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Association Between Pesticide Use and Incidence of Diffuse Large B-Cell Lymphoma

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Abstract. *Background/Aim: Exposure to pesticides has been reportedly associated with several types of cancer. Materials and Methods: In this study, we used data from The United States Geological Survey (USGS), United States Census, and the Surveillance, Epidemiology, and End Results (SEER) database to analyze the association between the area density of specific agricultural pesticides and the county level annual incidence of diffuse large B-cell lymphoma (DLBCL). Results: Incidence of DLBCL was significantly associated with an area density of 14 of the pesticides reported by USGS. Conclusion: This highlights the need for further investigation into the safety of the use of these pesticides. The importance of this study comes not only from the significant association it shows between pesticides and the incidence of cancer, but also from the fact that it included all compounds reported to USGS as being used in agriculture. This helps in prioritizing pesticides for further evaluation.*

Diffuse large B-cell lymphoma (DLBCL) is the most common type of adult aggressive non-Hodgkin lymphoma (NHL) (1). Despite its prevalence, the pathogenesis of DLBCL is not fully understood. Certain occupations and exposures, such as pesticide exposure, have been linked to an increased risk of DLBCL (2-5). The effect of many compounds used in agriculture on humans remains unstudied, and their association with an increased risk of developing cancer is unknown (6). Epidemiologic associations are an important step in the study of potential human carcinogens (7). In this study, we reviewed all the agricultural compounds reported in the United States Geological Survey (USGS) and analyzed their association to the incidence of DLBCL using the Surveillance, Epidemiology, and End Results (SEER) database.

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Materials and Methods

International Classification of Diseases for Oncology (ICDO-3) code 9680 was used to extract all patients diagnosed with DLBCL in 2012 from Lymphoma-Leukemia dataset of the Surveillance, Epidemiology, and End Results database (SEER*Stat 18 November 2015 submission) (8). Patients were grouped into counties by Federal Information Processing Standards (FIPS) codes (9). United States Census data were used to obtain population estimates for each FIPS code in 2012 (9). USGS data were used to extract area densities (kilograms per square kilometer harvested crop) for all reported agricultural chemical use in the year of 1992 per FIPS code (10). The USGS method of handling acreages with no reported use of a particular chemical as missing data (high use estimation) was used for analysis. The incidence of DLBCL per FIPS code was calculated from data extracted from SEER and census data, and then matched to pesticide use from USGS data based on FIPS code. SPSS software (version 25) was used for statistical analysis. Association between the level of pesticide use and incidence of DLBCL was analyzed using Pearson correlation analysis. Two-tailed p value of <0.05 was used for statistical significance and sequential modified Bonferroni correction with a Benjamini-Hochberg method (alpha of 0.05) was used to reduce risk of false discovery (11). University of Hertfordshire Pesticides Properties Database was used to extract uses and chemical classes of the pesticides (12). Identified chemicals were cross-referenced with the World Health Organization Pesticide Data Sheets (13). Epi Info 7 software was used for maps creation (14). Maps boundaries file was downloaded from the Census website (9).

Results and Discussion

A total of 2,258 patients with diagnosis of DLBCL in 2012 were extracted from SEER Lymphoma-Leukemia dataset using ICDO-3 code 9680. These patients were distributed over 167 counties that also had pesticide application data. USGS data

Table I. *Pesticides significantly correlated with incidence of diffuse large B-cell lymphoma (DLBCL). Chemical class, median and range are reported for each pesticide.*

