Received: 18 December 2023 | Revised: 23 February 2024 | Accepted: 26 February 2024

DOI: 10.1002/pbc.30954

Pediatric Blood & Cancer

RESEARCH ARTICLE

Registration, incidence patterns, and survival trends of central nervous system tumors among children in Germany 1980–2019: An analysis of 40 years based on data from the German Childhood Cancer Registry

Maike Wellbrock[1,2] | Mathias Voigt[3] | Cecile Ronckers[3] | Desiree Grabow[3] | Claudia Spix[3] | Friederike Erdmann[1,2]

[1]Research Group Aetiology and Inequalities in Childhood Cancer, Division of Childhood Cancer Epidemiology, Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

[2]Department of Prevention and Evaluation, Leibniz Institute for Prevention Research and Epidemiology - BIPS, Bremen, Germany

[3]German Childhood Cancer Registry/Division of Childhood Cancer Epidemiology, Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

Correspondence
Maike Wellbrock, Research Group Aetiology and Inequalities in Childhood Cancer, Division of Childhood Cancer Epidemiology, Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), University Medical Center of the Johannes Gutenberg University Mainz, Langenbeckstraße 1, 55131 Mainz, Germany.
Email: mwellbro@uni-mainz.de

Funding information
Tour der Hoffnung; Federal Ministry of Health; Health Ministries of the 16 federal states of Germany

Abstract

Background: Tumors of the central nervous system (CNS) are the second most common type of pediatric cancer in Germany. We aimed to describe registration practice, incidence, and survival patterns for childhood CNS tumors in Germany for the past 40 years.

Procedure: Including all CNS tumor cases in children diagnosed at ages 0–14 years registered at the German Childhood Cancer Registry (GCCR) in 1980–2019 (for survival analysis 1980–2016), we calculated age-specific and age-standardized incidence rates (ASIR) over time, average annual percentage changes (AAPC), and 1- and 5-year overall survival.

Results: While we observed a pronounced increase in ASIR after the establishment of the GCCR during the 1980s, ASIR for all pediatric CNS tumors combined continued to increase markedly from 28.6 per million in 1990–1999 to 43.3 in 2010–2019 (AAPC = 2.7% in 1991–2010, AAPC = 0.3% in 2010–2019). The 5-year overall survival from CNS tumors improved from 63% in the 1980s, 70% in the 1990s to 79% in 2010–2016. These improvements have occurred across all age groups. Children diagnosed with ependymomas and choroid plexus tumors experienced the strongest increase (from 54% to 81%).

Conclusions: Observed increases in incidence rates for pediatric CNS tumors are likely only partially caused by actual increasing case numbers. The majority is a function of improved registration and, to a minor extent, improvements in diagnostics. Survival from pediatric CNS tumors has, by and large, improved consistently, leading to a growing population of childhood cancer survivors with diverse health biographies and risk of lifelong adverse impact on health and wellbeing.

Abbreviations: AAPC, average annual percentage change; ASIR, age-standardized incidence rate; CI, confidence interval; CNS, central nervous system; GCCR, German Childhood Cancer Registry; HR, hazard ratio; ICCC, International Classification of Childhood Cancer; ICD-O, International Classification of Diseases for Oncology; SPN, subsequent primary neoplasm.

Maike Wellbrock and Mathias Voigt contributed equally to this work.

[Correction added on 15 April 2024, after first online publication: The copyright line was changed.]

KEYWORDS
childhood cancer, German Childhood Cancer Registry, incidence, pediatric central nervous system tumors, survival, time trends

1 | INTRODUCTION

Tumors of the central nervous system (CNS) are the second most common type of pediatric cancers in most high-income countries, and account for roughly 25% of all cancers in children between the ages 0 and 14 in most European countries.[1] CNS tumors comprise a heterogeneous group of entities with substantial differences in biology, incidence pattern, histology, and prognosis.[2–4] Its two most common subtypes in children, pilocytic astrocytoma and medulloblastoma, are rarely seen in adults, whereas the two most common subtypes that occur in adults, glioblastoma and meningioma, are rarely seen in children.[2]

Reported incidence rates have increased steadily in Europe over the past decades.[5] Observed age-standardized incidence rates (ASIR) ranged from 30 to 42 cases per million, while temporal trends vary by region.[5–7] Albeit their relative importance for the overall cancer burden in children, which is enhanced by a comparatively poor prognosis for some tumor types and many life-years ahead along with a high risk for tumor- and treatment-related somatic late effects, the etiology of CNS tumors remains largely unknown. About 5% of all CNS tumors can be traced back to genetic predisposition syndromes, like neurofibromatosis.[8,9] A higher risk is also frequently observed for children with exposure to high doses of ionizing radiation in utero (transplacental carcinogenesis)[10,11] or during childhood,[12–14] and for children with high or low birth weight.[2,15,16] The increases in incidence rates that were observed since the 1980s lead to hypotheses that environmental factors play a role in the development of pediatric CNS tumors. Despite a growing body of research, no toxin or other environmental factor could, so far, be found to undoubtedly fill this etiological role.[9,11,17] Another explanation for the perceived increase in incidence rates was sought in changes of coding and classification schemes, improvements in reporting, and new means of diagnosis, such as the increasing availability of MRI (magnetic resonance imaging)[18] scans, which coincided with the uptick in reported CNS tumor incidence rates, especially for low-grade gliomas.[19]

The survival from pediatric CNS tumors has notably improved over the past decades,[20,21] although for some tumor types the prognosis remains poor compared to other childhood cancer types. Two comprehensive assessments reported remarkably increasing 5-year survival estimates over the past decades to recently 73% (all CNS diagnoses combined) in Europe[22–24] and 79% in Germany.[21] Yet, when only malignant CNS tumors were considered, survival estimates were substantially worse; 5-year survival probabilities remained at 59%[24] and 66%,[21] respectively. While the survival probability of the most common CNS tumor type, low-grade gliomas, has improved substantially, these improvements were not observed in medulloblastomas and the majority of malignant gliomas.[18]

With this article, we offer an overview about registration, incidence patterns, and survival trends in childhood CNS tumors in Germany for the past 40 years, by taking advantage of the high-quality population-based data from the German Childhood Cancer Registry (GCCR). The GCCR was established in 1980 and is one of the few, long-standing national childhood cancer registries in the world. The longitudinal data offer a high granularity to describe the epidemiology of childhood CNS tumors and discuss influencing factors on incidence and survival patterns at different time points during 40 years of registration.

2 | MATERIALS AND METHODS

2.1 | Study population and data

The study population comprised all children diagnosed with a primary CNS tumor between the ages 0 and 14 years (including subsequent primary neoplasms [SPNs]) registered at the GCCR from 1980 to 2019. The GCCR has been recording and monitoring incident cases of all pediatric malignancies and non-malignant intracranial and intraspinal tumors in Germany for more than 40 years. At first, only pediatric cancer cases from West Germany were registered. Since 1991, the GCCR also covers the population of former East Germany.

The registration process of the GCCR is based on voluntary reporting by all pediatric hematology-oncology units in Germany and written informed consent of the respective parents and patients. In case no written consent is given, incident cancer diagnoses are registered without any personal identifiable information. During the initial build-up phase from 1980 to about 1987, the GCCR quickly established a close and well-functioning network with all treating hospitals and the German Society of Paediatric Oncology and Haematology, the association of pediatric oncology professionals in Germany (including the commitment of the GPOH to report all new cancer diagnoses to the GCCR), which ensures the coverage of virtually all pediatric cancer cases that are diagnosed and treated in a pediatric oncology unit. Some pediatric CNS tumor patients, primarily of adolescent age or when no chemotherapy is required, are treated in neuro-oncology facilities for adults, which do not report reliably to the GCCR. Excellent coverage for almost all cancer types is achieved since about 1987, with completeness of registration being estimated to exceed 95% (diagnosed before the age of 15, all cancer types combined). CNS tumors tended to be somewhat underreported, particularly during the build-up period,[4] but to a minor extent likely up to the present day. Consequentially, the incidence rates and temporal patterns reported for the early 1980s, most likely do not reflect actual changes in incidence over time but rather improvements in the completion of the registry.

CNS tumors reported to the GCCR were initially classified according to the first International Classification of Childhood Cancer [ICCC] by Birch and Marsden).[25] After each introduction of a new ICD-O (International Classification of Diseases for Oncology) edition, all diagnoses were retrospectively recoded and reclassified according to the respective ICCC edition (since 2003 according to the third edition [ICCC-3]).[26] The main differences (on main diagnostic group level), between the Birch and Marsden edition and ICCC-3 concern ICD-O-3 morphology codes 9060–9102 (intracranial and intraspinal germ cell tumors), which have been removed from group III and added to group X.[25,26] As the symptoms and prognoses are similar to malignant CNS tumors, intracranial and intraspinal tumors of non-malignant or uncertain behavior are included in the ICCC. Following the ICCC-3 classification, we present the respective CNS tumor types in our analysis: ependymomas and choroid plexus tumors (group III(a)), astrocytomas (group III(b)), intracranial and intraspinal embryonal tumors (group III(c)), other gliomas (group III(d)), other specified intracranial and intraspinal neoplasms (group III(e)), unspecified intracranial and intraspinal neoplasms (group III(f)). The latter group is just included in the descriptive results but excluded from analysis. At the time of our study (data extraction: January 15, 2022), registry data on incident diagnoses were available for the period from 1980 to 2019.

