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Examining Spatial Distribution of Adult Glioma Incidence using SEER Data 2001-2014

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ABSTRACT

EXAMINING SPATIAL DISTRIBUTION OF ADULT GLIOMA INCIDENCE USING SEER DATA 2001-2014

By

MARISSA J. HICKS

APRIL 19, 2018

INTRODUCTION: Gliomas are most common and fatal primary brain neoplasms, with few known risk factors. High dose ionizing radiation is the only known environmental risk factor. Previous studies show Caucasians having greater rates compared to African Americans, and higher rates of glioblastoma found in areas with higher socio-economic status (SES), suggesting involvement of SES-related factors. We examine spatial distribution of glioma incidence in Caucasians and African Americans to determine geographical disparities related to race, SES, and radon.

AIM: To determine whether geospatial clusters of high glioma incidence exist, intending to identify potential environmental risk factors in areas with high glioma risk.

METHODS: Data from Surveillance, Epidemiology, and End Results (SEER) Program 2001-2014 were used to generate descriptive statistics for adult glioma. Global Moran's I test was performed for glioma rates, radon levels, and SES contextual factors and predicated use of Local Indicator of Spatial Association analysis, and results were compared.

RESULTS: Glioma rates per 100,000 were highest for ages 70-79 (18.85, 95% CI: 17.96-19.75). Incidence rates were more than twice greater for Caucasians, 7.86 (7.65-8.07), compared to African Americans, 3.48 (2.66-4.30), and other races 2.83 (1.48-3.80). County rates varied from 0 to 27.84 for all races combined.

CONCLUSION: High and low rates of glioma are not spatially random, indicating environmental risk factors for glioma. Racial disparity in glioma is persistent. An inverse relationship with low SES is demonstrated, while a positive correlation is seen with radon. Understanding risk factors and focus on high-rate areas could lead to development of prevention.

Keywords: Glioma, geospatial distribution, radon, socioeconomic status, risk factor

EXAMINING SPATIAL DISTRIBUTION OF ADULT GLIOMA INCIDENCE USING SEER
DATA 2001-2014

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APPROVAL PAGE

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Author's Statement Page

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Marissa J. Hicks

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CHAPTER I

REVIEW OF THE LITERATURE

1.1 INTRODUCTION

Gliomas are primary neoplasms that originate from glial or glial precursor cells and aggressively invade the surrounding parenchyma from which they arise (Pisapia, 2017). These tumors are characterized by lack of recognized premalignant lesions as well as lack of screening methodologies that yield tissue specimens (Pisapia, 2017). Malignant glioma is associated with high morbidity and mortality and poor survival outcomes, with a 5-year survival of less than 40% and decreasing with age, and 5% for glioblastoma (Bondy et al., 2008). The risk for recurrence is high even with surgery, and like most other cancers, there is no known cure for this brain tumor.

Gliomas can be classified as astrocytoma (including glioblastoma), oligodendroglioma, ependymoma, oligoastrocytoma (mixed glioma), malignant glioma, not otherwise specified (NOS), and a few rare histologies (Ostrom et al., 2017). However, the World Health Organization (WHO) has updated the classification of gliomas of all histologic grades to be subdivided broadly into 3 groups dependent on codeletion status of chromosomal arms 1p and 19q, and the mutational status of Isocitrate Dehydrogenase (IDH) 1, or its mitochondrial cousin, IDH2 (Pisapia, 2017). The three groups of gliomas are astrocytoma IDH mutant, astrocytoma IDH-wild type, and oligodendroma IDH-mutant and 1p/19q-codeleted (Pisapia, 2017). There is a fourth possible type of 1p/19q-codeleted tumors without the IDH mutation, but it is extremely rare, 0% cases out of 1,087 gliomas (Pisapia, 2017). The WHO does classify some astrocytoma or oligodendroglioma tumors with a “not otherwise specified” modifier so that clinicians or researchers know that the case will require additional molecular workup or that the molecular results that were obtained are irregular in some fashion (Pisapia, 2017).

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Different classifications of glioma can make it difficult to compare results across studies. In addition to histologic criteria changing over time, there is inter-rater variability in the histopathological diagnosis of glioma, meaning that incomplete, incorrect, or alternatively stated diagnoses in pathology reports or medical records can lead to an inappropriate reporting of the details of a given case (Ostrom et al., 2017). For the purpose of consistency, the definition used for this study is that defined by the Central Brain Tumor Registry of the United States (CBTRUS) as the International Classification of Disease for Oncology third revision (ICD-O-3) codes 9380-9384 and 9391-9460.

Although gliomas are a rare disease, they represent approximately 26.5% of all primary brain and other central nervous system (CNS) tumors and 80.7% of malignant tumors (Ostrom et al., 2017). Unlike most cancers for which African Americans tend to have higher rates and worse outcomes, glioma is seen more often in Caucasians. According to the Central Brain Tumor Registry of the United States (CBTRUS), the annual average age-adjusted incidence rates for tumors of neuroepithelial tissue is 7.09/100,000 for Caucasians, and 3.98/100,000 for African Americans using SEER data from 2010-2014 (Ostrom et al., 2017). In 2018 it is estimated that there will be 23,830 new cases of primary malignant brain tumors diagnosed (“CBTRUS - 2016 CBTRUS Fact Sheet,” n.d.).

It is thought that adult glioma is different from pediatric glioma. Data from different national cancer registries support the idea that brain tumors in children are epidemiologically different from brain tumors in adults (Bondy et al., 2008). The glioma incidence rate for children is approximately 0.18 per 100,000 person-years (compared to 14.07 per 100,000 person-years in adults), which is extremely rare (de Robles et al., 2015) even though brain and other

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central nervous system (CNS) tumors are the most common form of solid tumors in children ages 0-19 (Ostrom, 2017).

