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Spatio-Temporal Analysis of Childhood Retinoblastoma and CNS Tumors in Kentucky, from 1995 through 2014

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Spatio-Temporal Analysis of Childhood Retinoblastoma and CNS Tumors in Kentucky, from 1995 through 2014

CAPSTONE PROJECT PAPER

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ABSTRACT

Objectives
Childhood cancer poses a significant public health burden, both globally and in the United States (US). The most common childhood cancers affect the brain and central nervous system (CNS). Age-adjusted childhood brain tumor (CBT) incidence rates in Kentucky are larger than in the rest of the US; these rates are also higher in Appalachian Kentucky than in the rest of the state. This study determined if high-rate clusters of either CNS tumor or retinoblastoma existed in Kentucky.

Methods
Data for this study were retrieved from the Kentucky Cancer Registry for the years 1995 through 2014. Cases were individuals between the ages of 0 and 19 years that were diagnosed with either retinoblastoma (N=81) or a CNS tumor (N=1042). Population data for demographic subgroups defined by binary combinations of age, sex, and race were obtained from the CDC WONDER Bridged-Population database. Spatial scan statistics, used to identify high-rate clusters of CBT, were implemented using SaTScan Version 9.4.4. Clusters were mapped using ArcGIS version 10.4.1.

Results
One significant high-rate cluster of CNS tumor cases was identified across the northern part of Appalachian Kentucky and northern and central parts of Kentucky ($p<0.0001$), but there were no significant high-rate clusters of retinoblastoma cases.

Conclusions
The significant cluster identified by the spatial scan statistic somewhat corresponds to previous findings indicating a higher rate of these cancers in the Appalachian region, but it was not confined to Appalachia. Future aims of this pilot study are to identify possible risk factors that may be causing this increase.

INTRODUCTION

Childhood cancer poses a significant global public health burden, with between 175,000 and 250,000 incident cases annually.[1] While approximately 90% of childhood cancer cases occur in developing countries, the American Cancer Society (ACS) estimates that, in 2017, 10,270 incident cases of cancer will be diagnosed among children, aged 14 years and under, in the United States (U.S.), where incidence rates for childhood cancers have increased annually by 0.6% since 1975.[1,2] Although mortality rates have decreased from 6.5 to 2.0 (per 100,000 persons) between 1969 and 2014, it is estimated that 1,190 deaths from childhood cancer will occur in 2017; the US relative survival rate for all childhood cancers is 83%.[2]

The most common solid tumors that affect children occur in the brain and central nervous system (CNS) (26% of all childhood cancers), with a five-year survival rate of 79%.[2] The histological subtypes of childhood brain tumors (CBTs) include gliomas (which arise from glial cells) and tumors of embryonic cells (which develop if these cells are present in the CNS post-partum).[3-5] The most common CBT in children, aged 14 years and under, is pilocytic astrocytoma, which comprises 17% of all CNS tumors in children; incidence rates are between 0.74 to 0.9 (per 100,000 persons), with a 10-year survival rate greater than 96%.[3,6] Retinoblastoma comprises 2% of all cancers diagnosed in children under age 5 years and has a five-year survival rate of 95%.[7] Less common forms of CBT include brain stem glioma, diffuse astrocytoma, high-grade astrocytoma, primitive neuroectodermal tumor (PNET), medulloblastoma, and atypical teratoid/rhabdoid tumor (ATRT).[3,5]

There are currently few recognized risk factors for CBTs, including ionizing radiation exposure and certain cancer syndromes, though there have been several studies where researchers examined other potential risk factors[3,8-30] These include advanced parental age, parental exposures (i.e., maternal nutrition, cigarette smoking, proximity to radiofrequency electromagnetic fields, paternal occupational exposure to radiation or chemicals), high socioeconomic status, birth defects, markers of fetal growth, genotype interactions, residential pesticide exposure, and certain infections.

Previously, researchers conducted a study comparing pediatric brain tumor incidence in Appalachian versus non-Appalachian regions to determine if astrocytoma risk among Appalachian children was greater than national rates. From the North American Association of Central Cancer Registries (NAACR), for the years 2001 through 2011, Huang, et. al., identified CNS tumor cases, diagnosed in approximately 27,000 non-Appalachian and 2,200 Appalachian individuals between the ages of 0 and 19. Here, researchers determined that pediatric CNS tumor incidence rates (reported per 100,000 with 95% confidence intervals (CIs)) were greater among Appalachian (3.31, 3.17-3.45) cases than among non-Appalachian cases (3.06,3.02-3.09). Additionally, from the years 2004 through 2011, researchers determined that World Health Organization (WHO) grade I astrocytomas were greater in Appalachia (0.63, 0.56-0.70) than in non-Appalachia (0.44, 0.43-0.46).[31]

Presenters to the Interim Joint Committee on Health and Welfare (September 21, 2016) observed that age-adjusted childhood cancer incidence rates, from 1999 through 2013 (per 1,000,000), when compared to the entire state of Kentucky and to the U.S., are larger in Appalachian Kentucky; that is, 184.0 compared to 176.0 and 174.0 in Kentucky

and in the U.S.[32] These differences were statistically significant ($p<0.05$) among males (age-adjusted incidence of 202.0 per 1,000,000 compared to 188.0 for the entire state and 182.0 for the U.S.). Incidence rates for CNS cancers were also significantly higher when comparing Appalachian Kentucky to the U.S. (approximately 40.0 per 1,000,000 versus approximately 32.0 per 1,000,000).

Table 1.1 shows age-adjusted incidence rates (per 1,000,000) and 95% confidence intervals (CIs) for pediatric CNS tumors and retinoblastoma for individuals between ages 0 and 19 years from 2010 through 2014.[33,34] Rates are shown for Appalachian Kentucky, the whole state of Kentucky, and the U.S.; these are considered significantly different from each other since CIs do not overlap. During this time period, incidence rates of CNS tumor were significantly greater in Appalachian Kentucky (45.7, 35.4-58.0) and the whole state of Kentucky (40.5, 35.4-46.1) than in the U.S. (32.2, 31.6-32.7). The incidence rate for retinoblastoma cases in Appalachian Kentucky during this period was not stable from 2010 to 2014 because the case count was less than 15; this is marked in the table with an asterisk. There were no statistically significant differences when comparing incidence rates for retinoblastoma.

