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Geographic Patterns of Childhood and Adolescent Germ Cell Tumor Incidence in Georgia and Their Association with Toxic Release Inventory RSEI Scores

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Environmental Health - Epidemiology

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B.S., Florida State University, 2021
Emory University
2023

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Abstract

Geographic Patterns of Childhood and Adolescent Germ Cell Tumor Incidence in Georgia and Their Association with Toxic Release Inventory RSEI Scores

By Addison Goldstein

Germ cell tumors (GCTs) are a group of neoplasms arising from germ cells. While rare in younger children, GCTs are the most common solid tumor in those aged 15 to 19. The etiology of GCTs is widely unknown. There is a strong hereditary component but rising rates of pediatric GCTs over the past decades indicate the presence of exogenous risk factors. Previous studies suggest associations between environmental chemicals and GCTs. Using Surveillance, Epidemiology, and End Results (SEER) data, we captured 199 cases of GCTs in those aged 0 to 19 in Georgia from 2013-2019. We used EPA Toxic Release Inventory data to investigate RSEI scores, a metric used to quantify the composite health risk associated with a facility's toxic releases. We aggregated cases and RSEI scores by county, and by cancer registries associated with the facilities and case's county - Rural Georgia, Greater Georgia, and Atlanta (Metro) registries. Using U.S. Census population data, we found age and sex specific population sizes. Our hypothesis was that registries with counties with higher RSEI scores would have a higher incidence of GCTs. Using Poisson regression, we modeled the association between cancer registry, RSEI score, and incident GCT cases, while controlling for age group and sex, and offset by log(population). We found no statistically significant associations between RSEI scores or cancer registries and incident GCTs. The risk of GCTs in counties in Greater Georgia was 2.02 (0.11, 39.67) times the risk of GCTs in Rural counties ($p=0.62$). The risk of GCTs in counties in Atlanta (Metro) was 2.04 (0.11, 38.92) times the risk in Rural counties ($p=0.63$). Finally, a one unit increase in the log of the average cumulative RSEI score for all counties in each of the cancer registries resulted in a 1.23 (0.72, 2.10) times higher risk of GCTs ($p=0.46$). While these models showed no statistically significant associations between RSEI scores and GCT incidence, we still believe the association between residential proximity to toxic releases and GCTs should be explored.

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Table of Contents

I. Introduction

Germ Cell Tumors

Germ cell tumors (GCTs) represent an extremely heterogeneous mix of neoplasms that are categorized together because they all arise from primordial germ cells (PGCs) [1]. GCTs occur throughout the body in a spatial distribution thought to reflect the migration patterns of PGCs during embryogenesis [2]. In young children, GCTs are relatively rare, accounting for only 3% of cancers in those under 15 years of age. However, among adolescents aged 15 to 19 years, GCTs represent 14% of all cancers, making them the most common solid tumor in this age group [3].

Approximately 90% of GCTs develop in the gonads (ovaries and testes), but they can be extragonadal as well [3,4]. The two kinds of gonadal germ cell tumors are ovarian and testicular GCTs which are categorized as seminomas (slow-growing tumors) and nonseminomas (fast-growing tumors). These are typically diagnosed during or after puberty. Extragonadal GCTs arise from gametes, or egg and sperm cells, that migrate throughout the body, normally developing along the midline. Most commonly, they will occur in the mediastinum, an area in the middle of the thoracic cavity, but they can appear anywhere from the pineal gland to the coccyx. These are more likely to be diagnosed in early childhood. Malignant extragonadal GCTs can be further categorized as embryonal carcinomas, malignant teratomas, and yolk sac tumors. Sacrococcygeal teratomas are another subcategory of germ cell tumors that are usually diagnosed before or directly after birth. Germinomas, teratomas, and choriocarcinomas are further categories of germ cell tumors. Overall, gonadal GCTs have a good prognosis a with 5-year survival rate of 90% in children younger than 15 and 93% in adolescents between the ages of 15

and 19 years [3]. The prognosis is much poorer for extragonadal GCTs, which carry a 4-year survival rate of 70% [5].

The etiology of GCTs is widely unknown [3]. Many inherited defects are associated with an increased risk of developing GCTs, and the familial risk of testicular GCTs is much higher than most cancers, pointing to the importance of hereditary factors [6]. However, there has been a sustained increase in pediatric GCT incidence rates over the past several decades, indicating the presence of exogenous risk factors as well [6,7,8]. Recently, it has been postulated that early life exposure to a variety of environmental chemicals may increase the risk of developing GCTs [9].

Toxic Release Facilities and RSEI Scores

Exposure to endocrine-disrupting chemicals and other environmental chemicals are of great interest in evaluating potential exogenous risk factors [10]. Numerous studies have been conducted to explore the associations between environmental chemicals and cancer. Researchers have found an association between residential proximity to cropland and pesticide applications in California and GCTs, among other cancers [11]. One study found that children whose mothers lived near industries under the Toxic Release Inventory during pregnancy were more likely to have brain cancer, particularly if their address was within one mile of the industrial emissions site [12]. Additional studies have been done investigating the relationship between Wilms' tumors, breast cancer, childhood leukemia, and other cancers, and exposure to nuclear sites, hazardous landfills, traffic pollution, and other environmental toxicants [13]. Investigating the relationship between residential proximity to toxic release facilities public health issues that implement geographic information and geospatial techniques is relatively new. Though this kind

of research is in its infancy, many studies are highlighting significant associations between proximity to toxic release sites and adverse health outcomes [13].