Pesticide	Chemical class	R Coeff	*p*-Value	Median (kg/km^2)	Range	N
Pebulate	Thiocarbamate	0.6700	0.0030	16.70	0.20-188.80	17
Mecoprop	Aryloxyalkanoic acid	0.3580	0.0000	38.30	0.10-144.70	113
Imazethapyr	Imidazolinone	0.3490	0.0000	674.90	0.10-3707.30	131
Nicosulfuron	Sulfonylurea	0.3430	0.0000	44.20	0.10-461.20	143
Trelse Ifluralin	Dinitroaniline	0.3320	0.0000	2,732.10	1.60-42219.00	159
Hexazinone	Triazinone	0.3230	0.0000	119.75	0.60-6283.20	130
Metolachlor	Chloroacetamide	0.3150	0.0000	16,556.45	0.20-184353.70	154
Paraquat	Bipyridylium	0.3080	0.0000	344.00	0.10-3733.30	158
Ethalfluralin	Dinitroaniline	0.3080	0.0000	1,108.80	0.10-4123.80	129
Bromoxynil	Hydroxybenzonitrile	0.2820	0.0000	488.90	0.10-11969.20	151
Methyl_Parathion	Organophosphate	0.2790	0.0000	340.90	0.20-2401.20	153
Cyanazine	Triazine	0.2750	0.0010	11,721.40	0.10-125509.80	151
Pendimethalin	Dinitroaniline	0.2690	0.0010	4,821.90	0.90-26457.60	157
Dicamba	Benzoic acid	0.2560	0.0010	1,771.00	1.40-19579.00	159

N represents the number of counties with data for both DLBCL and chemical area density.

included 290 compounds reported as being used in agriculture. Of these compounds, 65 were excluded due to no reported use in the studied counties. The remaining 225 were included in the analysis. To investigate the correlation between compounds' exposure and the incidence of DLBCL, the quantity used of each compound (kg/km^2) was matched to the 167 counties that had DLBCL cases reported. Pearson correlation analysis was then applied and showed a statistically significant correlation ($p<0.05$) between the incidence of DLBCL and area density of 40 compounds from the 225. Only one (Pendimethalin) of the 40 compounds was listed as a probable carcinogen by the International Agency for Research on Cancer (IARC) (15), and none are listed in the latest Report on Carcinogens from the United States National Toxicology Program (7). This number decreased to 14 compounds after applying Benjamini-Hocheberg method with alpha set to 0.05 to account for false discovery (Table I). None of the 14 compounds were on the WHO list of obsolete pesticides (16). Only one (Methyl-Parathion) had a WHO hazard classification >3 for acute toxicity based on animal-model LD50. To visually show the correlation between area density of pesticide application and incidence of DLBCL, we used Epi Info software to generate maps for incidence as well as pesticide. These maps show that areas with higher application of the 14 pesticides correspond to areas with increased DLBCL incidence (Figure 1).

To analyze how these pesticides are being used in agriculture, we used University of Hertfordshire Pesticides Properties Database to extract the use as well as the chemical class of the compounds with significant correlation. Of the 14 compounds, 13 are used as herbicides; Methyl Parathion is an organophosphate used as an insecticide. Other organophosphate chemicals have been associated with cancer development (7, 8). However, other compounds belong to different chemical classes with dinitroaniline being the most frequent (Table I). Analysis of the underlying mechanism of action of these compounds is needed to uncover any possible common pathway, such as their effects on hematopoietic cell mutagenesis, B cell hyperstimulation, alteration of intestinal microbiome, and other potential mechanisms for carcinogenicity. Glyphosate, is a herbicide that has been extensively studied due to its association with NHL (17); it was used in 160 (95.8%) of the studied counties in 1992 with a total of 0.2 million pounds applied, and was not significantly associated with diagnoses of DLBCL in 2012. In 1992, 0.8 million pounds were applied to all US crops compared to 78.2 million pounds in 2001 (18).

This analysis advances our understanding of a dose response relationship between the quantity of pesticides used in a particular county and the incidence of DLBCL. The identified compounds warrant study as possible carcinogens. A significant effect size was recently reported in a cohort of 244 French patients with DLBCL, with a 2-year event-free survival hazard ratio adjusted for confounders of 3.5 for patients with occupational exposure to pesticides (9). Future investigations using genetic data can identify whether exposure to pesticides is associated with specific mutational patterns.

