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A comprehensive analysis of neuroblastoma incidence, survival, and racial and ethnic disparities from 2001 to 2019

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Abstract

Background: We characterize the incidence and 5-year survival of children and adolescents with neuroblastoma stratified by demographic and clinical factors based on the comprehensive data from United States Cancer Statistics (USCS) and the National Program of Cancer Registries (NPCR).

Methods: We analyzed the incidence of neuroblastoma from USCS (2003–2019) and survival data from NPCR (2001–2018) for patients less than 20 years old. Incidence trends were calculated by average annual percent change (AAPC) using joinpoint regression. Differences in relative survival were estimated comparing non-overlapping confidence intervals (CI).

Results: We identified 11,543 primary neuroblastoma cases in USCS. Age-adjusted incidence was 8.3 per million persons [95% CI: 8.2, 8.5], with an AAPC of 0.4% [95% CI: −0.1, 0.9]. Five-year relative survival from the NPCR dataset (n = 10,676) was 79.7% [95% CI: 78.9, 80.5]. Patients aged less than 1 year had the highest 5-year relative survival (92.5%). Five-year

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CONFLICT OF INTEREST STATEMENT

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relative survival was higher for non-Hispanic White patients (80.7%) or Hispanic patients (80.8%) compared to non-Hispanic Black patients (72.6%).

Conclusion: Neuroblastoma incidence was stable during 2003–2019. Differences in relative survival exist by sex, age, race/ethnicity, and stage; patients who were male, older, non-Hispanic Black, or with distant disease had worse survival. Future studies could seek to assess the upstream factors driving disparities in survival, and evaluate interventions to address inequities and improve survival across all groups.

Keywords

epidemiology; neuroblastoma; outcomes research

1 | INTRODUCTION

Neuroblastoma, an embryonal malignancy of neural crest cells, is the second most common solid tumor in pediatrics behind brain tumors.[1] Young children represent the majority of cases, with the median age at diagnosis being 17 months. Less than 5% of diagnoses occur after 10 years of age.[2] Neuroblastoma is renowned for its clinical heterogeneity, with some patients experiencing spontaneous regression of their tumors without intervention, whereas others have aggressive, hard-to-cure disease necessitating intensive multimodal therapeutic approaches. While neuroblastoma accounts for 8%–10% of all pediatric cancers, it accounts for 12%–15% of cancer-related deaths in children.[2]

Significant changes in staging and classification systems for neuroblastoma, as well as advancements in care, have occurred in the past two decades. In 2009, the International Neuroblastoma Risk Group (INRG) published the INRG Staging System (INRGSS) and risk classification criteria.[3] This new staging system allowed for a new risk classification system to be created that was based upon image-defined risk factors of the original tumor, rather than degree of surgical resection, thus allowing for pretreatment risk stratification. These changes have occurred in parallel with advancements in therapy, such as dual transplant followed by autologous hematopoietic stem cell rescue for high-risk patients, and immunotherapy. Previous epidemiological studies of neuroblastoma have predominantly utilized data collected prior to the implementation of these changes. Studies relying on data from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) program covered less than 30% of the US population.[4] INRG data only includes patients who were enrolled on a biological or clinical trial.[5] Given the advancements in staging and classification and the limited sample sizes of prior studies in the United States, analysis of a larger, more comprehensive dataset is necessary to elucidate recent epidemiological trends in neuroblastoma incidence and outcomes.

The purpose of this study was to describe recent trends in the epidemiology of neuroblastoma in the United States, including patient characteristics and outcomes. We analyzed the United States Cancer Statistics (USCS) database and the National Program of Cancer Registries (NPCR) survival database to interrogate how incidence and outcomes may differ based on several factors, including epidemiological, clinical, economic status, and race/ethnicity. We explored whether outcomes changed from the time period of 2001–2009

to 2010–2018 given alterations in classification and advances in treatment between these time periods.

2 | METHODS

2.1 | Databases

Incidence data were obtained from USCS database from 2003 to 2019, which covered 99.1% of the US population and included 49 states (excluded Nevada) and the District of Columbia.[6] USCS comprises data from the Centers for Disease Control and Prevention's (CDC) NPCR database and the SEER database.[7] Survival data are from NPCR-funded registries that conducted active case follow-up or linkage with the CDC's National Death Index. This database covered cases diagnosed during 2001 to 2018, with follow-up through December 2018, and covered 87.5% of the US population, including the District of Columbia and all states except for Connecticut, Hawaii, Iowa, Massachusetts, Michigan, Nevada, New Mexico, South Dakota, and Virginia.

2.2 | Inclusion criteria for incidence and survival analyses

Neuroblastoma was defined according to the International Classification of Childhood Cancer diagnostic Group IVa,[8]which includes neuroblastoma and ganglioneuroblastoma (*International Classification of Diseases for Oncology, Third Edition* [ICD-O-3] histology codes 9500 and 9490, respectively).[9] Cases involving patients aged less than 20 years with malignant, microscopically confirmed neuroblastoma were included in this analysis. Only cases involving initial diagnosis of malignancy were included. Autopsy-only or death certificate-only cases were excluded.

2.3 | Variables

We stratified neuroblastoma case incidence and 5-year survival data by variables including sex, age, tumor stage, race/ethnicity, rural–urban status by county population, economic status by county, and date of diagnosis. Age was stratified by the pre-set database age categories of less than 1, 1–4, 5–9, 10–14, 15–19 years for incidence analysis (19 age groups—Census P25–1130). Race and ethnicity were grouped as non-Hispanic White, non-Hispanic Black, non-Hispanic American Indian or Alaska Native (AIAN), non-Hispanic Asian or Pacific Islander (API), and Hispanic. Tumor stage was categorized as local, regional, or distant based on merged summary stage.[10] Economic status was obtained utilizing county of residence at diagnosis and stratified by percentile (bottom 25%, 25%–75%, and top 25%), as defined by the most recent Appalachian Regional Commission data (2017–2021), which draws from the most recent American Community Survey and comparable Census population estimates.[11]

2.4 | Incidence rates and trends

Rates from the USCS database are expressed per 1,000,000 persons, and were age-adjusted to the 2000 US standard population. Adjusted relative risk of incidence was estimated using multivariable negative binomial regression. Predictors included age group, sex, race/ethnicity, economic status, and metropolitan area status. Trends in incidence are described

using average annual percent change (AAPC) calculated by the Joinpoint Regression Program. Statistically significant AAPCs were different from zero ($p < .05$).