To investigate this phenomenon, the present study focused on identifying regions of Kentucky where clusters of CBTs exist. CBTs of interest for this study include CNS cancers defined by site groupings specified by the International Classification of Childhood Cancer (ICCC). These site groupings are based on the International Classification of Diseases for Oncology (ICD-O-3) and the World Health Organization (WHO) Classification of Tumors of Haemotopoietic and Lymphoid Tissues (2008) (ICD-O-3/WHO 2008); groupings are based on site and histology combinations. Cancer groups

for this project include “III CNS and miscellaneous intracranial and intraspinal neoplasms” and “V Retinoblastoma”.[35] Throughout this paper, these defined cancer groups will be referred to as CNS tumor and retinoblastoma.

The results of this study will be used to guide further research into this topic, including later identifying possible risk factors that may be associated with increased risk of either CNS tumor or retinoblastoma within significant clusters. After determining risk factors within clusters, these results can be used to target interventions and reduce pediatric CNS tumors and/or retinoblastoma in high-rate areas.

LITERATURE REVIEW

A literature review was completed using PubMed, an online database containing peer-reviewed publications that pertain to life and biomedical sciences; this is maintained by the United States National Library of Medicine at the National Institutes of Health. The following keyword searches were performed to identify pertinent resources: “childhood brain tumors”, “childhood astrocytoma risk”, and “childhood CNS tumors risk”. Results were restricted to those publications that were published within the past 10 years and studied human subjects.

Prenatal Factors/Parental Exposures

Several researchers have assessed the relationship between CBTs and prenatal risk factors, including environmental exposures among parents (i.e., maternal nutrition, parental smoking, and parental environmental exposures).

These studies show that dietary factors and nutritional supplements may have a protective effect against CBTs. In an international case-control study looking at cases diagnosed between 1982 and 1992 Pogoda, et. al., revealed that maternal consumption of

cruciferous vegetables and fresh fish significantly reduced the risk of anaplastic astrocytoma and astroglial tumor.[29] Milne, et. al. (2012), in an Australian case-control study conducted between 2005 and 2011, showed that mothers who used folic acid supplements prior to pregnancy had children with the lowest risk of CBT; risk was also lower among children of mothers that used supplements during pregnancy.[22] A different study identified a possible negative association between pre-pregnancy folic acid supplementation and CBT risk where a mother, father, or child has the MTRR 66GG genotype; this genotype alone, however, does not significantly decrease the risk when it is present in a child or father.[30] Conversely, Mortensen, et. al., who conducted a population-based cohort study in Norway reported that there was not an association between maternal supplemental folic acid use and CBT tumor risk in their offspring.[25]

Published literature indicates that there are no significant associations between CBT risk and parental smoking either during or prior to pregnancy. Huang, et. al., performed a meta-analysis and found that relative risks were not greater for children of either mothers or fathers that smoked; results were consistent when assessing if risk increased with dose of cigarette smoke.[19] Milne, et. al. (2013), in an Australian population-based case-control study reported similar results, with no significant ORs for any parental smoking.[23] Barrington-Trimis, et. al., in a case-control study examining polymorphism genotypes using neonatal dried blood spots, found that high-risk genotype *EPHX1* H139R increased risk of CBT, with an additional dose-response pattern for paternal smoking; these results, however, were not statistically significant.[9]

Multiple researchers have conducted case-control studies to assess other parental exposures. Assessing maternal exposure to mobile phone base stations during pregnancy,

Elliott, et. al., reported no significant associations to CBT risk.[16] Keegan, et. al., considered paternal occupation and social class, as derived from fathers' occupations at the time of their child's birth, and observed significantly increased CNS tumor risk for children with fathers exposed to farm animals (OR=1.40, 95% CI 1.01-1.94) and to lead (OR=1.18, 95% CI 1.01-1.39). Increased risk associated with exposure to farm animals may be related to pesticide exposure, and the effect of lead was only significant after adjusting for social class.[21] In a study of parental occupational solvent exposure, Peters, et. al., reported a significantly increased risk for children with fathers who were exposed to aromatic solvents other than benzene (OR=1.76, 1.10-2.82).[28]

Perinatal Risk Factors

Several researchers have conducted studies to determine if associations exist between the development of CBTs and several perinatal risk factors (i.e., fetal growth, maternal/familial history, maternal infections, and birth defects).

High fetal growth is a term used to describe the development of infants who are large for gestational age (LGA).[14] An infant that is LGA has a birthweight that is greater than the 90th percentile for their gestational age. LGA can occur for multiple reasons, including genetic factors, a mother gaining excessive weight during pregnancy, and maternal diabetes. Many of the problems associated with LGA children include increased incidence of birth defects, low blood sugar (LBS or hypoglycemia) after delivery, and respiratory distress.[36]

Multiple researchers have recognized that there is an association between high fetal growth and an increased risk for CBTs.[10,14,27] O'Neill, et. al., in a population-based case-control with study data from the U.S. and the United Kingdom (U.K.), observed

high birth weight was associated with an increased risk of CNS tumors in both datasets, reported as odds ratios (ORs) with 95% CIs (U.S. OR=1.10, 1.06-1.13; U.K. OR=1.07, 1.04-1.10).[27] Crump, et. al., in a Swedish cohort study that followed subjects born between 1973 and 2008, observed that subjects with high fetal growth had significantly increased risk, independent of gestational age; results here suggest that growth factor pathways may be important to the etiology of certain brain tumors.[14] Bhatti, et. al., in a Washington state case-control study testing for circulating vitamin D3 levels from neonatal blood spots in birth records, observed that children with higher birth weights had greater vitamin D3 levels in their blood and were at greater risk of developing CBT; ORs, presented with 95% CIs, comparing higher to lower birth weight children in quartiles of vitamin D3 levels (2^{nd}=1.7, 1.0-3.3; 3^{rd}=2.4, 1.2-4.8; 4^{th}=2.6; 1.2-5.6).[10] Since vitamin D3 concentrations are affected by insulin-like growth factor 1 (IGF-1), this may be a growth factor pathway influencing the results of the above Swedish study.[10] Milne, et. al. (2008), who conducted a Western Australian population-based cohort study using intra-uterine growth measures rather than birth weight, however, observed that there was little evidence that fetal growth was associated with CNS tumor development.[24]

