

An Exploratory Study of the Relation of Population Density and Agricultural Activity to Hematologic Malignancies in North Dakota

Patricia L. Watkins, MS; John M. Watkins, MD

ABSTRACT

Introduction: Established risk factors for hematologic cancers include exposure to ionizing radiation, organic solvents, and genetic mutation; however, the potential roles of environmental and sociological factors are not well explored. As North Dakota engages in significant agricultural activity, the present investigation seeks to determine whether an association exists between the incidence of hematologic cancers and either population density or agricultural occupation for residents of south central North Dakota.

Methods: The present study is a retrospective analysis. Cases of hematologic malignancies and associated pre-malignant conditions were collected from the regional Central North Dakota Cancer Registry, and analysis of study-specific demographic factors was performed.

Results: Significantly higher incidence of hematologic cancers and pre-malignant disorders was associated with residence in an “urban” county and rural city/town. Within the latter designation, there was a higher rate of self-reported agricultural occupation (40% vs 10%, $P < 0.0001$).

Conclusions: The increased incidence of hematologic cancer in low population density areas of south central North Dakota supports the need for more detailed prospective research centered on agricultural exposures.

INTRODUCTION

Hematologic malignancies include such diseases as acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), myelomatous disorders, and Hodgkin and non-Hodgkin lymphoma (NHL).¹⁻⁷

Established risk factors for hematologic cancers include exposure to ionizing radiation;⁸ however, potential roles of socioen-

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Author Affiliations: University of North Dakota, School of Medicine and Health Sciences, Southwest Campus–Bismarck; c/o Bismarck Cancer Center, Bismarck, ND.

Corresponding Author: John M. Watkins, MD, Bismarck Cancer Center, 500 N 8th St, Bismarck, ND 58501; phone 701.222.6100; fax 701.222.6150; e-mail john.m.watkins.md@hotmail.com.

vironmental factors are not well explored. Specific to agricultural exposure, several investigations have demonstrated associations more specific to pesticide use, including its handling,⁹ chemical type,^{10,11} and timing of exposure with respect to child-birth.^{12,13}

As a formal descriptive study of potentially associated sociodemographic factors specific to North Dakota has yet to be performed, the present study seeks to determine whether a correlation exists between hematologic malignancies and agricultural activity in North Dakota. It is hypothesized that increased exposure to agricultural activities in North Dakota will be associated with an increased incidence of hematologic malignancies and associated premalignant conditions (such as myelodysplastic syndrome

[MDS]). Findings consistent with this hypothesis would support larger research efforts aimed at delineating specific hazards associated with agriculture in North Dakota that may increase risk of hematologic cancers.

METHODS

The present study was a retrospective review of medical records designed to examine differences in incidence of hematologic cancers between rural and urban regions of North Dakota. Following approval by the Institutional Review Boards (IRBs) at the University of North Dakota School of Medicine (Grand Forks, ND) and the 2 participating institutions (St Alexius Hospital and MedCenter One, Bismarck, ND), a research database was created.

Eligible cases were identified by query of the Central North Dakota Cancer Registry. Inclusion criteria were clinically defined hematologic malignancy or MDS diagnosed between 2002 and 2010, age > 18 at diagnosis, and residence in the following North

Dakota counties: Burleigh, Morton, Grant, Hettinger, Stark, or Emmons (selected due to dominance of the adult hematology/oncology practices of the participating institutions and thus anticipated near-complete capture and retention of patients diagnosed within the region).

Study Objectives

The principal objective of this investigation is to determine whether an association exists between incidence of hematologic malignancies and agricultural activity for residents of south central North Dakota, employing available population and demographic data.

