Pediatr Blood Cancer 2011;56:65–69

Incidence of Childhood Central Nervous System Tumors in the Nordic Countries

Lisbeth Samsø Schmidt, MD,[1,*] Kjeld Schmiegelow, MD, DMSC,[2,3] Paivi Lahteenmaki, MD, PhD,[4] Catarina Träger, MD, PhD,[5] Tore Stokland, MD,[6] Katrine Grell, MSc,[1] Göran Gustafson, MD,[5] Astrid Sehested, MD,[2] Ole Raashou-Nielsen, PhD,[1] Christoffer Johansen, MD, PhD, DMSC,[1] and Joachim Schüz, PhD[1]

Background. The incidence rates of childhood central nervous system (CNS) tumors in the Nordic countries remain among the highest in the world. Large geographical and temporal variations in the incidence rates of CNS tumors have been reported. Increasing incidence rates would be a public health concern, as they might indicate increased exposure to environmental risk factors. ***Methods.*** All 3,983 children 0–14 years of age registered with a primary CNS tumor in 1985–2006 in the national cancer registries of the Denmark, Finland, Norway, and Sweden were identified. Tumors were classified according to the International Classification of Childhood Cancer version 3 (ICCC-3). Join-point analysis was used to detect changes in trends and to estimate annual changes in incidence rates. ***Results.*** The mean annual incidence rate of CNS tumors was 42 per million. No statistically significant change in time trends of incidence rates was observed during 1985–2006. Furthermore, the incidence by birth cohort was relatively stable during the study period. ***Conclusion.*** The incidence rates of childhood CNS tumors in the Nordic countries remain among the highest in the world. The stable incidence rates during the last 22 years indicate that major changes in environmental risk factors are unlikely. Pediatr Blood Cancer. 2011;56:65–69.

Key words: astrocytoma; child; CNS tumor; incidence; Nordic countries

INTRODUCTION

Monitoring changes in incidence rates of childhood cancers has drawn considerable attention, since such changes could reflect changes in exposures to environmental risk factors, and hypothesis-driven research could lead to preventive measures. The incidence rates of childhood CNS tumors varies considerably internationally, with annual incidence rates ranging from 20 to 40 per million [1]; the highest incidence rates in the world are reported in the Nordic countries [2–5]. Increasing incidence rates have been reported in various parts of the world including Europe, Australia and USA [4,6–9], including the Nordic countries [2,5,10]; however, recent publications suggested that the incidence rates are leveling off [3,11–14] or even decreasing [15,16]. It remains to be determined whether the variations over time reflect a true biological phenomenon or a change in the registration of benign tumors [17], better case ascertainment [18], changes in classification criteria [19], improved diagnostic tools [8,20], or social inequality in access to health care. Childhood tumor registration in the Nordic countries provides a unique tool for addressing these questions, as the Nordic cancer registries have a history of more than half a century; they are mandatory and regulated by law; and they are validated or supplemented with other independent data sources, such as pathology registries, hospital discharge registries, death certificate registries and independent childhood cancer registries, which ensure almost 100% coverage. In the present study, we describe the temporal trends of childhood CNS tumors in the Nordic countries in 1985–2006, overall and by histological subgroup according to the International Classification of Childhood Cancer, 3rd edition (ICCC-3) [21].

METHODS

The cases were all primary CNS tumors in children 0–14 years of age with a diagnosis made between 1 January 1985 and 31 December 2006, who resided in Denmark, Norway, Sweden, or Finland at the time of diagnosis. CNS tumors were defined according to main group III of ICCC-3 [21], which includes both benign and malignant primary tumors of the CNS but excludes germ cell tumors and lymphomas located in the CNS. Cases were identified from the national cancer registries [22]. In addition, we searched for incident cases in the childhood cancer registries of Sweden and Denmark and in the Nordic Society of Paediatric Haematology and Oncology database of solid tumors in Norway. Furthermore, diagnostic information on the Swedish and most of the Danish cases was re-abstracted and recoded on the basis of information from the medical records in connection with previous studies [3,5]. For tumors classified as gliomas, data from the Finnish Cancer Registry were supplemented with data from pathology reports in order to characterize them to a more specific level than that available in the Registry. Calculation of the incidence is based on yearly population data from the national population registries, which are continuously updated on an individual level regarding vital status and migration.