Researchers have also examined the relationship between maternal and familial history.[11,14] Cantwell, et. al., in a Northern Ireland population-based cohort study that following persons born between 1971 and 1986, found that the risk of CBT was significantly greater among children born into larger families or to mothers with an obstetric history of miscarriage, reported with a 95% CI (OR=1.68, 1.16-2.42).[11] In the previously mentioned Swedish study, Milne, et. al., (2008), observed that risk of CBT was greatest among those with a first degree history of brain tumor and those born to

mothers with high educational achievement.[14] This may relate to the findings of a California study that reported risk of glioma increased with maternal age over 35 years (OR=1.87, 1.00-3.52).[26] In a U.S. population-based case-control study of data pooled from five states, Carozza, et. al., reported a similar association, recognizing that ORs for astrocytoma were reduced by 30 to 40% for lower parental education levels.[12] Johnson, et. al., in a similar multi-state study, observed a significant increase in childhood CNS tumors, with positive linear trends per five-year maternal age increase (OR=1.07, 1.03-1.10).[20]

Related studies have been conducted to assess the relationship between maternal infections, childhood birth defects, and CBT risk in California. In a case-control study of children under age 16 years diagnosed with CNS tumors between 1988 and 2008, Oksuzyan, et. al., found that mothers with genital herpes or blood/immune disorders during pregnancy had children with significantly greater risk of CNS tumors (respectively, 2.74, 1.16-6.51; and 2.28, 1.08-4.83). Researchers also observed a protective effect for mothers with non-sexually transmitted infections (STIs) during pregnancy (0.28, 0.09-0.85).[26] Fisher, et. al., in a population-based cohort study of children born between 1988 and 2004, recognized that childhood cancer risk is greater in children with chromosomal birth defects, reported as hazard ratio (HR) with a 95% CI (HR=12.44, 10.10-15.32); risk was also greater with non-chromosomal birth defects, especially for brain and other solid tumors (1.58, 1.33-1.87).[17]

Childhood Exposures

Fewer researchers have assessed the role of childhood exposures. Dobbins, et. al., in a case-control study considering the influence of genotype on asthma and glioma risk

found that the single nucleotide polymorphism (SNP) region rs7216389 tags the 3' flanking region of *ORMDL3* at 17q21; this is significantly associated with both asthmas and increased risk of glioma, reported as OR with 95% CI (1.10, 1.01-1.19).[15] In a multi-national case-control study that assessed social contacts and CNS tumor risk Andersen, et. al., found that children with at least four sick days per month in their first six years of life had a significantly increased risk of glioma, reported with 95% CI (OR=2.93, 1.57-5.50).[8] These results make sense in the context of increased CBT risk observed by Cantwell, et. al., in children born into families with at least three other children.[11]

Summary

The current literature provides evidence that several risk factors may be associated with an increased risk for CBT, including parental occupational exposure to animals, lead, and some aromatic solvents; higher circulating vitamin D3 levels in neonates; high birth weight; being born into a larger family; being born to a mother with a history of miscarriage; maternal age; maternal genital herpes; maternal blood/immune disorders during pregnancy; being born with birth defects; having a genotype that predisposes one to asthma; and frequent infections in the first six years of life. Evidence, however, is most robust for the following risk factors: non-chromosomal birth defects, paternal exposure to non-benzene aromatic solvents, high fetal growth that may be related to circulating vitamin D3 levels, and maternal age over 35 years.

METHODS

Study Design and Data

This cross-sectional study was approved by the institutional review board of the University of Kentucky on March 28, 2017. The Kentucky Cancer Registry (KCR)

supplied data on CBT cases diagnosed from January 1, 1995 through December 31, 2014. The KCR is Kentucky's mandatory population-based central cancer registry and is part of the Markey Cancer Control Program's integrated cancer control effort; the KCR has collected uniform data for all cancer cases among Kentucky residents since 1995.[37] Data for this study were obtained from the KCR for all cases of retinoblastoma and CNS tumors in Kentucky for individuals aged 0 to 19 years from 1995 to 2014. The retinoblastoma dataset included tumors identified for three histological subtypes; the CNS tumor dataset included tumors for 56 histological subtypes.

Spatial scan statistics were used to identify high-rate clusters of CBT incidence in Kentucky from 1995 to 2014. This technique was chosen because brain cancer is a rare event, and county-level incidence rates are thus highly unstable. Spatial scan statistics, unlike other common local cluster analysis options (e.g., local Moran's I and Getis-Ord Gi*), enable a Poisson-based analysis based on case and population counts. Spatial scan statistics were implemented using SaTScan version 9.4.4.

SaTScan is a free software that analyzes spatial, temporal, and space-time data using scan statistics. It was developed by Martin Kulldorff in association with Information Management Services Incorporated, with financial support from multiple divisions within the National Cancer Institute (NCI), the Alfred P. Sloan Foundation, the Centers for Disease Control and Prevention (CDC), the National Institute of Child Health and Development, and the National Institute of General Medical Sciences.[38]

Several researchers have used spatial scan statistics to identify high-rate brain cancer clusters.[39-41] Kulldorff, et. al., utilized spatial scan statistics to determine if rates of brain cancer were not greater than expected in the Los Alamos neighborhood of New

Mexico.[39] Smith, et. al., used spatial scan statistics, in addition to other methods, to determine if there were geographical clusters of childhood astrocytoma cases in Sweden.[40] Fang, et. al., used spatial scan statistics to investigate descriptive statistics that indicated geographical differences of brain cancer mortality in the U.S.[41]

In a spatial scan statistic, circular or elliptical scan windows of varying sizes, are centered on the centroids of every region, and are generated across the study area to identify groups of contiguous regions that have significantly higher (or lower) rates of disease than expected. These scan windows represent potential clusters, and sizes vary continuously until the maximum population at risk is in the window. Windows in which disease rates are greater (or less) than regions outside of the scan window are identified as clusters. Space-time scan statistics are calculated using cylindrical scan windows, the heights of which correspond to time periods for potential clusters. A Monte Carlo simulation is used to determine p-values for scan statistics, comparing the calculated test statistic to statistics that were generated under the null hypothesis that disease clusters did not exist.[38] Within clusters, p-values indicate the probability that disease rates are higher (or lower) than rates in the rest of the study area.