All facilities in specific sectors are required to submit annual data to the EPA on accidental and deliberate releases of over 600 specified chemicals through any medium (air, surface water, etc.) [14]. The data on these releases is then analyzed in conjunction with toxicity information, population exposure, and models of fate and transport through the environment, among other things, to add context to toxic release information. Ultimately, this data is used to create a single value that represents the composite health risk generated by toxic releases called the Risk-Screening Environmental Indicators (RSEI) score. The RSEI score is one metric used to quantify the danger imposed by toxic release facilities. They are unitless values related to risk that incorporate a multitude of factors, including: the size of the chemical release, the fate and transport of the chemical through the environment, the size and proximity of the exposed population, and the chemical's toxicity [15]. Figure 1 depicts the different variables that are considered when calculating RSEI scores. The best way to interpret the RSEI scores of different facilities is to compare them with each other. For instance, a facility with an RSEI score twice as high as another suggests that the risk posed by that facility is approximately twice as high [15].

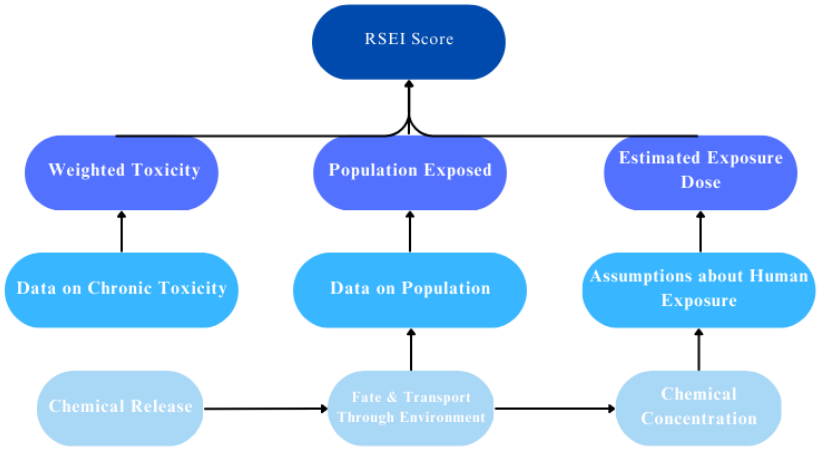


Figure 1. Different variables used to calculate RSEI scores.

II. Methods

Data Sources

De-identified incident cases of germ cell tumors were obtained using the Surveillance, Epidemiology, and End Results (SEER) registry [16]. We used SEER*Stat statistical software version 8.4.0.1 to create frequency tables from the database titled "Incidence - SEER Research Plus Limited-Field Data. 22 Registries, Nov 2021 Sub (2000-2019)" using a Frequency Session. We selected germ cell tumor diagnoses in children and adolescents aged 0 to 19 years from 2013 to 2019 in Georgia. These diagnoses included germ cell tumors, trophoblastic tumors and neoplasms of the gonads. The cases were initially separated into the following age groups: 0 years, 1 to 4 years, 5 to 9 years, 10 to 14 years, and 15 to 19 years. We later collapsed the age groups into 0 to 4 years, 5 to 9 years, 10 to 14 years, and 15 to 19 years to correspond with the U.S. Census population estimates age grouping. Georgia's cancer registries are separated into three geographic groups: the Atlanta (Metro) registry, which is comprised of Clayton, Cobb, Dekalb, Fulton, and Gwinnett counties; the Rural Georgia registry, including Glascock, Greene, Hancock, Jasper, Jefferson, Morgan, Putnam, Taliaferro, Warren, and Washington counties; and the Greater Georgia registry, which encompasses the rest of the state. For the majority of the analyses, incident GCT cases were aggregated by which of the three cancer registries they were reported to. We did not collect other demographic factors of those diagnosed in this age group (0 to 19 years) and time period (2013 to 2019) due to patient privacy. In total, we captured 199 germ cell tumor diagnoses. Figure 2 shows a map of Georgia counties color-coded by which cancer registry they contribute to.