2.5 | Relative survival analysis

Relative survival is an estimate of cancer survival in the absence of other causes of death. Expected survival was calculated in SEER*Stat using socioeconomic status/geography/race annual life tables. Data from patients with less than 5 years of follow-up were included using the complete method. We calculated 5-year relative survival stratified by age group, sex, race and ethnicity, rural–urban status, and calendar year of diagnosis. Relative survival analyses were performed using SEER*Stat 8.3.8.[12]

2.6 | All-cause survival analysis

Survival curves were generated using the Kaplan–Meier method from the NPCR database. Non-Hispanic API and non-Hispanic AIAN cases were grouped into the category non-Hispanic all other races to allow for comprehensive analysis given the limited number of cases in these groups. Diagnosis during 2001–2009 was compared to diagnosis during 2010–2018 to align with treatment changes instituted by the Children's Oncology Group.[13] Statistical testing for survival curves was performed using the log-rank test. Multivariable Cox proportional hazards regression modeling was conducted to examine the effects of selected demographic and clinical variables on 5-year all-cause survival. Age group, sex, race and ethnicity, diagnosis year, economic status, metropolitan area status, stage, and histology were included as candidate predictors. Missing data were imputed ($m = 10$ imputations) using the aregImpute function from the Hmisc package in R. All candidate predictors and the outcome variables were included in the multiple imputation process. Missing data were imputed for stage ($n = 813$), race and ethnicity ($n = 155$), economic status ($n = 6$), and metropolitan area ($n = 2$). The remaining predictors had complete data. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were generated for each of the variables in the model. A HR greater than 1 between compared groups indicates a higher risk of death, with statistical significance determined at $p < .05$. Multivariable analysis and generation of survival curves were performed using SAS version 9.4 and R version 4.2.1. Kansas and Minnesota were excluded from all-cause survival analysis as economic data were not reported from these states.

3 | RESULTS

3.1 | Demographic and clinical characteristics

We identified 11,543 cases diagnosed during 2003 to 2019 within the USCS database (Table 1), and 10,676 cases diagnosed during 2001 to 2018 within the NPCR survival database (Table 2). Most cases were male (52.7% of USCS; 53.0% of NPCR). Non-Hispanic White, Hispanic, and non-Hispanic Black patients made up most neuroblastoma cases (65.0%, 15.9%, and 12.8% of USCS; 64.1%, 16.5%, and 12.8% of NPCR, respectively). The majority of cases lived in a metropolitan county with a population over 1 million people at the time of diagnosis (56.6% of USCS; 57.8% of NPCR). By stage, 46.9% of cases in the USCS database and 46.7% of cases in the NPCR database involved distant stage at diagnosis.

3.2 | Incidence

The overall incidence of neuroblastoma cases in the United States during 2003–2019 was 8.3 per million persons (Table 1). The overall annual incidence of neuroblastoma cases was stable during this time period, with an AAPC of 0.4% (95% CI: −0.1% to 0.9%) (Figure 1). Significant AAPCs in incidence occurred among patients with ganglioneuroblastoma (AAPC = 1.4%, 95% CI: 0.2%–2.6%) and among non-Hispanic White patients (AAPC = 0.7%, 95% CI: 0.2%–1.2%). We observed significant increases in annual incidence among cases in the 5–9-year-old (AAPC = 2.4%, 95% CI: 1.2%–3.7%) and 15–19-year-old (AAPC = 3.3%, 95% CI: 0.6%–1.6%) age groups. A significant AAPC in incidence was also observed amongst localized cases (AAPC = 2.6%, 95% CI: 1.8%–3.4%) and regional cases (AAPC =−1.9%, 95% CI: −3.0% to −0.9%).

Relative risk of neuroblastoma among the 1–4-, 5–9-, 10–14-, and 15–19-year-old age groups compared to less than 1-year-old group was 0.42 (95% CI: 0.37–0.47), 0.07 (0.06–0.08), 0.02 (0.02–0.02), and 0.01 (0.01–0.01), respectively. Non-Hispanic White patients had a higher relative risk of developing neuroblastoma compared to all other race/ethnicity groups. Compared to non-Hispanic White patients, the relative risks were 0.54 (95% CI = 0.47–0.61) for Hispanic, 0.64 (95% CI = 0.54–0.76) for non-Hispanic API, 0.69 (95% CI = 0.54–0.88) for non-Hispanic AIAN, and 0.73 (95% CI = 0.64–0.83) for non-Hispanic Black patients (Table 1).

3.3 | Relative survival

Five-year relative survival of neuroblastoma cases diagnosed during 2001–2018 was 79.7% (95% CI: 78.9%–80.5%) and increased from 76.8% (95% CI: 75.6%–78.0%) for cases diagnosed during 2001–2009 to 83.2% (95% CI: 82.0%–84.3%) for those diagnosed during 2010–2018 (Table 2). Five-year relative survival increased between those diagnosed during 2001–2009 and those diagnosed during 2010–2018 in age less than 1 year (92.4% vs. 92.6%), 1–4 years (69.6% vs. 78.1%), 5–9 years (64.5% vs. 78.7%), 10–14 years (64.6% vs. 84.8%), and 15–19 years (58.7% vs. 73.6%), although CIs overlapped for ages less than 1 and 15–19 years. By race and ethnicity, relative survival increased from 2001–2009 to 2010–2018 for non-Hispanic White patients (from 78.1% to 84.2%) and non-Hispanic Black patients (67.3% vs. 79.6%); relative survival increased for non-Hispanic API patients (74.7% vs. 81.2%) and Hispanic patients (78.3% vs. 83.3%), although CIs overlapped. Increases were noted for patients with either regional stage (91.8% vs. 95.3%) or distant stage (60.0% vs. 70.0%); survival for patients with local disease increased (96.6% vs. 97.3%), but CIs overlapped. Improvements in relative survival were observed by rural–urban status, with non-overlapping 95% CIs noted for metropolitan populations of more than 1 million and less than 250,000. By economic status, increased survival between 2001–2009 and 2010–2018 with non-overlapping CIs was seen for patients from the top 25% and 25%–75% of counties.