Since a discrete Poisson distribution was used to model the probability of high-rate clusters, we obtained population data from the CDC WONDER database Bridged-Race Resident Population Estimates United States, State and County for the years 1990-2015. CDC WONDER data, rather than KCR data, was used for the population denominator because population counts within specific demographic categories were necessary to conduct adjusted analysis. Although KCR data uses Census data to provide population estimates, these estimates are aggregated and are not provided by age, race, or

sex. The CDC WONDER data, which comprise population estimates for each county in Kentucky, were downloaded on April 17, 2017.[42] We used the SaTScan software, along with the population data and the case data, to calculate outcome rates within each county and for each group defined by potential confounders (i.e., age, race, and sex).

For the years 1990 through 2009, inter-censal estimates of the July 1 resident population were used; starting in 2010, July 1 post-censal estimates were used. Inter-censal estimates are determined by taking into account two completed censuses and adjusting post-censal series of estimates for differences between census population counts and previously-calculated estimates; post-censal estimates are determined using measures of population change. For the years where inter-censal estimates were used, county-level data differs from state- and national-level data because rounding created some negative population counts that were changed to a value of zero.

Variable Selection

We stratified the data by type of cancer. Thus, one case dataset included retinoblastoma cases (N=81) only, and another dataset included all other CNS tumor cases (N=1042). Variables available for analysis included year of diagnosis, county of residence at time of diagnosis, age at diagnosis, sex, and race (white or non-white). The geographical unit of analysis for this study was county of residence at time of diagnosis. A new age variable was created by categorizing age at diagnosis as either 0 to 4 years of 5 to 19 years; these categories were chosen to maintain consistency with data previously presented at the Interim Joint Committee on Health Welfare.[32] Among the cases of retinoblastoma, one individual's race was "unknown"; there were 14 cases for whom race was "unknown" in the CNS tumor dataset. Rather than excluding these cases, "unknown"

race was changed to "white", since the great majority of Kentucky's population is white. According to the 2010 US Census, 81% of Kentucky's population ages 0 to 19 years is "white"; this demographic was estimated as 79% in 2015.[43]

Analysis was adjusted for age, sex, and race to adjust for population differences across regions of Kentucky. Population data, gathered for the years 1995 through 2014, therefore, were stratified by age (using the age categories described above), sex, and race. This created eight new demographic sub-groups, including white males aged 0 to 4 years, white males aged 5 to 19 years, white females aged 0 to 4 years, white females aged 5 to 19 years, non-white males aged 0 to 4 years, non-white males aged 5 to 19 years, non-white females aged 0 to 4 years, and non-white females aged 5 to 19 years. This data was collected for each county for each year during this time period.

Statistical Analysis

The number of cases in each county is Poisson distributed because the dataset provides case count information, and CBT diagnoses occur independently. Therefore, the discrete Poisson model was used for SaTScan analysis. Under this model, it is expected that the number of diagnoses in each county is proportional to its population size. Since we adjusted for demographic variables, an expected number of cases was calculated (using SaTScan) for each of the eight demographic subgroups– combination of binary age, race, and sex categories – across the study period. The purpose of adjusted analysis was to account for effects of these covariates on retinoblastoma or CNS tumor incidence. As previously mentioned, population differences exist across the regions of Kentucky, and such factors may be related to development of CBT.

A preliminary and purely spatial analysis – using a circular scan window with a maximum 50% of the population at risk – was conducted first. Spatio-temporal analyses - using circular scan windows with maximums of 50% and 25% of the population at risk – were then conducted. After conducting these preliminary analyses, a second spatio-temporal analysis was conducted – using an elliptical scan window with a maximum of 25% of the population at risk – to characterize more specific temporal and spatial patterns. For the spatio-temporal analyses, time was aggregated to year of diagnosis. A significance level of 0.05 was used to determine if clusters had statistically significant higher rates of either retinoblastoma or CNS tumor compared to the rest of Kentucky. This analysis was conducted twice, once for retinoblastoma and once for CNS tumors. Additionally, an analysis was conducted combining the retinoblastoma and CNS tumor data to compare to results from the stratified analysis.

RESULTS

Table 2.1 and 2.2 provide a summary of demographics for cases of retinoblastoma and CNS tumors, as well as the total populations within each demographic category in Kentucky from 1995 through 2014.[42] Total population information is provided for comparison because case data was aggregated over this time period. Retinoblastoma disproportionately affects males (60.5% of cases compared to 51.3% males aged 0 to 19 years in KY) and children aged 0 to 4 years (98.8% of cases compared to 24.3% of the 0-to-4 year old population during this period). The majority of retinoblastoma cases diagnosed between the ages of zero and four years is consistent with an average age of three years reported in the literature.[44] Additionally, the majority of retinoblastoma cases (90.1%) were white. Among cases of CNS tumor, 48.7% were male and 51.3% were

female. The majority of cases (73.6%) were between the ages of 5 and 19 years, and 91.2% of cases were white.

Tables 3.1 and 3.2 provide a summary of the elliptical scan statistics that were calculated for cases of retinoblastoma and CNS tumors. None of the clusters identified in the retinoblastoma dataset were significant. One statistically significant cluster was identified in the CNS tumor dataset. The time frame for this cluster was January 1, 2007 to December 31, 2014. The relative risk within the cluster was 1.87, with a p-value of less than 0.0001. This indicates that risk of developing a CNS tumor within these counties during this period was approximately 87% greater than in the rest of the state.

Figures 1.1 and 1.2 show the clusters identified using elliptical scan windows and setting the maximum population at risk to 25%. In these figures, the counties of Appalachia are shown in grey. Figure 1.1 shows four high-rate clusters of retinoblastoma, two of which lie in Appalachia; none of these clusters were statistically significant. Figure 1.2 shows three high-rate clusters of CNS tumors, two of which are statistically nonsignificant (indicated by black outlines). The statistically significant cluster has red outlines and encompasses 40 counties. Approximately half of this cluster lies across part of Appalachian Kentucky.[45]

Table 3.3 provides a summary of the analysis conducted for retinoblastoma and CNS tumor cases combined. Similar to CNS tumor cases, one large significant cluster (p=0.0004) was identified across the northern part of Appalachian Kentucky and the northern central part of Kentucky; the time frame for this cluster was also January 1, 2007 through December 31, 2014 and included only four additional cases. Four other clusters were identified, all of which were non-significant. Clusters 2 and 3 were similar

in location to the non-significant clusters identified for CNS tumor, but had different time frames than clusters identified for either retinoblastoma or CNS tumor. Additional non-significant clusters were identified in the north western part of Kentucky. The locations of these clusters are shown in Figure 1.3.