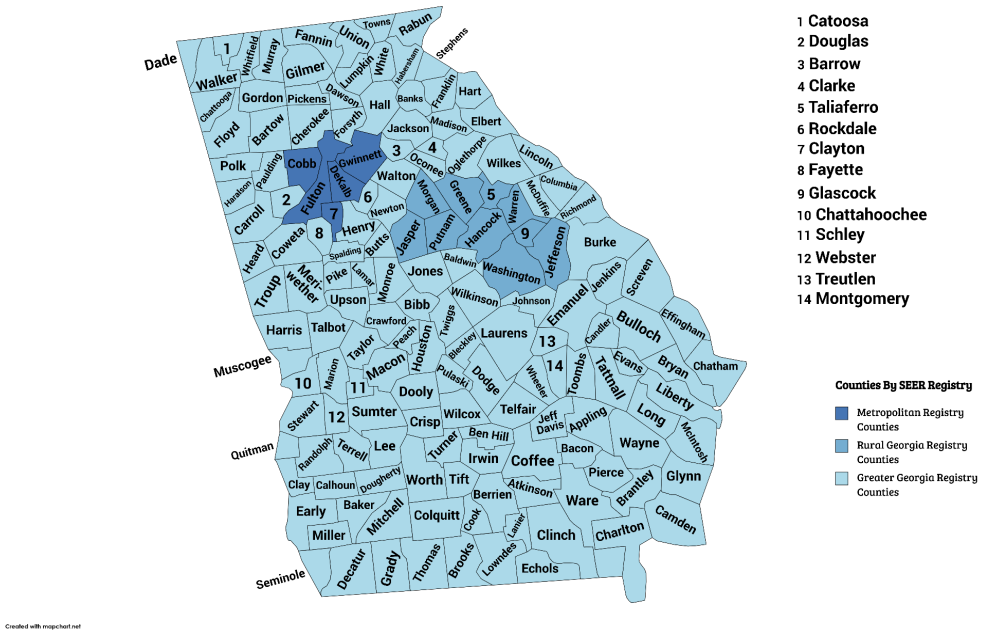


Figure 2. Color coded map of Georgia counties by which cancer registry they contribute to.

Data on the population sizes of age groups in 5-year intervals (0 to 4, 5 to 9, 10 to 14, and 15 to 19) in each county was obtained from the U.S. Census Bureau [17]. Starting in 2013, we collected data of the population estimates for the age groups of 0 to 4, 5 to 9, 10 to 14, and 15 to 19 by sex and by county. The Census population estimates were from 7/1/2013 to 7/1/2019 and captured on a yearly basis. The population size for these age groups was aggregated by cancer registry and year to estimate the size of the children and adolescent population that was at risk of developing a germ cell tumor. In other words, we summed all population estimates for the age groups (0 to 19 years) by county, and then summed all the counties in each of the three cancer registries.

Toxic release inventory (TRI) data was obtained from the Environmental Protection Agency's (EPA) EasyRSEI Dashboard version 2.3.11 [18]. We created a custom export table including the following variables on toxic release facilities in Georgia: facility name, reporting year, county, chemical, industry sector, parent company, total releases, waste managed, and

RSEI score. RSEI score will be the metric we use as the primary predictor variable for exposure to toxic releases. We summed all reported RSEI scores by county and year, and then by registry to find a cumulative RSEI score for each cancer registry every year from 2013 to 2019. We hypothesized that the registry with the highest county-sum RSEI score would have the most incident cases of germ cell tumor diagnoses each year after controlling for sex and age group. We offset by the size of the population at risk for each age group within the counties that make up each registry.

Statistical Analysis

All analyses were carried out using SAS v. 9.4 (SAS Institute, Inc., Cary, NC, USA). We found descriptive statistics on both the TRI and SEER data. We used one-way analysis of variance (ANOVA) to determine if there was a statistically significant difference between the average cumulative RSEI score in the Atlanta (Metro) registry, the Rural Georgia registry, and the Greater Georgia registry. We also examined the trends in GCT incidence using Poisson multivariate regression models. First, we aggregated GCT cases by county and then by cancer registry. The age categories were 0 to 4 years, 5 to 9 years, 10 to 14 years, and 15 to 19 years. When determining risk, we further collapsed the age groups to 0 to 9 years and 10 to 19 years for both females and males. We aggregated the facilities' RSEI scores by the county they were in, and then summed all the RSEI scores for the counties in each Georgia cancer registry by year from 2012 to 2019. This resulted in 8 values of RSEI score for each cancer registry. Two Poisson regression models were run. The first model used the cancer registry as the class and controlled for sex and age group and was offset by the log of the population size for each corresponding age group and sex in all counties contributing to the registry. The next regression looked at registry-level total RSEI score each year from 2013 to 2019 and was regressed over the number of GCT

diagnoses reported to that registry in the same year. Again, we controlled for age group and sex, and we offset by the log of the total population of each age group and sex for all counties within the registry.

