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Maternal Occupation and Pediatric Brain Cancer in Kentucky

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Maternal Occupation and Pediatric Brain Cancer in Kentucky

THESIS

A thesis submitted in partial fulfillment of the
requirements for the degree of Master of Public Health in the
College of Public Health
at the University of Kentucky

By

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Lexington, Kentucky

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ABSTRACT OF THESIS

Maternal Occupation and Pediatric Brain Cancer in Kentucky

Pediatric brain cancer is a rare and potentially deadly diagnosis that affects children in Kentucky at a higher incidence than those nationally. Limited exposures in children early in life to warrant the development and progression of brain cancer point to the role parental exposures experienced in the period prior to conception and throughout pregnancy may play in its development. Many of these exposures may be experienced through occupation. Data on a subset of pediatric brain cancer cases in Kentucky was compared to all cases diagnosed in the state from 1995 to 2019. Survey data of the study sample was collected and work-related characteristics of biological mothers of the sample were standardized using industry codes and analyzed to identify occupation fields with potential associations to pediatric brain cancer. Cases diagnosed at a younger age and those from metropolitan areas were over-represented in the sample. The maternal occupation of the sample varied slightly from the occupational prevalence of the general population. However, since the comparison was made to all working women in the United States 16 years and older, the comparison is flawed. Additional research is needed to verify these findings and identify additional exposures that may contribute to cancer development.

KEYWORDS: Maternal Occupation, Prenatal Exposure, Pediatric Brain Cancer, Childhood Brain Tumor

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Introduction

Pediatric brain cancer is a rare diagnosis in the United States, with an incidence of 31 cases per 1,000,000 children per year. (National Cancer Institute, n.d) Among male and female children in Kentucky, the incidence of brain and central nervous system tumors was 41.6 and 38.1 per 1,000,000 children, respectively, as of 2017 (Kentucky Cancer Registry, 2020) The state rates and the rates in the Appalachian region of Kentucky, in particular, are significantly higher than the national rates. (Kentucky Cancer Registry, 2020) Despite its rarity, brain and central nervous system tumors are the leading cause of cancer death among children. (Curtin et al., 2016) The elevated incidence and aggressiveness of this form of cancer have led to questions regarding exposures and pathways leading to the development of cancer this early in life.

Because children have limited exposures early in life and most cancers have a relatively long latency, parental exposures both before conception and throughout the prenatal period may play an important role in the development of childhood cancer. (National Cancer Institute, n.d) For this reason, the excess pediatric brain cancer cases observed in Kentucky may be due to exposures experienced by biological parents immediately prior to conception and throughout pregnancy prior to birth. Research has indicated that exposure to toxic agents has been shown to affect male and female fertility, especially sperm and egg quality. (Sheiner, Sheiner, Hammel, Potashnik, & Carel, 2003) (Mendola, Messer, & Rappazzo, 2008) Additionally, previous research has indicated the ability of carcinogens and other chemical substances to enter the fetal bloodstream by crossing the placental barrier. (Mueller & Gurney, 1992) While the presence of such

exposures has the potential to cause harm, the timing of these exposures may also be critical in the growth of brain tumors. (Anderson, Diwan, Fear, & Roman, 2000)

Despite the knowledge that exposures while in utero can cause harm to a fetus, the effect of one major path of exposure, parental occupation, continues to be met with uncertainty. Many occupations enable exposure to potential carcinogens and occupational exposures are often at a higher dosage and are sometimes more prolonged than exposures sustained in the general environment. (Semple, 2005) Due to these factors the effect of parental occupation in the year prior to birth warrants more study, particularly when it comes to the occupational exposures of the individual carrying the fetus. This is especially important to consider given that between 2016 and 2019, 66.4% of pregnant women worked in some capacity during pregnancy. (Scherer, 2022)