DISCUSSION

The purpose of this study was to identify high-rate clusters of retinoblastomas or other CNS tumors in Kentucky between the years 1995 and 2014 for individuals aged 0 to 19 years, after adjusting for basic demographic factors. No significant high-rate clusters of retinoblastoma were observed. One significant high-rate cluster was observed among those diagnosed with a CNS tumor, even after adjustment for race, sex, and age. This finding was somewhat consistent with preliminary analysis suggesting that age-adjusted childhood cancer incidence rates in Appalachian Kentucky are higher than in the rest of the state.[32] This cluster of high rates, however, extended into portions of Central and Northern Kentucky that are not generally considered Appalachia.

Comparison with Other Studies

Previous studies have indicated the utility of using spatial scan statistics to identify high-rate clusters of brain cancer incidence.[39-41] Kulldorff, et. al., used the spatial scan statistic to confirm the findings of a public health review in New Mexico that excess brain cancer mortality was not significantly higher in the region surrounding a nuclear research facility in Los Alamos.[39] Similarly, in this study we investigated findings from a previous study that claimed higher CBT incidence in one region of Kentucky. As this is a pilot study, however, additional studies will need to be conducted to investigate what

factors may be associated with increased diagnoses of CNS tumors in the cluster that was identified.

Smith, et. al., conducted a population-based study of pediatric brain tumors in Sweden, and found that there were no statistically significant clusters (either spatial or temporal) found for cases of either astrocytoma or all cases of CNS tumor.[40] Similarly, we found a significant spatio-temporal cluster for cases of CNS tumor. This study, however, included a broader age range (0 to 19 years versus 0 to 15 years) and had defined geographic boundaries throughout the entire study period (Sweden's parishes have experienced minor geographic boundaries changes, so a geographically constant standard had to be used). The risk factors of these populations are likely also different, highlighting the need for geographical analyses of CBT incidence in different regions.

Investigating previously published descriptive statistics on brain cancer mortality in the United States, Fang, et. al., used the spatial scan statistic to determine if high-rate geographical clusters existed in certain regions. In that study, significantly higher mortality was found among all adults in Southern west Kentucky and among men in of Western Kentucky and Tennessee, in addition to higher rates in other parts of the U.S.[41] Although this study used a similar methodology, it focused on the United States as a whole rather than Kentucky. Additionally, a cluster of individuals under age 20 years in Western Kentucky and Tennessee were non-significant.[41] This may be due to less mortality among children compared to adults, but also to smaller case counts. The only cluster we identified in this region of Kentucky was for retinoblastoma – which has a five-year survival rate of 95% – and was also non-significant.[7]

Possible Risk Factors for CNS Tumor

The present study identified a region of Kentucky with greater than expected diagnoses of CNS tumors in children; currently, evidence is inconsistent about risk factors. The Kentucky Birth Surveillance Registry (KBSR), which provides birth statistics for Kentucky from 2005 through 2014, produced a map (Figure 2.1) displaying rates of major non-chromosomal birth defects (including neural tube defects) by region.[46] The statistically significant cluster shown in Figure 2.2 encompasses two of the regions with the highest rates of birth defects, but also includes regions with lower rates. It is not possible, however, to conclude there is an association between birth defects and the identified cluster because it is not possible to compare rates at different scales. There is limited data available for infant birth weight and maternal age by either county or region in Kentucky, and recent requests for data from the Kentucky Cabinet for Health and Family Services have not been successful. In future analysis, it would be beneficial to link vital statistics records to cases in the KCR dataset, to determine if rates of CNS tumor are greater in regions with LGA infants and/or mothers age 35 years and older. Data is not available regarding paternal occupational exposures to non-benzene aromatic solvents.

Strengths and Limitations

The main strength of this study was the completeness of the datasets from the KCR and the CDC WONDER database. KCR data has been uniformly collected since the registry was mandated in 1995, providing twenty years of information on case demographics and county of residence. Therefore, it was possible to compare data over the study period to identify where clusters existed within the study. This is also beneficial

for determining possible causes of increased CBT rates within clusters. The CDC WONDER database uses census information to estimate population counts, and has a defined method for calculating population in non-census years. Therefore, it was possible to create defined demographic subgroups to conduct adjusted analysis.

This study had multiple limitations. Kentucky consists of 120 counties, some having considerably smaller populations than others and would have expected rates of retinoblastoma or CNS tumor close to zero. Compared to counties with larger populations, this could increase the rate of diagnosis in a county or region in some years and increase the spatial scan statistic within a cluster, influencing where high-rate clusters were identified. Adjusting for age, race, and sex, however, reduced these effects. Small populations also influence the maximum population at risk, as more counties would have to be included in a cluster to meet the pre-determined window size. To minimize the radius of scan windows and ensure that only counties with truly higher rates of diagnoses were included in clusters, the maximum population at risk was defined as 25% rather than 50%.

Small case counts exist because cancer, especially retinoblastoma, is a rare event. Regions in which retinoblastoma cases were diagnosed, therefore, sometimes appear to have high incidence rates when any diagnoses were made. Analyzing data over a long time period increases case counts, and may lead to the identification of significant clusters. The earlier presentation to the Interim Joint Committee on Health and Welfare – that indicated high incidence rates of CNS tumors (significant) and retinoblastoma (non-significant) – analyzed data from diagnoses made between 1999 and 2013. Therefore, we

looked at cases from 1995 through 2014. No significant clusters of retinoblastoma were identified however, so future analysis would benefit from additional years of data.

Race was "unknown" and changed to "white" for fifteen cases. This may have influenced analysis because of the small case counts in each year of the study period. Although race was adjusted for in analysis, changing race in the dataset could lead to an underestimation of retinoblastoma or CNS tumor incidence among those who are non-white.