Annual population estimates by age and sex were obtained from the German Federal Statistical Office.[27]

The study population for the survival analyses included cases with a primary CNS tumor (including SPNs) diagnosed between 1980 and 2016 (data base as of December 31, 2021). The GCCR regularly collects follow-up data on vital status using information from relevant therapy trials, treating hospitals, and local population registries.[4] Follow-up of patients without written consent is prohibit (as they were registered without any personal identifiable information), and follow-up after emigration from Germany is generally not possible.

2.2 | Statistical analysis

Age-specific and age-standardized incidence rates (ASIR) per million were calculated for all CNS tumors combined and by tumor type. The ASIRs were calculated through direct standardization, using the Segi 1960 World Standard Population.[28] The analyses were stratified by CNS tumor types (see above), age at diagnosis (grouped by 0, 1–4, 5–9, 10–14 years), sex (female/male), and behavior (malignant/non-malignant). For the graphical representation of reported incidence trends over time, we applied a cubic spline smoother to the ASIRs per calendar year. To evaluate if the magnitude or direction of ASIR trends changed over time, we used Joinpoint regression.[29] This method allowed us to calculate the average annual percentage changes (AAPC) in incidence rates.[30] The Joinpoint model applies Monte Carlo permutation tests to detect points in time marking significant changes in magnitude or direction of temporal trends (the so-called joinpoints). As recommended by National Cancer Institute,[31] we allowed for up to five joinpoints for each model. Where joinpoints were detected, the AAPC and its 95% confidence interval (CI) were reported for the time (segment) between two adjacent joinpoints.

Overall survival was defined as the period between the date of diagnosis and death from any cause. Follow-up information was available until December 31, 2021. Observation time was censored at 5 years after diagnosis; patients were followed until death from any cause, emigration, or end of follow-up, whichever came first. We calculated 1- and 5-year overall survival for each of the above-mentioned stratification variables with the lifetable method. For graphical presentation, a locally estimated scatterplot smoothing (LOESS) with cubic interpolation was applied to the 5-year overall survival estimates per calendar year. For the analysis on determinants influencing survival, we used Cox proportional hazard regression to model hazard ratios (HR) and corresponding 95% CIs for the risk of dying in a multivariable setting.

Analyses were performed using R version 4.1.1 (10.08.2021), SAS Software 9.4[32] and Joinpoint Regression Program, version 4.9.0.0, National Cancer Institute.[31]

3 | RESULTS

In total, 14,576 children (45.2% females) diagnosed with a CNS tumor at ages 0–14 years were reported to the GCCR during the 40-year study period (1980–2019) (Table 1). Of those, 1.2% were SPNs. Children diagnosed at ages 5–9 accounted for 33.9% of the total cases, followed by children in the ages 1–4 (30.4%), 10–14 (28.9%), and infants (6.8%). Astrocytomas represented the most frequently diagnosed CNS tumor type (44.3%) (Table 1). The incidence of CNS tumors differed notably by tumor type and age at diagnosis (Table S1, Figure S1). Figures S2 and S3 show the distribution of tumors behavior (malignant/non-malignant) by diagnostic subgroups and vice versa.

3.1 | Incidence rates

The average ASIR for the entire study period (1980–2019) was 32.9 per million with an AAPC of 3.3% [95% CI: 1.8–4.9] (Tables 1 and 2). For the period 1991–2010, the Joinpoint analysis revealed a moderately increasing trend (AAPC: 2.7%, 95% CI: 2.0–3.4), followed by rather stable rates during 2010–2019 (Table 2 and Figure 1A).

The age-specific analysis indicated substantial increases of the reported CNS tumor incidence rates for each age group. For children diagnosed during infancy, the incidence rate ranged between 29.3 per million in 1990–1999 and 42.4 per million in 2010–2019. The increases in reported incidence rates were slightly disproportionally distributed in terms of timing and magnitude. For the 1- to 4-year olds, the best fitting model suggested an AAPC of 2.1% [95% CI: 1.7–2.5] for the entire period and did not identify any joinpoints, suggesting a relatively consistent trend. Both age groups, 5–9 and 10–14, experienced substantial increases during the 1980s with an AAPC of 13.4% [95% CI: 7.1–20.1] and 15.2% [95% CI: 3.3–28.3], respectively, while incidence rates increased more moderately in subsequent periods (with AAPCs

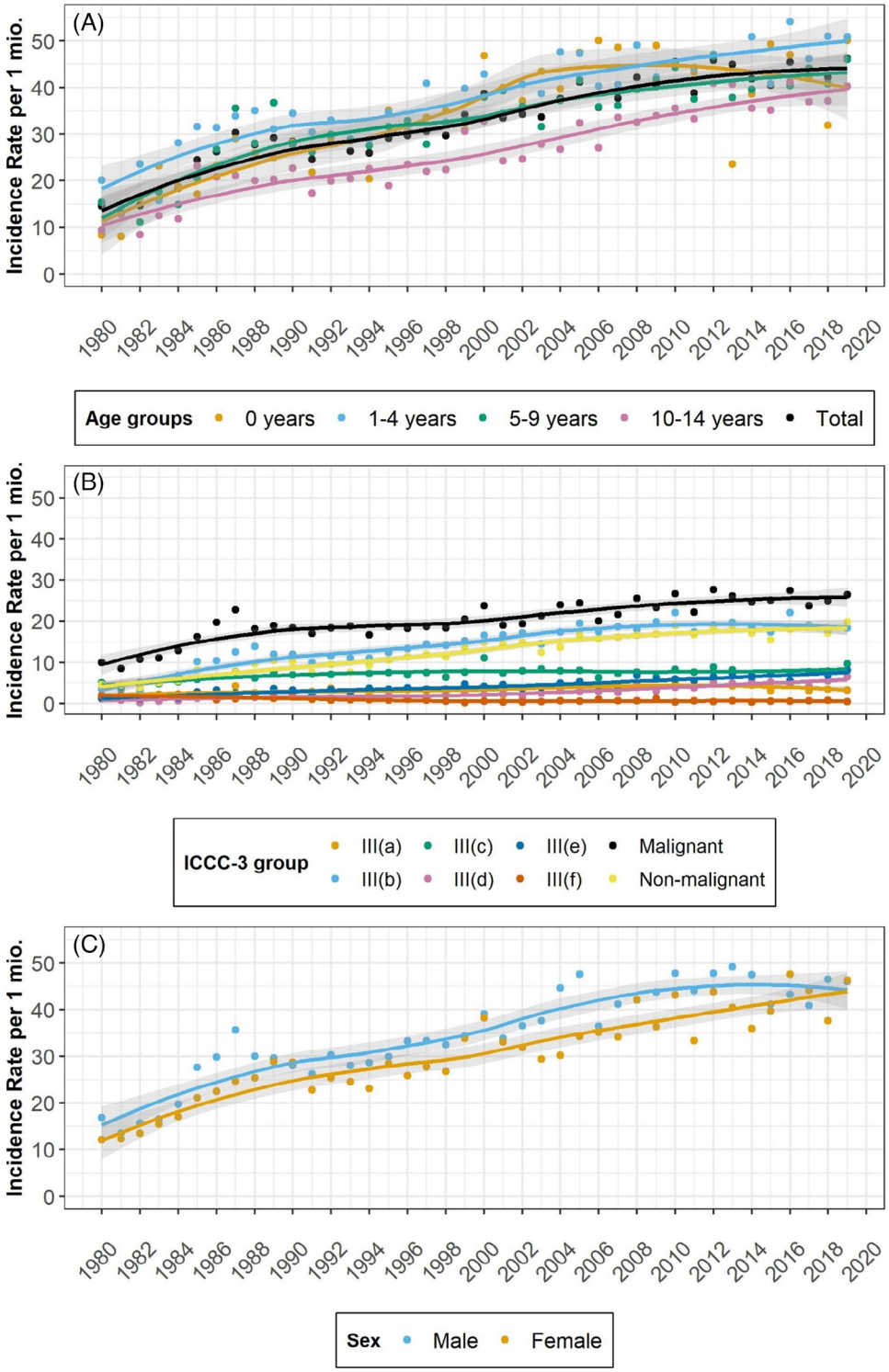

FIGURE 1 Age-specific and age-standardized incidence rates of central nervous system (CNS) tumors in children aged 0–14 years at diagnosis by (A) age group at diagnosis, (B) tumor type/behavior, and (C) sex from 1980 to 2019 in Germany. ASIRs were directly age-standardized according to the Segi 1960 World Standard Population. Tumor types are classified according to the International Classification of Childhood Cancer – third edition (ICCC-3): Ependymomas and choroid plexus tumors (ICCC-3 group III(a)), Astrocytomas (ICCC-3 group III(b)), Intracranial and intraspinal embryonal tumors (ICCC-3 group III(c)), other gliomas (ICCC-3 group III(d)), Other specified intracranial and intraspinal neoplasms (ICCC-3 group III(e)), and Unspecified intracranial and intraspinal neoplasms (ICCC-3 group III(f)). A cubic spline smoother was applied to the ASIRs per calendar year.