Prior research has indicated some occupational and environmental exposures as established risk factors for the development of pediatric brain cancer. Previous meta-analyses have indicated a significantly increased risk of brain cancer in children of parents using pesticides at their residential address both prior to and after birth. (Van Maele-Fabry, Gamet-Payrastre, & Lison, 2017) (Johnson et al., 2014) A meta-analysis examining occupational exposure to extremely low frequency and magnetic fields, such as those encountered during electrical utility work and welding operations, indicated a significant increased risk (OR 1.16 95% CI (1.06, 1.26)) of CNS tumors in children of exposed mothers. (Su et al., 2018) In addition to exposures, both advanced maternal and paternal age have been found to be associated with an increased risk of childhood brain tumors. (Johnson et al., 2014)

Although not well-established, previous studies have found associations between specific occupations or common occupational exposures and pediatric brain cancer. An international, case-control study observed an increased odds of paternal work with petroleum (OR 3.4, 95% CI (1.4, 8.2)) in cases of childhood astroglial brain cancer and an increased odds of maternal work in the textile industry (OR 1.7, 95% CI (1.1, 2.7)) in cases of childhood brain cancer. (Cordier et al., 2001) Another study indicated that cases of childhood brain tumors had greater odds of maternal work as a general farmer (OR 3.8, 95% CI (1.3, 11)), maternal farm work involving potential contact with animals (OR 2.3 95% CI (1.2, 4.7)), agricultural chemicals such as fertilizers and pesticides (OR 1.9 95% CI (1.3, 2.8)), and animal manure (OR 2.0 95% CI (1.3, 3.2)) all within the 5 years preceding the child's birth. (Efird et al., 2003) Although these and several studies have indicated an association between maternal occupation and pediatric brain cancer in a variety of industries, the results are inconsistent and often contradictory. (Mueller & Gurney, 1992)

This study explored the relationship between maternal occupation during the prenatal period and the occurrence of pediatric brain cancer through analysis of population-based survey data. The purpose was to examine the prevalence of occupations in mothers of pediatric brain cancer cases in comparison to the prevalence of the same occupations in the general population of women workers nationally.

Methods

Data Collection

Participants for this study were recruited from the Kentucky Cancer Registry (KCR), which is mandated by law to collect information on all cancer cases diagnosed and treated among Kentucky residents. KCR is a part of the Surveillance, Epidemiology, and End Results (SEER) Program, which is an authoritative and comprehensive source of information for cancer statistics in the United States. (SEER, n.d.) Ongoing quality control ensures that data collected is accurate and complete. (SEER, n.d) Cases eligible for contact in this study were those that had agreed to have their contact information released to KCR for recruitment in future studies. Cases and/or their parent/guardian were contacted via telephone or, if not reachable after six attempts, text message. Those cases that were reached—or, if deceased, unavailable, or underage, their surviving family members—were asked to take part in a survey that included questions detailing past environmental exposures and parental occupation in the months leading up to conception and throughout pregnancy. Informed consent was obtained prior to survey completion via telephone or Zoom call. Survey data were combined with standard registry data collected by the Kentucky Cancer Registry. These data included KCR's standard variables available for research, including sex, age, race, cancer stage, and county of residence, among others. As this was an ongoing study, the data included in this analysis were current as of May 24, 2023.

Analysis of Study Population and All Diagnosed Cases

To determine if those completing the survey were representative of all pediatric brain cancer cases over the same time period, demographic characteristics of the

surveyed cases were compared to the same characteristics among all cases diagnosed in Kentucky from 1995 to 2019. A chi-square test for independence was used to determine if any differences were statistically significant. Significance was set at $p<0.05$. All analyses were performed using SAS 9.4. (SAS Institute, Inc, Cary NC)

The number of surveyed cases and all diagnosed cases in each county were mapped using a geographic information system (QGIS version 3.16) in order to visualize any differences in geographic distribution of cases. In these maps, the exact number of cases was censored for counties with fewer than five cases.

