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The Development and Use of a Geographic Information System for Evaluating the Association between Pesticide Exposure and Prostate Cancer

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

by

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Preface

This doctoral thesis includes three studies, presented in Chapters 2-4, that have been prepared as manuscripts for specific journals.

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Abstracts

THE DEVELOPMENT AND USE OF A GEOGRAPHIC INFORMATION SYSTEM FOR EVALUATING THE ASSOCIATION BETWEEN PESTICIDE EXPOSURE AND PROSTATE CANCER

Abstract 1 – A Geographic Information System for Evaluating
Residential Pesticide Exposure and Prostate Cancer Incidence

Abstract 2 – Spatial Analysis of Prostate Cancer Incidence and
Residential Pesticide Exposure in Iowa

Abstract 3 – Multilevel Analysis of Residential Pesticide Exposure and
Prostate Cancer Incidence

By Kristen M. Wells, MPH

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor
of Philosophy at Virginia Commonwealth University.

Virginia Commonwealth University, 2010.

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Abstract 1 – A Geographic Information System for Evaluating Residential Pesticide Exposure and Prostate Cancer Incidence

Agricultural pesticide exposure is hypothesized to be a risk factor for prostate cancer, and such exposures are of particular concern for men living in farming communities where large-scale pesticide applications occur. Prostate cancer incidence data were obtained from the State Health Registry of Iowa for the years 1996 through 2006, and county and census tract level age-adjusted incidence rates were calculated. Historical crop-specific land use records and pesticide sales data for the state of Iowa during 1990 were integrated into a geographic information system (GIS), where estimates of predicted exposure to the four most commonly used pesticides in Iowa (atrazine, metolachlor, cyanazine, alachlor) were produced. Ecological correlation between pesticide exposure and prostate cancer incidence was evaluated using Spearman's (rank) correlation coefficient and linear regression analysis. Statistically significant associations between prostate cancer incidence and percent of acres of corn and soybean crops were found at both the county ($r=0.22$, $p=.031$ and $r=0.33$, $p=.001$, respectively) and census tract ($r=0.10$, $p=.007$ and $r=0.13$, $p<.001$, respectively) level. The associations between percent of land exposed to the specific pesticides and prostate cancer were not statistically significant. Our findings suggest that residential proximity to corn and soybean fields, and by association the pesticides used on those crops, is correlated with increased prostate cancer risk, but that the increase in risk is not correlated with exposure to the four most commonly used pesticides in Iowa in 1990. Findings from this study underscore the need for continued investigation of the association between agricultural exposures and prostate cancer incidence.

Abstract 2 – Spatial Analysis of Prostate Cancer Incidence and Residential Pesticide Exposure in Iowa

A statistically significant positive association between prostate cancer incidence and residential proximity to corn and soybean fields in Iowa exists. Research suggests that exposure to pesticides used on these crops increases prostate cancer risk. The objective of this study was to investigate clustering of prostate cancer risk in the presence of potential exposure to pesticides in Iowa. Prostate cancer incidence data (1996-2006) were obtained from the State Health Registry of Iowa. Using SaTScan software, clusters of high and low prostate cancer risk were identified. Ecological correlation between exposure to the four most commonly used pesticides (atrazine, metolachlor, cyanazine, alachlor) in Iowa during 1990 and residence in a cluster of relatively high or low prostate cancer incidence was evaluated using Pearson's chi-square test statistic and logistic regression analysis. Clusters of increased prostate cancer risk were associated with a greater percentage of land used for all crops of interest (i.e., corn and soybean farming ($p < 0.001$), corn farming ($p < 0.001$), soybean farming ($p < 0.001$)) and low exposure to alachlor ($p = 0.032$) than did clusters with decreased risk of prostate cancer. After adjustment for percent of land used for each crop type, no association between pesticide exposure and prostate cancer risk was observed. Residence in or near agricultural communities increases prostate cancer risk. Our findings suggest that residential proximity to exposures specific to corn and soybean farming increases prostate cancer risk. Evaluation of exposure to less commonly used pesticides and those used in lower quantities is needed.

Abstract 3 – Multilevel Analysis of Residential Pesticide Exposure and Prostate Cancer Incidence

An association between residential exposure to factors specific to corn and soybean farms in Iowa exists. The objectives of this study were to statistically assess spatial autocorrelation in prostate cancer incidence in Iowa and to evaluate the effect of residential exposure to the most commonly used pesticides for corn and soybean farms in Iowa in 1990 on prostate cancer incidence. Prostate cancer incidence data were obtained from the State Health Registry of Iowa for the years 1996 through 2006. Spatial patterning of age-adjusted incidence rates was assessed via Moran's I global index of spatial autocorrelation. A hierarchical regression modeling approach with an assumed Poisson distribution was used to characterize the relationship between census tract level prostate cancer incidence and exposure to pesticides. Statistically significant spatial patterning of prostate cancer incidence, corn and soybean fields and pesticide use ($p < .001$ for all variables) was observed. After adjustment for individual and area level characteristics, prostate cancer risk increased by approximately 25% for each percentage point increase in percent of land used for corn and soybean crops. Prostate cancer risk was approximately 25% higher for Black men exposed to corn and soybean fields compared to white men exposed to corn and soybean fields. Results from this study support the need for further evaluation of residential exposure to environmental hazards specific to corn and soybean farming.

Chapter 1: Background and Significance

Rationale

Prostate cancer is the most commonly diagnosed cancer among men in the United States, excluding basal and squamous cell skin cancers. Approximately one out of every six men in the United States will be diagnosed with prostate cancer during his lifetime (1). In 2010, it is estimated that 217,730 new prostate cancer cases will be diagnosed in the United States (2), which represents approximately 28% of new cancer cases diagnosed among men (2). Prostate cancer is the second leading cause of cancer-related mortality in American men (3). An estimated 2.3 million men are currently living with prostate cancer in the United States (4).

Certain prostate cancer risk factors are well established, and include age, race and family history. Approximately 65% of prostate cancer diagnoses are in men age 65 and older (5). The probability of being diagnosed with prostate cancer increases with increasing age. Men ages 40 to 59 have a 1 in 41 chance of being diagnosed with an invasive prostate tumor whereas the probability is 1 in 16 for men between 60 and 69, and 1 in 8 for men age 70 and older (5).

African American men disproportionately suffer the burden of prostate cancer incidence and mortality. Between 2001 and 2005, the incidence rate for prostate cancer was approximately 59% higher in Black men compared to white men, and Black men were more likely than white men to be diagnosed with advanced-stage prostate cancer (6). Black men have the highest death rate from prostate cancer of any race in the United States and worldwide (7). Despite declines in the death rate for both white and

Black American men since the early 1990s, the death rate for Black men remains 2.4 times higher than for white men (6). Racial disparities in prostate cancer incidence and mortality persist after controlling for socioeconomic status (7, 8).

Men with a family history of prostate cancer are between two and three times more likely to develop prostate cancer than men without a family history (9-11). This risk increases with an increasing number of first-degree relatives diagnosed (9, 11, 12).

The role of other hypothesized risk factors in the development of prostate cancer is less clear. Variations in diet (e.g. increased fat consumption and vitamin D deficiency) (13-15), hormones (e.g. testosterone) (16, 17), occupational exposures (e.g. farming, rubber manufacturing) (18-22), exposure to environmental (e.g. pesticides, bisphenol A) (23) and infectious agents (e.g. human papillomavirus, *Propionibacterium acnes*) (24-26), lifestyle factors (e.g. smoking, obesity, marital status) (27-31), and demographic characteristics (e.g. socioeconomic status, education level) (32-34) have been posited to influence prostate cancer risk. Findings from a series of studies indicate that the interaction between known and hypothesized risk factors increases prostate cancer risk, particularly with regard to family history of prostate cancer and exposure to certain organochlorine pesticides (35).

Environmental Exposures and Prostate Cancer Risk

The role of environmental exposures in prostate cancer has gained considerable attention in recent decades (36, 37) . An association between exposure to low doses of environmental estrogens (23); certain agricultural pesticides, including methyl bromide, captan, and chlorpyrifos (18-20, 35); and laboratory studies of certain trace metals and

prostate cancer has been demonstrated, although the current epidemiological literature is insufficient to establish a causal association.

To date, the majority of the literature examining the association between prostate cancer incidence and pesticide exposure has focused on occupational studies of farmers. Despite lower alcohol use and smoking prevalence as well as lower all-cause mortality compared to the general male population (38, 39), farmers are at an elevated risk of being diagnosed with and dying from prostate cancer (19, 38, 40-42). Further, despite declines in prostate cancer incidence in the general population, the risk of prostate cancer appears to be increasing in farmers (40).

In a recent cohort study of 55,332 male licensed pesticide applicators in Iowa and North Carolina, a two-fold increase in prostate cancer risk was observed among pesticide users compared to subjects who reported that they did not use pesticides (35). A dose response relationship between frequency of use and lifetime application days for the organohalogen fumigant methyl bromide and prostate cancer risk was identified. Among men with a family history of prostate cancer, a statistically significant increase in prostate cancer risk following occupational exposure to six commonly used herbicides and insecticides was observed. Interestingly, four of the six pesticides belong to the organochlorine class of chemicals.

The organochlorine pesticides are a class of commonly used insecticides that were introduced to the U.S. agricultural market in the 1940s. Although the use of some organochlorines was outlawed in the U.S. during the 1970s and 1980s, many are still in use today. Chemicals in the organochlorine class are known endocrine disruptors, and may modulate the production and bioavailability of or mimic the action of steroid sex

hormones, particularly with regard to estrogen or testosterone activity (43).

Organochlorines are confirmed animal carcinogens (43) and are classified as probable human carcinogens (44). Additionally, they are bioaccumulative (45, 46, 46, 47) (i.e., the rate of accumulation exceeds the elimination rate). As a result, large amounts of organochlorine pesticides persist in the environment (48-50), which can lead to unintentional exposure. Although a direct link between human exposure to endocrine disrupting compounds and prostate cancer has not been established, the known hormonal basis for the disease and the demonstrated ability of organochlorines to act as endocrine disruptors, coupled with the strength of the association in animal models and the widespread use of pesticides in the U.S. (51), necessitates further study of its association in humans.

Several studies have attempted to characterize prostate cancer incidence and mortality in agricultural communities (52-55). Mills obtained pesticide use data from the California Department of Pesticide Regulation to evaluate the correlation between pounds of active ingredient used and cancer incidence at the county level. In a series of papers evaluating cancer mortality and agriculture activity in northern wheat-producing states, Schreinemachers used crop type as a surrogate for pesticide active ingredient. Chrisman et al. estimated residential exposure using pesticide sales data in a study evaluating pesticide exposure and cancer mortality in Brazil. However, numerous limitations have been noted in previous studies attempting to characterize the association between residential pesticide exposure and prostate cancer incidence, including: the inability to account for latency (52), lack of specificity regarding active ingredient used (55), exposure and disease misclassification in study populations with

high residential mobility (52) and the lack of ability to account for pesticide drift across political boundaries (52-55).

Quantifying Pesticide Exposure

One of the most complex issues surrounding the assessment of unintentional pesticide exposure is the quantification of dose. The typical “gold standard” for estimating human exposure to pesticides and other environmental contaminants is through the measurement of pesticide metabolites in urine samples collected over multiple 24-hour time periods (56, 57). However, such methods are expensive and time-consuming, and may result in misclassification of exposure or underestimation of dose due to noncompliance with study protocols that result in missing urine. The effects of underestimation are of particular concern for individuals whose exposure estimates are above toxicological significance levels and for individuals with fluctuating exposure levels, such as those living in farming communities who are not directly working with pesticides (58, 59).

Epidemiologic studies attempting to quantify long-term exposures to pesticides often rely on self-reported data from study subjects. However, in an agricultural community setting, residents often cannot accurately self-report potential sources of exposure, resulting in a lack of specificity regarding the type of pesticide used (particularly with regard to the active ingredient in the formulation), the target pest and the amount of pesticide applied (60). Differential recall of exposure variables has been demonstrated in studies assessing pesticide exposure and health outcomes (61, 62). In a study assessing proximity of residence to crop fields, approximately 66% of mothers

of children with neural tube defects accurately reported the distance of their house from the location of “any crops,” compared to 50% of mothers of children without neural tube defects. The specificity for reporting location from crops was similar between case and control mothers, suggesting that control mothers were more likely to underreport their proximity to crops (61).

Pesticide Exposure in Residential Communities

Exposure to pesticides is of particular concern for individuals living in farming communities, where residences are often located in close proximity to agricultural fields where large-scale pesticide applications occur. Individual exposures can occur through inhalation of aerosolized particles, ingestion via food or water and dermal contact with contaminated soil or dust. For persistent pesticides, particularly those belonging to the organochlorine and organohalogen families, the risk of unintentional exposure remains for years after the spray, and is magnified by the ability of the compound to accumulate in the environment.

A direct relationship between proximity to agricultural fields and residential pesticide concentrations is well-established. In multiple studies conducted in Washington (63-66), Iowa (67, 68) and California (69), higher levels of pesticides in household dust and soil were found in the homes of agricultural workers and homes located in close proximity to agricultural fields compared to homes located farther away. A study designed to assess household pesticide residue concentrations in the homes of individuals who work in the agricultural industry and live near agricultural fields found a seven-fold increase in the median house dust concentrations of pesticides in the homes

of agricultural families compared to homes located at least one-quarter mile from the nearest agricultural field (65). Urinary pesticide metabolite concentrations have been demonstrated to be positively associated with house dust pesticide concentrations (68, 70). Drift from pesticide spraying applications has been identified up to 1,000 meters from the source (71, 72).

Quantifying Pesticide Exposure Using Geographic Information Systems (GIS)

Several key areas of attention for researchers attempting to quantify residential pesticide exposures have been identified in the literature, and include: characterization of temporal variability in pesticide use patterns, particularly with regard to the potential for a resident to be exposed to more than one active ingredient (60); characterization of the exposure source, including the rate and method of application (60, 73); and the characterization of key factors of human exposure, including the distance from the residence to the exposure source (65, 74, 75) and the presence of natural boundaries that could affect the movement of chemicals through the environment. The application of geographic information systems (GIS) technologies to the study of environmental exposure assessment provides a means by which investigators can integrate a variety of spatially referenced factors that can influence residential exposure to pesticides, including: historic and current records of pesticide use and crop-specific locations of agricultural fields.

GIS has been used in several studies assessing the association between pesticide exposure and health, with outcomes including breast cancer (76), non-Hodgkin's lymphoma (77, 78), leukemia (79) and adverse health events in military

personnel exposed to Agent Orange (80). In a series of studies assessing residential exposure to pesticides on Cape Cod, Massachusetts, researchers found a modest association between exposure to pesticides and breast cancer risk (76). However, it is likely that misclassification of exposure occurred. Data on the type, frequency, amount and method of pesticide application on each land parcel were not available. Additionally, the study was conducted in a town where approximately 50% of the population during the spring and summer spraying periods is seasonal and whose population demographics have shifted towards a retiree population in the last 25 years (81). Thus, it is unlikely that this study captured the full life-range of pesticide exposure.