TABLE 1 Descriptive overview and age-standardized/age-specific incidence rates of children diagnosed with a CNS tumor at ages 0–14 years between 1980 and 2019 in Germany by diagnostic decade.

	Abs. Freq.	Rel. Freq.	Age-standardized[a] and age-specific incidence rate per million [95% CI] per diagnostic decade				
	N	%	1980–2019	1980–1989	1990–1999	2000–2009	2010–2019
Total	14,576	100.0	32.9 [29.5–36.8]	21.2 [20.3–22.2]	28.6 [27.7–29.6]	37.4 [36.2–38.5]	43.3 [42.1–44.6]
Age at diagnosis (years)							
Age 0	987	6.8	36.1 [27.0–47.3]	20.1 [16.7–24.0]	29.3 [25.7–33.3]	42.3 [39.9–44.7]	42.4 [37.8–47.4]
Age 1–4	4435	30.4	38.3 [30.6–47.4]	26.3 [24.3–28.4]	33.4 [31.5–35.4]	46.1 [41.2–51.3]	50.3 [47.7–52.9]
Age 5–9	4942	33.9	32.8 [27.3–39.2]	22.1 [20.4–23.8]	29.8 [28.2–31.5]	37.6 [35.7–39.6]	42.0 [39.9–44.2]
Age 10–14	4212	28.9	26.3 [21.6–31.8]	15.1 [13.9–16.4]	22.1 [20.7–23.5]	29.4 [27.8–31.1]	37.6 [35.7–39.7]
Tumor type[b]							
III(a) Ependymomas and choroid plexus tumor	1407	9.7	3.2 [2.2–4.8]	2.6 [2.3–3.0]	3.0 [2.7–3.4]	3.8 [3.5–4.2]	4.1 [3.7–4.6]
III(b) Astrocytomas	6457	44.3	14.7 [12.4–17.4]	7.9 [7.4–8.5]	12.5 [11.9–13.1]	17.5 [16.8–18.3]	19.1 [18.3–20.0]
III(c) Intracranial and intraspinal embryonal tumors	3110	21.3	7.2 [5.6–9.3]	5.8 [5.3–6.3]	7.2 [6.7–7.7]	7.9 [7.4–8.4]	7.9 [7.4–8.5]
III(d) Other gliomas	1217	8.4	2.8 [1.9–4.2]	1.2 [1.0–1.4]	1.7 [1.5–1.9]	2.8 [2.5–3.1]	4.9 [4.5–5.4]
III(e) Other specified intracranial and intraspinal neoplasms	1997	13.7	4.3 [3.1–5.9]	2.1 [1.8–2.4]	3.4 [3.1–3.8]	4.7 [4.3–5.1]	6.7 [6.2–7.2]
III(f) Unspecified intracranial and intraspinal neoplasms	388	2.7	0.9 [0.4–2.0]	1.6 [1.3–1.9]	0.8 [0.7–1.0]	0.6 [0.5–0.8]	0.6 [0.4–0.7]
Sex							
Female	6587	45.2	30.4 [25.7–36.0]	19.0 [17.8–20.4]	26.7 [25.4–28.1]	34.4 [32.9–36.0]	41.1 [39.4–42.9]
Male	7989	54.8	35.3 [30.4–41.1]	23.3 [21.9–24.7]	30.5 [29.1–31.9]	40.2 [38.5–41.8]	45.4 [43.7–47.3]
Tumor behavior							
Malignant	8879	60.9	20.3 [17.6–23.4]	14.8 [14.0–15.6]	18.4 [17.6–19.1]	22.2 [21.3–23.1]	25.4 [24.5–26.4]
Non-malignant	5697	39.1	12.6 [10.6–15.1]	6.5 [5.9–7.0]	10.3 [9.7–10.9]	15.2 [14.5–15.9]	17.9 [17.1–18.7]
Diagnostic period							
1980–1989	1980	13.6					
1990–1999	3593	24.7					
2000–2009	4333	29.7					
2010–2019	4670	32.0					
Second primary neoplasm	174	1.2					

Abbreviations: Abs., absolute; CI, confidence interval; CNS, central nervous system; *N*, number; Rel., relative.

[a]Age-standardized according to the Segi 1960 World Standard Population.

[b]Tumor types are classified according to the International Classification of Childhood Cancer—third edition (ICCC-3): ependymomas and choroid plexus tumors (ICCC-3 group III(a)), astrocytomas (ICCC-3 group III(b)), intracranial and intraspinal embryonal tumors (ICCC-3 group III(c)), other gliomas (ICCC-3 group III(d)), other specified intracranial and intraspinal neoplasms (ICCC-3 group III(e)). Unspecified intracranial and intraspinal neoplasms (ICCC-3 group III(f)).

of 1.4% [95% CI: 1.1–1.8] and 2.5% [95% CI: 2.1–2.9], respectively). More details about age-specific contributions can be found in Tables 1 and 2, Figure 1A, and Table S1.

For almost all tumor types, the increases in reported incidence rates were stronger during the early 1980s compared with other periods (Table 2 and Figure 1B). The tumor types have contributed dissimilarly to the observed trends in the overall ASIR (Table 2 and Figure 1B). We observed the largest ASIR increase for astrocytomas, with an AAPC of 5.1% [95% CI: 3.1–7.0] for the entire study period—particularly from 1980 to 1987 (build-up period) when the ASIR for astrocytomas grew on average 25.2% [95% CI: 18.3–33.2] a year. Finally, ASIRs reached 19.1 per million in 2010—2019 (Tables 1 and 2). For the second largest group of CNS tumors, intracranial and intraspinal embryonal tumors, we estimated an AAPC of 1.6% [95% CI: 0.6–2.6], and identified a sharp increase in ASIR with one significant joinpoint in 1989, followed by plateauing incidence rates (Table 2). The reported ASIR for other

TABLE 2 AAPC in the incidence rates of childhood CNS tumors between 1980 and 2019 in Germany by tumor type, sex, and age at diagnosis.

	Entire study period	AAPC [95% CI]	Slope 1	AAPC [95% CI]	Slope 2	AAPC [95% CI]	Slope 3	AAPC [95% CI]	Slope 4	AAPC [95% CI]
Total	1980–2019	3.3% [1.8; 4.9]	1980–1987	13.4% [8.8; 18.3]	1987–1991	−3.2% [−14.1; 10.1]	1991–2010	2.7% [2.0; 3.4]	2010–2019	0.3% [−1.4; 2.1]
Age at diagnosis (years)										
Age 0	1980–2019	2.4% [1.3; 3.5]	1980–2007	4.3% [3.2; 5.5]	2007–2019	−1.8% [−4.4; 0.8]				
Age 1–4	1980–2019	2.1% [1.7; 2.5]								
Age 5–9	1980–2019	3.5% [2.4; 4.6]	1980–1987	13.4% [7.1; 20.1]	1987–2019	1.4% [1.1; 1.8]				
Age 10–14	1980–2019	4.0% [2.6; 5.5]	1980–1985	15.2% [3.3; 28.3]	1985–2019	2.5% [2.1; 2.9]				
Tumor type[a]										
III(a) Ependymomas and choroid plexus tumor	1980–2019	1.6% [0.9; 2.3]								
III(b) Astrocytomas	1980–2019	5.1% [3.1; 7.0]	1980–1987	25.2% [18.3; 33.2]	1987–1991	−6.1% [−19.0; 8.9]	1991–2005	4.1% [2.8; 5.5]	2005–2019	0.1% [−0.9; 1.2]
III(c) Intracranial and intraspinal embryonal tumors	1980–2019	1.6% [0.6; 2.6]	1980–1989	5.9% [1.7; 10.2]	1989–2019	0.3% [−0.2; 0.8]				
III(d) Other glioma	1980–2019	4.2% [−4.0; 13.2]	1980–1982	−50.7% [−83.3; 45.8]	1982–1985	62.2% [−9.4; 190.4]	1985–2019	5.5% [4.5; 6.6]		
III(e) Other specified intracranial and intraspinal neoplasms	1980–2019	3.7% [3.2; 4.2]								
Sex										
Female	1980–2019	3.6% [2.5; 4.7]	1980–1987	11.4% [4.8; 18.4]	1987–2019	2.0% [1.6; 2.4]				
Male	1980–2019	3.2% [0.7; 5.6]	1980–1987	14.3% [9.2; 19.7]	1987–1990	−6.9% [−30.6; 24.9]	1990–2010	2.8% [2.0; 3.5]	2010–2019	−0.6% [−2.6; 1.4]

Abbreviations: AAPC, average annual percentage changes; CI, confidence interval; CNS, central nervous system.