Occupational Analysis

Occupational category was the exposure of interest. It was derived from survey questions regarding previous maternal employers, job titles, industries, and duties. To standardize this information for analysis, O*NET OnLine was used to determine probable industry and occupation codes for each respondent. (O*NET OnLine, n.d.) The system for industry and occupation codes was the Standard Occupational Classification (SOC), which is the federal coding system for comparing occupational data. (US Bureau of Labor Statistics, n.d.) The job title and/or job description were placed into the occupation keyword search bar on the O*NET website, yielding a list of similar occupations. The listed occupation most similar to the information provided by the respondent was selected as the industry and occupation code for that observation.

Analysis was limited to maternal occupations in the year leading up to the birth of the case. The analysis focused on the primary occupation during this period, if more than one was reported. For those that worked multiple jobs in the year prior to giving birth, the primary occupation was selected based on the highest number of hours worked per week,

or, if weekly hours were the same or not indicated, the occupation listed first by the respondent (n=2). Age at diagnosis, sex, and race were obtained from case data and were collected at diagnosis.

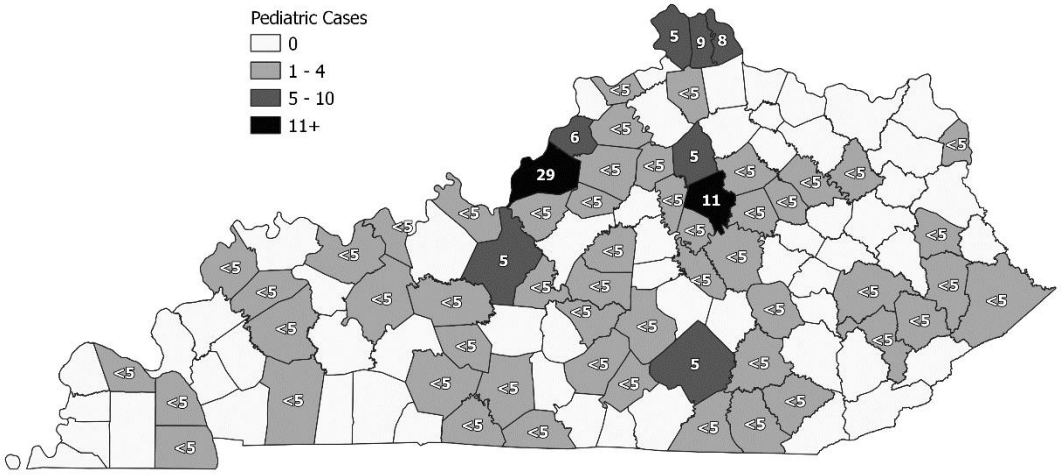
Tables of work-related variables were created for the biological mothers of surveyed cases. Variables included whether the mother worked during pregnancy, number of jobs worked, number of hours worked weekly, education level, and income. All variables were measured via self-report from the survey respondents. Due to some mothers reporting varying levels of income in the year prior to giving birth, reported income at the time of birth was used as an indication of income level.

Given the limited size of the cases enrolled in the study (n=172), the SOC codes were collapsed from 22 major groups into 6 broad categories. The national data on women's employment for those 16 and older was obtained from the Current Population Survey, which is conducted by the Bureau of Census for the Bureau of Labor Statistics. Estimates for those that were unemployed were also obtained from this source. These estimates were from 2022. Because the national estimates were for all women, including those exceeding reproductive age, an estimate of the population of women 65 years and older was taken from 2020 Census estimates and subtracted from the unemployed estimate to generate more accurate proportions. (Blakeslee et al., 2023) Military occupations were excluded from analysis as their estimates were not collected by the Current Population Survey. The proportion of mothers working each occupational category according to these collapsed codes and those unemployed were tabulated and compared to the proportion in the national population of women both employed and unemployed.