The proposed research seeks to improve upon previous studies of pesticide exposure from agricultural applications and prostate cancer incidence by estimating historical pesticide exposure that transcends political boundaries via the integration of historical crop-specific land use coverage data and pesticide sales data in Iowa. The resulting GIS will be used to address the gaps in exposure assessment found in the current epidemiological literature, particularly with regard to exposure misclassification and simplification of the pesticide exposure matrix.

Use of Spatial Statistics to Evaluate Risk

One of the most fundamental goals in spatial epidemiology is the identification and description of locations of populations at risk for increased exposure to a suspected environmental hazard. When mapping the complex association between environmental exposures and cancer outcomes, this is often accomplished through cluster analysis, with the statistical significance of identified clusters quantified through the use of a

spatial scan statistic. The purpose of a spatial scan statistic is to identify groups of spatially referenced cases of a disease that are least consistent with the fundamental geographical modeling processes of stationarity (the statistical characteristics do not change with time) and isotropy (statistical characteristics are dependent upon the direction of measurement), which state that the relationships between two identified events rely only on their relative position to each other and their distance from each other; in other words, the events could have occurred anywhere in the study space. Through the use of spatial scan statistics employed in cluster analysis, the unequal geographic distribution of disease can be detected, and attempts at the identification of the underlying reasons for the nonrandom distribution of cases can be made.

Modeling cancer case count data, such as those data obtained from a cancer registry, is often complicated by the fact that the data frequently are not normally distributed, which violates an assumption required for traditional statistical tests. Mapped cancer count data often reveal geographical units that have no cases and others that contain multiple cases, which results in a dataset that is right-skewed. The Poisson distribution provides an alternative to the normal distribution that can be applied to cancer count data, where the goal is to model the number of cases that occur during a fixed time interval and in a fixed geographical area (82).

When applying spatial scan statistical methods to geographically referenced count data with an assumed Poisson distribution, the underlying spatial process can be either homogeneous or heterogeneous. The homogeneous process can be described by the concept of complete spatial randomness (CSR), which states that the location of one case is equally likely to occur at any location within a study area, regardless of the

location of the other identified cases; in other words, the location of each case is independent of the location of the other cases (83). The heterogeneous spatial Poisson process can be described by the constant risk hypothesis, which states that each person in a study area has the same risk of disease, regardless of their location within the study area. When modeling disease clustering over a large area, where the population is expected to vary based on location (e.g., urban versus rural status), the constant risk hypothesis is often used, as it allows the researcher to account for population variance; it is assumed that more cases will be identified in areas with more people at risk, and, consequently, it allows the interpretation of clustering above what would be expected to occur due solely to varying population densities (83). To account for variation in population concentrations between urban, suburban, and rural census tracts and counties in Iowa, the heterogeneous spatial Poisson process was assumed.

Several types of spatial scan statistics have been identified in the epidemiologic literature, and include Tango's elliptical scan statistic (84), global Moran's I, generalized additive models (GAM) (85), Bayesian disease mapping (BYM) (86), and Kulldorff's spatial scan statistic (87). One of the critical factors defining a scan statistic is the null hypothesis upon which the statistic is based. When studying environmental exposures and cancer outcomes, where some sort of spatial pattern is almost always present, the concept of CSR is not plausible (88). One of the most commonly identified spatially related patterns is variation in incidence due to population size differences, and the inability of a statistical test to detect clustering in the presence of varying population size has been demonstrated to lead to the false identification of statistically significant clusters (88). For the detection of localized clustering, such as that that is hypothesized

to occur with environmental exposures and cancer outcomes, Kulldorff's spatial scan statistic, or SaTScan, is preferred (89).

The SaTScan software package utilizes Kulldorff's spatial scan statistic for the analysis of spatio-temporal trends of disease. The software was developed by Martin Kulldorff and Information Management Services (IMS) through funding provided by the NCI, the Alfred P. Sloan Foundation, the Centers for Disease Control and Prevention (CDC), and the National Institute of Child Health and Development, and is freely available via Internet download. The SaTScan spatial scan statistic utilizes a series of circular "windows" with variable radii that range from the smallest observed distance between a pair of cases to an upper distance that is defined by the user. Identification of the optimal search window size in this study was based on a combination of the population size of the smallest census tracts and observation of the size of the clusters produced by each window. An initial maximum search window of 50% of the total population was used and then progressively smaller windows of 25%, 10%, 7%, 5% and 0.5% of the population total were used. Window sizes smaller than 0.5% could not be considered as Iowa's smallest census tracts contained approximately 0.11% of the state's population. An infinite number of circular windows may be used to characterize the study space. The circular window moves over the defined study area and identifies areas where the disease rate in the window is different than the rate outside of the window. Statistical assessment of clustering is based on maximum likelihood estimation. The spatial scan statistic has the ability to model data with either a Bernoulli or Poisson distribution; the SaTScan Poisson model is recommended by the developers of the software for count data relating to a continuous risk factor (87) .

A number of advantages to using the spatial scan statistic for disease clustering have been identified. In a study comparing the power to detect disease clusters, SaTScan demonstrated more power to detect clusters in rural and mixed rural/urban areas and higher overall power than the GAM and BYM statistics (90, 91). Further, the spatial scan statistic has the ability to both detect the presence and the precise location of clusters (87). In part for this reason, the spatial scan statistic has been recommended for publishing cancer spatial pattern maps and for characterizing clusters (89). The spatial scan statistic performs best at a finer spatial resolution, and more information is retained in the analysis (92). In addition, computationally, SaTScan is simpler than other tests, as it easily allows for the incorporation of point locations of cases (90). Also, the spatial scan statistic makes no *a priori* assumptions about the existence of clustering and has the ability to adjust for categorical covariates.

The spatial scan statistic is frequently used in epidemiological literature. In a descriptive study of colorectal cancer detection by stage at diagnosis, Pollack and colleagues were able to identify areas in California where the number of observed late-stage colorectal cancer cases was different than expected (93). DeChello, Abe, and Klassen evaluated the geographical distribution of prostate cancer incidence at the state level in Maryland, and were able to characterize the racial, socioeconomic and age variations that contributed to clustering (94-97). Additional applications of the spatial scan statistic in cancer cluster detection include cancers of the breast (98, 99) and gastrointestinal tract (100) and leukemia (101).

Modeling Spatial Correlation

In cohort studies, the association between pesticide exposure and health outcomes is traditionally assessed via regression analysis. Statistical assessment of regression analysis model fit is carried out in part through the examination of the model's observed error terms, or residual analysis. A regression model's error terms are assumed to be independent and normally distributed, with a mean of 0 and constant variance. If the model is appropriate for the data, the residual terms should reflect the same assumptions as the observed error; however, when the assumption of independence is violated the terms are said to be correlated.

When extending regression analysis to spatially referenced data such as those obtained from a cancer registry, a violation in the assumption of independence across a georeferenced space is called spatial autocorrelation (102). Spatial autocorrelation in regression modeling occurs when a spatially varying covariate is omitted from a model (83, 102) or in situations where the locations of spatially referenced data points are not independent; i.e. when area effects (e.g. area-level measures of socioeconomic status) are present (83). Ignoring spatial autocorrelation in regression modeling will result in a deflation of the model's standard error terms, which will lead to downward biased β coefficients and the artificial inflation of the chances of finding a statistically significant association (103, 104). Thus, to reduce the potential for bias in parameter estimates it is imperative that predictive models consider potential spatial autocorrelation (83).

The presence of spatial autocorrelation at the census block group (105) and neighborhood (106, 107) levels has been identified. In a study of socioeconomic status and nitrogen dioxide exposure, strong spatial correlation (as identified through model

Akaike Information Criterion (AIC) comparison) at the census block group level was demonstrated (105). Bell et al. identified spatial autocorrelation at the neighborhood level (as identified through the joint-count statistic) in unintentional third party injury. Throughout the study area (Vancouver, BC), men who were hospitalized for severe assault-related injury were three to five times more likely to reside in neighboring areas than would be expected under a random spatial pattern of residence (106).

In the assessment of complex environmental exposures and health outcomes, where the exposure-disease relationship is often confounded by the presence of individual- and area-level effects, and the assumption of statistical independence between health events is not valid, predictive models incorporating spatial variation outperformed ordinary least squares models (103, 108). In an analysis of water quality trends, Chang et al. found that spatial regression models explained 10% or more of the variation in water quality (as measured by R^2) than ordinary least squares models when values of Moran's I were high. When the value of Moran's I was lower, there was little change in the R^2 values (108). These findings suggest that the incorporation of the spatial relationship between water sources into regression models provides a more complete assessment of water quality. In a study of air pollution and heart disease, Cakmak et al. found that spatial regression models provided more accurate estimates of the uncertainty in the regression estimates compared to models without spatial predictors. When the spatially autocorrelated error structure was included in the model, the unexplained variance was significantly lower compared to the model that did not include a spatial location variable (103).

The incorporation of spatial correlation in predictive prostate cancer modeling is limited in the published literature to studies of spatio-temporal trends in prostate cancer incidence. In a study of temporal changes in prostate cancer incidence cases reported to the Louisiana Cancer Registry following implementation of prostate specific antigen (PSA) testing, Mather et al. successfully identified spatio-temporal trends in incidence, while maintaining the ability to control for confounders (109). To date, no known study of the assessment of residential pesticide exposure and prostate cancer has utilized a regression modeling approach that incorporates measures of spatial autocorrelation.

Specific Aims

The specific aims of this study are to: (1) map the prostate cancer incident cases diagnosed between 1996 and 2006 for the state of Iowa, (2) assess prostate cancer incidence for spatial clustering, and (3) conduct a geographical correlation study designed to assess the association between prostate cancer incidence and exposure to pesticides. These aims will be accomplished through the following primary objectives:

1. Develop a geographic information system (GIS) that incorporates prostate cancer incidence, pesticide use and environmental and land data
2. Investigate the clustering of prostate cancer cases in the state of Iowa
3. Investigate the independent effect of environmental exposure to pesticides on prostate cancer incidence in Iowa

The secondary objectives of the proposed study include:

1. The identification of “hot spots” of potentially increased pesticide exposure risk in Iowa and describe these areas using data obtained from the GIS
2. A descriptive analysis of prostate cancer in Iowa in relation to corn and soybean crop fields and the pesticides used on these fields.

Study Setting

This study assessed residential exposure to pesticides and prostate cancer risk in the state of Iowa. Located in the Midwestern region of the United States, Iowa is one of the nation's leading producers of corn, soybean, oats and hogs. Approximately 90% of Iowa's land is used for agricultural purposes, and 4% of Iowa's population over the age of 16 is employed in agriculture (110).

Approximately 75% of Iowa's 2000 population was born in Iowa, ranking Iowa as fourth in the nation for the percent of its residents born in the current state of residence (111). Iowa has a relatively stable population. Between 2005 and 2007, 83% of Iowa's population at least one year old lived in the same residence the previous year. Of the 17% who did not live at the same residence, 10% moved from a residence in the same county and 4% moved from another county in Iowa (110).

Iowa is a Surveillance, Epidemiology, and End Results (SEER) registry state and has an extensive repository of geospatial data available for public use. The availability of these data, coupled with Iowa's stable population, provides a unique opportunity to develop a GIS-based database that integrates historical pesticide sales and use data and validated land coverage data for the study of pesticide exposure and cancer incidence.

Data Sources

Prostate Cancer Incidence. Prostate cancer incident cases (1996 to 2006) were obtained from the State Health Registry of Iowa. Data obtained from the registry included: patient race (Black, white, other), ethnicity (Hispanic/non-Hispanic), age at

diagnosis in five-year increments; cancer stage and grade at diagnosis; and county and census tract of residence at the time of diagnosis.

Pesticide Sales. Pesticide sales data were obtained from the Iowa Department of Agriculture and Land Stewardship for the 1990 calendar year. This agency routinely collects pesticide sales data for all purchases atrazine and for sales of other active ingredients over \$3,000 per calendar year, which is indicative of large-scale commercial pesticide applicator purchasing. Agricultural pesticide active ingredients purchased in quantities significant enough to warrant reporting to the agency during 1990 were identified as: atrazine, metolachlor, cyanazine, alachlor and simazine. The pesticide use profile for the four most commonly used active ingredients, which accounted for 99.9% of required- reported pesticide sales for the 1990 calendar year, for the year closest to the study year (alachlor: 1985, atrazine: 1990, cyanazine: 1993, metolachlor: 1985) was obtained to determine the crop(s) for which the active ingredient was indicated.

Pesticide Use. The interpolated density surface of annual pesticide sales data file was obtained from the Iowa Department of Natural Resources for the 1990 calendar year. These data layers were developed by the Iowa Water Monitoring Section using a Kernel modeling approach to distribute point of origin pesticide active ingredient sales throughout the state. The resulting data set detailed approximate zones of pounds of active ingredient sold per square mile.

Land Cover. The 1990 Iowa Land Cover Data Set was obtained from the Iowa Department of Natural Resources (IDNR) (112) and imported into a GIS. The raster digital data set was compiled by the IDNR from Landsat 5 satellite TM imagery and other ancillary data sets collected at multiple time points during the spring and summer

months of 1989 through 1991. The approximate accuracy of the maps is ± 30 meters. Land cover is classified into 17 categories, of which six are types of agricultural fields. Agricultural fields are identified as grazed and ungrazed pasture, alfalfa, corn, soybean and unplanted crop fields.

Additional Variables. County and census tract boundary files for the 1990 census year were downloaded from the U.S. Census Bureau's TIGER files (available online: <http://www.census.gov/geo/www/tiger/>).

Area-Level Demographic Variables. Area-level demographic variables were obtained from the U.S. Census Bureau summary tape file 3A at the county and census tract level. Datasets included: ratio of income to poverty and percent rural status. Area-level indicators of poverty have been demonstrated to serve as adequate proxies for individual socioeconomic status for public health research (113).

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Chapter 2: A Geographic Information System for Evaluating Residential Pesticide Exposure and Prostate Cancer Incidence

Introduction

Associations between pesticide exposure and increased adverse health risks, including reproductive and birth outcomes (1-3), certain cancers (4-7), respiratory ailments (8-10) and neurological disorders (11-13), have been demonstrated in several recent studies. Pesticide exposure is of particular concern for individuals living in farming communities, where residences are often located in close proximity to agricultural fields where large-scale pesticide applications occur. Residential proximity to agricultural fields is directly related to the concentration of pesticide residues in house dust (14, 15). Urinary pesticide metabolite concentrations have been demonstrated to be positively associated with house dust pesticide concentrations (16, 17), indicating that ambient exposure can result in an internal dose.