Future Directions

In the present study, it was not possible to assess the relationship between possible risk factors and the high-risk CNS tumor cluster that was identified because necessary data was not available. Following this exploratory analysis, future plans are to explore what factors are contributing to increased rates of CNS tumor in the cluster detected by the spatial scan statistic. Since it is not possible, with data from the KBSR, to conclude that birth defects are greater in the cluster region than in the rest of the state, it would be worthwhile to obtain birth defect data to conduct further analysis. Additionally, data for birth weight and maternal age need to be examined to compare CNS tumor rates in this region to the rest of the state after adjusting for those factors. This could be done by linking birth records to cases in the KCR dataset. To further investigate the impact of paternal occupational exposure to solvents, a case-control study could be conducted within the region of the statistically significant cluster.

CONCLUSIONS

This preliminary study identified one statistically significant high-rate cluster for cases of CNS tumor for individuals aged 0 to 19 years in Kentucky between 1995 and

2014, but did not identify significant high-rate clusters of retinoblastoma. This cluster was across the northern part of Appalachian Kentucky and northern and central parts of the state. While this somewhat corresponds to previous findings, it is important to note that this cluster was not confined to Appalachia. Because there are currently not data available to investigate why this cluster exists, future aims as a result of findings from this pilot study are to identify possible risk factors that may be causing this increase.

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Appendix

Table 1.1: Age-adjusted incidence rates of Pediatric CNS tumor and retinoblastoma cases per 1,000,000, Ages 0 to 19 Years, 2010 through 2014

	Appalachian KY	State of Kentucky	United States
CNS tumors	45.7 (35.4-58.0)	40.5 (35.4-46.1)	32.2 (31.6-32.7)
Retinoblastoma	6.8 (3.3-12.5)*	4.0 (2.5-6.0)	3.3 (3.1-3.4)

Table 1.1 displays age-adjusted incidence rates per 1,000,000 of CNS tumor and retinoblastoma from 2010 through 2014, for individuals aged 0 to 19 years.[33,34] Shown in parentheses are 95% confidence intervals. Rates are significantly different when confidence intervals do not overlap. An asterisk (*) indicates that rates are unstable do to case counts under 15.

Table 2.1: Retinoblastoma Case Demographics, Kentucky, 1995 through 2014

	Retinoblastoma Cases (N=81) n (%)	Kentucky (N=22,459,624) n (%)
Race		
White	73 (90.1%)	19,818,448 (88.2%)
Non-White	8 (9.9%)	2,641,176 (11.8%)
Sex		
Male	49 (60.5%)	11,525,495 (51.3%)
Female	32 (39.5%)	10,934,129 (48.7%)
Age		
0-4 Years	80 (98.8%)	5,447,740 (24.3%)
5-19 Years	1 (1.2%)	17,011,884 (75.7%)

Table 2.1 displays the demographics of retinoblastoma cases, in addition to demographics for all individuals aged 0 to 19 years in Kentucky from 1995 through 2014.

Table 2.2: CNS Tumor Case Demographics, Kentucky, 1995 through 2014

	CNS tumor (N=1042) n (%)	**Kentucky (N=22,459,624) n (%)**
Race		
White	950 (91.2%)	19,818,448 (88.2%)
Non-White	92 (8.8%)	2,641,176 (11.8%)
Sex		
Male	507 (48.7%)	11,525,495 (51.3%)
Female	535 (51.3%)	10,934,129 (48.7%)
Age		
0-4 Years	275 (26.4%)	5,447,740 (24.3%)
5-19 Years	767 (73.6%)	17,011,884 (75.7%)

Table 2.2 displays the demographics of CNS tumor cases, in addition to demographics for all individuals aged 0 to 19 years in Kentucky from 1995 through 2014.

Table 3.1: Retinoblastoma Spatial Scan Statistic Summary Using Elliptical Scan Window with 25% Maximum Population at Risk, Kentucky, 1995 through 2014

	Time Frame	Number of Cases	Expected Cases	Observed/ Expected	Relative Risk	Test Statistic	p-value
Cluster 1	1/1/2010 to 12/31/2011	8	0.92	8.68	9.52	9.93	0.171
Cluster 2	1/1/1999 to 12/31/2000	2	0.028	71.59	73.38	6.59	0.928
Cluster 3	1/1/2013 to 12/31/2013	4	0.24	16.54	17.35	6.54	0.935
Cluster 4	1/1/2009 to 12/31/2009	2	0.039	50.71	51.97	5.80	0.983

Table 3.1 displays summary values from calculating spatial scan statistics for the retinoblastoma dataset. There were no statistically significant high-rate clusters in this dataset.

Table 3.2: CNS Tumor Spatial Scan Statistic Summary Using Elliptical Scan Window with 25% Maximum Population at Risk, Kentucky, 1995 through 2014

	Time Frame	Number of Cases	Expected Cases	Observed/ Expected	Relative Risk	Test Statistic	p-value
Cluster 1	1/1/2007 to 12/31/2014	179	104.04	1.72	1.87	20.19	>0.0001
Cluster 2	1/1/2009 to 12/31/2009	6	0.56	10.68	10.73	8.78	0.551
Cluster 3	1/1/2004 to 12/31/2013	64	34.86	1.84	1.89	7.58	0.878