Results

Figure 1. Maps of pediatric brain cancer cases participating in the study and all cases in Kentucky by county

1A. Sample of Kentucky cases participating in the study as of May 24, 2023



1B. All pediatric brain cancer cases in Kentucky from 1995-2019, Kentucky Cancer Registry

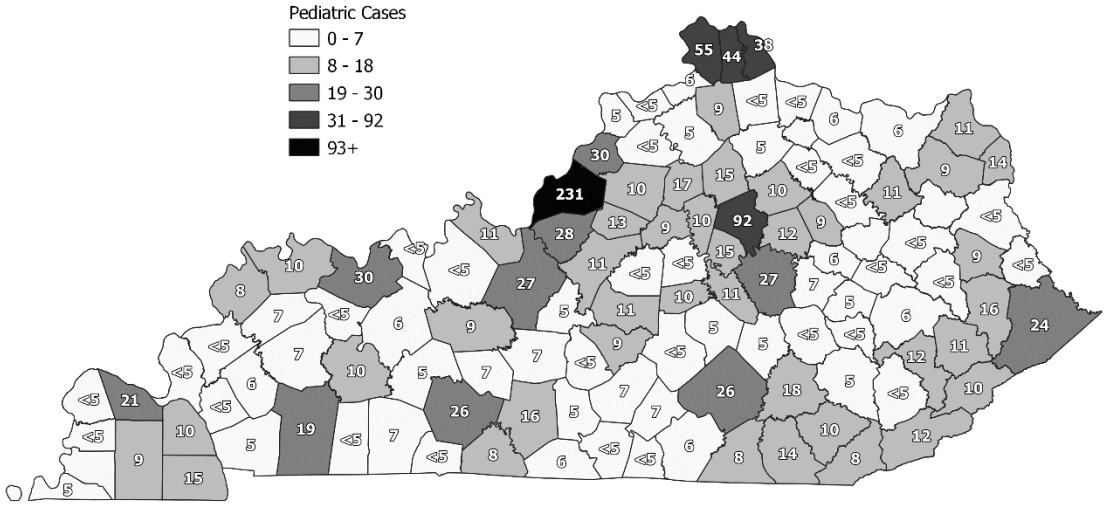


Figure 1 shows the number of pediatric brain cancer cases by county in Kentucky for both those participating in the study (Figure 1A) and all recorded cases from 1995 to 2019 (Figure 1B). The geographic distribution of cases is similar between the two groups as most cases are concentrated in urban centers and surrounding areas.

Demographic characteristics of the study population and all cases of brain cancer in those 19 and younger from 1995 to 2019 are shown in Table 1. There were significant differences between the populations in regard to age at diagnosis, race, and metropolitan status. In comparison to all cases, those responding to the survey were diagnosed younger, with 61.0% diagnosed under the age of 10. The study population was also made up of more white individuals (96.5%) compared to the overall population of cases (89.1%). More of the surveyed cases resided in metropolitan counties (67.4%) than the overall population of cases (56.8%).

Table 1. Comparison of descriptive characteristics between cases in the study population and all recorded cases in Kentucky from 1995-2019

		Study Population (n=172)	All Cases 1995-2019 (N=1436)	
Variable		n (%)	n (%)	p-value[1]
Age at diagnosis				
	0 to 4	52 (30.23)	363 (25.28)	0.0045
	5 to 9	53 (30.81)	344 (23.69)	
	10 to 14	42 (24.42)	349 (24.30)	
	15 to 19	25 (14.53)	380 (26.46)	
Sex				
	Male	94 (54.65)	704 (50.97)	0.1631
	Female	78 (45.35)	732 (49.03)	
Race				
	White	166 (96.51)	1279 (89.07)	0.0002
	Black	5 (2.91)	129 (8.98)	
	Other	1 (0.58)	28 (1.95)	
Metropolitan Status				
	Metropolitan County	116 (67.44)	815 (56.75)	0.0073
	Non-Metropolitan County	56 (32.56)	621 (43.25)	
Appalachia Status				
	Appalachian County	40 (23.26)	415 (28.90)	0.1204
	Non-Appalachian County	132 (76.74)	1021 (71.10)	

[1]Chi-square test or Fisher's exact test in the case of race

Characteristics related to work and exposures in the home experienced by the biological mothers in the year prior to the cases' birth are shown in Table 2. The majority of mothers worked throughout pregnancy (70.4%), and a small proportion worked more than one job throughout this period (5.8%). Most mothers worked full-time, with 16.3% working over 40 hours a week in the year prior to giving birth. In this sample of cases, the biological mothers were highly educated, with 76.2% having at least some college education and 46.5% completing a bachelor's degree or greater. In the year prior to giving birth, approximately two-thirds of biological mothers used pesticides of some sort at their residence and 16.3% were exposed to smoking in their home.