The most consistent evidence of an association between prostate cancer incidence and pesticide exposure is found in occupational studies of farmers (18, 19). While farmers have lower alcohol use and smoking prevalence as well as lower all-cause mortality compared to the general male population (20, 21), they are at an elevated risk of being diagnosed with and dying from prostate cancer (20, 22-25). In Iowa, the risk of prostate cancer appears to be increasing in farmers despite declines in prostate cancer incidence in the general population (23). Epidemiologic evidence suggests that human exposure to endocrine disrupting chemicals increases prostate cancer risk (26), and laboratory studies have characterized multiple pesticides, including

atrazine, metolachlor, alachlor and cyanazine, as probable endocrine disruptors (27, 28).

Several studies have attempted to characterize prostate cancer incidence and mortality in agricultural communities (29-32). Mills obtained pesticide use data from the California Department of Pesticide Regulation to evaluate the correlation between pounds of active ingredient used and cancer incidence at the county level. In a series of papers evaluating cancer mortality and agriculture activity in northern wheat-producing states, Schreinemachers used crop type as a surrogate for pesticide active ingredient. Chrisman et al. estimated residential exposure using pesticide sales data in a study evaluating pesticide exposure and cancer mortality in Brazil. However, numerous limitations have been noted in previous studies attempting to characterize the association between residential pesticide exposure and prostate cancer incidence, including: the inability to account for latency (29), lack of specificity regarding active ingredient used (32), exposure and disease misclassification in study population with high residential mobility (29) and the lack of ability to account for pesticide drift across political boundaries (29-32).

The objective of this study was to develop a geographic information system (GIS) for estimating historical pesticide exposure via the integration of historical crop-specific land use coverage data and pesticide sales data in Iowa. Using the GIS, a geographical correlation study was conducted to investigate the relationship between residential pesticide exposure from large-scale agricultural pesticide applications and prostate cancer incidence in Iowa.

Methods

Study Population

Pathologically confirmed incident prostate cancer cases between 1996 and 2006 were obtained from the State Health Registry of Iowa. Variables included: age at diagnosis (five-year age groups), race (white, Black, other), ethnicity (Hispanic, non-Hispanic), tumor stage and grade, and county and census tract of residence at the time of diagnosis.

GIS Development

A GIS was constructed using ArcGIS (Environmental Systems Research Institute, Redlands, CA) to identify areas of potentially high exposure to pesticides. To account for the plausible prostate cancer latency period and the availability of historical agricultural activity data, we used data from the 1990 calendar year, which was the first and only year these data were available.

County and census tract boundary files for the 1990 census year were downloaded from the U.S. Census Bureau's TIGER files. The state of Iowa is divided into 99 counties, which are further subdivided into 793 census tracts. The Iowa Land Cover Data Set – which classifies land use – was obtained from the Iowa Department of Natural Resources (33). The digital data set was compiled from satellite imagery and other ancillary data sets collected at multiple time points during the spring and summer months of 1989 through 1991. The approximate accuracy of the maps is ± 30 meters. In 1990, 86.3% of Iowa's overall land was designated farmland, with corn and soybean crops comprising over 90% of all agricultural planting. Over 95% of the corn and

soybean crops were treated with relevant pesticides from the late 1970s through the 1980s (34). Because the overwhelming majority of pesticide application in Iowa was on corn and soybean fields, these analyses were conducted using pesticides identified primarily for corn and soybean crops in Iowa.

Pesticide sales data were obtained from the Iowa Department of Agriculture and Land Stewardship for the 1990 calendar year. This agency routinely collects pesticide sales data for all purchases of atrazine and all other active ingredients over \$3,000 per calendar year, which is indicative of large-scale commercial pesticide applicator purchasing. Agricultural pesticide active ingredients purchased in quantities significant enough to warrant reporting to the agency during 1990 were identified as: atrazine, metolachlor, cyanazine, alachlor and simazine. The pesticide use profile for the four most commonly used active ingredients, which accounted for over 99.9% of required-reported pesticide sales for the 1990 calendar year, for the year closest to the study year was obtained to determine the crop(s) for which the active ingredient was indicated (Table 2.1).

The interpolated density surface of annual pesticide sales data file was obtained from the Iowa Department of Natural Resources. These data layers were developed by the Iowa Water Monitoring Section using a Kernel modeling approach to distribute point of origin pesticide active ingredient sales throughout the state. The resulting data set detailed approximate zones of pounds of active ingredient sold per square mile.

Classification of Pesticide Exposure

Corn and soybean crops fields located within the zones of highest concentrated sales were identified using the GIS (Table 2.1). We calculated the approximate acres of crop contained within each zone of highest sales to ensure that the total acres of crop identified did not exceed the total acres treated with each active ingredient during the study year. Note that the total percentage of acres treated sums to greater than 100% as acres may be treated with more than one type of pesticide.

Previous studies have identified pesticide residues as far away as 1000 meters from the source of application (14, 15). Thus, we calculated a 1000 meter buffer around the centroid of each corn and soybean field located within the zone of highest concentrated sales for each pesticide. The percent of land at the county and census tract level that was contained within this buffer and thus potentially exposed to the pesticide was calculated.

Statistical Methods

Prostate cancer incidence rates were calculated at the county and census tract level and were age-adjusted to the 2000 U.S. standard population. To account for small population counts in some counties and census tracts, a median-based smoothing algorithm called “headbanging” (35) was applied to the data. The headbanging algorithm uses population counts in neighboring geographical units as weights to stabilize the incidence rate of a sparsely populated geographical unit. Headbanging allows for visualization of regional variation in incidence rates while maintaining patterns inherent in the raw data (35).

Geographical correlation between estimated pesticide use at the county and census tract level and area-level prostate cancer incidence was assessed via Spearman's (rank) correlation coefficient and its associated p -value. A logit transformation was applied to the smoothed incidence rates and a linear regression analysis was performed to assess the relationship between percent of land used for corn and soybean crops and prostate cancer incidence after controlling for exposure to the four most commonly used pesticides in Iowa in 1990. All statistical analyses were conducted using SAS 9.2.

Results

Agriculture Activity

The total percent acreage in row crop (corn and soybean) at the county level ranged from 15.3% (Allamakee County) to 86.8% (Calhoun County), and at the census tract level ranged from 0% to 91.8%. By crop at the county level, the total percent acreage in corn ranged from 10.7% (Decatur County) to 45.9% (Hancock County), while soy ranged from 1.6% (Allamakee County) to 53.5% (Lyon County). At the census tract level, the percent of acreage in corn ranged from 0% to 52.1%, and the percent of acreage in soy ranged from 0% to 60.7%. At the county level, the highest concentrations of corn and soybean crop were generally located in the north-central region of Iowa (Figures 2.1a and 2.1b). At the census tract level, the census tracts with the smallest percent of acreage in corn were generally located in urban areas (Figures 2.1c and 2.1d).

Pesticide Exposure

Figures 2.2 and 2.3 detail county and census tract level exposure to each pesticide. The percent of land potentially exposed to metolachlor was highest in the north-central region of the state (county and census tract level range: 0-100%) while the percent of land potentially exposed to cyanazine was highest in the southwest and southeast regions of Iowa (county and census tract level range: 0-100%). The percent of land exposed to alachlor was highest in a concentrated area located in the central region of Iowa (county level range: 0-76.7%; census tract level range: 0-100%). For atrazine, the percent of land exposed was highest in the southwest and central eastern regions (county level range: 0-92.7%; census tract level range: 0-100%).

Prostate Cancer Incidence

A total of 23,147 pathology confirmed incident cases of prostate cancer were reported to the State Health Registry of Iowa between 1996 and 2006. The highest percentage of cases was diagnosed in men between the ages of 70 and 74 (19.5%), followed by men between the ages of 65 and 69 (19.0%) and 75 and 79 (15.7%). Approximately 96% of the cases were in non-Hispanic white men and the overwhelming majority (84%) of cases were diagnosed in the localized stage.

Smoothed age-adjusted prostate cancer incidence rates ranged from 1.196 cases per 1,000 males to 1.835 cases per 1,000 males at the county level. At the census tract level, prostate cancer incidence ranged from 0.72 cases per 1,000 males to 2.31 cases per 1,000 males. In general, prostate cancer incidence rates were highest in the northwest and south-central regions of the state (Figure 2.4)

Association between exposure to agricultural activity, pesticides and prostate cancer incidence

At the county level, we observed statistically significant positive correlations between percent of land used for corn crop ($r=0.22$, $p=.031$), soybean crop ($r=0.33$, $p=.001$) and corn and soybean crop ($r=0.33$, $p=.001$). At the census tract level, statistically significant positive correlations between percent of land used for corn crop ($r=0.10$, $p=.007$), soybean crop ($r=0.13$, $p<.001$) and corn and soybean crop ($r=0.16$, $p<.001$) were identified. The associations between specific pesticide exposures and cancer incidence were not statistically significant at the county or census tract level (Table 2.2).

Results from multiple linear regression analysis with adjustment for percent of land exposed to atrazine, alachlor, metolachlor and cyanazine showed that the associations between percent of land at the county and census tract level used for corn crop ($p=0.046$ and $p<.001$, respectively) and soybean crop (county and census tract level, $p<.001$) remained.

Discussion

This study found statistically significant positive correlations between percent of land planted with corn and soybean crop at the county and census tract level and prostate cancer incidence. Analysis of exposure to the top four corn and soybean pesticides used during the study period did not find a statistically significant correlation between the percent of land at the county and census tract level exposed to each pesticide and prostate cancer incidence.

Our findings are consistent with previous studies that have identified a statistically significant positive correlation between the amount of land used to grow crops and prostate cancer incidence (30, 36). St-Hilaire et al. found a statistically significant positive correlation between the amount of land used to grow crops and prostate cancer incidence in the United States. Geographical variation in risk suggested that crop-specific variation in pesticide use due to factors such as weather could be, in part, responsible for the observed variation. Our study used interpolated pesticide sales grids to identify regions of highest sales of each pesticide to account for variation in specific pesticide used on each crop throughout the state. While our study lacked the ability to validate this method, communication with licensed pesticide applicators in Iowa indicated that pesticides are typically purchased within 30 miles of their target fields, as transportation of pesticides is expensive and time consuming. However, we cannot exclude the possibility of exposure misclassification based solely on this information. It is likely that exposure misclassification exists in this data set.

The literature examining the health effects of pesticide exposure is inconclusive with regard to prostate cancer. Animal studies have demonstrated an association between exposure to atrazine and prostate cancer incidence (37); however, studies examining occupational exposures of farmers (38) and atrazine manufacturers (39, 40) have failed to find an association between atrazine exposure and prostate cancer. In a geographical correlation study of county level prostate cancer incidence and atrazine exposure, Mills et al. found a statistically significant positive correlation between residential exposure to atrazine and prostate cancer incidence in African American men in California ($r=0.67$). In our study, approximately 96% of prostate cancer cases were in

white males, and 3.6% of Iowa's 1990 male population was Black. Due to the small number of cases in, and the low proportion of, African American men in the majority of counties and census tracts in Iowa, we did not stratify incidence by race. Future studies in Iowa should be limited to geographical areas with a substantial proportion of the population of African American race to determine if the association between atrazine exposure and prostate cancer varies by race.

Our study represents the first published study investigating residential exposure to alachlor, metolachlor and cyanazine. Our findings are consistent with occupational exposure studies (41-44), which have failed to find a strong statistically significant association between exposure to these pesticides and prostate cancer. However, failure to find an association between exposure to these pesticides and prostate cancer does not confirm that exposure to pesticides does not increase prostate cancer risk. Increasing laboratory and epidemiologic evidence suggests that exposure to environmental endocrine disruptors, including cadmium (45) and pesticides in the organochlorine family (18), increases prostate cancer risk, although the current epidemiological literature is insufficient to establish a causal association. Future work should examine residential exposure to these compounds, as well as the interaction between agricultural risk factors, and prostate cancer incidence.

The methodology utilized in this study overcomes several of the limitations present in previous studies of residential pesticide exposure and prostate cancer. First, due to the long latency period between exposure to a potential human carcinogen and disease onset, it is important that researchers consider historical exposures. Access to historical data detailing specific crops grown and pesticides used is often a limiting

factor in estimating previous pesticide exposure patterns. Our study evaluated pesticide exposure between six and sixteen years prior to diagnosis of prostate cancer, which coincides with the approximate latency period of prostate cancer.

Second, the potential for exposure misclassification due to residential mobility over time is increased in studies of disease with a long latency period. Our study was conducted in a state with relatively low residential mobility (46, 47), thus reducing the impact of residential mobility on our findings.

Third, previous studies have examined county-level pesticide use and prostate cancer incidence, which prevented the researcher from evaluating pesticide residues that drift beyond political boundaries. Using a GIS, we were able to identify areas of land that were potentially exposed to pesticides via drift from applications in neighboring counties and census tracts, and compute the percent of land in neighboring counties and tracts that were potentially exposed to pesticides used in neighboring counties and census tracts.

This study has several limitations. Due to the ecological nature of our study, we were not able to evaluate individual-level risk factors for prostate cancer, most notably race, family history of prostate cancer, obesity and occupation, which have been shown to influence prostate cancer risk. However, with regard to occupational pesticide exposure confounding is minimal, as less than 4% of Iowa's population is employed in agriculture (46). Additionally, the potential for exposure misclassification exists. Our GIS identified crop fields located within regions of high amounts of pesticide-specific sales, but the ecological nature of our study prevented us from evaluating individual characteristics that could influence exposure and intake of pesticides, including amount

of time spent at the home, age and physical activity level. Our study did not take into account the possibility that counties and census tracts are spatially correlated. The probability that geographical units in close proximity to one another share characteristics that influence the type of crop grown and/or the pesticide used on that crop is high, as crop type and pesticide use are dependent upon factors such as soil type, climate and elevation, which are independent of political boundaries. Finally, our study evaluated exposure to the most commonly used pesticides in Iowa during 1990. However, pesticides other than those evaluated in our study were used on corn and soybean crops during this time period. It is possible that exposure to a pesticide other than the ones we evaluated, or exposure to a combination of pesticides used on corn and soybean crop in Iowa in 1990, is responsible for our finding of a statistically significant correlation between exposure to corn and soybean crops and increased incidence of prostate cancer. Similarly, due to temporal variability in pesticide use, individuals living in agricultural communities are likely exposed to a variety of pesticides throughout their lifetime. Future work should evaluate exposure to pesticides other than those evaluated in this study and cumulative lifetime exposure to pesticides.

Our findings underscore the need for continued investigation of the association between agricultural exposures and prostate cancer incidence. Future work should elucidate potential risk factors for both exposure to pesticides and the probability of being diagnosed with prostate cancer, including socioeconomic status, stage at diagnosis, and urban/ rural status of residence.

Tables

Table 2.1: Agricultural crop pesticide application data, Iowa, 1990.