[a]Tumor types are classified according to the International Classification of Childhood Cancer—third edition (ICCC-3): ependymomas and choroid plexus tumors (ICCC-3 group III(a)), astrocytomas (ICCC-3 group III(b)), intracranial and intraspinal embryonal tumors (ICCC-3 group III(c)), other gliomas (ICCC-3 group III(d)), other specified intracranial and intraspinal neoplasms (ICCC-3 group III(e)). Unspecified intracranial and intraspinal neoplasms (ICCC-3 group III(f)) were excluded from analysis due to small numbers.

gliomas increased from 1.2 per million in 1980–1989 to 4.9 per million during the most recent diagnostic decade (Table 1). The group of other specified intracranial and intraspinal neoplasms showed a substantial but steady increase in reported incidence rates over time (AAPC: 3.7% [95% CI: 3.2–4.2]) (Table 2).

The ASIRs for males and females increased at a similar rate, including the strong incline in the early 1980s (Figure 1C). Males had a higher overall ASIR compared to females. This pattern held true for the most recent period, with an ASIR of 45.4 [95% CI: 43.7–47.3] per million for males versus 41.1 [95% CI: 39.4–42.9] for females (Table 1). However, considering the formal trend analysis, ASIRs in males have developed unevenly in some periods and showed indications of a decrease in ASIR in recent years (Table 2).

3.2 | Survival

Of 12,894 cases diagnosed with a primary CNS tumor between 1980 and 2016, complete follow-up information for at least 5 years was available for 93.0% (Table 3). In all, 3344 deaths were confirmed within 5 years after diagnosis during the follow-up period (until December 31, 2021). One- and 5-year overall survival from all CNS tumors combined improved markedly over time, reaching 91.1% and 79.0% in 2010–2016, respectively. Survival estimates, HRs, and temporal trends by different age groups, tumor types, and sex are shown in Table 3 and Figure 2A–C.

The 5-year survival probability by age at diagnosis showed improvements for all age groups within the study period and, generally, a higher survival probability if the CNS tumor was diagnosed later in childhood (Figure 2A and Table 3). Children who were between the ages of 10 and 14 years at diagnosis had the highest 5-year survival in three out of four periods (82.1% in 2010–2016). Children diagnosed during infancy had the least favorable prognosis across the entire study period. This is underlined by results from the Cox regression, which yielded adjusted HRs for the risk of dying among infants that ranged between 1.4 [95% CI: 1.1–1.7] in 2000–2009 and 2.1 [95% CI: 1.7–2.7] in 1990–1999, when compared to children diagnosed at ages 10–14.

Children diagnosed at age 0 and 1–4 experienced the most remarkable improvements in 5-year survival. It increased by 19 and 21 percentage points and reached 71.7% and 79.4% in 2010–2016, respectively. For the other age groups, 5-year survival improved by about 12 percentage points over time. While the incidence of tumor types varies between age groups, these age-specific changes did not explain the difference in survival between tumor types (Table S1 and Figure S1).

Even though 5-year survival improved for most CNS tumor types, the temporal trends vary to some extent. The 5-year survival improvements in ependymomas and choroid plexus tumors have levelled-off at around 80% since the Millennium. While the bulk of the survival enhancements occurred in the first 20 years of the observation period, survival improvements for astrocytomas were evident over the entire period. Among children, astrocytoma presents predominantly as low-grade astrocytoma; its 5-year survival probability reached 84.4% in 2010–2016 (Table 3 and Figure 2B). For the subgroup of "Other gliomas," 5-year survival remained stable over time (59.4% during the 1980s and 56.3% in 2010–2016).

Males and females showed overall similar survival probabilities, which reached 78.6% and 79.4%, respectively, in the most recent period.

Tumor behavior is an important determinant of CNS tumor prognosis. While the probability to survive at least 5 years post diagnosis increased from 77.3% to 98.0% for non-malignant CNS tumors during the study period, malignant CNS tumors had much poorer prognoses (Table 3 and Figure 2C). Although, their 5-year survival increased from 57% before the Millennium to 65.4% in 2010–2016, the results from the Cox regression demonstrated that the HRs increased substantially over time. In 2010–2016, risk of death for children with malignant CNS was estimated to be around 20 times higher (HR 19.9, 95% CI: 13.3–29.9) versus children with non-malignant CNS tumor (Table 3).

4 | DISCUSSION

With this study, we provide a comprehensive assessment of temporal incidence and survival patterns of childhood CNS tumors in Germany, covering a period of 40 years, from 1980 to 2019. We observed an increase in the incidence rates for pediatric CNS tumors across all age groups and some tumor types. While we observed a pronounced increase in ASIR immediately after the establishment of the GCCR during the 1980s, the continued albeit less marked increase in observed incidence rates seemed to be disproportionally fueled by astrocytomas. The 1- and 5-year survival probabilities improved substantially across all age groups and virtually all tumor types. We observed exceptional improvements for children diagnosed at ages 1–4 and for those diagnosed with ependymomas and choroid plexus tumors.

Overall, the observations of the present analysis must be interpreted in light of the longstanding and ongoing efforts to improve the reporting of CNS tumors in Germany. As outlined above, the decade from 1980 to 1989 was marked by the initial build-up of the GCCR register population. Rapid improvements in registration in the early and mid-1980s have consequently led to an extreme, artificially inflated increase in ASIRs for this period. A national and international comparison of ASIRs from this period is therefore challenging, and a certain extent of under-ascertainment of diagnoses in the first decade after the register was established should be taken into consideration.

Current incidence rates for pediatric CNS tumors in Germany likely are still affected by minor underestimation. In fact, while the GCCR reports completeness levels of above 95% for all other neoplasms combined since the late 1980s, the completeness of registration of pediatric CNS tumors continues to be challenging.[33,34] This, however, concerns today primarily adolescent patients (>14 years at diagnosis), who were not part of the present assessment. Some pediatric CNS tumor patients, especially when no chemotherapy is required or when patients are of older adolescent age, are often treated in neuro-oncological facilities for adults, who often do not report to the GCCR.[8,35]

TABLE 3 One- and 5-year overall survival and estimated hazard ratios (with 95% confidence intervals) of overall survival from childhood CNS tumors in Germany by age group, sex, tumor type, and tumor behavior per diagnostic period.