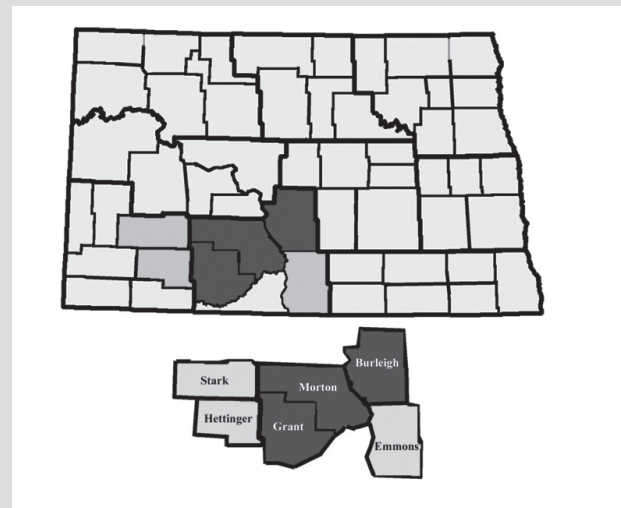
Population Stratification

In order to assess frequency of hematologic cancers by level of agricultural activity, several stratifications were employed. First, individuals were classified by the county of residence at diagnosis, stratified into “urban” and “rural” agricultural activity levels. Counties were designated as “urban” if <50% of acreage was devoted to cropland, and “rural” if >50%. Data on percentage of acreage devoted to cropland was obtained from publicly available data at the United States Department of Agriculture, National Agricultural Statistics Service database.¹⁴ Classification of counties is demonstrated in Figure 1. A second measure was population density, stratified into high vs low and classified based upon city/town of residence at the time of diagnosis. Cities were categorized as high population density if the city contained above the 25th percentile of total state residents in the 2000 census, and low if below the 25th percentile. These data were acquired from the North Dakota State Data Center database.¹⁵ Third, patients’ charts were reviewed to determine whether documented occupation in agriculture (eg, any farming activity) was noted at or prior to the time of diagnosis.

Statistical Analysis

All statistical analyses were performed using SPSS Version 10 (SPSS, Inc.; Chicago, Illinois). Frequencies and relative percentages were computed for demographic and clinical characteristics of patients. The Mann-Whitney U test was employed to assess differences between comparison populations in age at presentation, smoking status, or percent of individuals reporting agricultural work. Missing data were excluded from analysis. Incidence of hematologic disorders was recorded as a number per thousand derived from the group incidence divided by the population of represented cities, as obtained from the North Dakota State Data Center database.¹⁵ Chi-Square test was performed to test for differences in hematologic cancer incidence between rural and urban as well as high and low population densities. An alpha level of .05 was employed for this study, with statistical significance accepted where *P*-value was <.05.

Figure 1. Map of North Dakota, with Included Regions Highlighted



Classification of agricultural activity: dark gray = urban; medium gray = rural.

Table 1. Study Population Characteristics

Characteristic	Study Population ^a n (%)
Age at diagnosis	
Median	70
(range)	(19 - 89)
Gender	
Male	321 (53)
Female	286 (47)
Smoking history	
Yes	271 (44)
No	278 (45)
Not recorded	64 (11)
Agriculture occupation	
Yes	92 (15)
Hematologic disease	
Acute lymphoblastic leukemia	8 (1)
Acute myelogenous leukemia	58 (9)
Chronic lymphocytic leukemia	85 (14)
Chronic myelogenous leukemia	23 (4)
Hairy cell leukemia	8 (1)
Multiple myeloma	52 (8)
Plasmacytoma	7 (1)
Myelodysplastic syndrome	118 (19)
non-Hodgkin lymphoma	231 (38)
Hodgkin lymphoma	23 (4)

^aMissing data was excluded from analysis; 6 patients without gender, 64 patients without smoking history, and 108 patients without occupation data.

RESULTS

Patient Characteristics

Between 2002 and 2010, 613 patients were identified for inclusion in this study. Patient and disease data are shown in Table 1. A comparison of patient factors by county

Table 2. Population Characteristics by Agricultural Activity

	Low n = 496 (%)	High n = 117 (%)	P-value
Age			
Median	72	68	0.171
Gender			
Male	262 (54)	59 (50)	0.554
Female	228 (46)	58 (50)	
Smoking history			
Yes	220 (49)	51 (50)	0.801
No	228 (51)	50 (50)	
Agriculture occupation			
Yes	63 (16)	22 (21)	0.201

Table 3. Population Characteristics by Population Density

	High n = 484 (%)	Low n = 129 (%)	P-value
Age			
Median	70	71	0.443
Gender			
Male	247 (52)	74 (57)	0.251
Female	231 (48)	55 (43)	
Smoking history			
Yes	214 (49)	57 (50)	0.797
No	222 (51)	56 (50)	
Agriculture occupation	42 (10)	44 (40)	<0.0001 ^a

^aStatistically significant with an alpha level of 0.05.

cropland (“urban/rural”) classification is demonstrated in Table 2, and city/town high vs low population density in Table 3.