1.2 Risk Factors

Glioma has few known risk factors. High dose ionizing radiation exposure is the most well studied risk factor associated with glioma with evidence accumulating since the 1950s (Ostrom et al., 2014). Epidemiological studies done on populations exposed to radiation, such as atomic bomb survivors and radiotherapy patients, have shown an increase in cancer risk at doses above 100mSv (“WHO | Ionizing radiation, health effects and protective measures,” n.d.). Medical use of radiation accounts for 98% of population dose contribution from artificial sources, and 20% of total population exposure (“WHO | Ionizing radiation, health effects and protective measures,” n.d.). X-rays used for medical purposes are the largest source of man-made radiation exposure and increased frequency of use has been associated with higher glioma rates in individuals with a history of cancer in their family (Davis, Il'yasova, Rankin, McCarthy, & Bigner, 2011). There has also been evidence suggesting that cancer risk could increase at doses between 50-100 mSV based on epidemiological studies on people exposed to medical radiation during childhood (“WHO | Ionizing radiation, health effects and protective measures,” n.d.)

Radon is the main source of natural radiation that emanates from rock and soil (“WHO | Ionizing radiation, health effects and protective measures,” n.d.). It is biologically plausible that radon exposure could be a risk factor for glioma as well as other types of malignant neoplasms. If exposed to indoor radiation, the bronchial epithelium is suspected to be the tissue receiving the highest dose of ionizing radiation along with the upper respiratory tract, skin, and other organs such as the kidney and bone marrow receiving some level of exposure as well (López-Abente et

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al., 2018). If water containing radon is ingested, this would expose the stomach and other organs of the digestive system to radiation (López-Abente et al., 2018). A study done in Galicia, Spain, a region with known high radon levels, found a statistical association between indoor radon exposure and lung, stomach and brain cancer in women, with a risk ratio (interpreted as the increase in mortality for a twofold increase in exposure) of 1.28 [95% CI 1.13, 1.50] for brain cancer (López-Abente et al., 2018). It was speculated that the rates were seen higher for women because in this region women tend to spend more time indoors and drink more water when compared to men (López-Abente et al., 2018). This study was limited by a lack of data on tobacco use in this population, which is a known carcinogen and effect modifier, as well as a somewhat homogenous population that does not allow the results to be generalized to populations outside of Galicia, Spain (López-Abente et al., 2018).

Inherited susceptibility through genetic mutations is considered the only other highly agreed upon risk factor for glioma, but does not account for a large amount of cases. However, high rates of glioblastoma have been found in counties with high socioeconomic status (SES), with this association seen across all ages, sex, and races (Porter, Lachance, & Johnson, 2015), indicating that non-genetic factors can play a role in glioma risk. Due to glioma's rare nature, many previous studies have taken place within medical settings as mostly clinic-based case-control studies, which cannot address SES factors and is not ideal for examining environmental risk factors because the study sample is not generalizable to the general population. Glioma rates and mortality appear to be higher in more developed countries in comparison to less developed countries, but this could be attributed to progress in diagnostic technologies (Bondy et al., 2008).

Other suspected risk factors include cell phone use, occupational exposures and immune function, but research has yielded inconsistent and inconclusive findings regarding these risk

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factors. Studies on humans regarding cell phone use and brain cancers have yielded mixed results, and are not relatable to the general population, as many of them have been case-control studies (“Cellular Phones,” n.d.). Immune function, such as allergies and atopic diseases, have been associated with protective qualities and lower glioma risk, but this may not be consistent across all histological types of glioma (Ostrom et al., 2014). Occupational exposure to extremely low frequency magnetic fields have been mostly limited, without exposure-response relationships (Ostrom et al., 2014).

1.3 Importance of Study

This is the first study to address environmental component of glioma via examining its geospatial distribution. Previous glioma studies are mostly clinic-based case-control studies and have taken place within medical center settings allowing to recruit sufficient number of glioma cases, whereas population-based case-control studies would have to cover vast areas to identify a sufficient number of cases. Clinic-based study design cannot address SES risk factors and is not ideal to examine environmental risk factors, because the study population for each clinical center serving as the source of controls often does not represent the general population, especially with respect to SES factors (Middelburg Rutger A., Wiersum-Osselton Johanna C., Watering Leo M.G., & Bom Johanna G., 2013; Wacholder, Silverman, McLaughlin, & Mandel, 1992).

With this study we hope to lessen the gap in information regarding environmental risk factors of glioma that currently exists. Any correlations found between clusters of high or low rates of glioma with radon or SES constructs provides indication for future studies to focus on specific areas and risk factors. If no associations are found among glioma and the suspected risk factors, this cluster analysis could still be useful for finding similarities among the clusters that

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could point to an unsuspected risk factor. According to the Consensus from the Brain Tumor Epidemiology Consortium (BTEC), there is a "Pressing need for more researchers, especially junior investigators, to study brain tumor epidemiology," and specifically look at (potential) risk factors including inherited susceptibility, ionizing and nonionizing radiation, immune function, established neurocarcinogens, and metals. (Bondy et al., 2008). Little is known about the etiology of glioma and therefore it is important to try to identify populations of high risk with the ultimate goal to develop prevention strategies.

According to the United States Cancer Statistics, information obtained from population-based central cancer registries is essential for effective population-specific prevention of cancer as well as geographic prevention programs. Correctly utilized population-based information enables health care providers and policy makers to make informed decisions regarding which geographic areas or specific populations need to be equipped with specific cancer screening programs as well as diagnostic and treatment services.

Providing a geospatial analysis of this data could be very informative and useful in determining potential risk factors as well as identifying areas and populations that may need increased efforts allotted to prevention and screening programs. The results of this study could provide valuable information for following up with some of the previously suggested risk factors found in the various studies. Furthermore, if high-risk populations could be identified as a result of this study, actions and finances could be put into place to catch this disease early and prevent this aggressive disease from occurring.

1.4 Research question and Hypothesis:

This study aims to 1) determine whether the geospatial distribution of glioma is not random, and clusters with high and low rates of glioma exist in certain areas and 2) identify

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potential environmental risk factors based on the location of clusters of high rates of glioma.