Period	1980–1989			1990–1999			2000–2009			2010–2016		
	1923			3483			4294			3194		
N cases	1-year OS [95% CI][a]	5-year OS [95% CI][a]	HR [95% CI][b]	1-year OS [95% CI][a]	5-year OS [95% CI][a]	HR [95% CI][b]	1-year OS [95% CI][a]	5-year OS [95% CI][a]	HR [95% CI][b]	1-year OS [95% CI][a]	5-year OS [95% CI][a]	HR [95% CI][b]
All children	81.0%	63.3%		84.3%	69.5%		88.2%	76.2%		91.2%	79.0%	
	[79.2–82.7]	[61.1–65.5]		[83.1–85.5]	[68.0–71.1]		[87.2–89.2]	[74.9–77.5]		[90.0–92.0]	[77.5–80.4]	
Completeness 5-year follow-up (%)[c]	96.0	89.4		98.1	92.3		97.6	96.2		98.6	91.6	
Age at diagnosis (years)												
Age 0	65.5%	53.0%	2.0	71.9%	55.2%	2.1	77.3%	65.7%	1.4	80.0%	71.7%	1.7
	[56.1–73.4]	[43.4–61.6]	[1.5–2.7]	[65.5–77.3]	[48.4–61.5]	[1.7–2.7]	[72.3–81.5]	[60.2–70.6]	[1.1–1.7]	[73.8–84.9]	[64.9–77.4]	[1.2–2.2]
Age 1–4	79.3%	58.3%	1.4	82.6%	67.3%	1.3	87.7%	76.0%	0.9	92.9%	79.4%	1.1
	[75.9–82.3]	[54.2–62.2]	[1.2–1.8]	[80.2–84.7]	[64.4–70.1]	[1.1–1.5]	[85.7–89.4]	[73.5–78.3]	[0.8–1.1]	[91.1–94.4]	[76.7–81.9]	[0.9–1.3]
Age 5–9	80.8%	64.3%	1.2	84.7%	69.9%	1.2	89.7%	78.9%	0.8	89.8%	77.0%	1.2
	[77.5–83.7]	[60.3–67.9]	[1.0–1.5]	[82.6–86.6]	[67.2–72.4]	[1.0–1.4]	[88.0–91.9]	[76.7–80.9]	[0.7–0.9]	[87.7–91.5]	[74.3–79.5]	[1.0–1.4]
Reference: Age 10–14	86.6%	70.1%	1	89.0%	75.4%	1	89.9%	76.0%	1	92.9%	82.1%	1
	[83.4–89.2]	[65.9–73.9]		[86.8–90.9]	[72.4–78.1]		[88.1–91.4]	[73.5–78.3]		[91.1–94.4]	[79.5–84.3]	
Tumor type[d]												
III(a) Ependymomas and choroid plexus tumors	85.3%	53.6%	1.8	89.7%	65.5%	1.4	94.2%	80.4%	0.9	95.5%	80.5%	1.1
	[79.8–89.4]	[46.6–60.1]	[1.4–2.3]	[86.0–92.5]	[60.1-–0.2]	[1.1–1.7]	[91.5–96.1]	[76.1–84.0]	[0.7–1.1]	[92.6–97.3]	[75.6–84.5]	[0.8–1.5]
Reference: III(b) Astrocytomas	85.0%	74.6%	1	86.8%	76.7%	1	89.6%	79.8%	1	93.1%	84.4%	1
	[82.2–87.5]	[71.2–77.7]		[85.0–88.5]	[74.4–78.8]		[88.2–90.9]	[77.9–81.5]		[91.6–94.3]	[82.3–86.2]	
III(c) Intracranial and intraspinal embryonal tumors	77.5%	50.8%	2.2	77.3%	54.3%	2.2	84.8%	65.6%	1.8	85.7%	62.8%	2.6
	[73.6–80.8]	[46.4–55.2]	[1.8–2.6]	[74.4–79.9]	[51.0–57.6]	[1.9–2.6]	[82.2–87.0]	[62.3–68.6]	[1.7–2.1]	[82.4–88.3]	[58.5–66.8]	[2.1–3.1]
III(d) Other gliomas	73.1%	59.4%	1.9	67.5%	46.9%	3.0	66.1%	46.2%	3.5	75.5%	56.3%	3.5
	[63.8–80.4]	[49.4–68.0]	[1.4–2.7]	[60.7–73.4]	[39.8–53.6]	[2.4–3.7]	[60.6–70.9]	[40.7–51.6]	[2.9–4.2]	[70.6–79.6]	[50.9–61.3]	[2.8–4.3]
III(e) Other specified intracranial and intraspinal neoplasms	95.0%	86.3%	0.5	98.1%	94.2%	0.2	98.0%	95.1%	0.2	99.8%	96.1%	0.2
	[90.9–97.3]	[80.6–90.5]	[0.3–0.7]	[96.3–99.1]	[91.4–96.1]	[0.2–0.3]	[96.5–98.9]	[92.9–96.6]	[0.2–0.3]	[98.5–100.0]	[93.9–97.5]	[0.1–0.4]

(Continues)

TABLE 3 (Continued)

Period	1980–1989			1990–1999			2000–2009			2010–2016		
	1923			3483			4294			3194		
N cases	1-year OS [95% CI][a]	5-year OS [95% CI][a]	HR [95% CI][b]	1-year OS [95% CI][a]	5-year OS [95% CI][a]	HR [95% CI][b]	1-year OS [95% CI][a]	5-year OS [95% CI][a]	HR [95% CI][b]	1-year OS [95% CI][a]	5-year OS [95% CI][a]	HR [95% CI][b]
Sex												
Reference: Female	80.1%	65.2%	1	85.3%	71.1%	1	88.2%	77.4%	1	90.4%	79.4%	1
	[77.2–82.7]	[61.8–68.4]		[83.4–86.9]	[68.8–73.4]		[86.7–89.6]	[75.4–79.2]		[88.8–91.8]	[77.2–81.4]	
Male	81.7%	61.9%	1.0	83.5%	68.2%	1.1	88.2%	75.2%	1.1	91.7%	78.6%	1.0
	[79.3–83.9]	[58.8–64.8]	[0.9–1.2]	[81.8–85.1]	[66.1–70.3]	[1.0–1.2]	[86.9–89.5]	[73.4–76.9]	[0.9–1.2]	[90.3–92.9]	[76.6–80.5]	[0.9–1.2]
Tumor behavior												
Malignant	79.2%	57.1%	3.4	77.9%	56.9%	7.7	81.1%	61.8%	15.7	85.1%	65.4%	19.9
	[76.9–81.3]	[54.3–59.8]	[2.7–4.3]	[76.2–79.6]	[54.8–59.0]	[6.1–9.7]	[79.5–82.6]	[59.9–63.7]	[11.7–21.0]	[83.4–86.6]	[63.1–67.5]	[13.3–29.9]
Reference: Non-malignant	85.0%	77.3%	1	95.9%	92.5%	1	98.5%	97.1%	1	99.5%	98.1%	1
	[81.9–87.7]	[73.6–80.5]		[94.6–96.8]	[90.9–93.9]		[97.5–98.9]	[96.2–97.8]		[98.9–99.8]	[97.1–98.7]	

Abbreviations: CI, confidence interval; CNS, central nervous system; HR, hazard ratio; *N*, number; OS, overall survival.

[a]Survival probabilities are estimated with the lifetable method, and are based on the 1- and 5-year survival rates, respectively, for each category and a diagnosis date within the given observation period.

[b]Hazard ratios were calculated with an adjusted Cox proportional hazard model. The HRs are based on the probability of surviving at least 5 years after the initial diagnosis of CNS cancer. HRs of the comparison between age groups were adjusted for sex and tumor type, HRs of the comparison between tumor types were adjusted for age and sex, HRs of the comparison between sexes were adjusted for age and tumor type, and HRs of the comparison between tumor behavior were adjusted for age, sex, and tumor type.

[c]Completeness of 5-year follow-up refers to the follow-up information for the 5 years after diagnosis.

[d]Tumor types are classified according to the International Classification of Childhood Cancer—third edition (ICCC-3): ependymomas and choroid plexus tumors (ICCC-3 group III(a)), astrocytomas (ICCC-3 group III(b)), intracranial and intraspinal embryonal tumors (ICCC-3 group III(c)), other gliomas (ICCC-3 group III(d)), other specified intracranial and intraspinal neoplasms (ICCC-3 group III(e)). Unspecified intracranial and intraspinal neoplasms (ICCC-3 group III(f)) are not shown due to small numbers and heterogeneity.