3.4 | All-cause survival

Five-year all-cause survival of neuroblastoma cases diagnosed between 2001 and 2018 was 79.3%. Five-year survival was significantly different by age group ($p < .001$), with 91.6%, 73.1%, 71.8%, 73.6%, and 67.0%, of the less than 1-, 1–4-, 5–9-, 10–14-,and

15–19-year-old age groups achieving 5-year survival, respectively (Figure 2A). Females had significantly better 5-year survival compared to males, 81.3% and 77.6% ($p < .001$) (Figure 2B). Kaplan–Meier analysis yielded significant differences in 5-year survival by race and ethnicity: 5-year survival amongst Hispanic, non-Hispanic White, non-Hispanic Other, and non-Hispanic Black patients was 80.5%, 80.4%, 78.9%, and 72.2%, respectively ($p < .001$) (Figure 2C). Survival was significantly different based on date of diagnosis: only 76.6% of cases diagnosed before January 1, 2010 achieved 5-year survival, compared to 82.7% ($p < .001$) of cases diagnosed on or after this date (Figure 2D). As expected, survival was significantly better for cases with localized compared with distant disease, and ganglioneuroblastoma versus neuroblastoma (Figure 2E,F). Survival according to county-level economic status was significant ($p < .05$), with lower survival in counties with the lowest percentile. Rural–urban status did not significantly affect survival (Figure 2G,H). Multivariable Cox regression analysis of 5-year all-cause survival was used to estimate HRs related to selected characteristics adjusted for covariates (Table 3). The risk of death was higher for 1–4 years (HR = 2.76, 95% CI: 2.42–3.15), 5–9 years (HR = 2.77, 95% CI: 2.33–3.28), 10–14 years (HR = 3.46, 95% CI: 2.68–4.48), and 15–19 years (HR = 4.03, 95% CI: 2.80–5.81) age groups compared to age less than 1 year. Distant (HR = 8.86, 95% CI: 6.99–11.24) and regional stage (HR = 1.77, 95% CI: 1.34–2.33) demonstrated higher risk of death than local disease. Notably, non-Hispanic Black race and ethnicity were significant risk markers of lower survival (HR = 1.29, 95% CI: 1.14–1.46) relative to non-Hispanic White race and ethnicity. Other race and ethnicity groupings were not independent risk markers of change in 5-year all-cause survival. Diagnosis of neuroblastoma on or after January 1, 2010 was significantly associated with higher survival (HR = 0.69, 95% CI: 0.63–0.75). Ganglioneuroblastoma was associated with higher 5-year survival compared to neuroblastoma (HR = 0.56, 95% CI: 0.46–0.68). Females had borderline higher 5-year survival compared to males, although not statistically significant (HR = 0.91, 95% CI: 0.83–1.00, $p = .0552$). There were no differences in survival by rural–urban or economic status.

4 | DISCUSSION

Here, we report the most comprehensive incidence and survival assessment of neuroblastoma of pediatric neuroblastoma cases in the United States, which utilized databases that include 99.1% and 87.5% for US population coverage for incidence and survival, respectively. Our main findings included stable overall incidence rates of disease over time, increased survival over time, and survival disparities based on race and ethnicity.

In line with prior publications, we found that the overall incidence of neuroblastoma was stable. European data ranging from 1979 to 2016 of over 9000 patients demonstrate increased incidence in individuals aged 0–12 months, noting a varied range in the age-standardized incidence rate of cases per million: 9.5 in Australia, 10.1 in Southern-Eastern Europe countries, 13.7 in Germany, 13.8 in Italy, and 14.3 in France.[14–19] These differences were shown to be driven primarily by variation of incidence rates in the first year of life as well as variation in the human development index (HDI). It is hypothesized that higher HDI results in increased detection of neuroblastoma because of the availability of modern imaging technology and increased access to health care services,[20] the difference found in comparing our comprehensive US data with that of other nations may be in part due to

higher HDI in the United States. Additionally, we found significant increases in incidence in non-Hispanic White patients and patients with ganglioneuroblastoma.

Five-year relative survival during our entire study period increased over time, a finding consistent with prior reports.[14,19,21] This improvement may reflect systematic changes in staging, classification, and changes in therapy including the introduction of high-dose chemotherapy followed by stem cell rescue and immunotherapy. Gains in survival were observed for all characteristics examined, except in patients of non-Hispanic AIAN and non-Hispanic unknown race and ethnicity. The finding related to non-Hispanic AIAN populations may have been influenced by small reporting numbers. The largest survival increases observed were in older patients. Specifically, patients aged 5–9, 10–14, and 15–19 years experienced 5-year relative survival increases of 14.2%, 20.2%, and 14.9%, respectively, between 2001–2009 and 2010–2018. As these patients would be considered at least intermediate risk due to age, with the majority likely high risk, one may reason that improvements to survival are attributable to improvements in high-risk therapy.[2] A recent SEER study observed improved overall survival in high-risk patients who survive at least 1 year, suggesting the continuous advent of new treatments for this group has largely benefited a subset of high-risk patients who previously were at risk of progression during the later stages of therapy.[22] As expected, survival for patients diagnosed before 1 year of age remained excellent and were superior to relative 5-year survival outcomes when compared to all patients aged 1 year or older.