Active Ingredient	Crop(s)	Total Acres Treated	% of Acres Treated	Range of Pounds/Sq. Mi in Zones of Highest Sales
Atrazine	Corn	7,424,000	58	100.01-300.00
Metolachlor	Corn	4,480,000	35	
	Soybean	320,000	4	140.01-420.00
Cyanazine	Corn	2,304,000	18	135.01-270.00
Alachlor	Soybean	720,000	9	135.01-270.00

Table 2.2: Correlation between prostate cancer incidence, corn and soybean crop, and pesticide exposure.

	County Level r (p)	Census Tract Level r (p)
Corn and Soybean Crop	0.33 (0.001)	0.16 (<0.001)
Corn Crop	0.22 (0.031)	0.10 (0.007)
Soybean Crop	0.33 (0.001)	0.13 (<0.001)
Atrazine	-0.05 (0.607)	0.04 (0.241)
Alachlor	0.01 (0.909)	-0.18 (0.623)
Metolachlor	-0.03 (0.748)	0.03 (0.436)
Cyanazine	-0.08 (0.443)	0.04 (0.490)

Figures

Figure 2.1. Percent of land in corn and soybean crop, Iowa, 1990, at the county and census tract level

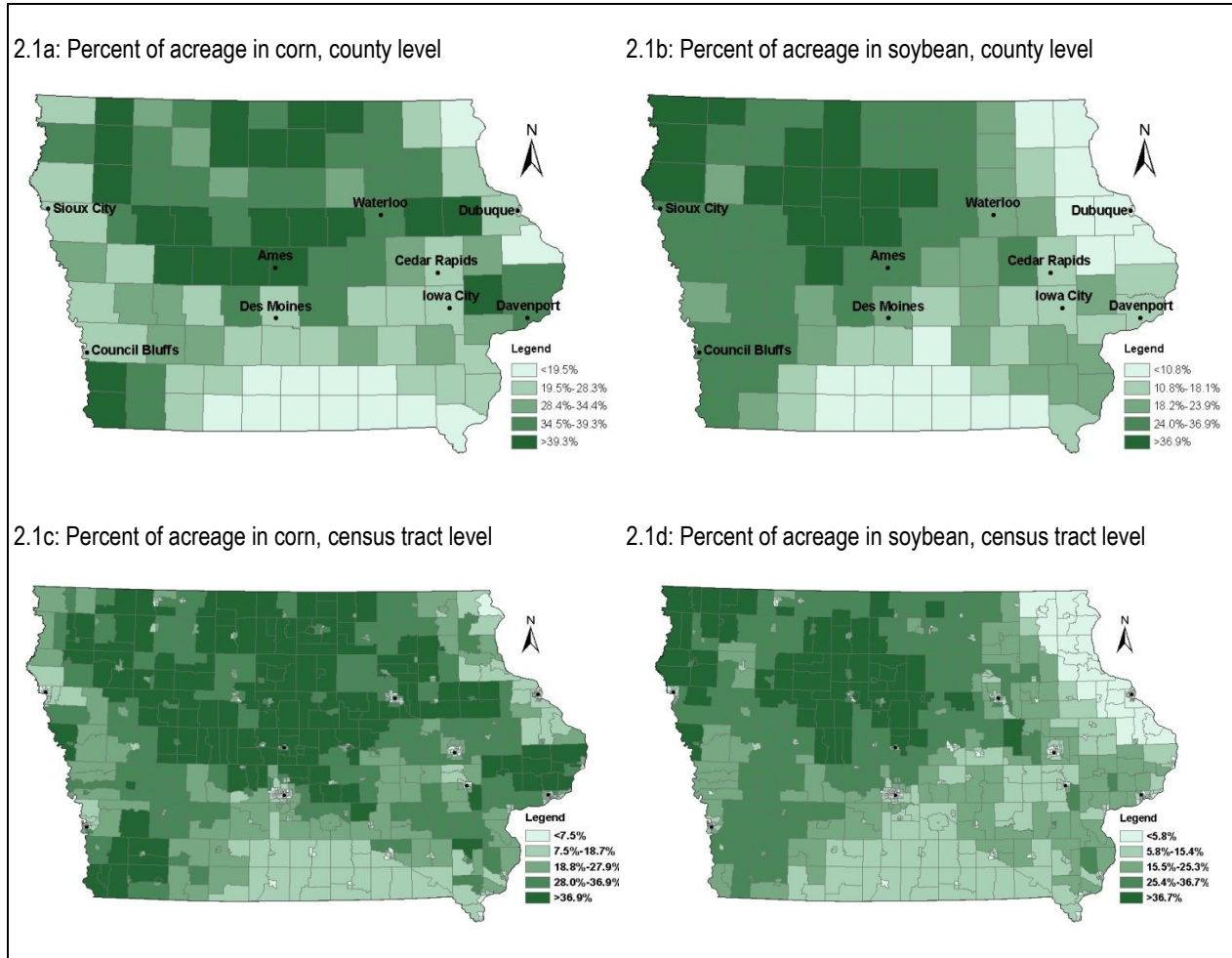


Figure 2.2: County percentage exposed to pesticides

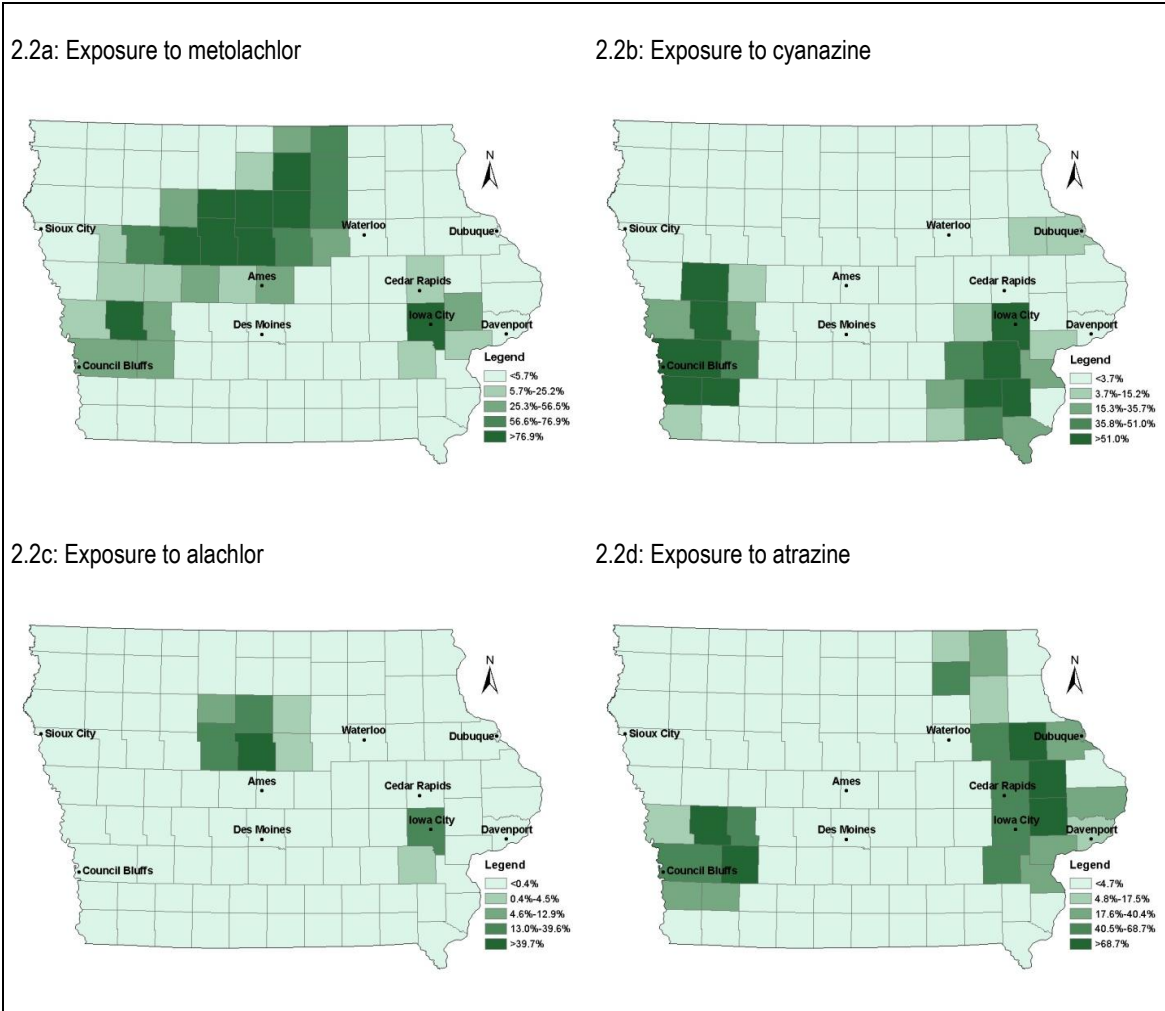


Figure 2.3: Census tract percentage exposed to pesticides

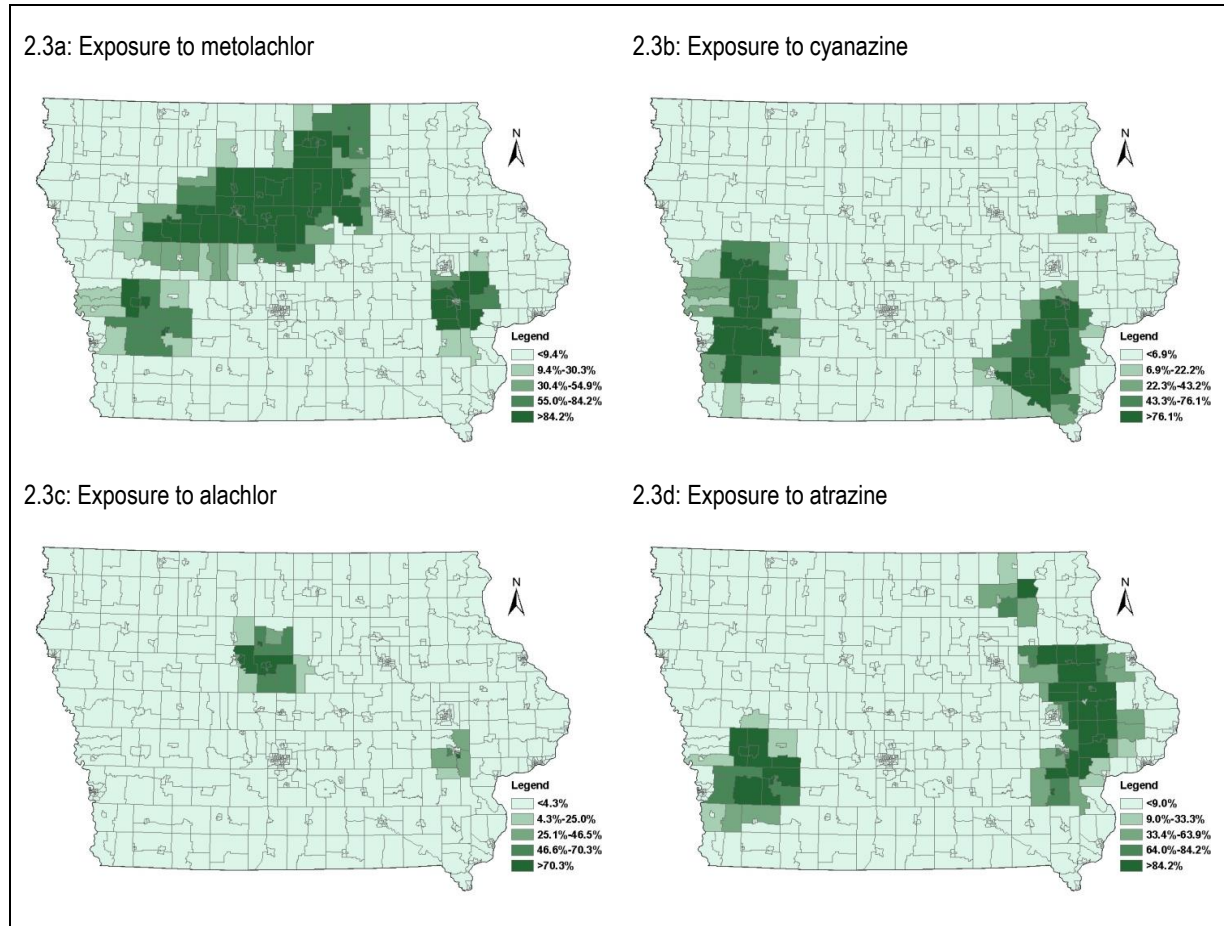
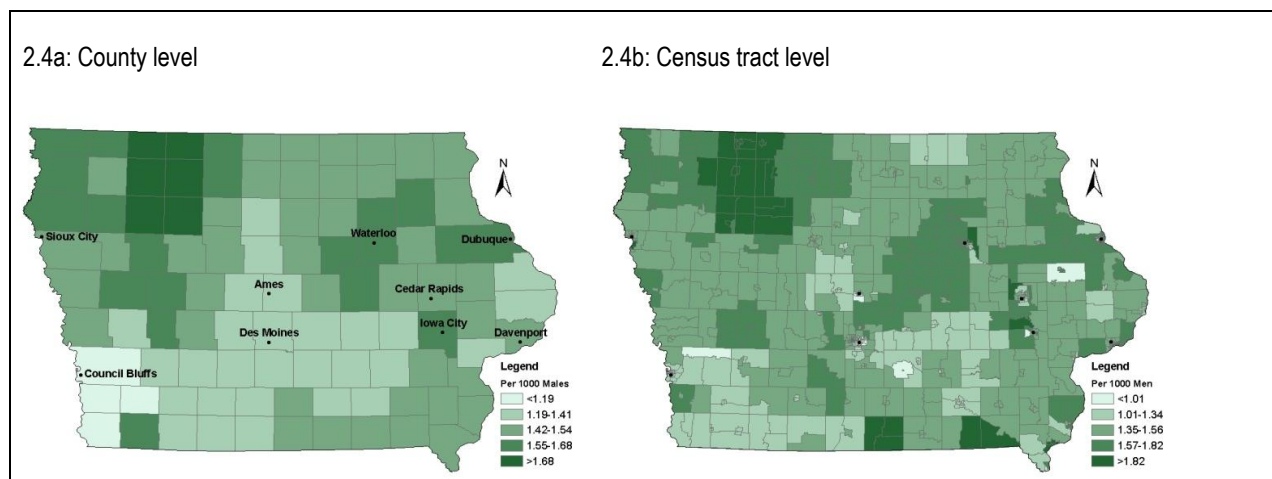


Figure 2.4: Prostate cancer incidence rates per 1000 males, smoothed



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Chapter 3: Spatial Analysis of Prostate Cancer Incidence and Residential Pesticide Exposure in Iowa

Introduction

The role of environmental pesticide exposure in prostate cancer has gained considerable attention in recent decades (1, 2). While the association between prostate cancer risk and pesticide exposure is most commonly evaluated in occupational studies of licensed pesticide applicators (3, 4), including farmers and nursery workers, pesticide exposure is also of concern to individuals who live in or near farming communities. Individual exposures can occur through inhalation of aerosolized particles, ingestion via food or water, and dermal contact with contaminated soil or dust. Pesticide residues from agricultural applications have been identified as far as 1,000 meters from the application source (5, 6).