This study makes use of high-quality data sets designed to reliably reflect geographic and temporal trends. Population-level data offer a broader perspective than prior case-control studies utilizing recall of chemical exposure in patients with lymphoma (19). Agricultural chemicals are used in the global food chain to improve productivity and reduce crop loss due to pests (20). The long-term effects of specific occupational chemicals should be investigated. With an increasing number

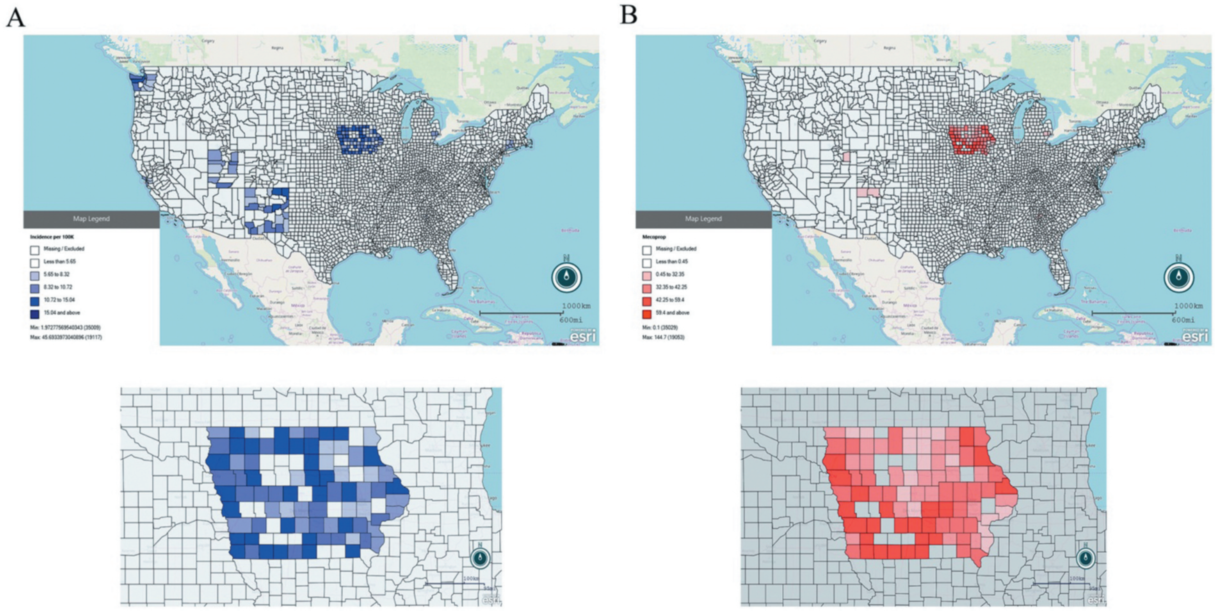

Figure 1. *Heat maps showing incidence of diffuse large B-cell lymphoma (DLBCL) (A) and use of Mecoprop (B), one of the pesticides reported in Table I. Areas with higher pesticides use corresponds to increase incidence of DLBCL. Enlarged areas shown under each map for clearer view. Heat maps for other pesticides reported in Table I are available upon request.*

of high-quality epidemiologic studies showing an association between pesticides exposure and incidence of cancer, the next step is to find specific associations that warrant multi-pronged analyses for carcinogenesis (21).

This study is limited by the SEER*Stat database only having data for 167 counties of the United States that also had pesticide application data, representing an estimated 15% of DLBCL diagnoses in 2012 (22). This lessens the power to detect associations between additional chemicals and the incidence of DLBCL. It is not unusual that multiple pesticides are used in the same area. This adds to the complexity of the analysis as these are not only confounding variables, but also can have important interactions with each other. The time lag between exposure and diagnosis biases our investigation toward the null hypothesis, since relocation and variable latency would be expected to dilute the association (23). Finally, it is important to note that while this study highlights an association to generate hypotheses, it does not establish causality. Further studies designed to mitigate the effect of confounding variables, discover putative biologic mechanisms, and evaluate dose-response relationships are needed to further characterize the apparent link between these pesticides and DLBCL.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

MGM conceived the idea. AA performed data extraction and analysis, MGM and LJH contributed to data analysis, AA created figures. All Authors contributed to writing the manuscript.

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