Age-standardized rates (ASR) were calculated by the direct method from the age-specific incidence rates for 5-year age groups with the weights for the World Standard Population 2000–2025 provided by the World Health Organization. A piecewise log-linear model called "join-point analysis" [23] was used to detect changes in trends and to estimate both annual percentage change (APC)

[1]Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen Ø, Denmark; [2]Department of Pediatrics, Copenhagen University Hospital, Copenhagen, Denmark; [3]The Medical Faculty, The Institute of Gynecology, Obstetrics and Pediatrics, University of Copenhagen, Copenhagen, Denmark; [4]Department of Pediatrics, Turku University Hospital, Turku, Finland; [5]Childhood Cancer Research Unit, Department of Women and Child Health, Karolinska Institutet, Stockholm, Sweden; [6]Department of Pediatrics, University Hospital Norway-North, Tromsø, Norway

The authors of this manuscript have no conflicts of interest to declare.

Kjeld Schmiegelow holds the Danish Childhood Cancer Foundation Professorship in Pediatric Oncology.

*Correspondence to: Lisbeth Samsø Schmidt, Institute of Cancer Epidemiology, Danish Cancer Society, Strandboulevarden 49, DK-2100 Copenhagen Ø, Denmark. E-mail: samsoe@cancer.dk

Received 1 December 2009; Accepted 22 March 2010

DOI 10.1002/pbc.22585
Published online 15 November 2010 in Wiley Online Library (wileyonlinelibrary.com).

TABLE I. Incident Cases With CNS Tumors by Age, Sex and Histology and Histology Specific Age Adjusted Incidence Rate

	0–4 years		5–9 years		10–14 years		0–14 years					
Histology[a]	Males	Females	Males	Females	Males	Females	Males	Females	Total	Sex ratio	ASR[b]	Average annual change (%)	95% CI
Ependymoma	115	103	63	42	45	37	223	182	405	1.2	4.2	−0.07	−1.43 to 1.32
Astrocytoma	314	310	293	281	261	251	868	842	1,710	1.0	17.9	−1.26	−1.94 to −0.19
Embryonal CNS tumors	172	131	159	96	81	53	412	280	692	1.5	7.3	0.97	0.02 to 1.94
Other gliomas	56	39	61	76	47	53	164	168	332	1.0	3.5	−0.61	−2.62 to 1.44
Other specified CNS tumors	74	60	99	76	131	101	304	237	541	1.3	5.7	4.17	−0.47 to 9.02
Unspecified CNS tumors	57	47	65	45	41	48	163	140	303	1.2	3.2	0.22	−2.12 to 2.62
Total	788	690	740	616	606	543	2,134	1,849	3,983	1.2	42.0	0.03	

[a]Classified according to the international classification of childhood cancer version 3. [b]Age adjusted according to the world standard population provided by WHO.

Fig. 1. Age-specific incidence rates of childhood CNS tumors by histological subgroup.

and average annual percentage change (AAPC) in incidence rates. The model was specified to include a maximum of four join-points, which could be placed in the middle of a year (e.g., 2003) or between two consecutive years (e.g., between 2003 and 2004). We denoted the latter join-points by adding 0.5 (e.g., 2003.5). We chose to let the model constrain the join-points to at least 2.5 years from each other and at least 3 years from the boundaries of the total study period. The best fitting model was searched on 4,499 randomly permuted datasets, according to the grid method [23] with overall significance level of 0.05, under the assumption of heteroscedastic variance and uncorrelated errors. Incidence rates by birth cohort were calculated by summarizing the incidence rates by increasing age group in consecutive years divided by the number of years of observation (i.e., 5 years for age groups and 15 years for the overall estimates). The study was approved by the national data protection boards in all four countries.

RESULTS

During 1985–2006, 4,263 children 0–14 years of age were registered with a primary CNS tumor. Of these, 280 were excluded (lipomas, hemangiomas, germ cell tumors, adenomas, neurofibromas), as they were not classified as CNS tumors in ICCC-3 main group III. Hence, the final number for analysis was 3,983 incident cases of CNS tumor (Table I). The overall age-adjusted incidence rate (ASR) was 42 cases per million; the rates were 43 in Denmark, 42 in Sweden, 40 in Norway, and 40 in Finland. The incidence of CNS tumors was slightly higher in males than in females, with a ratio of 1.2:1. Most of the difference was accounted for by a male predominance of embryonal CNS tumors (Table I). The most frequent tumor was astrocytoma, with an average annual incidence of 18 per million. The age-specific incidence rates varied by histological subgroup (Fig. 1). Most ependymomas occurred in the first 2 years of life. The age-specific incidence rate for embryonal CNS tumors was 10–12 per million in the first 2 years of life and lower after the age of 10 (incidence rate (IR) 3–4 per million). Two peaks of age-specific incidence rates were observed for astrocytoma, at age 4 and 12 years, with incidence rates of 27 and 18 per million, respectively.