Geographic studies of prostate cancer incidence and mortality can identify groups of spatially referenced cases of disease that are unequally distributed throughout a geographical area and, in conjunction with geographic information system (GIS) technologies, can help identify factors that are associated with the disease. When mapping the complex association between environmental exposures and cancer outcomes, cluster analysis is often used with the statistical significance of identified clusters quantified through the use of a spatial scan statistic. Previous studies using spatial scan statistics have detected spatial variation in prostate cancer incidence (7, 8) and mortality (9, 10).

In a recent study examining the association between prostate cancer incidence and agricultural activity in Iowa, geographic variation in age-adjusted incidence rates was observed at the county and census tract levels. Further, statistically significant associations between prostate cancer incidence and the percent of land used for corn and soybean crop production were identified (11). In the current study, we expand upon previous work by using the SaTScan spatial scan statistic to identify Iowa census tracts with increased risk of prostate cancer. Using a GIS, we compared the cancer cluster locations to historical pesticide use. To our knowledge, no published study has examined the spatial clustering of prostate cancer incidence in relation to agricultural activity and pesticide use.

Methods

Data Sets

Prostate cancer incidence cases

Pathology-confirmed incident prostate cancer cases (N=23,147) reported to the State Health Registry of Iowa between 1996 and 2006 were obtained. Individual-level variables included age at diagnosis in five-year increments, race (white, Black, other), ethnicity (Hispanic/non-Hispanic), tumor stage and grade, as well as county and census tract of residence at the time of diagnosis.

Area level data

Historical data were chosen for this study to better approximate area-level characteristics at the time of presumed relevant pesticide exposure given latency.

Specifically, census tract level demographic data for variables hypothesized to influence both risk of exposure to environmental agents and prostate cancer (i.e., age, race and ratio of income to poverty), were obtained from the U.S. Census Bureau for 1990. Position in the urban/rural continuum was based on the 1993 classification, which is the closest year to our study period for which these codes were published (<http://www.ers.usda.gov/Data/RuralUrbanContinuumCodes/>). Position in the urban/rural continuum was classified at the county level, and each census tract was assigned the urban/rural continuum code of the county in which it is located. Tracts were classified as: metropolitan (located in a metropolitan area with a population of any size), suburban (population 2,500 to 20,000 and adjacent to a metropolitan area), or rural (population <2,500). Previous work indicates that area-level socioeconomic status influences risk of exposure to environmental agents and prostate cancer risk.

The ratio of income to poverty is available at the census tract level in nine categories (i.e., <0.50, 0.50-0.74, 0.75-0.99, 1.0-1.24, 1.25-1.49, 1.50-1.74, 1.75-1.84, 1.85-1.99, and >2.0). Lower levels indicate a higher number of people in the census tract living in poverty. Consistent with previous work (12), the nine categories were collapsed into three categories: severe poverty (ratio ≤ 0.99), near poverty (ratio 1.00 to 1.99), and non-poverty (ratio ≥ 2.00). The percent of persons in each census tract living at each level of poverty was calculated, and the census tract was assigned the most prevalent poverty level in the tract.

The percent of lowa land exposed to each of four commonly used pesticides was calculated using methods previously described (11). Briefly, historical crop-specific land use records and pesticide sales data for 1990 were integrated into a GIS, as that was

the earliest and only year for which both of these data sets were available. Corn and soybean fields were identified, which accounted for over 90% of all agricultural planting in 1990 and were predominantly treated with one of the top four most-purchased pesticides in 1990 (i.e., atrazine, metolachlor, alachlor and cyanazine). Since pesticide residues can be found up to 1,000 meters from the application source (5, 6), a 1,000 meter buffer was calculated around the centroid of each corn and soybean field. The total area of each Iowa census tract that was located within each of four corresponding pesticide application buffers was calculated.

Cluster Identification

Statistical analysis of the spatial clustering of prostate cancer risk was assessed using the Poisson-based SaTScan version 7.0.3 spatial scan statistic (SaTScan™ SaTScan.org, Boston, MA) (13). Case counts were aggregated at the 1990 census tract level and were assigned the latitude and longitude coordinates of the centroid of the census tract, as defined by the SaTScan coordinates file (13).

The spatial scan statistic utilized “windows” of various shapes and sizes to scan the geographical area. As the scanning window moved across the study space, the probability distribution of the disease in the window was compared to that of the rest of the study area. Using the likelihood function, the most likely primary cluster and non-geographically overlapping secondary prostate cancer clusters were identified (13). Statistically significant clusters were defined by a p -value <0.05 . Visualization of identified clusters was performed using ArcMap.

Based on visualization of census tract level age-adjusted Iowa prostate cancer incidence rates and findings from previous studies, an elliptic scan window was chosen *a priori* for this study as it has been shown to outperform the standard circular window when a small- to moderate-sized window is used (14). Ellipses were user-defined in SaTScan by size, shape and angle, as well as the location of each centroid. Maximum window size was based on the percent of the study population that was included in the window, up to a maximum size of 50%. The maximum window size for this study was determined by visualizing clusters identified with a 0.5%, 5%, 7%, 10%, 25% and 50% maximum window size. Larger window sizes resulted in clusters that often contained geographically and demographically diverse census tracts and masked local variability, while smaller window sizes resulted in clusters that often contained only a few census tracts in urban areas, which resulted in a loss of detail in suburban and rural areas. A maximum window size of 5% of the population was selected for this study, as it produced clusters with sufficient geographic and demographic diversity, without a loss of detail in urban and suburban areas. Ellipse shape was determined by the ratio of the long to short axis, with a ratio of 1 indicating a perfect circle. For this study, ratios were set at 1.5, 2, 3, and 4, with the associated number of equal-sized angles set at 4, 6, 9, and 12, respectively.

All clusters were age-adjusted to the 2000 U.S. standard population, with further adjustments by census tract position in the urban/rural continuum and ratio of income to poverty (13).

Characterization of clusters

We used Pearson's chi-square test statistic to evaluate the relationship between agricultural activity and residence at the time of diagnosis in a statistically significant cluster of increased ($RR > 1.0$) or decreased ($RR < 1.0$) prostate cancer risk. Agricultural activity variables included the percent of land planted with corn, soybean and corn or soybean crops. Residential pesticide exposure variables included the percent of land exposed to the four most commonly used pesticides in Iowa in 1990 (i.e., atrazine, metolachlor, alachlor or cyanazine) (11). A logistic regression analysis was used to assess the relationship between percent of land used for corn and soybean crops and location in a cluster of statistically significant increased or decreased prostate cancer risk after controlling for exposure to the commonly used pesticides. All statistical analyses were conducted using SAS 9.2

Results

The majority 69.5% of cases were diagnosed in men over the age of 65. Over 96% of cases occurred in white males, and approximately 84% were diagnosed at the localized stage (Table 3.1).

The spatial scan statistic identified eighteen statistically significant clusters of increased or decreased prostate cancer risk after adjustment for age, position in the urban/rural continuum and poverty (relative risk of disease among statistically significant clusters: 0.16-1.81). Nine clusters had an increased relative risk of disease ($RR > 1.0$) and nine had a reduced relative risk of disease ($RR < 1.0$). (Figure 3.1).

SaTScan identified a large cluster of increased prostate cancer risk in the upper northwest region of the state. This cluster was comprised of 29 contiguous census tracts and contained 1,864 cases of prostate cancer. The overall relative risk of disease in this cluster was 1.67 ($p=.001$) with the census tract level relative risk of disease ranging from 1.26 to 2.67.

Clusters with increased risk of prostate cancer had a higher percentage of land used for all crops of interest (i.e., corn and soybean farming ($p < 0.001$), corn farming ($p < 0.001$), soybean farming ($p < 0.001$)) and lower exposure to alachlor ($p = 0.032$) than did clusters with decreased risk of prostate cancer (Table 3.2). After adjustment for exposure to each of the pesticides studied, the odds of living in a cluster of increased risk of prostate cancer increased with increasing percent of land used to grow corn crops ($\beta=0.82$, $p < .001$) and percent of land used to grow soybean crops ($\beta=0.69$, $p < .001$). After adjustment for type of crop grown, percent of land exposed to alachlor was no longer statistically significantly associated with location in a cluster of low or high prostate cancer risk.

Discussion

The spatial scan statistic identified nine clusters with statistically significant increased risk of prostate cancer and nine clusters with statistically significant decreased risk of prostate cancer. The primary cluster of increased prostate cancer risk was located in the northwest region of the state. Prostate cancer risks were higher in clusters with a higher percentage of land used for corn and soybean farming and were generally lower in urban and suburban areas with fewer crops.

Our findings are consistent with previous research that has identified an association between exposure to corn and soybean crop fields and prostate cancer (11, 15, 16). It is possible that environmental exposures specific to corn and soybean farming, including exposure to low doses of environmental estrogens (17), agricultural pesticides other than those examined in this study (3, 18-20) and certain trace metals, are responsible for the observed increase in prostate cancer risk.

In a recent cohort study of 55,332 male licensed pesticide applicators in Iowa and North Carolina, a two-fold increase in prostate cancer risk was observed among pesticide users compared to subjects who reported that they did not use pesticides (3). A dose response relationship between frequency of use and lifetime application days for the organohalogen fumigant methyl bromide and prostate cancer risk was identified. Among men with a family history of prostate cancer, a statistically significant increase in prostate cancer risk following occupational exposure to six commonly used herbicides and insecticides was observed. Interestingly, four of the six pesticides associated with increased prostate cancer incidence in men with a family history of prostate cancer belong to the organochlorine class of chemicals. Our study was designed to evaluate associations between prostate cancer incidence and exposure to the most commonly used pesticides in Iowa in 1990. Future research should evaluate the association between exposure to methyl bromide and pesticides in the organochlorine class and, where possible, evaluate the interaction between family history and residential exposure to these pesticides.

We identified a statistically significant lower percentage of land exposed to alachlor in clusters with a decreased risk of prostate cancer compared to clusters with

statistically significant increased risk. This difference did not persist after controlling for percent of land used for corn or soybean crop in logistic regression analysis. Alachlor is an aniline herbicide used for annual control of broad leaf weeds on corn and soybean crops. In 1990, alachlor was the most commonly used herbicide in the U.S., and the third most commonly used pesticide in Iowa. Toxicology studies have identified an association between exposure to high levels of alachlor and nasal turbinate (21) and thyroid (22) cancers in rats, although genotoxicity studies fail to support extrapolation of the associations to humans and other animals (23). Alachlor is classified as a probable human carcinogen at high doses by the EPA (24). Occupational studies of agricultural workers and pesticide manufacturers have identified an association between exposure to alachlor and colorectal (25) and lymphohematopoietic (26) cancers. Thorpe et al. (27) identified a potential association between groundwater exposure to alachlor and certain childhood cancers, including leukemia and bone cancer. The majority of epidemiologic evidence examining alachlor exposure and prostate cancer incidence are in the occupational setting, where studies have failed to find an association between exposure to alachlor and prostate cancer (25, 26, 28, 29). Our study is the first to evaluate residential exposure to alachlor.

Our study addresses many of the limitations of previous studies, including small sample sizes, limited periods of exposure and limited follow-up periods. Our population-based study included over 23,000 incident prostate cancer cases diagnosed in a state with relatively low residential mobility. The integration of geographically-referenced historical pesticide use and sales data using a GIS allowed for the estimation of area-level exposures prior to the diagnosis of prostate cancer.

This study was conducted using area-level data only, making interpretation of the results subject to the ecological fallacy. Data on factors specific to pesticide exposure at the individual level were not available, thus preventing the inclusion of these factors in the exposure matrix. Future studies should incorporate individual characteristics in the modeling of geographic variation in spatial patterns of disease. Further, prostate cancer risk may appear higher in areas with higher screening rates. To evaluate this, we obtained prostate specific antigen (PSA) screening data from the 2002 (30) and 2004 (31) Centers for Disease Control and Prevention's Behavioral Risk Factor Surveillance System (BRFSS) surveys (the only years during our study period that the optional PSA screening questions were asked). However, screening data at the county level were sparse, which prevented the calculation of county level PSA screening prevalence. Additionally, expansion of toxicological studies to primates and humans would allow researchers to better quantify the mechanisms by which exposure to pesticides affects biological systems.

Findings from our study reinforce previous findings of an association between residential proximity to agricultural fields and prostate cancer incidence, and highlight the need for further investigation of exposure to specific agricultural pesticides other than those evaluated in this study (i.e. potentially carcinogenic pesticides used less commonly and those used in lower quantities).