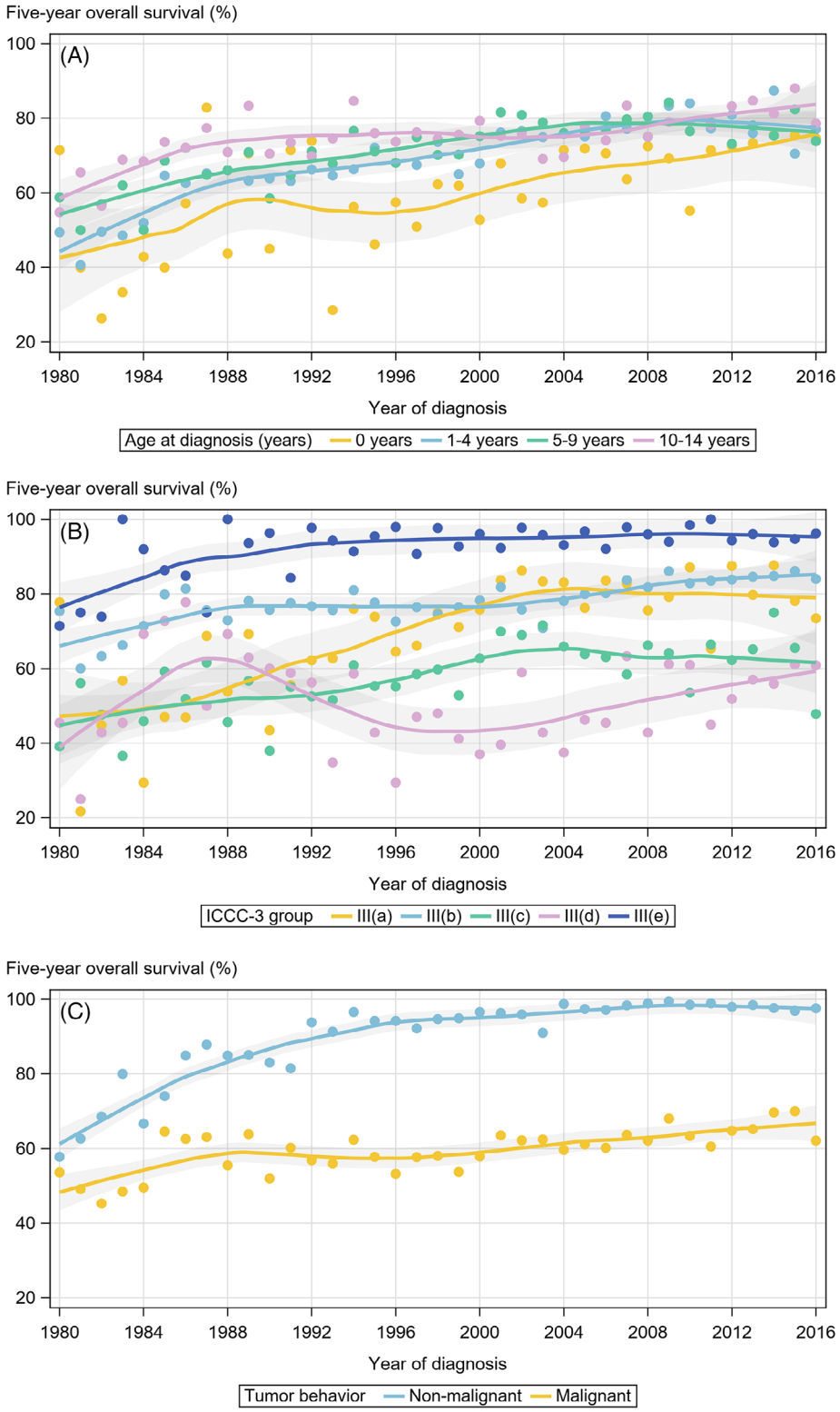

FIGURE 2 Estimated 5-year overall survival probability and corresponding 95% confidence interval (CI) over time by (A) age group, (B) ICCC-3 tumor types, and (C) tumor behavior for children aged 0–14 years at diagnosis in Germany (1980–2016). Survival probabilities are estimated with the lifetable method and based on the 5-year survival rates for cases of a category at a given year. Tumor types are classified according to the International Classification of Childhood Cancer – third edition (ICCC-3): Ependymomas and choroid plexus tumors (ICCC-3 group III(a)), Astrocytomas (ICCC-3 group III(b)), Intracranial and intraspinal embryonal tumors (ICCC-3 group III(c)), other gliomas (ICCC-3 group III(d)), Other specified intracranial and intraspinal neoplasms (ICCC-3 group III(e). Unspecified intracranial and intraspinal neoplasms (ICCC-3 group III(f)) were not shown due to small numbers and heterogeneity. A locally estimated scatterplot smoothing (LOESS) with cubic interpolation was applied to the 5-year overall survival estimates per calendar year.

Moreover, changes in diagnostics and registration practice of pediatric cancers have affected the reported ASIRs for astrocytoma. The accuracy with respect to reporting non-malignant CNS tumors, such as pilocytic astrocytomas, has improved substantially in recent years. The parallel continued decline in ASIRs of unspecified CNS tumors (ICCC-3 group III(f)), which we also observed in our data, appears to be a clear indicator.

Direct associations between variations in external risk factors and changes in incidence rates in pediatric CNS tumors are generally difficult to retrace due to the largely unknown etiology.[9] About 5%–10% of all CNS tumor cases diagnosed during childhood can be traced back to rare genetic syndromes, exposure to ionizing radiation, or the few other established risk factors.[18,36] Despite the continued efforts to reduce medical radiation,[37] many children have been exposed to low doses of diagnostic ionizing radiation in early life. Moreover, as cranial radiotherapy was and still is routinely used to treat most forms of brain tumors as well as acute lymphoblastic leukemia in some circumstances, a non-trivial group of childhood cancer survivors is at risk of subsequent CNS tumors. Of note though, the majority will manifest at adult ages, in view of latency SPNs.[13,38] Apart from these established risk factors, environmental pollutants such as pesticides, solvents and other chemicals, parental lifestyle, and occupational exposures have been studied to solve the etiological puzzle.[39–43] Generally, these studies have not shown convincing results. The main limitation has often been the difficulty to obtain reliable unbiased exposure data[44] and the need for time-sensitive exposure data, as timing appears to play a crucial role in the etiology of childhood CNS tumors.[16,45] Numerous epidemiological studies have used more data-driven approaches to compare various indirect factors, such as socioeconomic background, to examine the occurrence of pediatric CNS tumors. One reoccurring theme is that a higher socioeconomic status (at individual or spatial level) was found to be associated with a higher risk of CNS tumor diagnoses.[46–48]

CNS tumors account for 30.7% of all deaths recorded at the GCCR between 1980 and 2021, and thus contribute considerably to overall childhood cancer-related mortality in Germany.[4] Our study shows that 5-year overall survival from all CNS tumors combined has, however, constantly improved over the last 40 years, even considering the changing composition by tumor type. The 5-year survival probability of 79.0% for cases diagnosed in 2010—2016 is comparable to what was reported in the Nordic countries and the United Kingdom.[24]

Albeit remarkable improvements, the analysis of survival by tumor type showed highly dissimilar temporal trends. While the 5-year survival from ependymomas improved by almost 30 percentage points, "other gliomas" was a subgroup for which we did not observe improvements in 5-year survival over time. It was 59.4% in 1980—1989 and 56.3% in 2010—2016. Notably, besides improving diagnostics, substantial changes in CNS tumor classification altered the composition and proportion of malignant and non-malignant tumors in this group.[4] Considering later diagnostic years, when the proportion of malignant tumors was higher than during the 1980s, our findings yet suggest survival improvements of about 10 percentage points for "other gliomas." Although advances in treatment, diagnostic methods,[49] and organizational structures[50] were overall successful at improving survival from pediatric CNS cancer,[20,36] this is to show that its histological complexity continues to present an enormous challenge.[51] Accordingly, those advances in diagnostics including improved tumor allocation may have contributed to the increasing HRs for the association between tumor behavior and 5-year overall survival.

Apart from clinical risk factors, with respect to the survival from pediatric CNS tumors, there is a growing body of research on social and socioeconomic factors, which is trying to identify patterns and inequalities that derive from structural social differences.[52] This admittedly requires high-quality data, and the majority of such studies stem from high-income countries, like Switzerland,[53] Finland,[54] or Denmark.[55] Most studies revealed persistent disadvantages for individuals or areas with low levels of relative income, education, or wealth. These inequalities in the survival from childhood tumors and more specifically pediatric CNS tumors persist even in the context of high-quality healthcare and despite consistent efforts to reduce them.[53]

From an international perspective, the incidence rates reported in this study are similar to recently published ASIRs for other European countries.[5] Astrocytomas showed the highest increase in observed incidence rates for all tumor types over time, which is in line with findings from the United Kingdom and France.[56,57] The temporal trends do not quite replicate the patterns found in other European countries such as the United Kingdom and France. For the period after 1987, these countries have not observed the persistent incline that we observed in Germany.[5,56,57] A rise in CNS incidences rates did not occur in the Scandinavian countries during this 40-year period, which often serve as litmus test because of their highly accurate and complete cancer registration. ASIRs in Sweden and Denmark have been plateauing for over three decades.[58,59] However, in contrast to Germany, in the Nordic countries, there is a general legal obligation to report incident cancer cases to national cancer registries, including cancer diagnoses in children and adolescents. Those registries have reported pediatric CNS tumor incidence rates beyond 40 per million already since the early 1990s, and it is assumed that observed incidence patterns are not affected by changes in registration and reporting practice.

4.1 | Strengths and limitations

The present study uses the long-standing data from the GCCR, which is one of the longest operating, population-based childhood cancer registries worldwide. Another strength relates to the practically universal access to healthcare in Germany irrespective of socioeconomic conditions and a sizeable population of about 11 million children between the ages 0 and 14, which allowed for analyses with high statistical power. Due to the build-up period of registration at the GCCR, incidence rates have been grossly underestimated for the early period (1980–1987).[35] Moreover, the GCCR has no information about pediatric cancer cases for East Germany before the German reunification in 1991.[4] However, considering incidence time trends from the early 1990s, there was no or very little fluctuation in 1991—1992 following

the German reunification and the simultaneous consolidation of East and West German cancer registration systems.

Another limitation concerns the recoding and reclassification of diagnoses due to adapted editions of ICD-O and ICCC. One-to-one reclassification of diagnoses based on previous ICCC editions to ICCC-3 involved some specific diagnoses that were difficult to unequivocally reclassify. This may have somewhat—although likely to an unneglectable degree—affected our temporal observations. Also, with respect to the survival estimates, a minor impact from the incomplete follow-up information—especially from deceased patients—cannot be ruled out. Lastly, the GCCR lacks complete data about grading, which is, however, an important prognostic marker, and investigating the temporal pattern of the association between grading and survival was therefore not feasible.