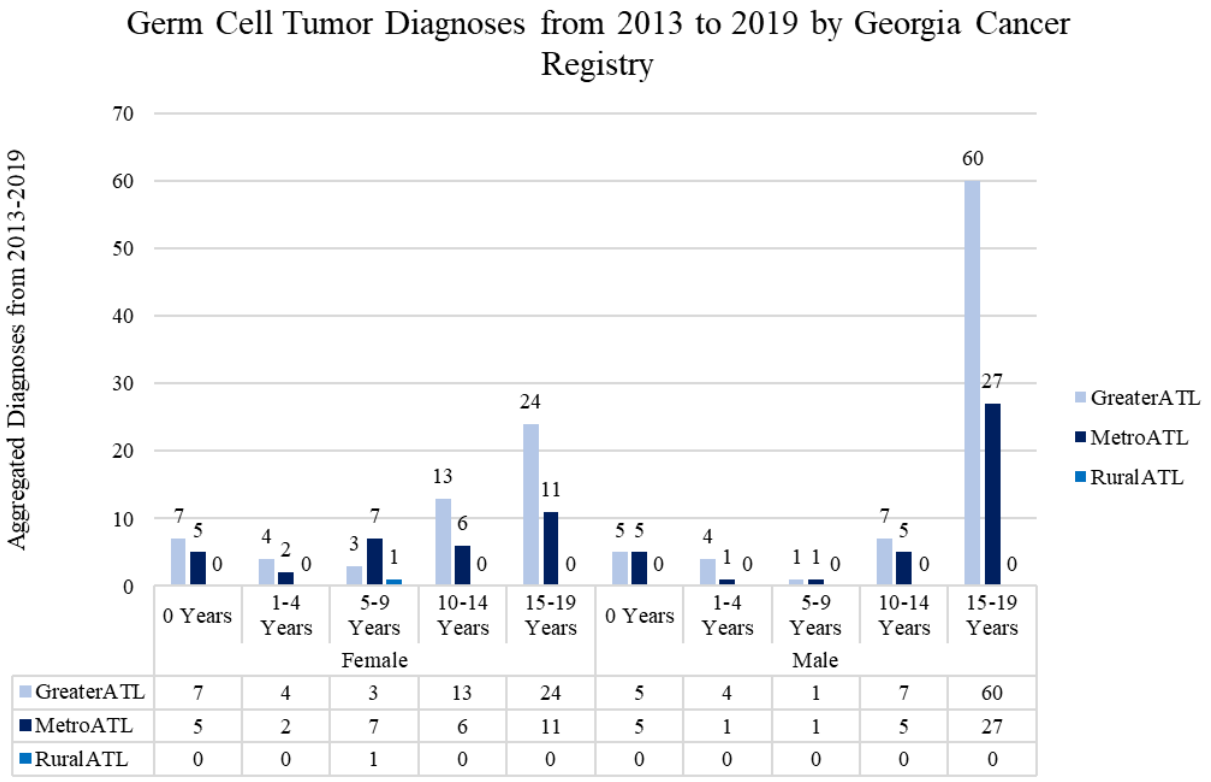
III. Results

Trends in Germ Cell Tumor Incidence

We captured a total of 199 incident cases of germ cell tumors from 2013 to 2019. 83 of these cases were in females (41.7%) and 116 (58.3%) were in males. As expected, the incident cases of germ cell tumors throughout the study period followed a bimodal distribution. In both males and females, there is a peak in germ cell tumor cases in the first year of age. The incidence then drops from ages 1 to 9 years and begins to rise again at 10 to 14 years. The second peak in later in childhood corresponds to the age of onset puberty [19].

The highest incidence in males and females occurs from 15 to 19 years of age. However, males had more than twice as many germ cell tumor diagnoses within this age range than females, with 87 cases and 35 cases, respectively. The Greater Georgia counties almost exclusively had the most cases, except for in females aged 5 to 9 years, where the Atlanta (Metro) counties had more, and in males aged 0 years and 5 to 9 years, where the Greater Georgia and Atlanta counties are equal. Figure 3 illustrates the counts of GCT diagnoses by age group, sex, and cancer registry. The risk of germ cell tumors was calculated over the range of years 2013-2019 for each registry. These risks were adjusted by age and sex. The risk of germ cell tumors in females aged 0 to 9 that live in counties in the Greater Georgia registry area was 4.95 per 1 million. The corresponding risk of germ cells in males was 3.41 per 1 million. In those aged 10 to 19, the risk for females in the Greater Georgia area was 11.89 per 1 million, and 20.61

per 1 million in males. In the Atlanta (Metro) registry counties, the risk of germ cell tumors for those aged 0 to 9 was 8.17 per 1 million in females and 4.01 per 1 million in males. For those aged 10 to 19 living in Atlanta registry counties, the risk was 9.80 per 1 million in females and 17.96 per 1 million in males.



	Female					Male				
	0 Years	1-4 Years	5-9 Years	10-14 Years	15-19 Years	0 Years	1-4 Years	5-9 Years	10-14 Years	15-19 Years
GreaterATL	7	4	3	13	24	5	4	1	7	60
MetroATL	5	2	7	6	11	5	1	1	5	27
RuralATL	0	0	1	0	0	0	0	0	0	0

Figure 3. Trends in GCT diagnoses in children and adolescents in Georgia from 2013 to 2019

Trends in RSEI Scores

The RSEI scores for all facilities in each county were added together to create a cumulative RSEI score by county. These values were then added again to create a cumulative registry RSEI score containing RSEI scores for all facilities in all counties within each of the three registries. The Greater Georgia registry counties had the highest cumulative RSEI score,

which was 16,883,762 in 2013. The average RSEI score from 2013 to 2019 in Greater Georgia registry counties was 5,932,829 with a standard deviation of 4,883,797. For Atlanta registry counties, the average RSEI score was 5,568,827 with a standard deviation of 5,386,369, and a maximum and minimum of 119,401,128 in 2015 and 835,121 in 2018, respectively. For Rural Georgia registry counties, the average RSEI score was 150,810 with a standard deviation of 88,712 and a maximum and minimum of 342,289 in 2013 and 92,425 in 2015, respectively. Table 1 displays the cumulative RSEI scores from all facilities in each cancer registry.