Urban vs Rural

Residence in an urban county (< 50% cropland) was associated with a significantly higher incidence of hematologic cancers and pre-malignant disorders as compared to rural (6.4 per 1000 vs 4.6 per 1000, $P = .0027$). When MDS was excluded, the difference was no longer statistically significant (5.0 per 1000 vs 4.0 per 1000, $P = .0576$).

High vs Low Population Density

The low population density group had a significantly higher incidence of hematologic cancers and premalignant disorders as compared to the high population density group (7.9 per 1000 vs 5.5 per 1000, $P = .0002$). When MDS was excluded, the difference remained statistically significant (6.7 per 1000 vs 4.4 per 1000, $P = .0001$).

DISCUSSION

Increased risk of hematologic malignancies for agricultural workers has been reported previously in several states with significant

agricultural activity.^{9-13,16} The present study suggests a similar increase in risk for agricultural workers in North Dakota. Patients residing in low population density areas, where a significantly higher number of patients self-reported an agricultural occupation, were found to have a significantly higher incidence of hematologic disorders. While the results obtained in high vs low population density groups supported the study hypothesis, the expected pattern of incidence was not observed in urban vs rural groups; indeed, the urban group had significantly higher incidence of hematologic malignancies.

Several possibilities exist for these findings. First, the definition of urban residence was determined at the county level, which was likely insufficiently sensitive to properly measure the effects of local agricultural activity to which the individual patient would have been exposed. This is substantiated by the subsequent study findings of increased malignancy risk with lower population density; thus, residence in lower population density areas of these “urban” counties increases risk. Whether this is due to differences in agricultural practices (eg, intensity of pesticide use) cannot be determined from the available data; however, it is noteworthy that there was no significant difference in agricultural occupation between the urban/rural designations. Second, an alternative characterization of urban vs rural (presently dichotomized to above/below 50% cropland) could be entertained.

As with all epidemiologic studies, the present investigation is limited by its retrospective nature. Agricultural occupation data was gleaned from social history information recorded by the physicians caring for each patient, and subsequently imported into the registry database. As such, level of occupational data available was insufficiently detailed, and no specific information on toxin exposure was recorded (eg, type, duration, age at exposure). Furthermore, patients residing in areas of agricultural activity, but whose work is not specifically agricultural, would be expected to have at least some exposure in common with agricultural workers. The low population density demographic would capture this, but data quantifying risk factors has not yet been prospectively collected. Additionally, the retrospective nature of this study limited the inclusion of factors measuring the duration of work in agriculture or residence in a specific location. Available records indicated only occupation and location of residence at the time of diagnosis.

Based upon the present study demonstrating an association between low population density and risk hematologic cancers, and increased probability of agricultural occupation in low population density areas the next steps of this investigation would be to prospectively evaluate occupational exposures and associated risk of hematologic cancer. As prior investigations have associated pesticides with risk of NHL,⁹⁻¹¹ and specified that length⁹ and intensity of exposure¹² correlate with risk, recording the types of pesticides used, length of exposure to each pesticide, and han-

ding practices during exposure would allow for more accurate examination of risk within our population.

The ability to generalize the results of this study may be limited by the nature of the population characteristics. First, as stated previously, the variability of pesticide type and level of exposure by region and crop could not be determined from the present study. As some pesticides have a stronger association with hematologic cancers than others,⁹ the results of the present study would be applicable only to regions with similar crop and pesticide use profiles. Second, North Dakota is relatively homogeneous with respect to ethnoracial heritage (predominantly northern/western European white), thus the results may not be generalizable to other agricultural workers.

The present study found a significantly higher incidence of hematologic cancers and premalignant conditions in low population density regions of North Dakota, which suggests that further investigation into specific agricultural activities (including pesticide agents used and exposure) is warranted.

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