The county-level incidence rates of glioma (annual number of cases per 100,000 person-years) for persons 20 years and older across several of the United States will be examined to reveal spatial patterns within the states using SEER data from years 2001-2014. We will compare aggregate rates from 2001-2014 for all races to Caucasians, and African Americans. If clusters are found, high-rate areas will be compared against low rate areas, SES contextual factors, and radon levels geographically.

Hypothesis:

The global Moran's I test will demonstrate that glioma incidence rates are not randomly distributed across the United States and the distribution of clusters is unlikely to be due to chance alone. Based on previous evidence, it is also hypothesized that there will be higher incident rates of glioma for Caucasians compared to African Americans and that high rates of glioma will be associated with higher levels of radon and socioeconomic status.

CHAPTER II

METHODS AND PROCEDURES

2.1 Data

In order to make this study financially and logically feasible, secondary data was utilized. Obtaining primary data for cancer cases across the country would be extremely expensive, time consuming, and difficult. Not to mention, the data that is needed already exists for a portion of the United States. The data used in this study is the data that makes up the United States Cancer Statistics (USCS) and was provided by central cancer registries participating in CDC's National Program of Cancer Registries (NPCR) and NCI's Surveillance, Epidemiology, and End Results (SEER) Program and submitted to CDC and NCI by November 2016. The NPCR and SEER incidence- USCS Research Data Agreement was completed and signed and submitted in exchange for access to the restricted-use database along with a SEER*Stat account. Access to the data was obtained by downloading the SEER*Stat software, distributed by the National Cancer Institute's SEER program. SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2016 (2000-2014) is the specific data set utilized in this research.

This passive surveillance system includes cancer cases diagnosed from 2000 to 2014. NPCR and SEER consider a cancer case reportable if it has a behavior code of 2 (in situ, noninvasive) or 3 (invasive, primary site only) in the International Classification of Diseases for Oncology, Third edition (ICD-O-3). The registry's sources for the cancer diagnosis are: "hospital inpatient/outpatient clinic, laboratory only, physician's office/private medical practitioner, nursing/convalescent home/hospice, radiation treatment centers, medical oncology clinics, and other hospital outpatient units/surgery centers (CDC, 2014)." Once a patient is diagnosed with cancer and the ICD-O-3 code has been entered into their medical record, medical

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facilities (hospitals, doctor's offices etc.) send information regarding the cancer incidence to their cancer registry. In most cases, highly trained registrars are the ones transferring information from the patient's medical record to the registry's computer software using specific standardized codes, and from there the data are sent to the central cancer registry. The data that is submitted contains clinical information (morphology, primary site, stage, etc.) as well as demographics, and geographic location at the time of the cancer incidence.

Contextual factors for SES were also used in this study. This data was obtained from the GeoDa Center calculated from American Community Survey (ACS) Census Bureau 2005-2009 and the U.S. Census Bureau, Small Area Health Insurance Estimates (SAHIE) program data from 2005. Categorical data estimating the predicted average radon screening levels of radon at the county level were obtained from the Environmental Protection Agency, year 2014. XPOV05 was taken from Small Area Health Insurance Estimates and put into an RTI database. N25UPL was created by the GeoDa center staff based on data taken from the American Community Survey (ACS) from years 2005-2009.

2.2 Sample

The eligible participants of this study are individuals in the United States who were diagnosed with cancer between 2000 and 2014 and had their cancer case submitted to NPCR by November 30, 2016 or to SEER by November 1, 2016. In order for the registry data to be included in the data file used for this study, the registry had to meet specific criterion: "5% or fewer cases were ascertained solely on the basis of a death certificate, 3% or fewer cases are missing information on sex, 3% or fewer cases are missing information on age, 5% or fewer cases are missing information on race, and 97% or more of the registry's records passed a set of single-field and interfiled computerized edits (NPCR and SEER Incidence-USCS 2001-2014

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Public Use Research Database).” The study sample includes the eligible participants who were 20 years or older when diagnosed between the years of 2001-2014 with (malignant) glioma, identified by “Site and Morphology ICD-O-3 histology/behavior, malignant” codes 9380–9384, and 9391–9460. The states that are included in this study are: California, Connecticut, Georgia, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, Utah, and the Seattle metropolitan area in Washington. The Detroit metropolitan area of Michigan was removed from this study because it only contained 3 counties, which was considered insufficient for performing a cluster analysis for noncontiguous data, given that the amount of adjacent neighboring counties is used in the analysis.

2.3 Measures

This study aims to identify clusters of high and low glioma incidence rates across the United States. Glioma is identified within the data set by the Site and Morphology ICD-O-3 histology/behavior, malignant variable that identifies the morphology of the cancer as malignant glioma with codes of 9380–9384, or 9391–9460, as defined by the CBTRUS. Age adjusted incidence rates of glioma are calculated per 100,000 person-years. While creating the data table in the SEER*Stat program, the data was manipulated to exclude year 2000 because starting in 2001 the registry began coding with only malignant in ICD-O-3, meaning that some data would not have been considered malignant if diagnosed under ICD-O-2 rules, which were diagnosis years <2001. Therefore, analysis begins with year 2001 through 2014 and includes the cases identified as malignant by ICD-O-3 for the purpose of consistency. Due to the rare nature of glioma, this study uses an aggregate rate created in SEER*Stat that takes the count and population by age for the cumulative 14 years and calculates the rate the same as the age adjusted rates for the individual year. This study focuses specifically on age categories that are

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20 years and older. A new age variable has been defined to create seven different levels of age categories. Race is divided into four levels including all races, white, black, and other. “All races” includes Caucasians, African Americans, American Indian/Alaska Natives, Asian or Pacific Islander, and unknown races. Other consists of American Indian/Alaska Natives and Asian or Pacific Islander. Not all of the United States have data at the county level for glioma incidence rates.