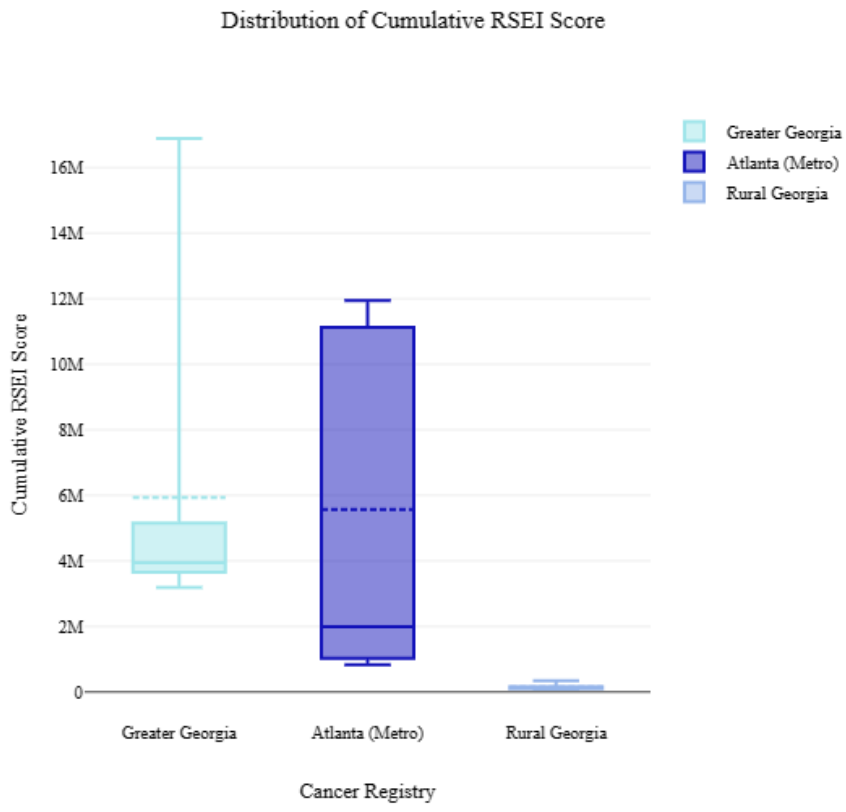


Figure 4. Distribution of cumulative RSEI scores from 2013 to 2019 by cancer registry.
F = 4.17 (p =0.033)

Table 1. *RSEI Score data aggregated by registry each year*

Registry	Year	Cumulative RSEI Score
Greater Georgia	2013	16883762.00
	2014	4925524.00
	2015	5237243.00
	2016	3728048.00
	2017	3942706.00
	2018	3628397.00
	2019	3184126.00
Atlanta (Metro)	2013	11279059.00
	2014	10681549.00
	2015	11940128.00
	2016	1306317.00
	2017	942167.00
	2018	835121.00
	2019	1997452.00
Rural Georgia	2013	342289.00
	2014	98806.00
	2015	92425.00
	2016	104790.00
	2017	106040.00
	2018	143994.00
	2019	167326.00

An analysis of variance was conducted to determine if the mean RSEI scores were significantly different by cancer registry. This test resulted in a statistically significant F-value of 4.17 with a p-value of 0.033, suggesting there was a statistically significant difference in mean RSEI score between at least one of the groups. We then ran a Tukey test post-hoc to determine where the difference was found. The average cumulative RSEI score was significantly different between Greater Georgia registry counties and Rural Georgia registry counties (p=0.048). There was a large difference between the cumulative RSEI scores in Metro registry counties and Rural registry counties, but this difference did not reach statistical significance at the 0.05 significance level (p=0.066) (see Appendix 1 for more details). Figure 4 depicts the distribution of the cumulative RSEI scores by registry and Table 2 provides the descriptive statistics for this distribution.

Table 2. *Distribution of the Cumulative RSEI Scores from 2012 to 2019 by Registry*

Groups:	**Greater Georgia**	**Atlanta (Metro)**	**Rural Georgia**
Sample Size:	8	8	8
Minimum	3,184,126.00	835,121.00	92,425.00
Q1:	3,678,222.50	1,124,242.00	1,017,98.00
Median:	3,942,706.00	1,997,452.00	106,040.00
Q3:	5,081,383.50	10,980,304.00	155,660.00
Maximum:	16,883,762.00	11,940,128.00	342,289.00
Mean:	5,191,225.75	4,872,724.00	131,958.75
Skewness:	2.22	0.62	1.40
Skewness Shape:	Right	Approx. Symmetrical	Approx. Symmetrical
Excess Kurtosis:	5.90	-2.15	3.55
Outliers	16,883,762.00	N/A	342,289.00

Poisson Models

Poisson regression models were used to evaluate the trends in germ cell tumor incident cases by geographic location (i.e., counties in the corresponding registries). Trends in incidence were found after adjusting for age (5-year age groups) and sex. To protect the privacy of patients,

registry data is de-identified. We did not get access individual level characteristics such as race, ethnicity, family history of cancer, smoking status, etc. All case counts were aggregated by age group, sex, and cancer registry. The first Poisson model looked at count as a function of age group, sex, and registry. This model was offset by the log of the population of those in the corresponding age group by sex.

Using the Rural Georgia registry as the reference group, we found the risk of GCTs in Greater Georgia to be 2.02 (0.11, 39.67) times higher (p=0.62). The RR for GCTs in Atlanta registry counties was similar, at 2.04 (0.11, 38.92) times higher than in Rural Georgia counties (p=0.63). These results are quite insignificant statistically, and it is more likely that there is no difference in GCT incidence between these geographic areas based on this model. The risk was 1.35 (0.88, 2.05) times higher in males than in females, after controlling for cancer registry and age group (p=0.1667). Again, this association appears to be statistically insignificant in this model. Compared with the age group with the lowest germ cell tumor risk, ages 5 to 9 years, the risk in those aged 0 to 4 years is 2.68 (1.03, 6.99) times higher (p=0.044). Among those aged 10 to 14 years, the risk of GCTs is 2.31 (0.88, 6.09) times higher (p=0.089) than those aged 5 to 9 years, and in those aged 15 to 19 years the risk of GCTs is highest, at 9.14 (3.89, 20.22) times the risk in those aged 5 to 9 years (p<0.0001). Overall, this model appears to show no association between incidence germ cell tumor cases and cancer registry (see Appendix 1 for more details). However, it does show statistically significant differences in the risk of GCT by age group, which agrees with that previous literature has found [3,4,5].