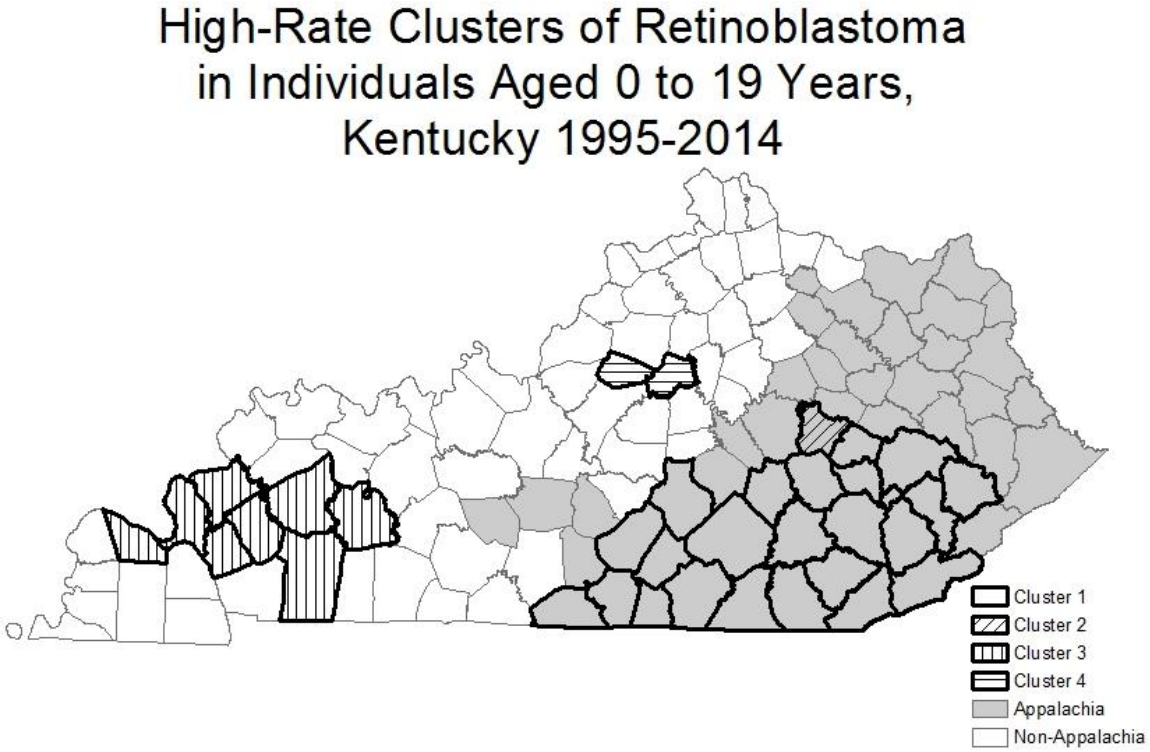
Table 3.2 displays summary values from calculating spatial scan statistics for the CNS tumor dataset. There was one statistically significant high-rate cluster (Cluster 1) in this dataset.

Table 3.3: Retinoblastoma and CNS Tumor Combined Analysis Spatial Scan Statistic Summary Using Elliptical Scan Window with 25% Maximum Population at Risk, Kentucky, 1995 through 2014

	Time Frame	Number of Cases	Expected Cases	Observed/ Expected	Relative Risk	Test Statistic	p-value
Cluster 1	1/1/2007 to 12/31/2014	183	110.60	1.65	1.78	17.93	0.0004
Cluster 2	1/1/2005 to 12/31/2014	30	11.05	2.71	2.76	9.67	0.353
Cluster 3	1/1/2006 to 12/31/2013	153	107.36	1.43	1.49	7.16	0.939
Cluster 4	1/1/2009 to 12/31/2010	10	2.64	3.79	3.81	5.98	0.999
Cluster 5	1/1/2004 to 12/31/2013	26	11.97	2.17	2.20	5.87	0.999

Table 3.3 displays summary values from calculating spatial scan statistics for the Retinoblastoma and CNS tumor datasets. There was one statistically significant high-rate cluster (Cluster 1) in this dataset.

Figure 1.1: High-Rate Clusters of Retinoblastoma Identified by Spatial Scan Statistics



This map displays the four high-rate clusters of retinoblastoma diagnoses identified by spatial scan statistics, none of which are statistically significant.

Figure 1.2: High-Rate Clusters of CNS Tumor Identified by Spatial Scan Statistics

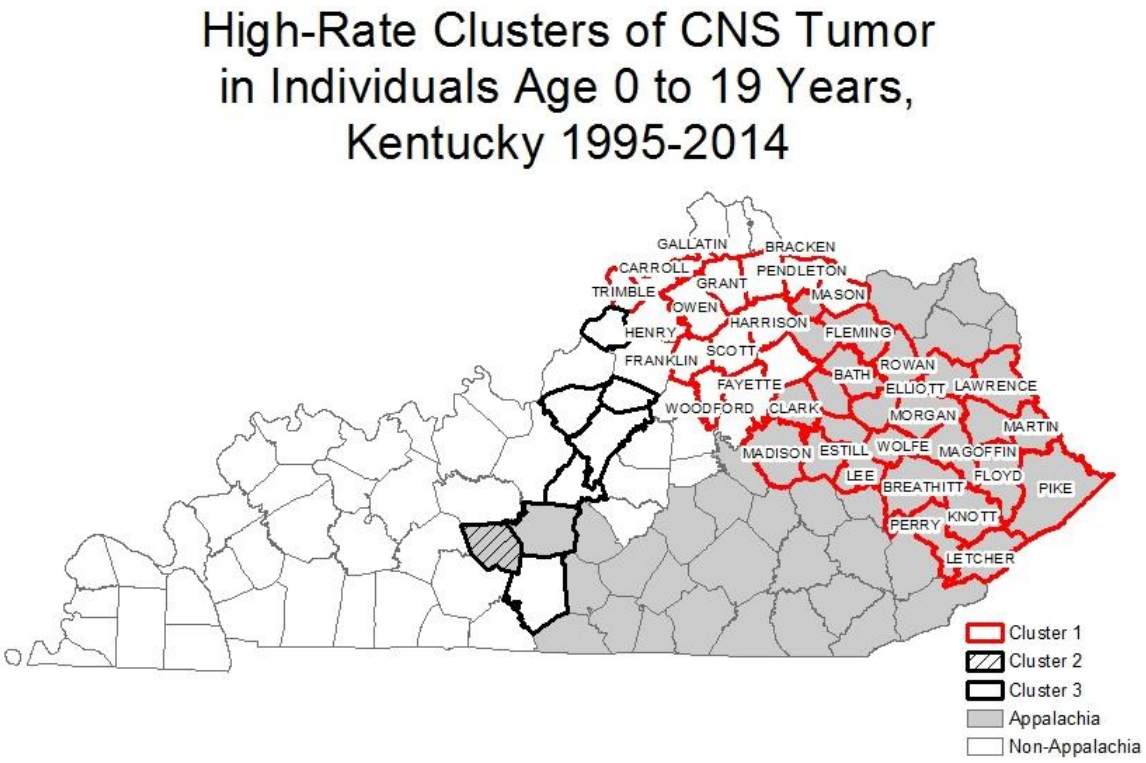


Figure 1.2 displays the three high-rate clusters of CNS tumor diagnoses identified by spatial scan statistics, only one of which is statistically significant (outlined in red, with counties labeled).