Survival disparities in neuroblastoma patients according to racial and ethnic differences in the United States have been previously reported.[23–26] In this study, we found that non-Hispanic Black patients experienced lower survival compared to non-Hispanic White patients in our multivariable Cox regression analysis, consistent with the unadjusted survival by Kaplan–Meier analysis. This disparity has been demonstrated before in neuroblastoma patients in a Children's Oncology Group study involving over 3500 patients, and was attributed partially to a higher incidence of high-risk disease in Black patients.[27] Our data add to the growing body of evidence demonstrating that non-Hispanic Black patients experience inferior survival across pediatric cancers.[23–26] Others have shown that socioeconomic status mediates the association of inferior survival by race/ethnicity in neuroblastoma and is likely due to disproportionate exposure to adverse social determinants of health driven by poverty.[28–30] Systematic collection of social determinants of health data, including individual-level family-reported poverty measures (e.g., family income, household material hardship, insurance), primary language, health literacy, and education, can offer insight into drivers of inequities.[31] While these individual-level data were not available in our dataset, we did explore the relationship between the economic status of county of residence and survival, and we did not find a significant association. Separately, others have demonstrated children with high-risk neuroblastoma and public insurance have inferior survival after treatment on immunotherapy trials, but also did not find a significant survival difference using neighborhood-level measures.[32] Further reports suggest the association of inferior survival in neuroblastoma and race and ethnicity is present regardless of differences in socioeconomic status.[30] Our data suggest that further investigation into factors that contribute to disparities, such as societal and structural factors stemming from systemic differences in care that might be related to systemic racism, are warranted.

A major strength of this report is the completeness of coverage. As noted, incidence and survival data were derived from data that cover 99.1% and 87.5% of the US population, respectively. Previous epidemiological reports of neuroblastoma incidence and survival in the United States rely on lower coverage of the population than our report or may only include patients who enroll on clinical trials, which may result in a selection bias. Of note, while clinical trial enrollment does not always reflect the general population, our race and ethnicity data are similar to what is reported for patients enrolled on prior clinical trials for patients with high-risk neuroblastoma.[32] Despite our unique ability to include almost complete coverage of the US population, a weakness of our reporting is the inability to divide the age variable at 18 months, as this age cutoff is utilized as prognostic in the staging of neuroblastoma patients. Thus, we were not able to distinguish between two groups of patients with very different outcome profiles. Additionally, the databases we utilized are not linked to specific patient information regarding treatment and tumor biology, prohibiting reporting of pertinent biological prognostic variables such as *MYCN*-amplification or segmental chromosomal aberrations, and did not contain an HDI variable.

5 | CONCLUSIONS

The overall incidence of pediatric neuroblastoma in the United States was stable in recent decades with increases in patients aged 5–9 and 15–19 years. The 5-year survival for patients diagnosed with neuroblastoma significantly increased since January 1, 2010. Despite these improvements in survival, disparities exist by age, tumor stage, and race or ethnicity, particularly of non-Hispanic Black patients. Analysis of the USCS and NPCR databases allowed for nearly complete coverage of all neuroblastoma cases in the United States between 2001 and 2019. These data may inform risk stratification of neuroblastoma cases and encourage the investigation of existing disparities in survival outcomes. Investigation into the societal and structural factors rooted in systemic racism that contribute to disparities among patients from racial and ethnic minority groups may further our understanding of inequities. This study represents the most comprehensive review of neuroblastoma incidence and survival over the past two decades, allowing for the most powerful analysis of trends in incidence and survival outcomes. These data may provide refined expectations for incidence moving forward and serve as a basis for the implementation of potential interventions, such as programs to increase clinical trial enrollment and address inequities in access to care, to address existing inequities in survival outcomes. Interventions addressing social determinants of health have been documented to be feasible and acceptable in pediatric oncology treatment settings.[33,34] Future evaluation may be needed to determine the effectiveness of similar approaches to addressing disparities in neuroblastoma survival.[35]

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request by contacting uscsdata@cdc.gov. The data are not publicly available because of privacy and legal restrictions. Information about accessing public use US Cancer Statistics can be found at https://www.cdc.gov/cancer/uscs/

Abbreviations:

AAPC	average annual percent change
AIAN	American Indian or Alaska Native
API	Asian or Pacific Islander
CI	confidence interval
GNB	ganglioneuroblastoma
HR	hazard ratio
INRG	International Neuroblastoma Risk Group
INRGSS	INRG Staging System
NB	neuroblastoma
NPCR	National Program of Cancer Registries
SEER	Surveillance, Epidemiology, and End Results
USCS	United States Cancer Statistics

REFERENCES

1. Siegel DA, King JB, Lupo PJ, et al. Counts, incidence rates, and trends of pediatric cancer in the United States, 2003–2019. J Natl Cance Inst. 2023:djad115. doi:10.1093/jnci/djad115
2. Irwin MS, Naranjo A, Zhang FF, et al. Revised neuroblastoma risk classification system: a report from the Children's Oncology Group. J Clin Oncol. 2021;39(29):3229–3241.
3. Sokol E, Desai AV. The evolution of risk classification for neuroblastoma. Children (Basel). 2019;6(2):27.
4. NIH. Surveillance, epidemiology, and end results (SEER) program SEER*stat database: incidence-SEER 9 regs research data. National Cancer Institute, Surveillance Research Program; 2021.
5. Cohn SL, Pearson AD, London WB, et al. The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report. J Clin Oncol. 2009;27(2):289–297.
6. National Program of Cancer Registries and Surveillance, Epidemiology, and End Results Program SEER*Stat Database: U.S. Cancer Statistics Incidence Analytic File. 1998–2019 (based on 2021 submission). United States Department of Health and Human Services, Centers for Disease Control Prevention; released June 2022.
7. National Program of Cancer Registries and Surveillance, Epidemiology, and End Results Program SEER*Stat Database. NPCR Survival Analytic File 2001–2018 (based on 2021 submission). United States Department of Health and Human Services, Centers for Disease Control Prevention; released June 2022.
8. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International classification of childhood cancer, third edition. Cancer. 2005;103(7):1457–1467.
9. Fritz APC, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S. International classification of diseases for oncology. World Health Organization; 2000.
10. Wu XC, Yu Q, Andrews PA, et al. Comparisons of directly coded SEER summary stage 2000 and collaborative staging derived SEER summary stage 2000. J Registry Manag. 2010;37(4):137–140.
11. Appalachian Regional Commission. Distressed designation and county economic status classification system. Appalachian Regional Commission; 2023.