Tables

Table 3.1: Descriptive statistics of Iowa prostate cancer incident cases (1996-2006)

	N (%)*
Age	
<55	1629 (7.0)
55-59	2178 (9.4)
60-64	3263 (14.1)
65-69	4402 (19.0)
70-74	4508 (19.5)
75-79	3623 (15.7)
80-84	2179 (9.4)
≥85	1365 (5.9)
Race	
White	22370 (96.6)
Black	357 (1.5)
Other	68 (0.3)
Unknown	352 (1.5)
Ethnicity	
Hispanic	108 (0.5)
Non-Hispanic	22651 (97.9)
Unknown	388 (1.7)
Stage	
Localized	19485 (84.2)
Regional	1366 (5.9)
Distant	1316 (5.7)
Unknown	980 (4.2)

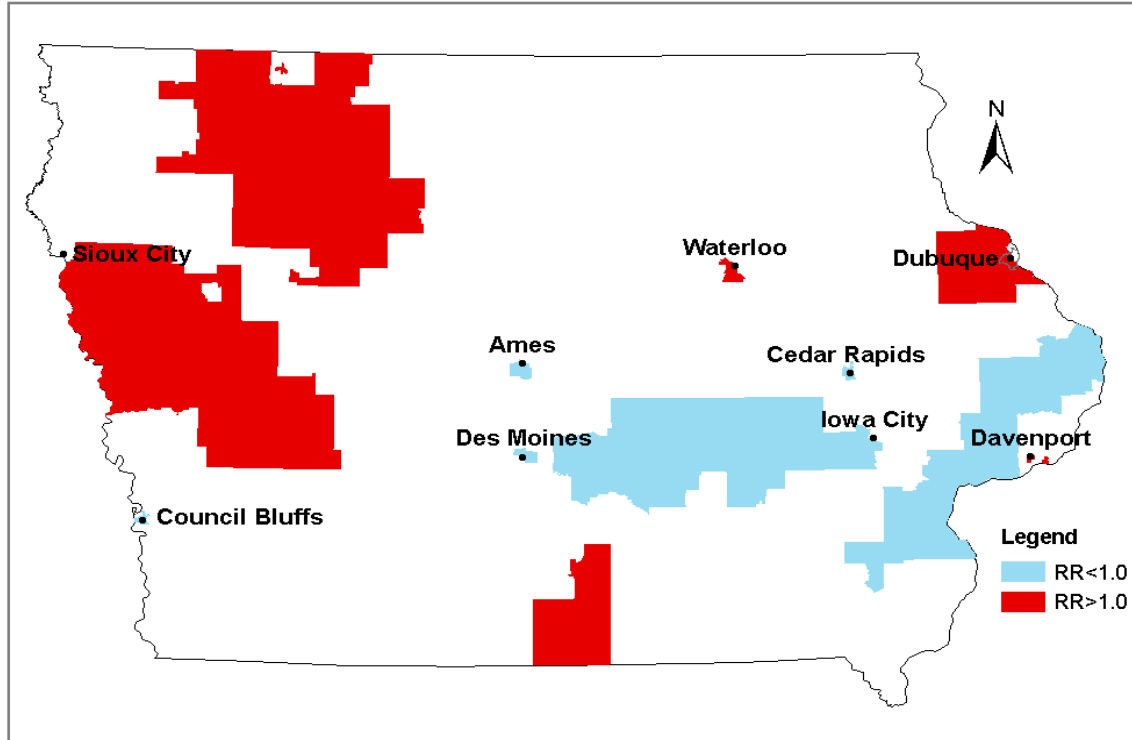
*Percentages may not add up to 100% due to rounding

Table 3.2: Comparison of agricultural characteristics among statistically significant clusters of high and low relative risk of prostate cancer incidence

	Percent of Land Covered		Unadjusted <i>p</i> -value	Adjusted <i>p</i> -value
	Clusters with RR <1.0 (n=9)	Clusters with RR >1.0 (n=9)		
Corn and Soybean	5.9	44.2	<0.001	<0.001
Corn	3.6	19.7	<0.001	-
Soybean	2.3	24.5	<0.001	-
Atrazine	4.3	3.6	0.801	0.706
Alachlor	3.4	0.0	0.032	0.812
Metolachlor	6.8	10.7	0.398	0.726
Cyanazine	13.7	5.3	0.055	0.289

Figures

Figure 3.1: Clusters of census tracts with high and low relative risk of prostate cancer



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Chapter 4: Multilevel Analysis of Residential Pesticide Exposure and Prostate Cancer Incidence

Introduction

Pesticide use is widespread in the United States, with as much as 80% of use occurring in the agricultural environment (1). For individuals living in agricultural communities, the potential for exposure exists through pesticide drift, which is the transport of a pesticide from its target organism and location to the surrounding area. An association between residential proximity to corn and soybean fields and prostate cancer incidence in Iowa has been observed in recent studies (2, 3). It is hypothesized that exposure to the pesticides used on crop fields increases prostate cancer risk, although the results of these studies are inconclusive.

In Iowa, approximately 90% of land is used for agricultural purposes, and approximately 90% of agricultural planting is corn and soybean crop. In the late 1980s and early 1990s, approximately 95% of corn and soybean crops in Iowa were treated with pesticides (4). Spatial variation and local clustering of prostate cancer incidence, corn and soybean fields, and pesticide use at the county and census tract level in Iowa has been observed (3). A statistically significant positive correlation between clusters of prostate cancer risk and corn and soybean crop has been identified (3).

In the assessment of complex environmental exposures and health outcomes, where the exposure-disease relationship is often confounded by the presence of individual and area-level effects, and the assumption of statistical independence between health events is not valid, predictive models incorporating spatial variation

have been shown to outperform ordinary least squares models (5, 6). However, the incorporation of spatial correlation in predictive prostate cancer modeling is limited in the published literature to studies of spatio-temporal trends in prostate cancer incidence. In a study of temporal changes in prostate cancer incident cases reported to the Louisiana Cancer Registry following implementation of prostate specific antigen (PSA) testing, Mather et al. successfully identified spatio-temporal trends in incidence while maintaining the ability to control for confounders (7). To date, no known study of the assessment of residential exposure to pesticides from large-scale agricultural use and prostate cancer has utilized a regression modeling approach that incorporates measures of spatial autocorrelation. The purpose of this study is to move beyond spatio-temporal trend analyses to statistically assess spatial autocorrelation in prostate cancer incidence in Iowa, and incorporate spatial autocorrelation into a hierarchical regression modeling process to assess the effect of agricultural pesticide exposure on prostate cancer incidence.

Methods

Variables

Pathology-confirmed incident prostate cancer cases reported to the State Health Registry of Iowa between 1996 and 2006 were obtained (N=23,147). Individual-level variables included age at diagnosis in five year increments, race (white, Black, other), ethnicity (Hispanic/ non-Hispanic), tumor stage and grade, and county and 2000 census tract of residence at the time of diagnosis.

Socioeconomic data were obtained from the U.S. Census Bureau (summary tape file 3A) for the 1990 census year (available at: <http://factfinder.census.gov>). Area level

data from 1990 were used for this analysis because they provided a historical context to the area level socioeconomic conditions that preceded the cancer diagnosis. The poverty level variable was calculated by the U.S. Census Bureau by determining the ratio of a family's household income to one of 48 poverty thresholds, which are based on the number of adults and dependent children living in the household. If a family's household income was below their assigned threshold value, then the individuals in that household were considered to live in poverty. These data were available at the census tract level in nine categories (<0.50, 0.50-0.74, 0.75-0.99, 1.0-1.24, 1.25-1.49, 1.50-1.74, 1.75-1.84, 1.85-1.99, and ≥ 2.0). Lower levels indicated a higher number of people in the census tract living in poverty. Consistent with previous work (8), the nine categories were further classified as severe poverty (ratio ≤ 0.99), near poverty (ratio between 1.00 and 1.99), and non-poverty (ratio ≥ 2.0). The percent of persons in each census tract living at each level of poverty was calculated, and the census tract was assigned the poverty level of the largest percent of the population in the tract.

Position in the urban/rural continuum was based on the 1993 classification, which is the closest year to our study period for which these codes were published (<http://www.ers.usda.gov/Data/RuralUrbanContinuumCodes/>). Position in the urban/rural continuum was classified at the county level and each census tract was assigned the urban/rural continuum code of the county in which it is located. Tracts were classified as: metropolitan (located in a metropolitan area with a population of any size), suburban (population 2,500 to 20,000 and adjacent to a metropolitan area) or rural (population <2,500). While position in the urban/rural continuum was evaluated in the descriptive statistics portion of this study, the variable was excluded from the

multiple logistic regression models due to a high level of collinearity with the poverty variable.

Estimation of percent of land exposed to pesticides has been described elsewhere (2). Briefly, historical crop-specific land use records and pesticide sales data for 1990, the earliest and only year that both of these data sets were available, were integrated into a geographic information system (GIS). Corn and soybean fields, which accounted for over 90% of all agricultural planting in 1990 and were predominantly treated with one of the four most commonly purchased pesticides in 1990 (i.e., atrazine, metolachlor, alachlor and cyanazine), were identified. A 1,000 meter buffer was calculated around the centroid of each corn and soybean field given pesticide residues can be found up to 1,000 meters from the application source (9, 10). The total area of each Iowa census tract that was located within each of four corresponding pesticide application buffers was calculated.

Evaluation of Race

Between 2001 and 2005, the incidence rate for prostate cancer in the United States was approximately 59% higher in Black men compared to white men (11). Previous work has identified an association between atrazine exposure and increased prostate cancer only in Black men (12). To evaluate the influence of race on the association between pesticide exposure and prostate cancer incidence, a data set containing only those cases located in a census tract with at least 12.3% Black, which is the average national Black population (percent “Black only” population, 2000 U.S. census) was created. Of the 32 Iowa census tracts that met this criterion, 14 had 12.3%

to 20% percent Blacks (51.9% of cases in census tracts with higher percent Black population), 5 had 20.1% to 30% percent Blacks (12.5% of cases in census tracts with higher percent Black population), and 13 had greater than 30.0% Blacks (35.8% of cases in census tracts with higher percent Black population).

Statistical Modeling

Age Adjustment

Census tract level prostate cancer incidence rates for men age 18 and over were calculated and age adjusted to the 2000 U.S. standard population (13). Population data were obtained from the 2000 U.S. Census Bureau summary tape file 3A for males age 18 and over.

Global Clustering

Spatial patterning of age-adjusted incidence rates for Iowa was assessed via Moran's I global index of spatial autocorrelation. The null hypothesis for the Moran's I index states that the observation being analyzed is randomly distributed throughout the study space. In this study, for example, the null hypothesis for the test of spatial autocorrelation of prostate cancer incidence is that census tract level incidence counts are evenly distributed throughout Iowa. Rejection of the null hypothesis indicates that the spatial distribution of census tracts with high and low counts is more spatially clustered than would be expected under the constant risk hypothesis. Values for Moran's I can range from -1 to 1, with higher positive values indicating greater autocorrelation. The higher the level of autocorrelation, the greater the degree of

clustering of higher and lower than expected census tract level counts throughout Iowa. Spatial correlation was considered present if the value of Moran's I was positive.

Spatial Autocorrelation Modeling

The *a priori* assumption for this study was that spatial autocorrelation due to both the dependence between observed data points and variation in prostate cancer incidence rates at the census tract level was present in these data. The hypothesis of spatial autocorrelation was assessed by performing the hierarchical modeling procedure both with and without the inclusion of a spatial autocorrelation structure. The model with the lowest Akaike information criterion (AIC) goodness of fit value was deemed most appropriate for the data.

Spatial autocorrelation was accounted for with conditional autoregressive models (CAR), which were designed to account for the spatial dependence of the case locations (14) and to account for unmeasured and/or unexplained residual correlation in the data (15). Neighborhood structure was defined as a continuous variable calculated as the distance between the centroids of neighboring census tracts. All models were weighted to account for population variations between census tracts, which is particularly important in population-based studies, as it adjusts for residual spatial autocorrelation due to population patterning (15).

A hierarchical regression modeling approach with an assumed Poisson distribution was used to characterize the relationship between census tract level prostate cancer incidence and exposure to pesticides. The hierarchical modeling approach was selected for this analysis because it allowed for census tract level

random effects, individual-level effects and spatial autocorrelation. All statistical modeling was performed using PROC GLIMMIX in SAS 9.2 (16).

Assessment of Racial Variation.

We used Pearson's chi-square test statistic and its associated p -value to evaluate differences in the characteristics of census tracts with a percent Black population above and below the national average. Using the hierarchical regression modeling approach described above, racial variation in prostate cancer incidence was evaluated.

Results

Prostate Cancer Incidence

Between 1996 and 2006, a total of 23,147 pathology-confirmed prostate cancer cases were reported to the State Health Registry of Iowa. The majority of cases (67.5%) were in white men over the age of 65. Over 84% of the cases were diagnosed in the localized stage (Table 4.1). Smoothed census tract level prostate cancer incidence ranged from 0.72 cases per 1,000 males to 2.31 cases per 1,000 males.

Men living in census tracts with a percent Black population above the national average were statistically significantly more likely to be of Hispanic ethnicity ($p<.001$) and diagnosed with advanced stage disease ($p<.001$) than men living in census tracts with a percent Black population below the national average. The prostate cancer incidence rates for white and Black men living in these census tracts was 1.57 per 1000 white males and 1.51 per 1,000 Black males respectively.

Spatial Autocorrelation

The global Moran's I test of spatial autocorrelation for prostate cancer incidence, percent of land used for corn and soybean fields and percent of land potentially exposed to alachlor, atrazine, cyanazine and metolachlor was highly significant ($p < .001$, Table 4.2), implying that the distributions of these variables in Iowa were spatially autocorrelated (i.e. the distributions are not random throughout the state). Further, inclusion of the spatial autocorrelation structure resulted in a reduced AIC value, indicating that inclusion of this dependence structure best fit these data. Thus, for these data, the null hypothesis of complete spatial randomness of prostate cancer incidence in Iowa was rejected, and the statistical models that included the spatial dependence structure were used.

In analyses without accounting for spatial autocorrelation, a statistically significant positive association between prostate cancer risk with exposure to corn and soybean crops ($\beta = 0.23$; 95% CI: 0.21, 0.25) and percent of land exposed to cyanazine ($\beta = 0.02$; 95% CI: 0.00, 0.05) and a statistically significant negative association between prostate cancer risk and percent of land exposed to metolachlor ($\beta = -0.08$; 95% CI: -0.10, -0.06) and alachlor was observed ($\beta = -0.06$; 95% CI: -0.11, -0.01; Table 4.3). After accounting for spatial autocorrelation, only the association between prostate cancer risk and exposure to corn and soybean fields remained statistically significant, representing a 23% increase in risk for each percent increase in the percent of land used for corn and soybean farming (95% CI: 0.20, 0.24; Table 4.3)

Census tracts with higher percent Black population

We identified 32 Iowa census tracts where the percent of the population of Black race was greater than or equal to the national percentage (12.3%). The percent of land in these census tracts used for corn and soybean crops ranged from 0.0% to 32.4%. Interestingly, none of the land in these census tracts was exposed to the four most commonly used pesticides during 1990. After adjustment for census tract level poverty status, a statistically significant increased risk of prostate cancer among Black men compared to white men was observed, representing a 22% increase in risk with each percent increase in the percent of land used for corn and soybean farming (95% CI: 0.11-0.32; $p < .001$). The association between prostate cancer risk and exposure to corn and soybean fields was statistically significant in unadjusted analysis ($p < .001$), but was not statistically significant after adjustment for race (Table 4.4).

Discussion

Overall, a high degree of spatial correlation was observed for prostate cancer incidence rates and the percent of land used for corn and soybean crops as well as those exposed to the four most commonly used pesticides in Iowa in 1990. The risk of prostate cancer incidence increased by approximately 25% (95% CI: 0.20, 0.24) with each percent increase in the percent of land used for corn and soybean fields.

Our finding of statistically significant global spatial patterning of prostate cancer incidence is consistent with previous studies, which have identified global and local clustering of prostate cancer incidence (17-20). Geographical variation in prostate cancer incidence is hypothesized to be due to factors such as differential PSA

screening rates (21); variation in population distribution by race (17); and environmental characteristics, such as fluctuations in vitamin D levels from sun exposure (18, 20). To evaluate the influence of area-level variation in prostate cancer screening rates on our findings, we obtained county-level PSA screening data from the Behavioral Risk Factor Surveillance System (BRFSS) of the Centers for Disease Control and Prevention for 2002 (22) and 2004 (23), which are the only years in our study period that the PSA screening module was administered. While state level screening rates remained stable between the 2002 and 2004 BRFSS surveys (58.7%), low response counts in many Iowa counties prevented the calculation of PSA screening prevalence by county. However, after collapsing the data at the county level, we found that the screening rate for counties with greater than 12.3% Black population was 60.9%, while the screening rate in counties with less than 12.3% Black population was 57.8%. This difference was not statistically significant ($p=0.47$), suggesting that variation in screening was not responsible for the observed increase in prostate cancer risk among counties with a higher percent Black population. Caution should be taken when interpreting these findings, as a county identifier was missing for 58.8% of male BRFSS respondents over the age of 50 in Iowa. However, the prostate cancer screening rate for men living in counties with a missing BRFSS county identifier was 52.1%, which was not statistically significantly different than that of men living in a county with an available county identifier ($p=0.29$), suggesting that the large proportion of missing county identifiers did not influence our findings.