Constructs for poverty and education are used to measure indicators for the SES of individuals at the county level and are compared to areas of high and low glioma incidence rates. The construct used to quantify levels of poverty was the estimated percent of people of all ages in poverty for income year 2005, as defined by the US Census based on the Federal Poverty Level, variable XPOV05. Education level was measured as the proportion of population aged 25 years or older with less than a high school diploma or equivalent from 2005-2009 and was calculated at the GeoDa Center from the Census ACS, 2005-2009, variable N25UPL.

Radon levels were also compared to glioma incidence rates. Data on the predicted average indoor radon screening levels from the Environmental Protection Agency (EPA) was used to create a “radon” variable for the three levels of radon indicated by the EPA (US EPA, 2014). The radon variable assigned a linearly increasing value for the increasing levels of radon for each county. Counties with predicted average indoor radon screening levels less than 2 pCi/L, which is considered zone 3 by the EPA, were assigned a 1. Counties with predicted average indoor radon screening levels from 2 - 4 pCi/L (zone 2), were assigned a 2, and counties with predicted average indoor radon screening levels greater than 4 pCi/L (zone 1), were assigned a 3.

2.4 Analysis

After the desired data was configured in SEER*Stat, it was exported to SAS and organized into a table that produced age-adjusted rates for all the counties for the 2001-2014 years, as well as the aggregate rate for all years 2001-2014. Due to the rare nature of glioma, only descriptive statistics were performed on the age-adjusted rates for the individual years. The Alaskan Native registry along with five counties that had missing data and/or were labeled as “unknown” were removed so as not to create holes in the map, leaving a total of 609 counties for the analysis. Descriptive statistics on race, age, and sex were produced using SAS (**Table 3.1**). To determine the effect of outliers, a sensitivity analysis was performed, producing descriptive statistics for a set of the data with the counties containing the top 5% of the “all races” incidence rates removed, and the counties containing the top 2% of the “all races” incidence rates removed. Five percent of the 609 counties was 30.6, and thus 30 counties were removed from the analysis. Two percent of the 609 counties was 12.24 and 12 counties were removed, depicted in **Tables 4.1-4.3**.

A shapefile of the 2001-2014 aggregate incidence rates for all races, Caucasians, and African Americans was created for spatial analysis to be performed in GeoDa and was then mapped using QGIS software. The same was done for percent of people of all ages in poverty for income year 2005, XPOV05, and the proportion of population aged 25 years or older with less than a high school diploma or equivalent from 2005-2009, N25UPL.

Data on the predicted average indoor radon screening levels from the Environmental Protection Agency (EPA) in 2014 was used to create a county level shapefile in QGIS using the created “radon” variable and then imported into GeoDa for the global and local Moran’s I test before being mapped in QGIS.

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The GeoDa software was used to perform the global Moran's I and Local Indicators of Spatial Association (LISA) tests to determine if there was a cluster pattern of glioma incidence rates, SES contextual factors, and radon, and if so, where these clusters exist.

The global Moran's I test is used to test the hypothesis of spatial randomness, and if rejected, predicates the use of the LISA test to identify the local clusters. A cluster is a core county with a high or low rate that is surrounded by neighboring counties that share that same type of high or low rate. There are four types of spatial clusters identified using the LISA statistic: high-high (counties with rates higher than average adjacent to rates that are also higher than average), low-low, high-low, and low-high. Positive values for the Moran's I statistic indicate positive spatial autocorrelation and clustering in glioma rates among the counties, represented by the high-high and low-low clusters, while negative values indicate dispersion and negative spatial autocorrelation, represented by the low-high and high-low clusters (Scott, Mobley, & Il'yasova, 2017). Local spatial clusters are the locations or sets of contiguous locations, for which the LISA is significant, meaning the null hypothesis of no local spatial association can be rejected (Anselin, 1995). The significance for the LISA test is established by bootstrapping, for which we used 99,999 randomized permutations to establish stability (Scott, Mobley, & Il'yasova, 2017). A weight matrix is used to define the correlation between a place (county) and its neighbors, and is then compared to the 99,999 correlations between the place and randomly chosen neighbors from all the other possible counties.

Because states with available cancer data are not contiguous across the country, the weights matrix used in the LISA analysis for this study was k-Nearest neighbors and the number of neighbors was chosen to be four because Hawaii has a total of five counties. GeoDa calculates actual correlation with neighbors by calculating the correlation between each county's glioma

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incidence rate and the neighbor's value for glioma incidence rate ((Scott, Mobley, & Il'yasova, 2017). When the correlation is in the far tail of the bootstrap distribution, the correlation is considered extremely unlikely to have occurred by chance alone and the hypothesis of spatial randomness can be rejected.

The clusters of high-high and low-low glioma rates were compared to the similarly constructed high-high and low-low LISA clusters for the SES contextual factors and predicted radon screening levels. A Wilcoxon Two-sample test was used to compare the underlying statistics for median poverty and education variables in the high-high and low-low glioma clusters to determine if there was a significant difference in the median poverty and education variables between high and low clusters of glioma. A Kruskal-Wallis test was used to compare the underlying statistics of the glioma rates within different radon zones, to determine if a significant difference exists in the rates dependent upon the level of radon. Finally, a chi-squared test was used to compare the frequencies of high-high and low-low glioma clusters to the frequencies of high-high and low-low clusters of poverty, education levels, and radon levels. This test was used to determine if the frequency of matched, high-high glioma crossed with high-high SES or radon, or mismatched, high-high glioma crossed with low-low SES or radon, cluster types was significant or simply due to chance.

CHAPTER III**RESULTS**

Age adjusted glioma incidence rates per 100,000 were consistent with previous studies. The rates were highest for adults ages 70-79, with a rate of 18.85, 95% CI [17.96, 19.75]. The age adjusted incidence rates were approximately two times higher for Caucasians, 7.86, [7.65, 8.07], compared to African Americans, 3.48, [2.66, 4.30], and other races, 2.83, [1.48, 3.80]. Higher rates were also seen in males, 8.67, [8.39, 8.96], compared to females, 6.06, [5.85, 6.28]. These descriptive statistics are depicted in **Table 3.1**. The glioma rates were consistently higher for males compared to females and Caucasians compared to African Americans across all ages as shown in **Figures 3.1** and **3.2**.