12. Mariotto AB, Zou Z, Johnson CJ, et al. Geographical, racial and socioeconomic variation in life expectancy in the US and their impact on cancer relative survival. PLoS One. 2018;13(7):e0201034.
13. Bagatell R, Irwin MS. Tandem transplant for high-risk neuroblastoma: next steps in the era of precision medicine. JAMA. 2019;322(8):729–731.
14. Georgakis MK, Dessypris N, Baka M, et al. Neuroblastoma among children in Southern and Eastern European cancer registries: variations in incidence and temporal trends compared to US. Int J Cancer. 2018;142(10):1977–1985.
15. Krejci D, Zapletalova M, Svobodova I, et al. Childhood cancer epidemiology in the Czech Republic (1994–2016). Cancer Epidemiol. 2020;69:101848.
16. Tas ML, Reedijk AMJ, Karim-Kos HE, et al. Neuroblastoma between 1990 and 2014 in the Netherlands: increased incidence and improved survival of high-risk neuroblastoma. Eur J Cancer. 2020;124:47–55.
17. Berthold F, Spix C, Kaatsch P, Lampert F. Incidence, survival, and treatment of localized and metastatic neuroblastoma in Germany 1979–2015. Paediatr Drugs. 2017;19(6):577–593.
18. Youlden DR, Jones BC, Cundy TP, et al. Incidence and outcomes of neuroblastoma in Australian children: a population-based study (1983–2015). J Paediatr Child Health. 2020;56(7):1046–1052.
19. Lacour B, Guyot-Goubin A, Guissou S, et al. Incidence of childhood cancer in France: National Children Cancer Registries, 2000–2004. Eur J Cancer Prev. 2010;19(3):173–181.
20. Shinagawa T, Kitamura T, Katanoda K, et al. The incidence and mortality rates of neuroblastoma cases before and after the cessation of the mass screening program in Japan: a descriptive study. Int J Cancer. 2017;140(3):618–625.
21. Coughlan D, Gianferante M, Lynch CF, Stevens JL, Harlan LC. Treatment and survival of childhood neuroblastoma: evidence from a population-based study in the United States. Pediatr Hematol Oncol. 2017;34(5):320–330.
22. Olsen HE, Campbell K, Bagatell R, DuBois SG. Trends in conditional survival and predictors of late death in neuroblastoma. Pediatr Blood Cancer. 2020;67(10):e28329.
23. Bhatia S Disparities in cancer outcomes: lessons learned from children with cancer. Pediatr Blood Cancer. 2011;56(6):994–1002.
24. Bhatia S, Sather HN, Heerema NA, et al. Racial and ethnic differences in survival of children with acute lymphoblastic leukemia. Blood. 2002;100(6):1957–1964.
25. Kahn JM, Kelly KM, Pei Q, et al. Survival by race and ethnicity in pediatric and adolescent patients with Hodgkin lymphoma: a Children's Oncology Group study. J Clin Oncol. 2019;37(32):3009–3017.
26. Gerbing RB, Smith FO, Meshinchi S, et al. Ethnicity and survival in childhood acute myeloid leukemia: a report from the Children's Oncology Group. Blood. 2006;108(1):74–80.
27. Henderson TO, Bhatia S, Pinto N, et al. Racial and ethnic disparities in risk and survival in children with neuroblastoma: a Children's Oncology Group study. J Clin Oncol. 2011;29(1):76–82.
28. Zheng DJ, Li A, Ma C, et al. Socioeconomic disparities in survival after high-risk neuroblastoma treatment with modern therapy. Pediatr Blood Cancer. 2021;68(10):e29127.
29. Valenzuela A, Hawkins A, Revette A, et al. "It's a lot of things": household material hardship among Black and Hispanic parents of children with cancer. Pediatr Blood Cancer. 2023:e30485. doi:10.1002/pbc.30485
30. Kehm RD, Spector LG, Poynter JN. Does socioeconomic status account for racial and ethnic disparities in childhood cancer survival? Cancer. 2018;124(20):4090–4097.
31. Umaretiya PJ, Vinci RJ, Bona K. A structural racism framework to guide health equity interventions in pediatric oncology. Pediatrics. 2022;149(5):e2021054634.
32. Bona K, Li Y, Winestone LE, et al. Poverty and targeted immunotherapy: survival in Children's Oncology Group clinical trials for high-risk neuroblastoma. J Natl Cancer Inst. 2021;113(3):282–291.
33. Umaretiya PJ, Revette A, Seo A, et al. PediCARE: development of a poverty-targeted intervention for pediatric cancer. Pediatr Blood Cancer. 2021;68(10):e29195.

34. Aziz-Bose R, Zheng DJ, Umaretiya PJ, et al. Feasibility of oncology clinical trial-embedded evaluation of social determinants of health. Pediatr Blood Cancer. 2022;69(11):e29933.

35. Winestone LE, Beauchemin MP, Bona K, et al. Children's Oncology Group's 2023 blueprint for research: diversity and health disparities. Pediatr Blood Cancer 2023;70(Suppl 6):e30592.