Table 2. Descriptive characteristics of the biological mothers of cases

Variable		N (%)
Smoking in home[1]		
	Yes	28 (16.28)
	No	134 (77.91)
	Missing	10 (5.81)
Pesticide use at home[1]		
	Yes	112 (65.12)
	No	57 (33.14)
	Missing	3 (1.74)
Worked throughout pregnancy		
	Yes	121 (70.35)
	No	48 (27.91)
	Missing	3 (1.74)
Number of jobs worked during pregnancy		
	One job	108 (62.79)
	Two or more jobs	10 (5.81)
	Did not work	48 (27.91)
	Missing	6 (3.49)
Hours worked weekly during pregnancy		
	25 hours or less	17 (9.88)
	26 hours to 40 hours	67 (38.95)
	Greater than 40 hours	28 (16.28)
	Did not work	48 (27.91)
	Missing	12 (6.98)
Education		
	Less than high school diploma	7 (4.07)
	Completed high school/GED	31 (18.02)
	Some college or Associate's degree	51 (29.65)
	4-year college degree or greater	80 (46.51)
	Missing	3 (1.74)
Income at time of birth		
	$0 to $34,999	16 (9.30)
	$35,000 to $74,999	69 (40.12)
	$75,000 to $99,999	20 (11.63)
	$100,000 or more	30 (17.44)
	Not sure/Missing	37 (21.51)

[1]Occurring anytime in the year prior to birth

The prevalence of biological mothers by collapsed occupational category compared to the overall working population of women is shown in Table 3. Of those completing the survey, approximately 30% did not work in the year prior to giving birth and nearly half worked in professional and related occupations (25.6%) or sales and

office occupations (20.1%). These proportions were slightly higher than the US population of working women in these fields which were 21.5% and 18.3%, respectively. The proportion of mothers of pediatric brain cancer cases working jobs in management, business, and financial operations, 6.1%, and service occupations, 11.0%, were lower than the proportions in the overall population of women, 12.3% and 14.25%, respectively.

Table 3. Comparison of maternal occupation prevalence in study population to overall population of US women

	Study Population (n=164)	**US Population[1] (Women 16+)**
	N (%)	N (%)
Management, Business, and Financial Operations Occupations	10 (6.10)	13,162,000 (12.93)
Professional and Related Occupations	42 (25.61)	21,921,000 (21.54)
Service Occupations	18 (10.98)	14,503,000 (14.25)
Sales and Office Occupations	33 (20.12)	18,649,000 (18.32)
Natural Resources, Construction, and Maintenance Occupations	2 (1.22)	818,000 (0.80)
Production, Transportation, and Material Moving Occupations	11 (6.71)	5,036,000 (4.95)
Not Employed	48 (29.27)	27,696,619 (27.21)

[1]Current Population Survey, 2022

Discussion

The objective of the study was to evaluate the similarity of the study sample to all cases of pediatric brain cancer in Kentucky from 1995 to 2019 as well as examine the prevalence of occupations in mothers of the cases sampled in comparison to the same occupations in the general population of women workers. The ultimate goal was to identify occupations worked in the prenatal period among mothers of children later

diagnosed with pediatric brain cancer to inform further investigation into their potential association with this rare diagnosis.