The spatial patterning of corn and soybean fields and the pesticides used on these fields likely reflects the characteristics that influence the type of crop grown and/or

the pesticide used on that crop, including soil type, climate, elevation and/or environmental regulations. Atrazine, an herbicide used to control weeds in corn and other row crops, is classified by the U.S. Environmental Protection Agency as a restricted use pesticide (RUP), due in part to the chemical's high potential for groundwater contamination (24). For example, in 1990, the Iowa Department of Agriculture and Land Stewardship implemented revised atrazine use regulations, which created atrazine restriction areas that severely limited the use of atrazine in areas with low clay or organic matter content, shallow bedrock aquifers, or agricultural drainage wells. Due to these restrictions, atrazine use is heavily restricted in the entirety of seven Iowa counties and in portions of sixteen additional Iowa counties (25). Similarly, alachlor, which was the most commonly used pesticide in the United States in 1990 and the third most commonly used pesticide in Iowa in 1990, is also classified as a RUP and was subject to the same usage restrictions as atrazine (26).

In the generalized linear mixed model not accounting for spatial autocorrelation, a statistically significant positive association between prostate cancer incidence and the percent of land used for corn and soybean crops and exposed to cyanazine was observed, while a statistically significant negative association between percent of land exposed to metolachlor and alachlor was observed. After adjustment for spatial autocorrelation, only the association between percent of land used for corn and soybean crops was statistically significant. It is plausible that the association between prostate cancer incidence and percent of land used for corn and soybean crops is due to environmental exposure characteristics specific to corn and soybean farming, including exposure to pesticides other than those evaluated in this study (27, 28). In

particular, recent studies have identified an association between exposure to endocrine disrupting pesticides, including the fumigant methyl bromine and pesticides in the organochlorine class, and prostate cancer incidence (28). Our study evaluated associations to the most commonly used pesticides in Iowa in 1990, and data on pesticides used in smaller quantities were not available at the time this study was initiated. Although a direct link between human exposure to endocrine disrupting compounds and prostate cancer has not been established, the known hormonal basis for prostate cancer coupled with the strength of the association in animal models and the widespread use of these pesticides in the U.S. (29) necessitates further study of the association in humans.

In a county-level ecological study evaluating residential pesticide exposure and prostate cancer incidence, Mills identified a statistically significant increase in prostate cancer risk amongst Black men exposed to atrazine (12). We attempted to evaluate this association among Black men living in Iowa. Due to the relatively homogeneous nature of the Iowa population with regard to race, we identified a subset of men residing in Iowa census tracts with a percent Black population above the national average ($\geq 12.3\%$). While none of the identified census tracts were identified as exposed to the four most commonly used pesticides in Iowa in 1990, the percent of land used for corn and soybean crops in these census tracts ranged from 0% to 31.1%. After adjustment for census tract level poverty status and the percent of land used for corn and soybean crops, prostate cancer risk for Black men was approximately 25% higher than for white men. This finding suggests that excess prostate cancer risk in Black men may be due, in part, to factors other than exposure to corn and soybean crops and pesticides.

Plausible hypotheses include genetic and lifestyle factors, including diet and screening behaviors. Future research should evaluate the interaction between prostate cancer incidence and race in the presence of exposure to pesticides other than those evaluated in this study.

Our study is the first to evaluate spatial autocorrelation in the evaluation of the association between prostate cancer incidence and residential pesticide exposure. The hierarchical modeling approach selected for this analysis allowed for the incorporation of census tract level random effects, individual-level effects and the incorporation of a spatial autocorrelation structure, which resulted in improved model performance as demonstrated in the reduction of the model's AIC value.

This study has multiple limitations. First, we did not have access to many individual-level variables that could influence prostate cancer risk, including family history of disease and occupation. Second, identified areas of increased prostate cancer risk might appear higher due to differential access to screening amongst geographical areas. While we attempted to incorporate county level screening rate data available through the Behavioral Risk Factor Surveillance System data set, low response counts at the county level prevented the calculation of county level screening rates. Third, we only used one year of pesticide exposure data (1990). It is likely that pesticide sales vary from year to year; thus, looking at several time points would strengthen future analyses. Due to the ecological nature of exposure estimates, we were unable to incorporate individual characteristics that could influence exposure, including actual exposure to pesticides and exposure to pesticides other than those evaluated in this study. Additionally, the potential for exposure misclassification exists.

Our GIS identified crop fields located within regions of high amounts of pesticide-specific sales, but the ecological nature of our study prevented us from evaluating individual characteristics that could influence exposure and intake of pesticides, including amount of time spent at the home, age and physical activity level.

Results from this study support previous findings of an increase in prostate cancer risk among men exposed to corn and soybean crops. The observed spatial variation in prostate cancer risk, percent of land planted with corn and soybean crops and the pesticides used on these crops generates hypotheses regarding environmental exposures specific to corn and soybean crop fields that could influence prostate cancer risk. Further evaluation of these exposures is warranted.

Tables

Table 4.1: Comparison of individual-level characteristics of men living in census tracts with a high and low percent population of Black race (1996-2006)

	All Cases N (%)*	In Census Tracts with <12.3% Black Race N (%)*	In Census Tracts with ≥12.3% Black Race N (%)*	p
Age				0.75
<55	1629 (7.0)	1583 (7.0)	46 (8.8)	
55-59	2178 (9.4)	2128 (9.4)	50 (9.5)	
60-64	3263 (14.1)	3172 (14.0)	91 (17.4)	
65-69	4402 (19.0)	4304 (19.0)	98 (18.7)	
70-74	4508 (19.5)	4401 (19.5)	107 (20.4)	
75-79	3623 (15.7)	3553 (15.7)	70 (13.4)	
80-84	2179 (9.4)	2139 (9.5)	40 (7.6)	
≥85	1365 (5.9)	1343 (5.9)	22 (4.2)	
Race				<.001
White	22370 (96.6)	22048 (97.5)	322 (61.5)	
Black	357 (1.5)	176 (0.8)	181 (34.5)	
Other	68 (0.3)	62 (0.3)	6 (1.1)	
Unknown	352 (1.5)	337 (1.5)	15 (2.9)	
Ethnicity				<.001
Hispanic	108 (0.5)	100 (0.4)	8 (1.5)	
Non-Hispanic	22651 (97.9)	22152 (97.9)	499 (95.2)	
Unknown	388 (1.7)	371 (1.6)	17 (3.2)	
Stage				<.001
Localized	19485 (84.2)	19054 (84.2)	431 (82.3)	
Regional	1366 (5.9)	1329 (5.9)	37 (7.1)	
Distant	1316 (5.7)	1273 (5.6)	43 (8.2)	
Unknown	980 (4.2)	967 (4.3)	13 (2.5)	

*Percentages may not add up to 100% due to rounding

Table 4.2: Values of global Moran's I for spatial clustering of prostate cancer incidence and pesticide use in Iowa

Variable	Moran's I	Z-score*
Prostate cancer incidence	0.62	6.48
Corn fields	0.60	6.27
Soybean fields	0.75	7.83
Alachlor	0.62	6.43
Atrazine	0.61	6.50
Cyanazine	0.88	9.41
Metolachlor	0.55	5.56

*All p-values <0.001.

Table 4.3: Generalized linear mixed model regression analysis of association between prostate cancer risk and exposure to pesticides in Iowa

	Unadjusted Analysis β (95% CI)	Model without Spatial Autocorrelation Structure β (95% CI)	Model with Spatial Autocorrelation Structure β (95% CI)
Individual Level			
Race			
White	Ref	Ref	Ref
Black	0.06 (0.02, .011)	0.02 (-0.04, -0.05)	0.05 (0.01, 0.08)
Other	-0.01 (-0.10, 0.09)	-0.01 (-0.03, 0.05)	0.01 (-0.02, 0.04)
Unknown	0.07 (-0.03, 0.10)	0.04 (-0.06, 0.07)	0.02 (-0.01, 0.05)
Ethnicity			
Hispanic	-0.04 (-0.07, -0.01)	-0.06 (-0.03)	-0.02 (-0.04, 0.00)
Non-Hispanic	Ref	Ref	Ref
Unknown	0.02 (-0.01, 0.05)	-0.03 (-0.07, 0.04)	-0.01 (-0.04, 0.03)
Stage			
Local	Ref	Ref	Ref
Regional	-0.01 (-0.03, 0.00)	0.01 (-0.01, 0.01)	0.00 (-0.01, 0.02)
Distant	-0.01 (-0.02, 0.00)	-0.02 (-0.05, 0.08)	-0.01 (-0.03, 0.05)
Unknown	-0.03 (-0.06, 0.00)	-0.01 (-0.03, 0.02)	-0.02 (-0.04, 0.00)
Area Level			
Poverty status			
Severe poverty	-0.01 (-0.04, 0.05)	0.15 (0.01, 0.32)	0.09 (0.01, 0.16)
Near poverty	-0.40 (-0.04, 0.05)	-0.44 (-0.61, -0.19)	-0.22 (-0.31, -0.16)
Non-poverty	Ref	Ref	Ref
Corn and Soybean*	0.20 (0.18, 0.22)	0.23 (0.21, 0.25)	0.23 (0.20, 0.24)
Chemical			
Atrazine	-0.01 (-0.18, 0.10)	-0.04 (-0.07, -0.01)	-0.03 (-0.08, 0.02)
Alachlor	-0.09 (-0.12, -0.06)	-0.06 (-0.11, -0.01)	-0.04 (-0.07, 0.03)
Cyanazine	-0.02 (-0.03, -0.01)	0.02 (-0.00, 0.05)	-0.01 (-0.04, 0.03)
Metolachlor	-0.04 (-0.05, -0.03)	-0.08 (-0.10, -0.06)	-0.05 (-0.08, 0.01)

Note: CI= Confidence Interval

*Percent of land used for corn or soybean fields

Table 4.4: Generalized linear mixed model regression analysis of association between prostate cancer risk and exposure to pesticides in Iowa census tracts with $\geq 12.3\%$ Black population

	Unadjusted Analysis β (95% CI)	Adjusted Analysis* β (95% CI)
Race		
White	Ref	Ref
Black	0.12 (0.53, 0.18)	0.22 (0.11, 0.32)
Other	-0.05 (-0.33, 0.23)	-0.12 (-0.55, 3.08)
Unknown	0.27 (0.08, 0.45)	0.42 (0.13, 0.69)
Corn and Soybean+	-0.19 (-0.26, -0.08)	-0.55 (-1.25, 0.13)
Atrazine‡	-	-
Alachlor‡	-	-
Cyanazine‡	-	-
Metolachlor‡	-	-

Note: CI= Confidence Interval

* Adjusted for census tract level poverty status

+ Percent of land used for corn and soybean fields

‡ No land exposed to chemical in the census tracts with $\geq 12.3\%$ Black population.

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Chapter 5: Summary and Implications

Summary of Findings

This study found statistically significant positive correlations between percent of land planted with corn and soybean crops at the county and census tract level and prostate cancer incidence. Analysis of exposure to the top four corn and soybean pesticides used during the study period did not find a statistically significant association between the percent of land at the county and census tract level exposed to each pesticide and prostate cancer incidence.

In the first stage of this study (Manuscript 1), historical pesticide sales data and crop-specific land cover data were successfully integrated into a geographic information system (GIS) where county and census tract level estimates of exposure to the most commonly used pesticides in Iowa in 1990 were calculated. In Iowa in 1990, the total percentage of land in row crop at the county level ranged from 15.3% to 86.8%, and at the census tract level ranged from 0% to 91.8%.

The percent of land potentially exposed to metolachlor was highest in the north-central region of the state (county and census tract level range: 0-100%) while the percent of land potentially exposed to cyanazine was highest in the southwest and southeast regions of Iowa (county and census tract level range: 0-100%). The percent of land exposed to alachlor was highest in a concentrated area located in the central region of Iowa (county level range: 0-76.7%; census tract level range: 0-100%). For atrazine, the percent of land exposed was highest in the southwest and central eastern regions (county level range: 0-92.7%; census tract level range: 0-100%).

A total of 23,147 pathology confirmed incident cases of prostate cancer were reported to the State Health Registry of Iowa between 1996 and 2006. The highest percentage of cases was diagnosed in men between the ages of 70 and 74 (19.5%), followed by men between the ages of 65 and 69 (19.0%) and 75 and 79 (15.7%). Approximately 96% of the cases were in non-Hispanic white men, and the overwhelming majority (84%) of cases was diagnosed in the localized stage. Smoothed age-adjusted prostate cancer incidence rates ranged from 1.19 cases per 1,000 males to 1.84 cases per 1,000 males at the county level and from 0.72 cases per 1,000 males to 2.31 cases per 1,000 males at the census tract level. In general, prostate cancer incidence rates were highest in the northwest and south-central regions of the state.

Ecological correlation and multiple linear regression analyses identified a statistically significant association between increased percentage of land used for corn and soybean fields and prostate cancer risk.

Stage 2 (Manuscript 2) of this study utilized Kulldorff's spatial scan statistic to identify clusters of increased and decreased prostate cancer risk in Iowa. The spatial scan statistic identified nine clusters with statistically significant increased risk of prostate cancer ($RR > 1.0$) and nine clusters with statistically significant decreased risk of prostate cancer ($RR < 1.0$) in Iowa. The primary cluster of increased prostate cancer risk was located in the northwest region of the state and had an overall relative risk of disease of 1.67 ($p < .001$). Prostate cancer risks were higher in clusters with a higher percentage of land used for corn and soybean farming and generally lower in urban and suburban areas with fewer crops. After adjustment for type of crop grown, no

statistically significant association between residence in a cluster of increased prostate cancer risk and exposure to the pesticides evaluated in this study was observed.

In stage 3 of this study (Manuscript 3), the probability of spatial autocorrelation of prostate cancer incidence and agricultural activity was evaluated. The probability that geographical units in close proximity to one another share characteristics that influence the type of crop grown and/ or the pesticide used on that crop is high, as crop type and pesticide use are dependent upon factors such as soil type, climate and elevation, which are independent of political boundaries. The global Moran's I test of spatial clustering of prostate cancer incidence, percent of land used for corn and soybean fields and percent of land potentially exposed to alachlor, atrazine, cyanazine and metolachlor was positive and highly statistically significant ($p < .001$ for each), implying that the distribution of these variables in Iowa was spatially autocorrelated. Inclusion of the spatial autocorrelation structure in hierarchical regression modeling resulted in a reduced AIC value, indicating that inclusion of the dependence structure best fit these data.