Table 3.1 *Descriptive Statistics of Mean Glioma Rates*

Variable	Years 2001-2014 Aggregated	
Age	N, (%)	Mean age-adjusted incidence rate/100,000, (95% CI)
All Cases	57,444, (100)	7.28, (7.08, 7.47)
20-29 years	3,559, (6.20)	2.62, (2.18, 3.06)
30-39 years	5,133, (8.94)	3.62, (3.32, 3.92)
40-49 years	7,895, (13.74)	5.13, (4.82, 5.45)
50-59 years	11,935, (20.78)	8.30, (7.89, 5.87)
60-69 years	12,680, (22.07)	13.68, (13.07, 14.28)
70-79 years	10,616, (18.48)	18.85, (17.96, 19.75)
80 + years	5,626, (9.79)	14.31, (13.29, 15.31)
Race		
White	50,931, (88.66)	7.86, (7.65, 8.07)
Black	3,118, (5.43)	3.48, (2.66, 4.30)
Other	3,142 (5.47)	2.83 (1.48, 3.80)
Sex		
Male	32,606, (56.76)	8.67, (8.39, 8.96)
Female	24,838, (43.24)	6.06, (5.85, 6.28)

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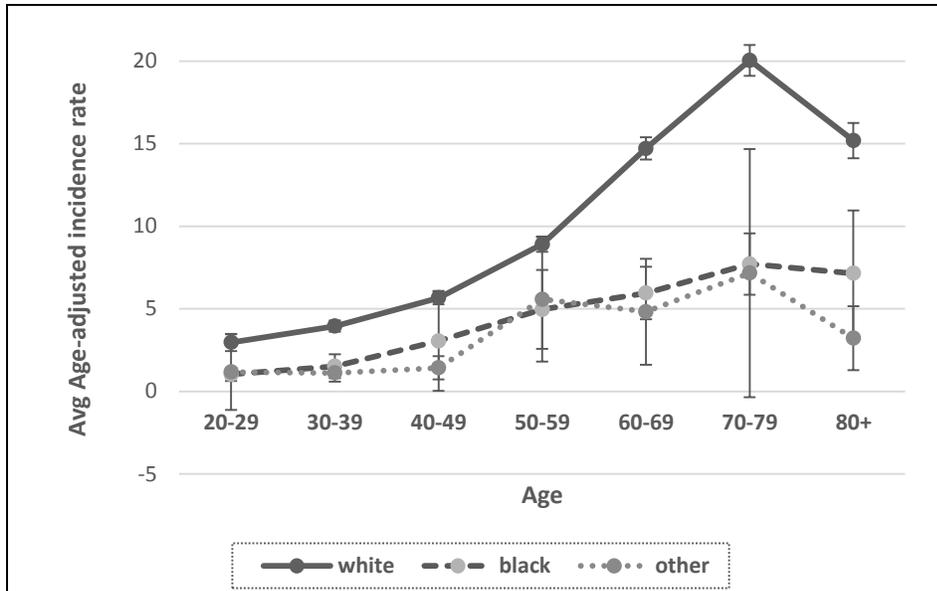


Figure 3.1 Glioma incidence rates comparing races across all ages

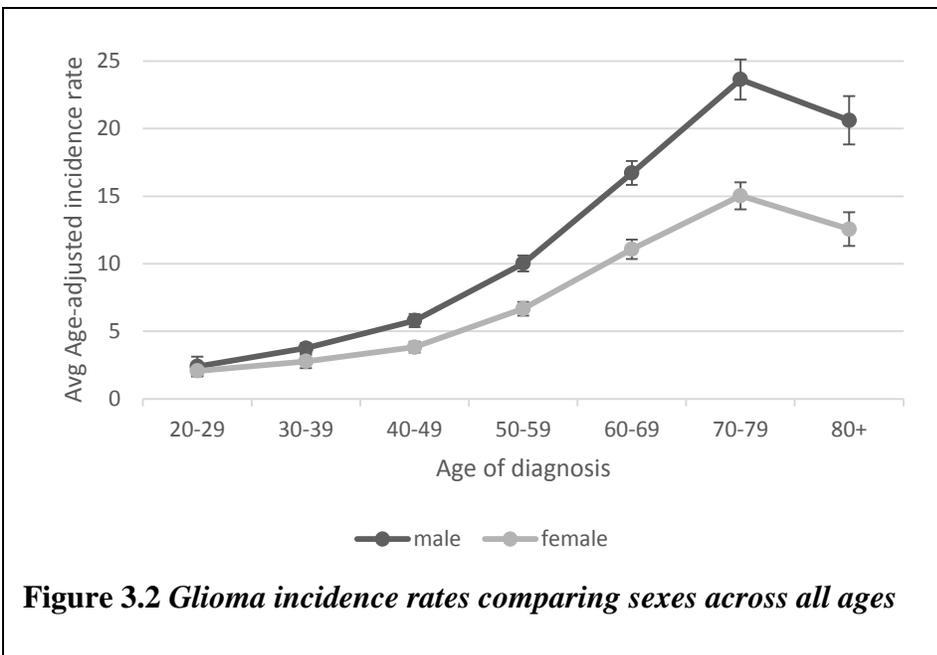


Figure 3.2 Glioma incidence rates comparing sexes across all ages

The global Moran’s I test showed positive autocorrelation, indicating the existence of clusters of glioma rates for all races with the Moran’s I value of 0.13116 and *p-value* <.01 (Table 3.2). The results of the global Moran’s I test for the radon level data and SES contextual factors are presented in Table 3.2. These results predicated the use of the LISA analysis, for

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which the results can be seen mapped in **Figures 3.3-3.6**. Results of the global Moran's I test for glioma rates for Caucasians and African Americans were not significant, and therefore the LISA test was not performed for an analysis on race. The LISA analysis found 30 high-high and 40 low-low county clusters of glioma rates within the 609 counties analyzed.