5 | CONCLUSION

We observed a continuous increase in incidence rates of pediatric CNS tumors in Germany even after the build-up phase of the register between 1987 and 2019, which was less marked and driven by a surge in astrocytoma diagnoses. While the gains have been equally distributed across age groups, the observed incidence rates indicate a growing number of non-malignant CNS tumor registrations, likely explained by improved diagnostics and improved completeness of reporting and registration. At the same time, we observed improving survival probabilities for most tumor types. This translates to a growing number of childhood CNS tumor survivors representing a susceptible group in the society, as a relevant proportion of survivors suffers from impairments and have particular needs. Follow-up care systems and guidelines will have to be developed to care for this growing subpopulation with special health biographies and lifelong adverse impact on health, quality of life, and socioeconomic consequences.[20,60–62]

AUTHOR CONTRIBUTIONS

Conceptualization: Maike Wellbrock, Mathias Voigt, and Friederike Erdmann. *Methodology*: Maike Wellbrock, Mathias Voigt, Friederike Erdmann, and Cecile Ronckers. *Formal analysis*: Maike Wellbrock and Mathias Voigt. *Data curation*: Friederike Erdmann, Claudia Spix, and Desiree Grabow. *Writing—original draft*: Maike Wellbrock and Mathias Voigt. *Writing—review and editing*: all authors; *Visualization*: Maike Wellbrock and Mathias Voigt; *Supervision*: Friederike Erdmann; *Project administration*: Maike Wellbrock, Mathias Voigt Friederike Erdmann. All authors contributed to the data interpretation, critically reviewed the manuscript for important intellectual content, and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

ACKNOWLEDGMENTS

We wish to thank Claudia Trübenbach for her technical support with data preparation for this article. Moreover, we are grateful to the German Society for Paediatric Oncology and Haematology (GPOH) and the pediatric hematology-oncology units for their data contributions to the German Childhood Cancer Registry. This research was partly funded by a grant from the "Tour der Hoffnung" foundation. The German Childhood Cancer Registry is part of the Division of Childhood Cancer Epidemiology at the Institute of Medical Biostatistics, Epidemiology and Informatics and is funded by the Federal Ministry of Health and the Health Ministries of the 16 federal states of Germany. The funding sources were not involved in the conceptualization, design, content, or preparation of the manuscript, nor the decision to submit for publication.

Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial, personal, or financial relationships with other people or organizations that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

Under the permission that national data protection requirements are fully met, access to aggregated or pseudonymized individual-level data may be made available upon reasonable request. All data access requests should be directed to the corresponding author.

ORCID

Maike Wellbrock https://orcid.org/0000-0002-5885-7002
Friederike Erdmann https://orcid.org/0000-0002-9982-3300

REFERENCES

1. Steliarova-Foucher E, Colombet M, Ries L, et al. International Incidence Of Childhood Cancer, volume III (electronic version). IARC. Accessed March 2, 2021. http://iicc.iarc.fr/results/
2. Erdmann F, Ghantous A, Schüz J. Environmental agents and childhood cancer. In: Nriagu J, ed. *Encyclopedia of Environmental Health*. Elsevier B.V.; 2019:347-359.
3. Spector LG, Pankratz N, Marcotte EL. Genetic and nongenetic risk factors for childhood cancer. *Pediatr Clin N Am*. 2015;62(1):11-25. doi:10.1016/j.pcl.2014.09.013
4. Erdmann F, Kaatsch P, Grabow D, Spix C. Annual report 2019 (1980–2018). Johannes Gutenberg University Mainz. Accessed January 22, 2021. https://www.kinderkrebsregister.de/dkkr/ergebnisse/jahresberichte/jahresbericht-2019.html
5. Steliarova-Foucher E, Fidler MM, Colombet M, et al. Changing geographical patterns and trends in cancer incidence in children and adolescents in Europe, 1991–2010 (Automated Childhood Cancer Information System): a population-based study. *Lancet Oncol*. 2018;19(9):1159-1169. doi:10.1016/s1470-2045(18)30423-6
6. Steliarova-Foucher E, Colombet M, Ries LAG, et al. International incidence of childhood cancer, 2001–10: a population-based registry study. *Lancet Oncol*. 2017;18(6):719-731. doi:10.1016/s1470-2045(17)30186-9
7. Withrow DR, Berrington de Gonzalez A, Lam CJK, Warren KE, Shiels MS. Trends in pediatric central nervous system tumor incidence in the United States, 1998–2013. *Cancer Epidemiol Biomarkers Prev*. 2019;28(3):522-530. doi:10.1158/1055-9965.Epi-18-0784
8. Schüz J, Kaletsch U, Kaatsch P, Meinert R, Michaelis J. Risk factors for pediatric tumors of the central nervous system: results from a German population-based case-control study. *Med Pediatr Oncol*. 2001;36(2):274-282. doi:10.1002/1096-911x(20010201)36:2⟨274::Aid-mpo1065⟩3.0.Co;2-d

9. McKinney PA. Central nervous system tumours in children: epidemiology and risk factors. *Bioelectromagnetics*. 2005;26(7):S60-S68. doi:10.1002/bem.20149
10. Adel Fahmideh M, Scheurer ME. Pediatric brain tumors: descriptive epidemiology, risk factors, and future directions. *Cancer Epidemiol Biomarkers Prev*. 2021;30(5):813-821. doi:10.1158/1055-9965.Epi-20-1443
11. Ostrom QT, Adel Fahmideh M, Cote DJ, et al. Risk factors for childhood and adult primary brain tumors. *Neuro Oncol*. 2019;21(11):1357-1375. doi:10.1093/neuonc/noz123
12. Miglioretti DL, Johnson E, Williams A, et al. The use of computed tomography in pediatrics and the associated radiation exposure and estimated cancer risk. *JAMA Pediatr*. 2013;167(8):700-707. doi:10.1001/jamapediatrics.2013.311
13. Pearce MS, Salotti JA, Little MP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet (London, England)*. 2012;380(9840):499-505. doi:10.1016/s0140-6736(12)60815-0
14. Hauptmann M, Byrnes G, Cardis E, et al. Brain cancer after radiation exposure from CT examinations of children and young adults: results from the EPI-CT cohort study. *Lancet Oncol*. 2023;24(1):45-53. doi:10.1016/s1470-2045(22)00655-6
15. O'Neill KA, Murphy MF, Bunch KJ, et al. Infant birthweight and risk of childhood cancer: international population-based case control studies of 40 000 cases. *Int J Epidemiol*. 2015;44(1):153-168. doi:10.1093/ije/dyu265
16. Schmidt LS, Schüz J, Lähteenmäki P, et al. Fetal growth, preterm birth, neonatal stress and risk for CNS tumors in children: a Nordic population- and register-based case-control study. *Cancer Epidemiol Biomarkers Prev*. 2010;19(4):1042-1052. doi:10.1158/1055-9965.Epi-09-1273
17. Baldwin RT, Preston-Martin S. Epidemiology of brain tumors in childhood–a review. *Toxicol Appl Pharmacol*. 2004;199(2):118-131. doi:10.1016/j.taap.2003.12.029
18. Pollack IF, Agnihotri S, Broniscer A. Childhood brain tumors: current management, biological insights, and future directions. *J Neurosurg Pediatr*. 2019;23(3):261-273. doi:10.3171/2018.10.Peds18377
19. Gnekow AK, Kandels D, Pietsch T, et al. Doubling recruitment of pediatric low-grade glioma within two decades does not change outcome—report from the German LGG studies [Verdopplung der Rekrutierungszahl niedrig-gradiger Gliome des Kindes- und Jugendalters innerhalb von 20 Jahren ändert die Überlebenschancen nicht]. *Klin Padiatr*. 2021;233(3):107-122. doi:10.1055/a-1471-5897
20. Erdmann F, Frederiksen LE, Bonaventure A, et al. Childhood cancer: survival, treatment modalities, late effects and improvements over time. *Cancer Epidemiol*. 2021;71(Pt B):101733. doi:10.1016/j.canep.2020.101733
21. Wellbrock M, Spix C, Ronckers CM, et al. Temporal patterns of childhood cancer survival 1991 to 2016: a nationwide register-study based on data from the German Childhood Cancer Registry. *Int J Cancer*. 2023;153(4):742-755. doi:10.1002/ijc.34556
22. Gatta G, Botta L, Rossi S, et al. Childhood cancer survival in Europe 1999–2007: results of EUROCARE-5—a population-based study. *Lancet Oncol*. 2014;15(1):35-47. doi:10.1016/s1470-2045(13)70548-5
23. Magnani C, Pastore G, Coebergh JW, Viscomi S, Spix C, Steliarova-Foucher E. Trends in survival after childhood cancer in Europe, 1978–1997: report from the Automated Childhood Cancer Information System project (ACCIS). *Eur J Cancer*. 2006;42(13):1981-2005. doi:10.1016/j.ejca.2006.05.006
24. Botta L, Gatta G, Capocaccia R, et al. Long-term survival and cure fraction estimates for childhood cancer in Europe (EUROCARE-6): results from a population-based study. *Lancet Oncol*. 2022;23(12):P1525-1536. 10.1016/S1470-2045(22)00637-4
25. Birch JM, Marsden HB. Classification scheme for childhood cancer. *Int J Cancer*. 1987;40(5):620-624.
26. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International classification of childhood cancer, 3rd ed. *Cancer*. 2005;103(7):1457-1467. doi:10.1002/cncr.20910
27. Genesis-online. Statistisches Bundesamt (Destatis). Accessed December 6, 2023. https://www.destatis.de/DE/Home/_inhalt.html
28. Segi M, Tōhoku D, Nippon Taigan K. *Cancer Mortality For Selected Sites In 24 Countries*. Japan Cancer Society; 1960.
29. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med*. 2000;19(3):335-351. 10.1002/(sici)1097-0258(20000215)19:3⟨335::aid-sim336⟩3.0.co;2-z
30. Clegg LX, Hankey BF, Tiwari R, Feuer EJ, Edwards BK. Estimating average annual per cent change in trend analysis. *Stat Med*. 2009;28(29):3670-3682. doi:10.1002/sim.3733
31. Joinpoint Regression Program, Version 4.9.0.0. Surveillance Research Program, National Cancer Institute; 2021.
32. SAS Software 9.4. SAS; 2016.
33. Kaatsch P. German Childhood Cancer Registry and its favorable setting [Das Deutsche Kinderkrebsregister im Umfeld günstiger Rahmenbedingungen]. *Federal Health J Health Res Health Protect*. 2004;47(5):437-443. doi:10.1007/s00103-004-0829-0
34. Grabow D, Spix C, Blettner M, Kaatsch P. Strategy for long-term surveillance at the German Childhood Cancer Registry—an update. *Klin Padiatr*. 2011;223(3):159-164. doi:10.1055/s-0031-1275352
35. Kaatsch P, Rickert CH, Kühl J, Schüz J, Michaelis J. Population-based epidemiologic data on brain tumors in German children. *Cancer*. 2001;92(12):3155-3164.
36. Smith MA, Altekruse SF, Adamson PC, Reaman GH, Seibel NL. Declining childhood and adolescent cancer mortality. *Cancer*. 2014;120(16):2497-2506. doi:10.1002/cncr.28748
37. Berrington de Gonzalez A, Pasqual E, Veiga L. Epidemiological studies of CT scans and cancer risk: the state of the science. *Br J Radiol*. 2021;94(1126):20210471. doi:10.1259/bjr.20210471
38. Casey DL, Vogelius IR, Brodin NP, et al. Risk of subsequent neoplasms in childhood cancer survivors after radiation therapy: a comprehensive PENTEC review. *Int J Radiat Oncol Biol Phys*. 2023. doi:10.1016/j.ijrobp.2023.07.025
39. Patel DM, Jones RR, Booth BJ, et al. Parental occupational exposure to pesticides, animals and organic dust and risk of childhood leukemia and central nervous system tumors: findings from the International Childhood Cancer Cohort Consortium (I4C). *Int J Cancer*. 2020;146(4):943-952. doi:10.1002/ijc.32388
40. Coste A, Bailey HD, Kartal-Kaess M, Renella R, Berthet A, Spycher BD. Parental occupational exposure to pesticides and risk of childhood cancer in Switzerland: a census-based cohort study. *BMC Cancer*. 2020;20(1):819. doi:10.1186/s12885-020-07319-w
41. Keegan TJ, Bunch KJ, Vincent TJ, et al. Case-control study of paternal occupation and social class with risk of childhood central nervous system tumours in Great Britain, 1962–2006. *Br J Cancer*. 2013;108(9):1907-1914. doi:10.1038/bjc.2013.171
42. Peters S, Glass DC, Greenop KR, et al. Childhood brain tumours: associations with parental occupational exposure to solvents. *Br J Cancer*. 2014;111(5):998-1003. doi:10.1038/bjc.2014.358
43. Raaschou-Nielsen O, Hvidtfeldt UA, Roswall N, Hertel O, Poulsen AH, Sørensen M. Ambient benzene at the residence and risk for subtypes of childhood leukemia, lymphoma and CNS tumor. *Int J Cancer*. 2018;143(6):1367-1373. doi:10.1002/ijc.31421
44. Zumel-Marne A, Castano-Vinyals G, Kundi M, Alguacil J, Cardis E. Environmental factors and the risk of brain tumours in young people: a systematic review. *Neuroepidemiology*. 2019;53(3-4):121-141. doi:10.1159/000500601
45. Krille L, Dreger S, Schindel R, et al. Erratum to: risk of cancer incidence before the age of 15 years after exposure to ionising radiation

