nebraska county. The relationship between nitrate and atrazine concentrations (in surface and groundwater) and the three most prevalent pediatric cancer types in Nebraska was also investigated.

Compared to Nebraska counties with surface water atrazine concentration in the reference group (group 1), counties with surface atrazine concentrations in groups 2, 3, and 4 had higher incidence rates of pediatric cancers (brain and other CNS cancers, leukemia, and lymphoma) after adjusting for nitrate concentrations in both surface and groundwater. Similarly, the incidence rate of pediatric cancers was higher in counties with groundwater atrazine concentration in group 3 (0.02 - 0.09 µg/L) after controlling for nitrate concentrations.

These findings add to the growing number of studies that have observed an association between atrazine levels in water and increased cancer incidence (Booth et al., 2015; Carozza et al., 2008; Fan et al., 2007; Freeman et al., 2011; Malagoli et al., 2016). For example, Freeman et al. (2011), with a small sample size, found an increased risk of ovarian cancer among females applicators of atrazine compared to female non-applicators. Furthermore, higher incidence rates of pediatric leukemia were observed in Illinois counties with greater than the corn's median acreage (Booth et al., 2015). Atrazine is one of the most common herbicides used in corn production; thus Booth et al (2015) in their study implied an association between atrazine use and pediatric leukemia (RR Leukemia = 2.09, 95 % CI = 1.31–3.32). Similarly, research showed an association between residence at the time of diagnosis in agriculturally intense areas and increased childhood cancer incidence. The assumption was that agriculturally intensive areas used many pesticides, including atrazine (Carozza et al., 2008). The risk of pediatric leukemia increased with arable crop production dominated by the use of atrazine, as suggested by Malagoli et al. (2016).

However, many other studies did not find an association between atrazine exposure and increased cancer risk (Rusiecki et al., 2004; Sathiakumar et al., 2011). Although Rhoades et al. (2013) in their research found that the odds of developing Non-Hodgkin lymphoma (NHL) were 2.9 times (CI: 1.1-7.4) higher in subjects exposed to both atrazine and nitrate in water, the study did not observe an association between NHL risk and nitrate or atrazine alone.

Although ecological, the present study has the advantage of large health databases and controlled for nitrate concentrations, a critical agrichemical used in Nebraska that could be a potential confounder of the findings.

After controlling for atrazine concentrations, this study also found that Nebraska counties with groundwater nitrate concentration in group 2 have higher incidence rates for all three major types of pediatric cancer than counties with groundwater nitrate concentration in group 1 (reference group). These findings suggest that intensive agriculture, the primary source of water contamination by nitrate, contributes to the excess rate of pediatric cancers in Nebraska. The current results will also enrich the body of evidence of a positive relationship between nitrate concentration and increased cancer risk in humans. Indeed, a significant number of studies have found an association between exposure to a relatively high nitrate concentration and the risk of developing cancer. Examples of such studies include case-control research conducted by Fathmawati et al. (2017) in Indonesia. The findings demonstrated (after adjusting for smoking history, age, and family history of cancer) an association between prolonged exposure (more than ten years) to nitrate concentration in drinking water above 11.29 mg/L of nitrate as N, with an increased risk of colorectal cancer occurrence (OR =4.31;95% CI: 1.32–14.09). Moreover, in a study conducted in Iowa, long-term ingestion ($\geq$ 4 years) of elevated nitrate in drinking water (> 5 mg/L of nitrate as N) was associated with an increased risk of bladder cancer among postmenopausal women, after adjusting for covariates such as smoking status and total trihalomethane levels (HR = 1.62; 95% CI: 1.06, 2.47) (Jones et al., 2016). Another study conducted in Iowa and controlled for confounders like trihalomethane levels demonstrated that high nitrate levels (> 5 mg/L of nitrate as N) in public water supplies were associated with an increased risk of renal cancer (HR=2.3, 95% CI:1.2–4.3) (Jones et al., 2017).

Strengths and Limitations

This ecologic study by design has the advantage of large health data and controlled for two major waterborne agrichemicals used in Nebraska. However, because aggregate rather than individual-level exposures were studied and other cancer risk factors were not accounted for, a causal relationship cannot be inferred. Additionally, the authors assumed that the county of residence at the time of diagnosis was the county where the exposure occurred, which may be reasonable in the study context, given Nebraska's population dynamics.

6. Conclusion

In this study, the authors determined the mean atrazine and nitrate concentrations and the age-adjusted pediatric cancer incidences in each county in Nebraska from 1987-2016. The age-adjusted pediatric brain incidence and other CNS tumors was higher than the national average in 63% of the Nebraska counties. The authors also examined the relationship between atrazine concentrations, nitrate concentrations, and pediatric cancers for the three most prevalent pediatric cancers in Nebraska (brain and other CNS, leukemia, and lymphoma). An association was found between relatively higher atrazine or nitrate concentration and an increased incidence rate of pediatric cancers (brain and other CNS, leukemia, and lymphoma). The runoff from fertilizer (nitrate) and herbicide (atrazine) application is the primary source of agrichemicals in water in farming areas. Nebraska is dominated by industrial agriculture; these results do not necessarily prove a causal relationship but suggest that the use of agrichemicals such as atrazine and nitrate poses a significant threat to pediatric health regarding brain and other CNS cancers, leukemia, and lymphoma occurrence. Further research is recommended to validate these findings, such as a case-control study to measure individual-level exposure and other potential confounders.

Acknowledgments

The authors wish to extend their gratitude to Sammy's Superheroes Foundation for funding this project and the Nebraska Department of Health and Human Services for granting access to the pediatric cancer data.

The authors declare no conflict of interest relevant to this study.

Data Availability

Some of the data used for this research are publicly available:

1. The 2010 US decennial census data and Nebraska county populations were obtained from the National Historical Geographic Information System database. https://www.nhgis.org/; accessed October 07, 2020.
2. Atrazine and nitrate data were retrieved from the water quality portal (https://www.waterqualitydata.us/portal/; accessed October 7, 2020) and Nebraska Quality-Assessed Agrichemical Contaminant Database (https://clearinghouse.nebraska.gov/Clearinghouse.aspx; accessed October 7, 2020).
3. The Nebraska state and county boundary shapefiles were extracted from the United States Census Bureau https://www2.census.gov/geo/tiger/TIGER2019/; accessed October 7, 2020.

Additional data (pediatric cancer data) supporting this research is available in Birth Defects Registration Partners and is not available to the public or research community unless access is granted by the Nebraska Department of Health and Human Services upon completion and approval of data uses agreement forms.

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