Table 3.2 Results of Global Moran's I analysis

Variable	Moran's I statistic	P-value
Glioma Rates All Races	0.131166	0.00001
Est. % of all ages in poverty 2005	0.720397	0.00001
Proportion population < H.S. Diploma 2005-2009	0.685047	0.00001
Radon Level	0.880465	0.00001

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Cluster Analysis of Glioma Incidence Rates /100,000 person years of All Races for Aggregate 2001-2014 years

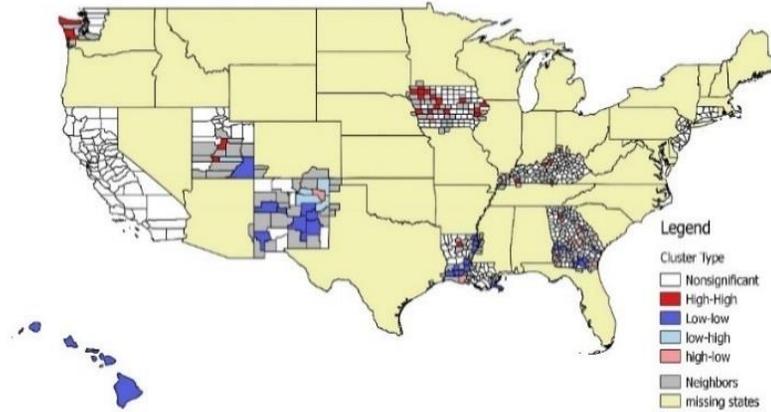


Figure 3.3 Clusters analysis of glioma rates

Cluster Analysis of Radon Levels from the Environmental Protection Agency

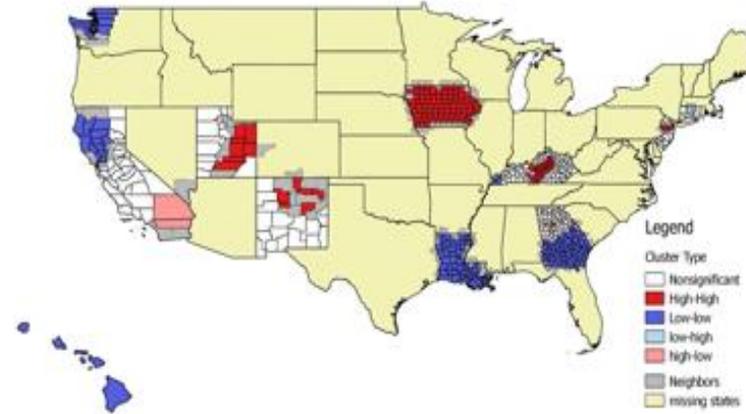


Figure 3.4 Clusters analysis of radon levels

Cluster Analysis of Proportion of Population aged 25+ yrs with Less than a High School Diploma or Equivalent from 2005-2009

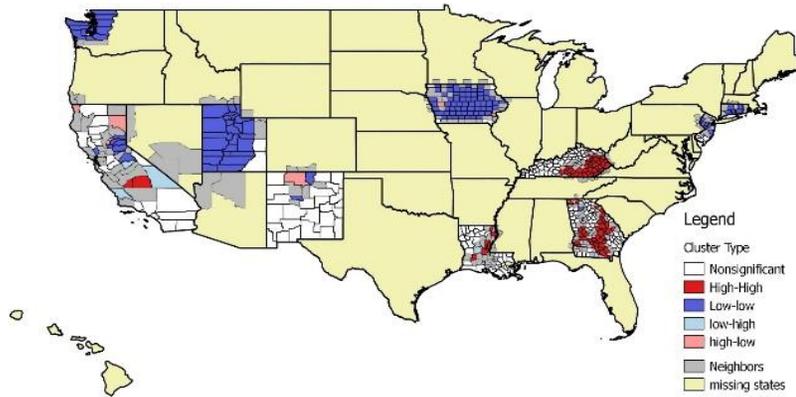


Figure 3.5 Clusters analysis of low education

Cluster Analysis of Estimated Percent of People of all ages in Poverty for Income year 2005

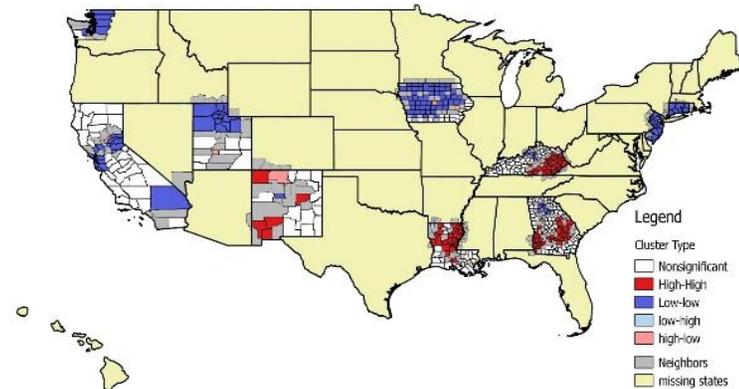


Figure 3.6 Clusters analysis of poverty

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The Wilcoxon two-sample test showed a statistically significant difference in the medians of the percent of poverty and proportion of population with low education in areas with high clusters of glioma compared to low clusters of glioma $p\text{-value} < .001$. The median values were approximately twice greater in areas of low glioma clusters compared to the areas of high clusters (**Table 3.3**). The Kruskal-Wallis test yielded significant results $p\text{-value} < .0001$ for comparing glioma rates in different radon zones. The mean highest rate of glioma, 8.30, was seen in zone 3 with the highest levels of radiation, and the lowest mean rate of glioma, 6.51, was seen in zone 1 with the lowest levels of radon (**Table 3.4**).