In analyses not accounting for spatial autocorrelation, a statistically significant positive association between prostate cancer risk with exposure to corn and soybean crops ($\beta = 0.23$; 95% CI: 0.21, 0.25; $p < .001$) and percent of land exposed to cyanazine ($\beta = 0.02$; 95% CI: 0.00, 0.05; $p = .002$) and a statistically significant negative association between prostate cancer risk and percent of land exposed to metolachlor ($\beta = -0.08$; 95% CI: -0.10, -0.06; $p < .001$) and alachlor ($\beta = -0.06$; 95% CI: -0.11, -0.01; $p < .001$) was observed. After accounting for spatial autocorrelation, only the association between

prostate cancer risk and exposure to corn and soybean fields remained statistically significant ($\beta = 0.23$; 95% CI: 0.20, 0.24; $p < .001$).

Comparison with Previous Work

Our findings are consistent with previous studies that have identified a statistically significant positive correlation between the amount of land used to grow crops and prostate cancer incidence and mortality (1, 2). St-Hilaire et al. found a statistically significant positive correlation between the amount of land used to grow crops and prostate cancer incidence in the United States. Geographic variation in risk suggested that crop-specific variation in pesticide use due to factors such as weather could be, in part, responsible for the observed variation. Our study represents the first published study investigating residential exposure to alachlor, metolachlor and cyanazine. Our findings are consistent with occupational exposure studies (3-6), which have failed to find a strong statistically significant association between exposure to these pesticides and prostate cancer incidence.

Upon completion of an extensive literature review preceding initiation of this study, an *a priori* hypothesis that an increase in prostate cancer risk would be observed as the percent of land used for corn and soybean crops increased, and that a statistically significant positive association between residential exposure to atrazine and prostate cancer incidence would be observed was developed. Animal studies have demonstrated an association between exposure to atrazine and prostate cancer incidence (7); however, studies examining occupational exposures of farmers (8) and atrazine manufacturers (9, 10) have failed to find an association.

In a geographical correlation study of county level prostate cancer incidence and atrazine exposure, Mills et al. found a statistically significant positive correlation between residential exposure to atrazine and prostate cancer incidence in African American men in California ($r=0.67$). In our study, approximately 96% of prostate cancer cases were in white males, and less than 3.6% of Iowa's 1990 male population was Black. Due to concerns about small numbers of cases and exposed Black men, we were unable to study the effect of race on the entire study population. To evaluate racial variation in prostate cancer risk in relation to agricultural exposures, we created a subset of prostate cancer cases located in census tracts with at least 12.3% of the population of Black race. However, none of the land in the census tracts with a high percentage of Black men was identified as being exposed to pesticides, preventing further evaluation of effect modification by race.

Although occupational studies have failed to find an association between exposure to the aniline herbicide alachlor, toxicology studies have identified an association between exposure to high levels of alachlor and nasal turbinate (11) and thyroid (12) cancers in rats. Occupational studies of agricultural workers and pesticide manufacturers have identified an association between exposure to alachlor and colorectal (3) and lymphohematopoietic (13) cancers. Thorpe et al. (14) identified a potential association between groundwater exposure to alachlor and certain childhood cancers, including leukemia and bone cancer. These findings, coupled with the observation that alachlor was the most commonly used herbicide in the U.S., and the third most commonly used pesticide in Iowa in 1990, provided a sound foundation for

studying the association between residential exposure to alachlor and prostate cancer incidence.

Both metolachlor, a pre-emergence herbicide used to control certain broadleaf and annual grassy weeds in corn, soybean and other crops, and cyanazine, a pre- and post-emergence herbicide, are classified as probable endocrine disruptors. This classification, coupled with the fact that metolachlor is moderately persistent in the environment with a half life of between 50 and 70 days (15), warrants the continued evaluation of health risks associated with exposure to these pesticides.

It is important to note that failure to find an association between exposure to these pesticides and prostate cancer incidence does not confirm that exposure to pesticides does not increase prostate cancer risk. Increasing laboratory and epidemiologic evidence suggests that exposure to environmental endocrine disruptors, including cadmium (16) and pesticides in the organochlorine family (17) increases prostate cancer risk, although the current epidemiological literature is insufficient to establish a statistical association.

Methodological Challenges

In the first stage of this analysis (Manuscript 1), we evaluated the association between exposure to corn and soybean fields and the four most commonly used pesticides in Iowa using prostate cancer incidence data at the county and census tract level from all 99 Iowa counties and 793 census tracts. In stage 2 (Manuscript 2), we isolated census tracts with statistically significantly increased and decreased risk of prostate cancer incidence and compared the characteristics of percent of land used for

corn and soybean crops and exposed to pesticides. In stage 3 (Manuscript 3), we moved beyond a straight ecological correlation study and used a hierarchical regression modeling approach with random effects that incorporated both individual and census tract level characteristics that can influence prostate cancer risk, including age at diagnosis, race, poverty and location in an urban or rural area.

While we theorize that exposure to pesticides other than those analyzed in this study could influence prostate cancer risk, it is important that risk factors for prostate cancer other than environmental pesticide exposure be considered. Among these characteristics are family history of prostate cancer and variation in prostate cancer screening rates. As previously stated, men with a family history of prostate cancer are between two and three times more likely to be diagnosed with prostate cancer than men without a family history of disease. This risk increases as the number of first degree relatives with prostate cancer increases. Our study used prostate cancer incidence data obtained from the State Health Registry of Iowa, which does not contain information on family history of disease.

Area level prostate cancer incidence rates could appear higher in census tracts with higher screening rates, as census tracts with higher screening rates will identify more men with disease than census tracts with lower screening rates. To evaluate area-level variation in prostate cancer screening rate in Iowa, we obtained prostate specific antigen (PSA) screening data from the Behavioral Risk Factor Surveillance System (BRFSS). While state level screening rates remained stable between the 2002 and 2004 BRFSS surveys (58.7%), low response counts in many counties prevented the calculation of county-level screening rates.

Hypothesis Generation

We hypothesize that environmental exposures specific to corn and soybean farming, including exposure to low doses of environmental estrogens (18), agricultural pesticides other than those examined in this study (17, 19-21) and certain trace metals, could be responsible for the observed increase in prostate cancer risk.

In a recent cohort study of 55,332 male licensed pesticide applicators in Iowa and North Carolina, a two-fold increase in prostate cancer risk was observed among pesticide users compared to subjects who reported that they did not use pesticides (17). A dose response relationship between frequency of use and lifetime application days for the organohalogen fumigant methyl bromide and prostate cancer risk was identified. Among men with a family history of prostate cancer, a statistically significant increase in prostate cancer risk following occupational exposure to six commonly used herbicides and insecticides was observed. Interestingly, four of the six pesticides associated with increased prostate cancer incidence in men with a family history of prostate cancer belong to the organochlorine class of chemicals.

Our study was designed to evaluate associations between prostate cancer incidence and exposure to the most commonly used pesticides in Iowa in 1990. However, pesticides other than those evaluated in our study were used during this time period. It is possible that exposure to a pesticide other than the ones we evaluated, or exposure to a combination of pesticides used on corn and soybean crop in Iowa, is responsible for our finding of a statistically significant correlation between exposure to corn and soybean crops and increased incidence of prostate cancer. Similarly, due to temporal variability in pesticide use, individuals living in agricultural communities are

likely exposed to a variety of pesticides throughout their lifetime. This study would be strengthened significantly with the inclusion of exposure data over multiple time points. At the time that this study was initiated, these data sets were not available. However, the data sets became available in June 2010, and access to these data has been requested. Upon receipt of these data sets, these analyses will be run using longitudinal exposure data.

The ecological nature of this study provided a firm foundation for generation of hypotheses of corn and soybean-specific exposures that could influence prostate cancer risk. Future research should evaluate the association between exposure to methyl bromide and pesticides in the organochlorine class and, where possible, evaluate the interaction between family history and residential exposure to these pesticides.

Study Strengths

The methodology utilized in this study overcomes several of the limitations present in previous studies of residential pesticide exposure and prostate cancer. First, due to the long latency period between exposure to a potential human carcinogen and disease onset, it is important that researchers consider historical exposures. Access to historical data detailing specific crops grown and pesticides used is often a limiting factor in estimating previous pesticide exposure patterns. Our study evaluated pesticide exposure between six and sixteen years prior to diagnosis of prostate cancer, which coincides with the approximate latency period of prostate cancer.

Previous studies evaluating pesticide exposure and cancer incidence have been limited by small sample size and/or a small number of disease cases. Our population-based study included over 23,000 incident prostate cancer cases.

Third, the potential for exposure misclassification due to residential mobility over time is increased in studies of disease with a long latency period. Our study was conducted in a state with relatively low residential mobility (22, 23), thus reducing the impact of residential mobility on our findings.

Finally, previous studies have examined county-level pesticide use and prostate cancer incidence, which prevented the researchers from evaluating pesticide residues that drift beyond political boundaries. Using a GIS, we were able to identify areas of land that were potentially exposed to pesticides via drift from applications in neighboring counties and census tracts, and compute the percent of land in neighboring counties and tracts that were potentially exposed to pesticides used in neighboring counties and census tracts.

Study Limitations

This study has several limitations. Due to the ecological nature of our study, we were unable to evaluate individual-level risk factors for prostate cancer, most notably race, family history of prostate cancer, obesity and occupation, which have been shown to influence prostate cancer risk. However, with regard to occupational pesticide exposure confounding is minimal, as less than 4% of Iowa's population is employed in agriculture (22).

Additionally, the potential for exposure misclassification exists. Our GIS identified crop fields located within regions of high amounts of pesticide-specific sales, but the ecological nature of our study prevented us from evaluating individual characteristics that could influence exposure and intake of pesticides, including amount of time spent at the home, age and physical activity level. While personal communication with pesticide regulators in Iowa revealed that pesticides are typically used within 30 miles of the point of sale due to the expense and regulation involved with transport, we cannot negate the possibility of exposure misclassification based solely on this knowledge. Ideally, the exposure estimates generated in this study would be validated by examining biological samples taken from homes and residents of agricultural communities for pesticide residues. However, due to the latency period of prostate cancer, annual variability in pesticides used, and the relatively short half-life of most pesticides, validation would have to occur with historical samples. No source of such samples is known to the authors of this work.

Further, prostate cancer risk may appear in areas with higher screening rates. We explored the use of area level prostate cancer screening data available through the BRFSS. However, sparse response counts in many Iowa counties prevented further evaluation of area level variation in screening rates across Iowa.

Protocol Revisions

The initial protocol developed for this study incorporated validated pesticide use data obtained from licensed pesticide applicators in Iowa that were enrolled in the Agricultural Health Study (AHS). However, through conversation with various AHS

principal investigators, I learned that the process of geocoding the farms of participants was not at a level that could be used for this protocol. At that time, the AHS investigators were confident in the county, census tract and zip code locations of the farms, but did not have validated latitude and longitude coordinates.

Following multiple conversations with one of the lead AHS investigators in which we discussed possible ways that this protocol could be modified to accommodate area-level farm location, it was decided that this was not the best way to go about estimating historical pesticide exposure. One of the strengths of the original protocol was the ability to use GIS to match survey results to individual land parcels, and area-level location of survey responses did not allow for this to occur. As a result, the following modifications to the original protocol were made:

1) Pesticide activity for individual land parcels was estimated using a combination of pesticide sales data and historical land cover data.

2) The pesticide air dispersion model was not used for this study. This model was appropriate only when validated parcel-specific pesticide spray activity data could be incorporated. Instead, pesticide concentration values were estimated utilizing GIS.

3) Only county and census tract-level prostate cancer incidence data rather than precise latitude and longitude coordinates of cases were used. The level of accuracy of the land parcel and pesticide sales layers is approximately 30 meters, which negated the need for precise estimates of residence.

Implications

As defined by the EPA, a pesticide is a substance that is designed to “prevent, destroy, repel, or mitigate a pest” (24). As indicated by this definition, a pesticide is designed to do some harm to a living organism, and this harm can be afflicted on unintended recipients, such as predators of those pests, as well as humans. However, pesticide use can also be beneficial to society. Pesticides control potential disease causing organisms, including certain bacteria and fungi; prevent the spread of weeds and insects that can reduce agricultural crop yields (25); and control potential disease transmitting organisms, including mosquitoes and ticks. Understanding risk of adverse health effects in humans from unintentional pesticide exposure is critical to achieving a balance between safety and worldwide food production needs.

Although a significant body of evidence surrounding the risk of prostate cancer following exposure to pesticides exists, few studies have focused on risk to individuals who live in agricultural communities. Individuals who live in close proximity to agricultural fields are at risk for exposure to pesticides through drift of pesticides from their target organism to the surrounding area. Drift from large scale pesticide applications has been identified up to 1,000 meters from the source of the spray. Pesticide use is widespread in agricultural communities, with over 80% of pesticide use in the United States in the agricultural environment.

One of the greatest challenges faced by scientists attempting to estimate the association between environmental exposure to pesticides and human health risks is the quantification of dose. The typical gold standard for estimating pesticide dose is through the collection and analysis of biological samples, including urine, hair and blood

over multiple time periods at different stages in the life cycle (26, 27). However, the expense and time commitment required for these protocols often results in missing biological samples, which could result in misclassification of exposure. Furthermore, residents of agricultural communities are often not aware of the pesticides used in close proximity to their residence (28-30), which limits the utility of self-reported residential pesticide exposure data.

In order to overcome these limitations, researchers are using GIS technologies to model environmental exposure to pesticides. Despite the rise in successful application of GIS to studies of pesticide exposure and health outcomes, this study is the first to use GIS for the study of residential pesticide exposure and prostate cancer incidence. As previously noted, the GIS developed for this study produced estimates of historical pesticide exposure that transcended political boundaries, thus overcoming several of the limitations of previous work.

Although our study did not find a statistically significant increase in prostate cancer risk following exposure to the most commonly used pesticides in Iowa during 1990, it is important from a public health standpoint to reinforce the possibility that exposure to pesticides other than those evaluated in this study could increase prostate cancer risk in agricultural communities. In this study, an increase in prostate cancer risk was associated with residential proximity to corn and soybean fields. It is imperative that future research continue to evaluate environmental exposures specific to farming activity.

Conclusion

Findings from our study reinforce previous findings of an association between residential proximity to agricultural fields and prostate cancer incidence, and highlight the need for further investigation of exposure to specific agricultural pesticides other than those evaluated in this study (i.e. potentially carcinogenic pesticides used less commonly and those used in lower quantities).

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Vita

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