A second model was used to determine if there was an association between GCT incidence and RSEI score. Incident cases were aggregated by sex, registry, year, and age group. This Poisson model looked at case count as a function of the log of the RSEI score, age group,

and sex. This model was also offset by the log of the population of those in the corresponding age group by sex. Using this model, we found the RR of a one-unit increase in log(RSEI Score) to be 1.23 (0.56, 2.68) times higher (p=0.61). Again, this model demonstrated that there appears to be no association between RSEI score and incident GCT rate. The RR for males to females produced by this model was 1.35 (0.89, 2.025) (p=0.15). The age group 5 to 9 years was used as the comparison group for this model as well. The RRs obtained for those aged 0 to 4 years, 10 to 14 years, and 15 to 19 years are 2.68 (1.06, 6.80) (p=0.038), 2.31 (0.80, 5.92) (p=0.080), and 9.14 (3.99, 20.96) (p<0.0001), respectively (see Appendix 2 for more detail).

IV. Discussion

We found that the previously known differences in germ cell tumor diagnoses between age groups and sex were present in this study population. In early ages, females tended to have a higher risk of germ cell tumors than their male counterparts. In both sexes, a decline in the risk of germ cell tumor diagnoses occurs from ages 5 to 9 years. New cases then spike after the onset of puberty, from ages 10 to 19 years. In the older age groups, males had a higher risk than females, which is consistent with previous research findings. The group in our study population most at risk for germ cell tumors are males aged 15 to 19 years. Overall, we found no evidence to support our initial hypothesis that germ cell tumor incidence rates would be higher in the Georgia registries made up of counties with higher RSEI scores.

There are a few important limitations to this study. As mentioned before, hereditary factors play an extremely significant role in the development of germ cell tumors. Familial risk of germ cell tumors is significantly higher than in most cancers. We could not control for family history of cancer, specifically germ cell tumors, in this study due to the SEER data being de-identified and not containing personal information and individual risk factors. We also could not

control for other factors that could potentially influence the risk of cancer like smoking, alcohol consumption, diet, exercise, etc. We also could not control for demographic factors like race, ethnicity, and socio-economic status. Using the registry that diagnoses were reported to as a proxy for geographic exposure to toxic release facilities is also potentially problematic. This does not take into consideration those who moved across counties or those who lived on the edge of county lines and potentially had exposure levels more influenced by facilities in other registry counties. There is huge variation in exposure levels geographically within each registry that our models could not account for in this study. Another important limitation comes from the way we needed to aggregate the data. Due to the overall rarity of germ cell tumor cases, we could not run these analyses at the county-level while still controlling for age and sex, as there were too few diagnoses over the years of our study and 159 different Georgia counties. This would have resulted in convergence issues with both of the Poisson models. As a result, we aggregated cases by age group, sex, diagnosis year and registry. The diagnoses in each year were further aggregated to obtain a single case count for each registry over the whole study period. To match the aggregation of the case data, we also had to find average cumulative RSEI scores despite large variations in these values. Each registry had very large standard deviations in RSEI scores, so using average cumulative estimates could have blurred important associations. Finally, we only looked at associations on a yearly basis. This would not account for past chronic exposures to toxic releases, and only accounts for the relationship between RSEI score for the year that the germ cell tumor was diagnosed.

V. Conclusion and recommendations

While this study found no statistically significant association between RSEI scores from toxic release facilities and child and adolescent germ cell tumor incidence, there is still evidence

that suggests the presence of exogenous risk factors in the literature [6,7,8]. These factors need to be explored. This study provided further support for the age and sex trends previously seen in germ cell tumor cases, as we saw a similar bimodal distribution by age, and different peaks in risk by sex.

Due to budgetary and timeline limitations, much of this data had to be condensed, resulting in the potential loss of associations that may have been important. Going forward, we believe it is still important to explore the association between residential proximity to toxic release facilities and germ cell tumor incidence. We would like to see the association between residential proximity to toxic release facilities and germ cell tumor incidence be explored over decades across the entire country. Again, as these cancers are quite rare, extending the study period and geographic area could capture more cases to produce more valid results. We also believe a case-control study design could produce a much clearer picture of the association between germ cell tumor diagnosis and potential exogenous risk factors, while controlling for important individual level characteristics and exposures. A more in-depth exposure assessment should also be done, rather than using RSEI score as a proxy for exposure levels.