Table 3.3 Median Values of High-High and Low-Low Glioma Clusters & Wilcoxon Two-Sample Test

Variable	Median of SES Characteristic Distribution		Wilcoxon Test
	High-High (n=30)	Low-Low (n=35)	P Value
Estimated percent of people (all ages) in poverty for income year 2005	11.2%	24.0%	<.0001
Proportion of population 25+ years with less than H.S. diploma or equivalent in 2005-2009	0.131	0.257	<.0001

Table 3.4 Kruskal Wallis test comparing rates of glioma in different radon zones

Radon Level	Number of counties	Glioma incidence rates/100,000 person-years			Kruskal-Wallis
		Mean	Median	Std. Error	P-Value
1	221	6.51	6.53	0.153	<.0001
2	227	7.32	7.16	0.172	
3	161	8.30	8.12	0.173	

The results of the chi-square test comparing the frequencies of high-high and low-low glioma clusters to the high-high and low-low clusters found within the radon cluster analysis and SES contextual factor cluster analysis are found in **Table 3.5**. Only comparisons with other high-high and low-low clusters in the radon and SES data are shown, leaving out high-low and

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low-high frequencies among the radon and SES data. Data from Hawaii was not available in the SES contextual factor data, therefore comparing a total of 35 low-low glioma clusters, rather than 40 against the SES factors. The observed results of the chi-square test were all statistically significant, $p\text{-value} < .0001$. High-high glioma clusters shared 16 high-high county clusters with radon, while low-low glioma clusters shared 31 low-low county clusters with radon. High-high and low-low clusters of poverty and low education levels had very few same-type clusters in common with glioma, but had high frequencies of opposing cluster types in common, i.e. high-high glioma matched with 16 low-low clusters of low education levels.

Table 3.5 *Chi-Square frequency table comparing high-high and low- low cluster*

Glioma Cluster	Radon Cluster			Poverty Cluster			Education Cluster		
	High-high	Low-low	Chi Square	High-high	Low-low	Chi Square	High-high	Low-low	Chi Square
High-high	16	3	<.0001	1	13	<.0001	1	16	<.0001
Low-Low	1	31		13	0		14	0	

CHAPTER IV

DISCUSSION AND CONCLUSION

4.1 Discussion

Table 3.1 shows that our findings are consistent with results from previous studies, i.e. with higher rates in men compared to women, Caucasians compared to African Americans and other races. Also, the highest age-specific rates were in adults between 70 and 79 years old. This was consistent across all races and sexes. **Figures 3.1** and **3.2** demonstrate that the glioma rates increase with age up until age 79, at which point the rates start to decline.

Based on the results of the global Moran's I test for glioma rates for all races, the null hypothesis that glioma rates are spatially random can be rejected. The Moran's I statistic showed positive autocorrelation of glioma rates for "all races", indicating clusters of high-high and low-low rates existing in the eleven states that were analyzed. The LISA analysis showed clusters of glioma in eight of the eleven states in **Figure 3.3**. California, Connecticut, and New Jersey did not have any significant clusters of glioma.

The results of the global Moran's I test suggest involvement of environmental risk factors associated with higher rates of glioma, otherwise the rates would show a random distribution, or negative autocorrelation. Identifying these clusters of glioma allows for a principally different search of environmental risk factors associated with high glioma risk.

Previous studies have indicated a higher risk for Caucasians compared to African Americans, and the incidence rates for glioma found in this study also indicated the same. However, clusters were not found to be significant by race. This could be due in part to the fact that only eleven states were included in this data and many of the counties within these states had very low populations of African Americans. Therefore, this study did not examine clusters by

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race, but rather by SES indicators, which have been previously found to be associated with glioma risk.

The global Moran's I test showed strong evidence of positive autocorrelation (clusters) for radon levels, poverty levels, and proportion of the populations with low education levels, as seen in **Figures 3.4, 3.5, and 3.6**. Clusters were seen in all eleven states for these potential risk factors, and when compared to the clusters of glioma, a positive correlation appears between radon and glioma rates, while the SES contextual factors demonstrate an inverse relationship. **Table 3.3** highlights the significant differences in percent of the population in poverty and proportion of the population with low education levels seen among high and low clusters of glioma. The difference is approximately twofold, making it evident that these clusters are very different from each other and that higher percentages of the population in poverty and higher proportions of the population with low education levels experience lower rates of glioma.

Conversely, **Table 3.4** demonstrates the positive correlation that radon shares with glioma rates. The mean rates seen in counties with lower levels of radon are significantly different from the higher rates seen in counties with high levels of glioma. The mean rates are also similar to the median rates and have small standard errors, indicating the reliability of the mean rates.

Perhaps the most informative information comes from **Table 3.5**, where the inverse relationship between glioma and the contextual factors indicating low SES is difficult to ignore next to the positive correlation between glioma and radon. Only one cluster is classified as high-high for both glioma and poverty and glioma and low education levels, with zero clusters being seen for both low-low clusters for both contextual factors while the discordant cluster types share more than 10 clusters each. The likelihood of this being caused by chance alone is thought to be

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extremely low and is confirmed by the *p-value* produced by the chi-square test. The opposite holds true for glioma compared to radon levels, in which discordant cluster types share 3 or less clusters, but concordant clusters have 16 or 31 clusters in common. This is very indicative of a positive correlation.

4.2 Strengths and Limitations

Epidemiological studies of glioma are complicated because these are relatively rare malignancies and they are histologically diverse. It is thought that specific histological subtypes present different etiological pathways. Incidence rates of glioma can vary significantly by histologic type, age of diagnosis, gender, race, and country (Ostrom, 2014). It is possible that there could be various risk factors for the different types. However, this study groups them all together, making inferences slightly less generalizable to each histology of glioma. Another complication in studying glioma is the fact that there are no premalignant lesions or screening methods. Essentially, the tumor could go unnoticed until severe symptoms prevent themselves, and therefore there could be a small population of glioma cases that go undiagnosed even after death. It is not expected that there would be a large population of undiagnosed glioma, but it could be a limitation.