In comparing the survey population to the overall population of cases both geographically and by descriptive characteristics, significant differences were observed in age at diagnosis, race, and metropolitan status. These differences may be due to selection biases that arose during data collection. While the methods of recruitment intended for all past cases to be contacted for participation, not all past cases may have been reachable due to inaccurate contact information or failure to respond to requests. Additionally, those that were contacted and chose not to participate may be different from those who chose to participate in terms of education and level of trust in the scientific community. White individuals and those that live in urban areas, both of which were more prevalent among the study population, are more likely to be more educated. (de Brey et al., 2019) It is possible that prior negative experiences with the medical system has resulted in a lack of trust in scientific research, and may have deterred participation among those with lower education and non-white race/ethnicity. The reported information on the biological mothers of the cases supports this as over three-fourths of the sample reported having at least some form of post-secondary education. In terms of age at diagnosis, those that participated in the study were diagnosed significantly younger than all recorded cases. It is possible that greater distress is experienced among families and individuals diagnosed at a younger age, which could lead to the desire to find answers for why this occurred and greater participation.

Analysis showed that professional and related occupations were more prevalent among the study sample while management, business, and financial operation

occupations and service occupations were less prevalent. Professional occupations include jobs in healthcare, sciences, engineering, and the arts among others. These occupations tend to have lower levels of chemical and biological exposures that may impact a fetus in utero. (Montano, 2014) In comparison, individuals working in service occupations are more likely to be exposed to potentially harmful agents, such as solvents and insecticides. (Montano, 2014) Those working in professional occupations tend to be of a higher socioeconomic status, which has been associated with a higher risk for development of some types of cancer, particularly brain tumors. (Ostrom et al., 2019) While it is not currently understood why this the case, it is possible that work-related stress and sedentary behavior associated with these jobs may play a role. It is also possible that this association may be due to factors other than work, such as increased access to healthcare and lifestyle factors like the use of pesticides inside and outside of the home.

Limitations

There are several limitations associated with this study. First, the information collected was both self-reported by mothers and reported by cases themselves. Because the information was not separately verified and some of the respondents to the survey were not the mother of the case themselves, there may be some inaccuracies that could not be accounted for in the analysis. Second, the coding of the occupational information to industry codes was based on the information that was provided by the respondent in the survey. Inputting this information into O*NET Online to yield similar professions may have resulted in industry codes that are not accurate when it comes to the mother's job duties during this period. Third, occupational group prevalence among the sample

was compared to the entire population of US women 16 years and older. Ideally, the comparison would have been made to the population of working women in Kentucky as occupational prevalence may differ by state. Additionally, limiting the comparison of only those of reproductive age would likely have resulted in greater accuracy. Fourth, the sample size of cases is small. With this small sample size, a comparison of industries worked by the mothers of cases to the general population of working women may not be accurate and lead to significant results just by chance. Lastly, while the study population was comprised of cases with many different types of brain cancer, the study combined all types due to small case counts. This may have resulted in the loss of potential valuable information as all cancer types, even of the same organ, may have different risk factors for their development.

Recommendations for Further Study

Due to the number of limitations associated with the study design and the lack of comparison group, this study mainly serves to generate hypotheses for further study. Given access to resources that result in the addition of a comparison group, additional research could be undertaken utilizing this same data in order to make inferences about potential risk factors related to maternal occupation. Due to the rarity of the diagnosis of pediatric brain cancer, a case-control study would be preferred. Controls may be recruited from school records, areas of residence of cases, or medical facilities. The controls and cases would be matched on the basis of age at diagnosis and area of residence, among other potential confounding factors. Ideally, multiple controls would be matched to each case to ensure statistical power. Given that this data has occupation information available in the form of a job title, it would be beneficial for professionals such as industry experts

and industrial hygienists to assess each job title for risk of exposure to classes of agents. Classes could include chemical, biological, and physical agents among others. Jobs would be grouped according to low, moderate, or high risk for each agent class. This would help to determine which type of occupation agent may be of the greatest concern in the development of pediatric brain cancer.

The findings of this study may be important in informing future research into potential occupational causes of pediatric brain cancer. In addition to this, more rigorous studies are needed to verify these findings. Additional studies into occupational industries most worked by mothers while pregnant with cases of pediatric brain cancer cases will be required to identify specific exposures that may contribute to cancer development. Research into the timing of occupational exposures during the prenatal period may also be important for identifying critical periods of development that increase the odds of brain cancer in children.

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