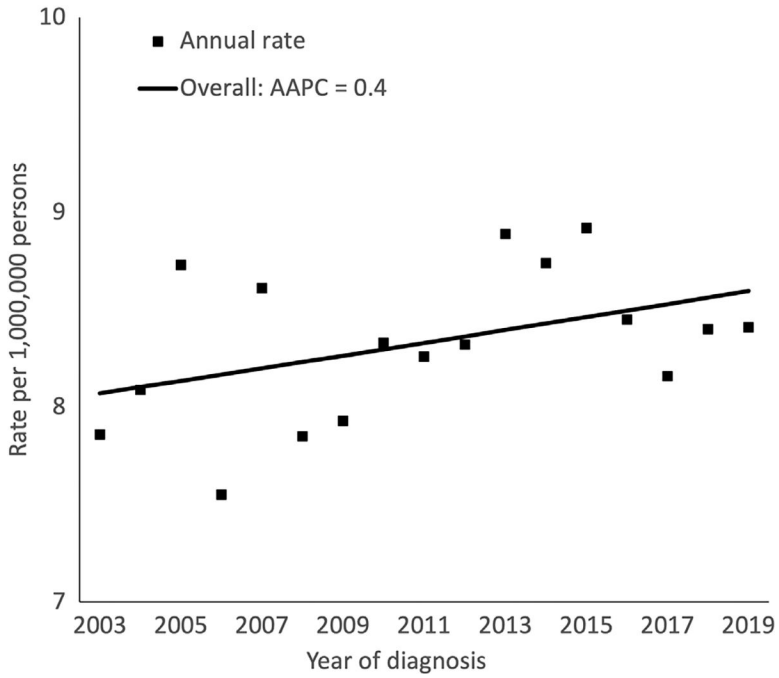

FIGURE 1.

Age-adjusted rates per 1,000,000 persons of neuroblastoma/ganglioneuroblastoma diagnosis in the United States from 2003 to 2019.

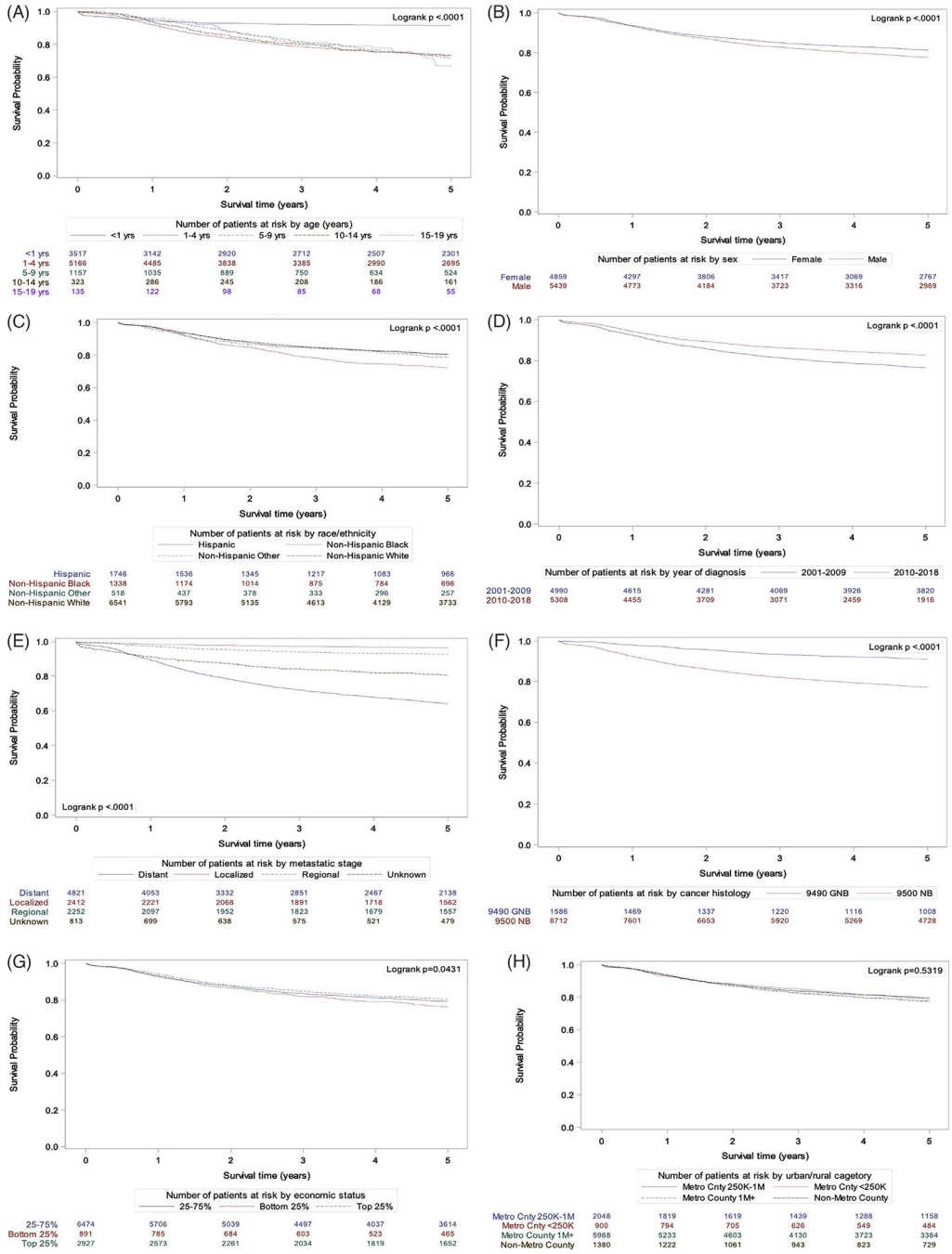

FIGURE 2.

Kaplan–Meier 5-year all-cause survival curves of neuroblastoma cases among children and adolescents from the National Program of Cancer Registries (NPCR) database (2001–2018). Data are stratified by (A) age, (B) sex, (C) race and ethnicity, (D) date of diagnosis, (E) stage, (F) histologic type, (G) economic status, and (H) rural–urban status.