VI. References

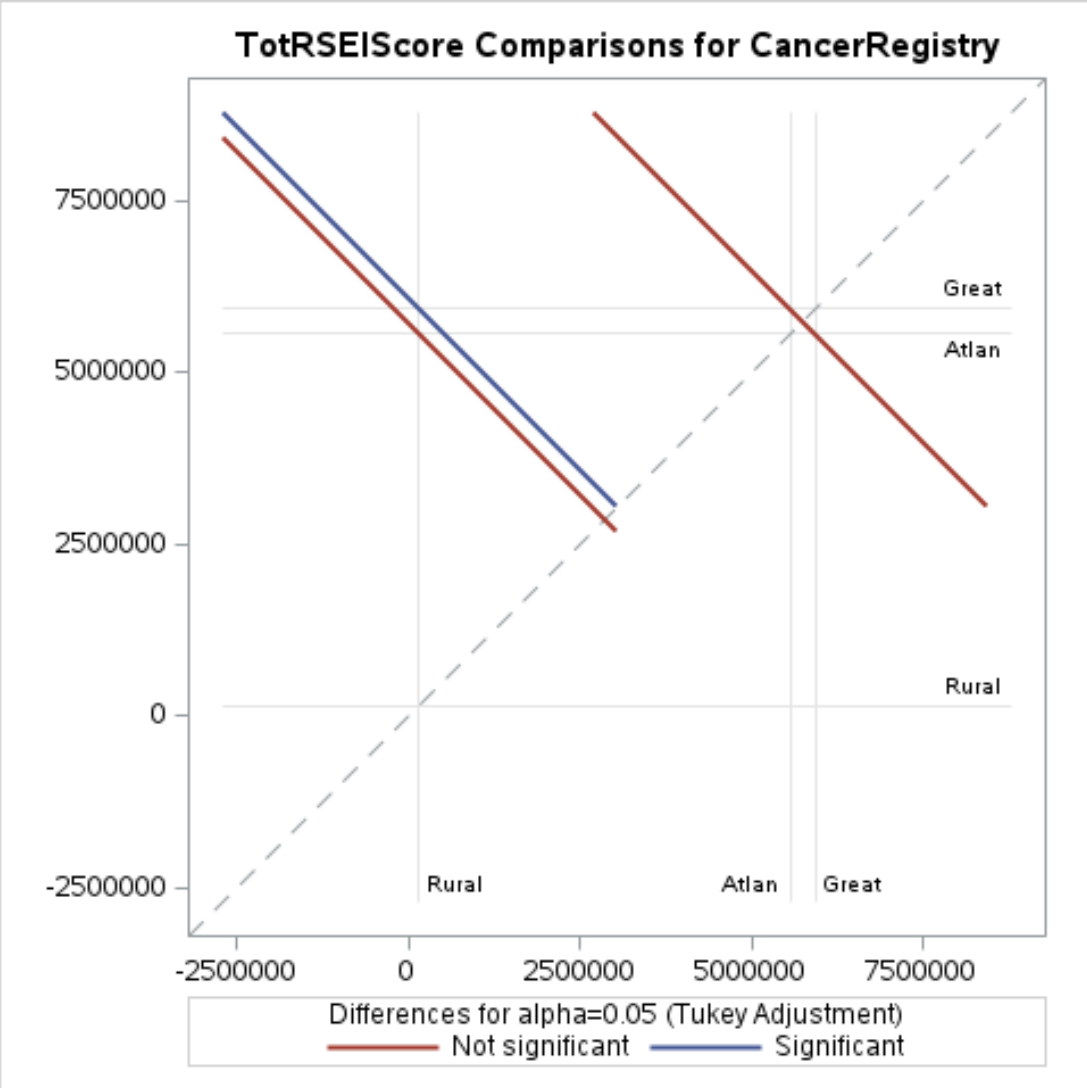
1. Jezierska, Michalina, et al. “Diagnostic, Prognostic and Predictive Markers in Pediatric Germ Cell Tumors—Past, Present and Future.” *Diagnostics*, vol. 12, no. 2, 21 Jan. 2022, p. 278., https://doi.org/10.3390/diagnostics12020278.
2. Ma, Y. T., Cullen, M. H., & Hussain, S. A. (2011). Biology of germ cell tumors. *Hematology/Oncology Clinics of North America*, *25*(3), 457–471. https://doi.org/10.1016/j.hoc.2011.03.004

3. Poynter, J. N., Amatruda, J. F., & Ross, J. A. (2010). Trends in incidence and survival of pediatric and adolescent patients with germ cell tumors in the United States, 1975 to 2006. *Cancer, 116*(20), 4882-4891. doi:10.1002/cncr.25454
4. Hassenfeld Children's Hospital at NYU Langone. (n.d.). *Types of germ cell tumors*. Types of Germ Cell Tumors. Retrieved April 15, 2023, from https://nyulangone.org/conditions/germ-cell-tumors-in-children/types
5. Giannandrea, F., & Fargnoli, S. (2017). Environmental Factors Affecting Growth and Occurrence of Testicular Cancer in Childhood: An Overview of the Current Epidemiological Evidence. *Children (Basel, Switzerland)*, *4*(1),1. https://doi.org/10.3390/children4010001
6. Horton, Z., Schlatter, M., & Schultz, S. (2007). Pediatric germ cell tumors. *Surgical oncology*, *16*(3), 205–213. https://doi.org/10.1016/j.suronc.2007.07.005
7. McGlynn, K. A., & Cook, M. B. (2009). Etiologic factors in testicular germ-cell tumors. *Future Oncology, 5*(9), 1389-1402. doi:10.2217/fon.09.116
8. Choi, H., Shim, Y., Kaye, W., & Ryan, P. (2006, July 01). Potential residential exposure to toxics release inventory chemicals during pregnancy and childhood brain cancer. Retrieved September 26, 2022, from https://open.library.emory.edu/publications/emory:twkd1/
9. Fukawa, T., & Kanayama, H. (2018). Current knowledge of risk factors for testicular germ cell tumors. International Journal of Urology, 25(4), 337-344. doi:10.1111/iju.13519
10. Reynolds, P., Von Behren, J., Gunier, R., Goldberg, D., Hertz, A., & Harnly, M. (2002, March). Childhood cancer and agricultural pesticide use: An ecologic study in California. Retrieved September 26, 2022, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1240773/