No time trend was observed in the join-point regression analysis, that is, the curve was compatible with a slope of 0 (Fig. 2). One

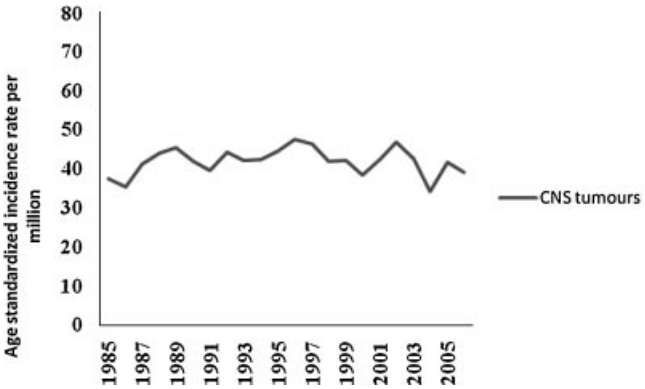

Fig. 2. Age standardized incidence of childhood CNS tumors in the Nordic countries 1985–2006. Including all histological subgroups classified as CNS by ICCC-3 (per million person years).

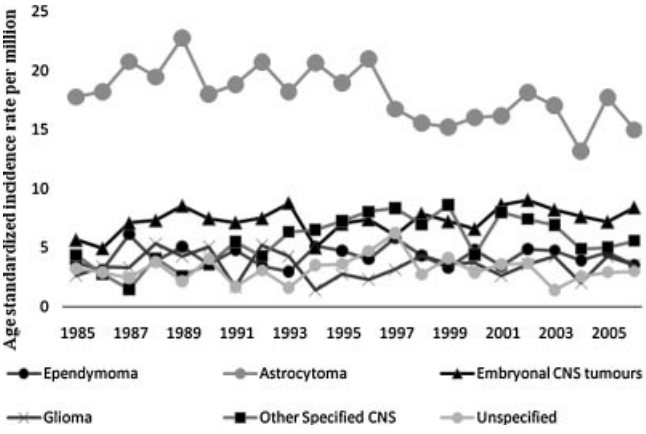

Fig. 3. Age standardized incidence rates by histological subgroup in the Nordic countries (per million person years).

join-point was found with the Danish data only; while the incidence rate increased initially (1985–1995.5: APC, 5.7; 95% CI, 3.4–8.0), it then decreased (1995.5–2006: −3.8 (−5.9 to −1.7)). No join-points were observed for the other three countries. A statistically significantly decreased annual percentage change in the incidence of astrocytoma of 1.26% was observed, whereas a nonsignificant increase was observed for embryonal CNS tumor and other specified CNS tumors (Table II and Fig. 3). After stratification by age group, the highest incidence was observed in the youngest cases, with rates of 46.9 per million at 0–4 years, 42.8 at 5–9 years and 35.7 at 10–14 years. A small, statistically significant increase in incidence rate was observed for children 10–14 years of age, with an annual increase of about 1% there was a small, statistically nonsignificant decrease for 5- to 9-year-olds and an average annual change of close to 0

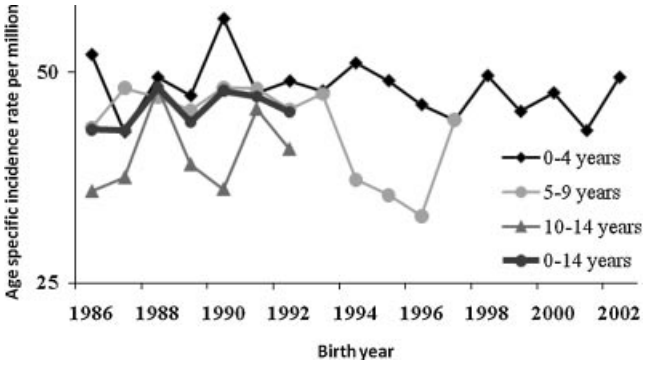

Fig. 4. Age specific incidence rate of CNS tumors by birth cohort in the Nordic countries (per million person years).

for 0- to 4-year-olds (Table II). As illustrated in Figure 4, the age-specific incidence rate by birth cohort was stable during the study period.

DISCUSSION

The incidence of childhood CNS tumors has been stable in the Nordic countries during the past 22 years. With an average annual age-standardized incidence of 42 per million, the incidence remains among the highest in the world [1]. Interestingly, recent publications from registries in United Kingdom, USA, and Eastern Germany, which include both malignant and benign tumors, have reported that the incidence is leveling off at a level close to that in the Nordic countries [9,17,24].