TABLE 1

Incidence and average annual percent change in neuroblastoma cases among children and adolescents from the USCS database (2003–2019) with multivariable negative binomial analysis.

Characteristic	Cases (%)	Incidence [per 1 million]	AAPC (%) [95% CI]	RR[b] [95% CI]	RR *p*-value
Overall	11,543(100%)	8.33 [8.18–8.48]	0.4 [−0.1 to 0.9]		
Sex					
Male	6088 (52.7%)	8.59 [8.38–8.81]	0.4 [−0.2 to 0.9]	Ref	
Female	5455 (47.3%)	8.05 [7.84–8.27]	0.4 [−0.2 to 1.1]	0.97 [0.88–1.07]	.601
Histology					
Neuroblastoma	9714 (84.2%)	7.00 [6.86–7.14]	0.2 [−0.4 to 0.8]		
Ganglioneuroblastoma	1829(15.8%)	1.33 [1.27–1.39]	1.4[a] [0.2 to 2.6]		
Age					
<1year	3924 (34.0%)	58.69 [56.87–60.56]	0.1 [−0.6 to 0.8]	Ref	-
1–4years	5761 (49.9%)	21.41 [20.86–21.97]	0.0 [−0.6 to 0.7]	0.42 [0.37–0.47]	<.001
5–9years	1315(11.4%)	3.88 [3.68–4.10]	2.4[a] [1.2 to 3.7]	0.07 [0.06–0.08]	<.001
10–14 years	376 (3.0%)	1.07 [0.97–1.18]	0.4 [−2.0 to 2.9]	0.02 [0.02–0.02]	<.001
15–19 years	167(1.5%)	0.46 [0.40–0.54]	3.3[a] [0.6 to 1.6]	0.01 [0.01–0.01]	<.001
Race and ethnicity					
NH White	7455 (65.0%)	9.99 [9.76–10.22]	0.7[a] [0.2 to 1.2]	Ref	
NH Black	1476(12.8%)	7.01 [6.65–7.37]	−0.6 [−1.6 to 0.4]	0.73 [0.64–0.83]	<.001
NH API	513(4.5%)	6.66 [6.09–7.26]	0.8 [−1.9 to 3.6]	0.64 [0.54–0.76]	<.001
NHAIAN	90 (0.7%)	6.46 [5.20–7.94]	3.5 [−1.5 to 8.7]	0.69 [0.54–0.88]	.004
Hispanic	1836(15.9%)	5.43 [5.19–5.69]	0.5 [−0.6 to 1.6]	0.54 [0.47–0.61]	<.001
NH unknown	173(1.5%)	-	-		
Stage					
Localized	2786(24.1%)	2.01 [1.94–2.09]	2.6[a] [1.8 to 3.4]		
Regional	2544 (22.0%)	1.83 [1.76–1.91]	−1.9[a] [−3.0 to −0.9]		
Distant	5408 (46.9%)	3.90 [3.80–4.01]	0.3 [−0.4 to 0.9]		
Unknown	805 (7.0%)	-			
Rural-urban status					

Characteristic	Cases (%)	Incidence [per 1 million]	AAPC (%) [95% CI]	RR[b] [95% CI]	RR *p*-value
Metro >1,000,000	6537 (56.6%)	8.49 [8.29–8.70]	0.3 [−0.2 to 0.8]	Ref	-
Metro 250,000–1,000,000	2405 (20.8%)	8.08 [7.76–8.41]	0.1 [−0.8 to 1.1]	0.88 [0.78–1.00]	.045
<250,000	1034 (9.0%)	8.32 [7.82–8.84]	0.5 [−1.4 to 2.3]	0.88 [0.76–1.02]	.094
Non-metro	1564(13.5%)	8.03 [7.64–8.44]	1 [−0.3 to 2.4]	0.82 [0.71–0.95]	.006
Economic status[c]					
Top 25%	3812 (34.1%)	9.01 [8.72–9.30]	0.4 [−0.2 to 1.1]	Ref	
25%–75%	6372 (57.0%)	8.12 [7.92–8.32]	0.3 [−0.4 to 1.1]	0.97 [0.86–1.08]	.573
Bottom 25%	973 (8.7%)	7.11 [6.67–7.57]	−0.1 [−1.6 to 1.5]	0.96 [0.84–1.11]	.606
Unknown	19 (0.2%)	-	-		

Abbreviations: AAPC, average annual percent change; AIAN, American Indian/Alaska Native; API, Asian or Pacific Islander; CI, confidence interval; metro, metropolitan; NH, non-Hispanic; RR, relative risk; USCS, United States Cancer Statistics.

[a]Indicates significant AAPC.

[b]RRfor histology and cancer stage were not included in the model, as they are cancer characteristics, not cancer predictors.

[c]Excluded cases from Kansas and Minnesota because economic data were not reported for these states.

Source: United States Cancer Statistics.

TABLE 2

Five-year relative survival of neuroblastoma cases among children and adolescents from the NPCR database (2001–2018).

Characteristic	Cases(%)	5-Year relative survival (%) [95% CI] 2001–2018, 2001–2009, 2010–2018
Overall	10,676 (100)	79.7 [78.9–80.5]
		76.8 [75.6–78.0]
		83.2 [82.0–84.3]
Sex		
Male	5658 (53.0)	78.0 [76.8–79.2]
		75.4 [73.8–77.0]
		81.3 [79.6–82.9]
Female	5018 (47.0)	81.6 [80.4–82.7]
		78.4 [76.7–80.0]
		85.3 [83.6–86.8]
Histology		
Neuroblastoma	9027 (84.6)	77.6 [76.7–78.5]
		74.8 [73.5–76.1]
		81.1 [79.7–82.3]
Ganglioneuroblastoma	1649(15.4)	91.0 [89.4–92.4]
		88.5 [86.0–90.6]
		94.0 [91.8–95.5]
Age		
<1year	3663 (34.3)	92.5 [91.5–93.3]
		92.4 [91.0–93.6]
		92.6 [91.1–93.8]
1–4years	5329 (49.9)	73.4 [72.1–74.7]
		69.6 [67.7–71.3]
		78.1 [76.3–79.8]
5–9years	1206(11.3)	71.3 [68.3–74.0]
		64.5 [60.3–68.4]
		78.7 [74.5–82.3]
10–14 years	334 (3.1)	73.4 [67.9–78.2]
		64.6 [56.6–71.6]
		84.8 [77.7–89.8]
15–19 years	144(1.4)	66.7 [56.7–74.9]
		58.7 [44.2–70.6]
		73.6 [58.6–83.8]
Race and ethnicity		
NH White	6848 (64.1)	80.7 [79.7–81.7]
		78.1 [76.6–79.4]
		84.2 [82.7–85.5]