11. Brender, J. D., Maantay, J. A., & Chakraborty, J. (2011). Residential proximity to environmental hazards and adverse health outcomes. American journal of public health, 101 Suppl 1(Suppl 1), S37–S52. https://doi.org/10.2105/AJPH.2011.300183
12. Childhood germ cell tumors. (n.d.). Retrieved September 26, 2022, from https://www.dana-farber.org/childhood-germ-cell-tumors/
13. Kaatsch, P., Häfner, C., Calaminus, G., Blettner, M., & Tulla, M. (2015). Pediatric germ cell tumors from 1987 to 2011: Incidence rates, time trends, and survival. Pediatrics, 135(1). doi:10.1542/peds.2014-1989
14. Ash, Michael, and James K. Boyce. "Racial Disparities in Pollution Exposure and Employment at US Industrial Facilities." *Proceedings of the National Academy of Sciences*, vol. 115, no. 42, 1 Oct. 2018, pp. 10636–10641., https://doi.org/10.1073/pnas.1721640115.
15. Environmental Protection Agency. (2022, July 8). Understanding RSEI Results. EPA. Retrieved April 10, 2023, from https://www.epa.gov/rsei/understanding-rsei-results#:~:text=A%20RSEI%20Score%20is%20a,population%2C%20and%20the%20chemical's%20toxicity.
16. Surveillance Research Program, National Cancer Institute SEER*Stat software (www.seer.cancer.gov/seerstat) version 8.4.0.1. SEER*Stat Database: Incidence - SEER Research Plus Limited-Field Data, 22 Registries, Nov 2021 Sub (2000-2019).
17. The U.S. Census Bureau. http://www.census.gov/ (accessed 04.23).
18. *EasyRSEI Dashboard v2.3.10*. (n.d.). https://edap.epa.gov/public/extensions/EasyRSEI/EasyRSEI.html
19. Fonseca, A., Frazier, A. L., & Shaikh, F. (2019). Germ cell tumors in adolescents and young adults. *Journal of Oncology Practice*, *15*(8), 433–441. https://doi.org/10.1200/jop.19.00190

VII. Appendices

Appendix 1: Diffogram displaying comparison of means of the total RSEI scores for the three Georgia registries.



Appendix 2: First Poisson Regression Output and Goodness of Fit Criteria. Dscale was used to correct overdispersion.

Analysis Of Maximum Likelihood Parameter Estimates								
Parameter		**DF**	**Estimate**	**Standard**	**Wald 95% Confidence**		**Wald Chi-**	**Pr > ChiSq**
Intercept		1	-11.7774	1.5503	-14.8160	-8.7388	57.71	<.0001
agegroupnew	0to4	1	0.9859	0.4888	0.0280	1.9439	4.07	0.0437
agegroupnew	10to	1	0.8393	0.4932	-0.1273	1.8060	2.90	0.0888
agegroupnew	15to	1	2.2128	0.4355	1.3592	3.0663	25.82	<.0001
agegroupnew	5to9	0	0.0000	0.0000	0.0000	0.0000	.	.
Sex		1	0.2967	0.2146	-0.1239	0.7173	1.91	0.1667
Registry	Greater	1	0.7437	1.4985	-2.1933	3.6806	0.25	0.6197
Registry	Metro	1	0.7151	1.5033	-2.2313	3.6614	0.23	0.6343
Registry	Rural	0	0.0000	0.0000	0.0000	0.0000	.	.
Scale		0	1.4926	0.0000	1.4926	1.4926		

Criteria For Assessing Goodness of Fit			
Criterion	**DF**	**Value**	**Value/DF**
Deviance	17	37.8760	2.2280
Scaled Deviance	17	17.0000	1.0000
Pearson Chi-Square	17	68.2705	4.0159
Scaled Pearson X2	17	30.6421	1.8025

Appendix 3: Second Poisson Regression Output and Goodness of Fit Criteria. Dscale was used to correct overdispersion.

Analysis Of Maximum Likelihood Parameter Estimates								
Parameter		**DF**	**Estimate**	**Standard**	**Wald 95% Confidence**		**Wald Chi-**	**Pr > ChiSq**
Intercept		1	-14.2271	6.2085	-26.3955	-2.0587	5.25	0.0219
agegroupnew	0to4	1	0.9858	0.4751	0.0547	1.9169	4.31	0.0380
agegroupnew	10to	1	0.8394	0.4794	-0.1002	1.7790	3.07	0.0799
agegroupnew	15to	1	2.2130	0.4233	1.3834	3.0426	27.33	<.0001
agegroupnew	5to9	0	0.0000	0.0000	0.0000	0.0000	.	.
Sex		1	0.2968	0.2086	-0.1120	0.7056	2.02	0.1547
logrsei		1	0.2044	0.3982	-0.5761	0.9849	0.26	0.6078
Scale		0	1.4508	0.0000	1.4508	1.4508		

Criteria For Assessing Goodness of Fit			
Criterion	**DF**	**Value**	**Value/DF**
Deviance	18	37.8872	2.1048
Scaled Deviance	18	18.0000	1.0000
Pearson Chi-Square	18	68.6143	3.8119
Scaled Pearson X2	18	32.5983	1.8110