The rare nature of glioma also created limitations in the ability to study the trends over time as year-specific estimates of adult glioma are unstable. An attempt was made to aggregate the rates for every three years, but there were so few cases that extreme outliers appeared to influence the results. Cases were not suppressed in the data, but for the purpose of comparing rates by races, the counties that had relatively small African American populations created extreme outliers if a case was seen in an African American within that county. A sensitivity analysis was performed to assess the effect that these outliers might have on the data. The

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variance appeared to be very large for the African American race, but this did not appear to critically affect the mean rates for the aggregate 2001-2014 when comparing the mean rates with all the data to the mean rates with 5% (30 counties) and 2% (12 counties) of the outliers removed. In **Tables 4.2** and **4.3** the results of the sensitivity analyses can be seen and compared to **Table 4.1** with all 609 of the counties included. The relationship between the races appeared to hold true across the sensitivity analysis for the mean and medians, with somewhat smaller values seen when 5% of the top outliers had been removed. All of the counties were included in the analysis in order to represent the data that was found because it is still important if one African American out of a population of 21 was diagnosed with glioma in a given county.

Table 4.1 *Descriptive statistics with all counties included*

Race	N	Mean	Median	Min	Max	Std Err	Var
All Races	609	7.285	7.29	0	27.84	0.1003	6.127
Caucasian	609	7.857	7.92	0	30.04	0.1090	7.242
African Am.	609	3.476	0	0	208.69	0.4283	111.740

Table 4.2 *Descriptive statistics for data with 2% outliers (12 counties) removed*

RACE	N	Mean	Median	Min	Max	Std Error	Var
All	597	7.127	7.20	0	12.420	0.088	4.635
Caucasian	597	7.696	7.88	0	23.490	0.097	5.632
African Am.	597	3.135	0.61	0	109.930	0.267	42.617

Table 4.3 *Descriptive statistics for data with 5% outliers (30 Counties) removed*

RACE	N	Mean	Median	Min	Max	Std Error	Var
All	579	6.987	7.14	0	11.15	0.085	4.144
Caucasian	579	7.561	7.830	0	23.49	0.095	5.176
African Am.	579	3.166	1.03	0	109.93	0.274	43.491

Lack of data for the continuous United States may have limited the statistical power of this study. When the global Moran's I test was performed for Caucasian and African American

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racess separately, significant clusters were not seen. The eleven states included in this study were not contiguous, limiting the ability to find neighbors of cores with similar rates across state borders. After finding significant results for glioma age adjusted rates for all races (all ages and all sexes), Georgia, California, and Iowa were tested individually for clusters of glioma for all races. California and Iowa were both statistically insignificant; Georgia showed significant clusters for all races, but not for Caucasians or African Americans.

In addition, the weight used for the cluster analysis was the K closest neighbors weight, searching for four of the closest neighbors. Ideally, a higher number of neighbors could be used to examine the sensitivity of the results to this specified parameter, but in order to include Hawaii in the study without pulling its neighbors from other states from the continuous United States, four neighbors had to be used due to Hawaii being made up of five counties. Hawaii could have been excluded from this study in order to utilize six neighbors in the weight, but this study already had so few counties included in the dataset and glioma is a very rare cancer, so it was included in the analysis.

Lastly, the data used to create the radon variable for the cluster map was not continuous data, but in fact, ordinal categorical data. This limits the ability to which the radon clusters can be interpreted.

4.3 Implications of Findings

The results of the Kruskal-Wallis test indicated that as the radon levels increased, glioma incidence rates showed a statistically significant increase as well. Radon and low-dose radiation are associated with higher glioma rates and prevention measures can be taken to reduce radon and low-dose radiation exposure. It is important that we utilize the knowledge of high rate clusters to implement prevention methods in these specific high rate areas, so as to maximize our

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efforts in reducing and preventing glioma incidence rates. Preventative measures can be taken to lower radon levels, such as radon screening tests and radon mitigation process. Perhaps an initiative needs to be taken to encourage homeowners to have their homes screened for radon.

Identification of areas with high glioma rates provide basis for a principally different search of environmental risk factors associated with glioma risk. Instead of conducting clinic-based studies, future glioma studies can be focused on high- and low-rate areas to determine exposures contributing to the risk of glioma.

4.4 Recommendations for Further Research

It is recommended that further research be done with more data collected from all over the United States, rather than limited to only eleven states. Glioma is such a rare disease, that more data needs to be made available in order to have sufficient data to analyze populations by race or other characteristics that could attribute to high risk.

As previously stated, future studies should focus on clusters of high glioma rates to find environmental and socioeconomic similarities among the geographically different populations so as to hone in on potential risk factors that these populations are exposed to. The geographic variability seen in glioma rates needs to be explained. Further research should be done to investigate what could link high SES and radon levels to glioma; perhaps more research is needed to determine if cell phone use or certain occupational exposures are associated with radon and higher SES.

Additionally, spatial regression could be used to perform a multivariate analysis of the relationships among glioma, radon, and SES contextual factors by state, and to determine if there is spatial lag or apparent contagion involved in the results seen in this study. This research could also be replicated using Empirical Bayes LISA analysis to look at counts of glioma within the

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population of the counties rather than the rates, which can be useful when dealing with rare diseases and counties with low populations. Perhaps this type of analysis would show different results when analyzing clusters by race.

4.5 Conclusion

This is the first study to address the environmental component of glioma via examining its geospatial distribution and provides evidence that clusters of glioma incidence rates are not spatially random, indicating environmental risk factors at play. In addition, there is evidence of an inverse association between glioma clusters and indicators for low SES clusters, agreeing with previously published findings that higher SES is associated with higher rates of glioma. There is a need to examine environmental factors present in clusters of high SES. This study also found evidence of an association between glioma and radon clusters, supporting the hypothesis that low dose radiation is a risk factor for glioma.

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