Characteristic	Cases(%)	5-Year relative survival (%) [95% CI] 2001–2018, 2001–2009, 2010–2018
NH Black	1367(12.8)	72.6 [70.0–75.1]
		67.3 [63.6–70.8]
		79.6 [76.0–82.8]
NH API	453 (4.2)	78.5 [73.9–82.3]
		74.7 [67.5–80.5]
		81.2 [74.9–86.1]
NH AIAN	86 (0.8)	81.6 [69.8–89.1]
		87.6 [71.4–94.9]
		69.3 [46.1–84.1]
Hispanic	1764(16.5)	80.8 [78.8–82.7]
		78.3 [75.3–81.0]
		83.3 [80.2–85.9]
NH unknown	158(1.5)	86.6 [79.5–91.4]
		91.1 [80.5–96.0]
		83.6 [72.8–90.3]
Stage		
Localized	2500 (23.4)	96.9 [96.1–97.6]
		96.6 [95.3–97.6]
		97.3 [96.1–98.2]
Regional	2389 (22.4)	93.3 [92.1–94.3]
		91.8 [90.0–93.2]
		95.3 [93.7–96.5]
Distant	4990 (46.7)	64.4 [63.0–65.8]
		60.0 [58.0–61.9]
		70.0 [67.8–72.0]
Unknown	837 (7.8)	80.8 [77.8–83.5]
		77.9 [73.6–81.5]
		84.8 [80.2–88.4]
Rural-urban		
Metro >1,000,000	6166 (57.8)	80.2 [79.1–81.2]
		77.2 [75.6–78.7]
		83.7 [82.2–85.2]
Metro 250,000–1,000,000	2091 (19.6)	79.8 [77.9–81.6]
		77.7 [75.0–80.1]
		82.4 [79.6–84.9]
<250,000	955 (8.9)	79.1 [76.1–81.7]
		74.7 [70.3–78.6]
		84.2 [80.3–87.5]
Non-metro	1462 (13.7)	77.9 [75.5–80.1]
		75.1 [71.7–78.2]
		81.4 [77.8–84.4]

Characteristic	Cases(%)	5-Year relative survival (%) [95% CI] 2001–2018, 2001–2009, 2010–2018
Economic status		
Bottom 25%	891 (8.7)	76.2 [73.0–79.1]
		73.7 [69.2–77.6]
		79.2 [74.3–83.4]
25%–75%	6474 (62.9)	79.6 [78.5–80.6]
		77.1 [75.6–78.6]
		82.6 [81.1–84.1]
Top 25%	2927(28.4)	80.6 [79.0–82.1]
		77.1 [74.8–79.2]
		85.0 [82.6–87.0]

Abbreviations: AIAN, American Indian/Alaska Native; API, Asian Pacific or Islander; CI, confidence interval; metro, metropolitan; NH, non-Hispanic; NPCR, National Program of Cancer Registries.

Source: National Program of Cancer Registries.

TABLE 3

Cox proportional hazards model predicting 5-year all-cause survival.

Characteristic	Wald χ^2	*p*-Value	Hazard ratio[a] [95% CI]
Age	251.30	<.0001	
<1year			1.0(ref)
1–4 years			2.76 [2.42–3.15]
5–9 years			2.77 [2.33–3.28]
10–14 years			3.46 [2.68–4.48]
15–19 years			4.03 [2.80–5.81]
Race/ethnicity[b]	15.88	.0012	
NH White			1.0(ref)
NH Black			1.29 [1.14–1.46]
Hispanic			1.11 [0.97–1.27]
Other[c]			1.05 [0.85–1.29]
Sex	3.67	.0552	
Male			1.0(ref)
Female			0.91 [0.83–1.00]
Diagnosis year	61.91	<.0001	
2001–2009			1.0(ref)
2010–2018			0.69 [0.63–0.75]
Stage[b]	595.14	<.0001	
Localized			1.0(ref)
Regional			1.77 [1.34–2.33]
Distant			8.86 [6.99–11.24]
Histology	35.97	<.0001	
Neuroblastoma			1.0(ref)
Ganglioneuroblastoma			0.56 [0.46–0.68]
Rural-urban[b]	2.17	.5384	
Metro >1,000,000			1.0(ref)
Metro 250K–1 M			0.99 [0.87–1.11]
<250,000			1.09 [0.92–1.30]
Non-metro			1.08 [0.93–1.26]
Economic status[b]	0.80	.6717	
Bottom 25%			1.09 [0.90–1.32]
25%–75%			1.03 [0.92–1.15]
Top 25%			1.0(ref)

Note: N = 10,298 with 1899 events. C-index = .758.

Abbreviations: CI, confidence interval; metro, metropolitan; NH, nonHispanic.

[a]A hazard ratio greater than 1 between compared groups indicates a higher risk of death, with statistical significance determined at $p < .05$.

[b] Multiple imputation was used to impute ($m = 10$) missing data for stage ($n = 813$), race/ethnicity ($n = 155$), economic status ($n = 6$), and rural-urban status ($n = 2$). All predictors and the outcome variables were included in the imputation models.

[c] Includes non-Hispanic American Indian/Alaska Native and non-Hispanic Asian/Pacific Islander.