Figure 1.2: High-Rate Clusters of Retinoblastoma and CNS Tumor Identified by Spatial Scan Statistics

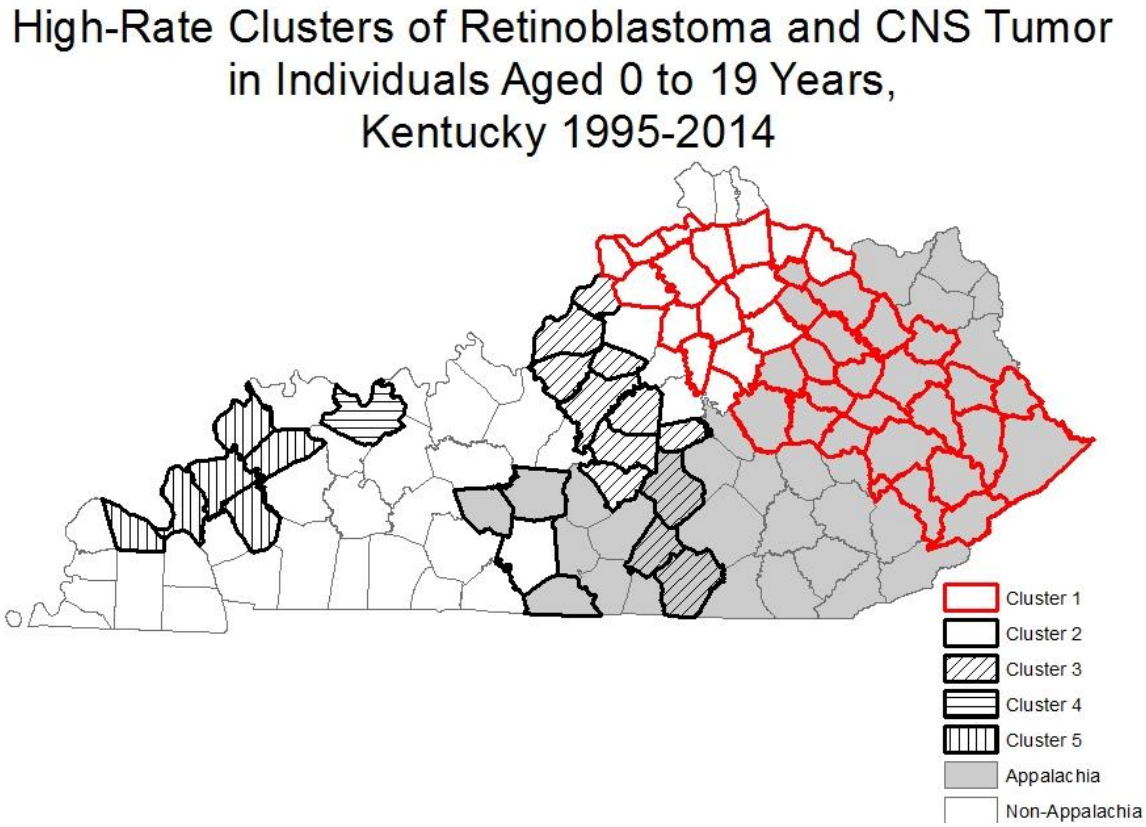
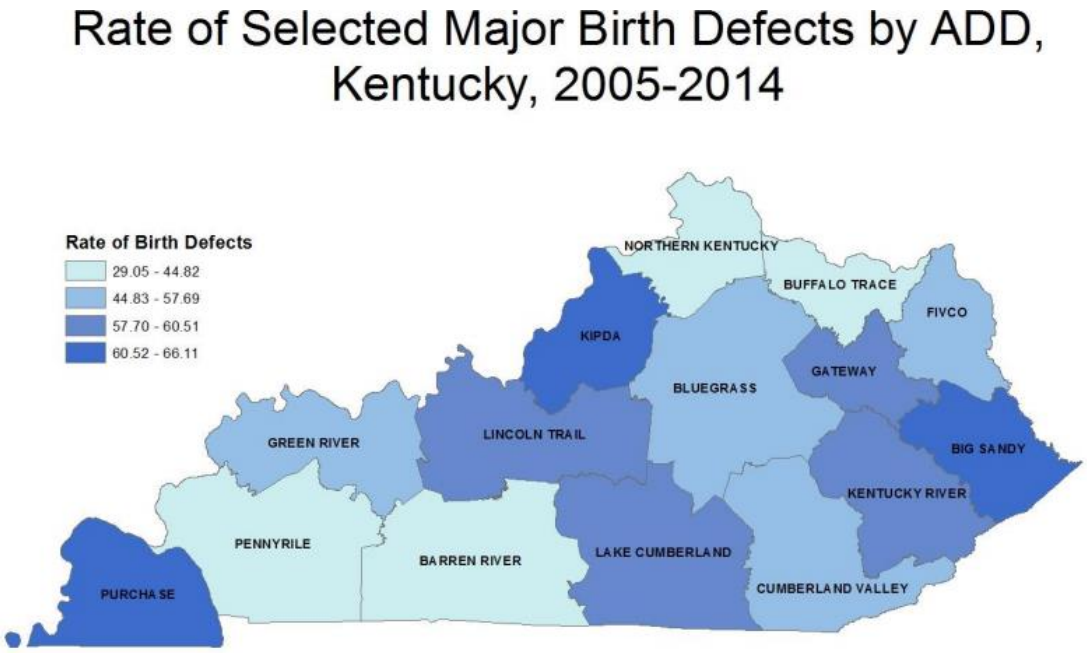


Figure 1.3 displays the five high-rate clusters of Retinoblastoma and CNS tumor diagnoses identified by spatial scan statistics, only one of which is statistically significant (outlined in red, with counties labeled).

Figure 2.1: Rate of Selected Major Birth Defects by ADD, per 10,000 Live Births, Kentucky, 2005 through 2014



This figure was prepared by Emily Ferrell, MPH CPH, from the Division of Maternal and Child Health at the Kentucky Department for Public Health, and was originally presented in the 2005-2014 Kentucky Birth Surveillance Report (KBSR), which was released August 2016.[46] Data used to create this figure was retrieved from the Kentucky Birth Surveillance Registry, Kentucky Live Birth Certificates, and Kentucky Stillbirth certificates. Selected major birth defects included critical congenital heart defects, orofacial clefts, down syndrome, neural tube defects, diaphragmatic hernia, and gastroschisis. Rates shown are per 10,000 live births.

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Biographical Sketch

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