from computed tomography: results from a German cohort study. *Radiat Environ Biophys*. 2017;56(3):293-297. doi:10.1007/s00411-017-0694-5
46. Erdmann F, Hvidtfeldt UA, Sørensen M, Raaschou-Nielsen O. Socioeconomic differences in the risk of childhood central nervous system tumors in Denmark: a nationwide register-based case-control study. *Cancer Causes Control*. 2020;31(10):915-929. doi:10.1007/s10552-020-01332-x
47. Ramis R, Tamayo-Uria I, Gómez-Barroso D, et al. Risk factors for central nervous system tumors in children: new findings from a case-control study. *PLoS One*. 2017;12(2):e0171881. doi:10.1371/journal.pone.0171881
48. Marquant F, Goujon S, Faure L, et al. Risk of childhood cancer and socio-economic disparities: results of the French Nationwide Study Geocap 2002–2010. *Paediatr Perinat Epidemiol*. 2016;30(6):612-622. doi:10.1111/ppe.12313
49. Chintagumpala M, Gajjar A. Brain tumors. *Pediatr Clin N Am*. 2015;62(1):167-178. doi:10.1016/j.pcl.2014.09.011
50. Pritchard-Jones K, Dixon-Woods M, Naafs-Wilstra M, Valsecchi MG. Improving recruitment to clinical trials for cancer in childhood. *Lancet Oncol*. 2008;9(4):392-399. doi:10.1016/s1470-2045(08)70101-3
51. Johnson KJ, Cullen J, Barnholtz-Sloan JS, et al. Childhood brain tumor epidemiology: a brain tumor epidemiology consortium review. *Cancer Epidemiol Biomarkers Prev*. 2014;23(12):2716-2736. doi:10.1158/1055-9965.Epi-14-0207
52. Mogensen H, Modig K, Tettamanti G, Erdmann F, Heyman M, Feychting M. Survival after childhood cancer-social inequalities in high-income countries. *Front Oncol*. 2018;8:485. doi:10.3389/fonc.2018.00485
53. Adam M, Rueegg CS, Schmidlin K, et al. Socioeconomic disparities in childhood cancer survival in Switzerland. *Int J Cancer*. 2016;138(12):2856-2866. doi:10.1002/ijc.30029
54. Tolkkinen A, Madanat-Harjuoja L, Taskinen M, Rantanen M, Malila N, Pitkäniemi J. Impact of parental socioeconomic factors on childhood cancer mortality: a population-based registry study. *Acta Oncol*. 2018;57(11):1547-1555. doi:10.1080/0284186x.2018.1478125
55. Erdmann F, Winther JF, Dalton SO, et al. Survival from tumours of the central nervous system in Danish children: is survival related to family circumstances? *Int J Cancer*. 2018;142(4):671-680. doi:10.1002/ijc.31082
56. Stiller CA, Bayne AM, Chakrabarty A, Kenny T, Chumas P. Incidence of childhood CNS tumours in Britain and variation in rates by definition of malignant behaviour: population-based study. *BMC Cancer*. 2019;19(1):139. doi:10.1186/s12885-019-5344-7
57. Desandes E, Guissou S, Chastagner P, Lacour B. Incidence and survival of children with central nervous system primitive tumors in the French National Registry of Childhood Solid Tumors. *Neuro Oncol*. 2014;16(7):975-983. doi:10.1093/neuonc/not309
58. Helligsoe ASL, Kenborg L, Henriksen LT, Udupi A, Hasle H, Winther JF. Incidence and survival of childhood central nervous system tumors in Denmark, 1997–2019. *Cancer Med*. 2022;11(1):245-256. doi:10.1002/cam4.4429
59. Lannering B, Sandström PE, Holm S, et al. Classification, incidence and survival analyses of children with CNS tumours diagnosed in Sweden 1984–2005. *Acta Paediatr*. 2009;98(10):1620-1627. doi:10.1111/j.1651-2227.2009.01417.x
60. Frederiksen LE, Pedersen C, Mogensen H, et al. Employment status and occupational positions of childhood cancer survivors from Denmark, Finland and Sweden: a Nordic register-based cohort study from the SALiCCS research programme. *Lancet Reg Health Eur*. 2022;12:100258. doi:10.1016/j.lanepe.2021.100258
61. Frederiksen LE, Erdmann F, Mader L, et al. Psychiatric disorders in childhood cancer survivors in Denmark, Finland, and Sweden: a register-based cohort study from the SALiCCS research programme. *Lancet Psychiatry*. 2022;9(1):35-45. doi:10.1016/s2215-0366(21)00387-4
62. Hudson MM, Ness KK, Gurney JG, et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. *JAMA*. 2013;309(22):2371-2381. doi:10.1001/jama.2013.6296

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wellbrock M, Voigt M, Ronckers C, Grabow D, Spix C, Erdmann F. Registration, incidence patterns, and survival trends of central nervous system tumors among children in Germany 1980–2019: An analysis of 40 years based on data from the German Childhood Cancer Registry. *Pediatr Blood Cancer*. 2024;71:e30954. https://doi.org/10.1002/pbc.30954