CNS tumors in children are a heterogeneous group, with more than 100 histological rare and distinct entities and variation in classification and registration practices complicates the characterization of temporal trends. The high incidence in the Nordic countries probably reflects the completeness of the registries, due to national coverage, compulsory registration of both benign and malignant tumors, registration from various sources and a public health-care system that is free and offers the same diagnostic and medical care for all citizens. Smith et al. [8] argued that the observed temporal variations in USA are due to differences in registration and diagnostic tools and do not represent real differences in incidence. They linked the rapid, although relatively small rise in CNS tumor incidence among children in the mid-1980s to the increased availability of magnetic resonance imaging, by demonstrating that the incidence did not increase steadily but rather jumped from a relatively constant level before 1984–1985 to a steady but higher level after 1985.

The age-standardized incidence in our study is slightly lower than the incidence reported for the Nordic countries (43.8/million) in the automated childhood cancer information system (ACCIS) [4]. The glioma rates are higher in the ACCIS study, whereas the astrocy-

TABLE II. Annual and Average Annual Percentage Changes in Incidence Rates by Sex and Age Groups

Sex/age	No. of cases	Period		Annual change (%)	95% CI	Average annual change (%)	95% CI
Males	2,134	1985	2006	0.11	−0.76 to 0.98	0.11	−0.71 to 0.93
Females	1,849	1985	2006	−0.11	−0.87 to 0.66	−0.11	−0.82 to 0.61
0–4 years	1,448	1985	2006	−0.02	−0.96 to 0.93	−0.02	−0.90 to 0.87
5–9 years	1,356	1985	2006	−0.67	−1.47 to 0.13	−0.67	−1.42 to 0.08
10–14 years	1,149	1985	2006	1.02	0.13 to 1.91	1.02	0.19 to 1.86

toma rates are lower. Several factors may explain these differences. First, the periods in which the studies were conducted overlap only partly (ACCIS: 1978–1997), and we included Sweden, with a total population of 9 million, instead of Iceland, with 300,000 citizens (Sweden was not part of the ACCIS). By cross-checking the different sources (national cancer and childhood cancer registries) in each country, we ensured a high degree of completeness in case ascertainment. Validation from medical records, including pathology and neuroimaging reports, is known to increase the validity of registered data [18,25], and this information was used in the present study [3,5]. The high incidence of astrocytoma in our study is consistent with previous Nordic reports [2,3,5,10] and appears to be the main determinant of the higher incidence in these countries. The discrepancy from the ACCIS report, in which other glioma were the most frequent tumors [4], is probably a result of the re-coding of the Finnish glial cell tumors according to pathology reports, so that tumors originally classified as gliomas were reclassified, mainly as astrocytoma and other gliomas.

The increasing incidence of childhood CNS tumors reported previously in Denmark [5] was reproduced in our study, as the join-point analysis suggested a peak in 1995. This was, however, followed by a decrease, leading to a stable trend over the entire period. However, it should be kept in mind that it is difficult to reliably detect changes in incidence rates of a rare disease such as CNS tumors in children in small countries and time trends become more stable when pooling data of the Nordic countries.

The international variation is also likely to reflect the use of many different, often not comparable classifications [21,24,26]. In order to meet the need for international standardization of childhood cancers, an international classification was proposed by Birch and Marsden [27] on the basis of ICD-O morphology and topography codes, with updates [21]. One disadvantage of the classification, however, is that the degree of malignancy is not taken into account. Unfortunately, many authors who report results according to the ICCC classification fail to state whether they excluded certain codes in the original version of the classification. Furthermore, if a cancer registry has different inclusion criteria, for example, excluding dysembryoplastic neuroepithelial tumors or other benign tumors, the incidence will not be comparable to international standards.

Overreporting is a potential problem in cancer registries such as those of the Nordic countries, which include hemangioma, lipoma and hamartoma as intracranial tumors, whereas they might be classified as unspecified CNS tumors if no conclusive biopsy is available and there is clinical uncertainty after radiological imaging. We attempted to avoid overreporting in the present study by re-abstracting, re-coding and cross-checking data from various sources. Changing diagnostic practice and the introduction of new histopathological entities can also affect the incidence rates of histological subgroups over time. A substantial interobserver variability of the pathological evaluation is well recognized and may add further to the variation of the reported incidences [28]. Furthermore, the increasing use of neuroimaging and surgery in searching for the structural causes of epilepsy [29] might have resulted in the diagnosis of more low-grade tumors such as dysembryoplastic neuroepithelial tumors, which might explain the increases in other specified CNS tumors observed in children 10–14 years of age. The differences in temporal trend by age group may also reflect random variation due to the small numbers of cases.

Detection of changing patterns in the incidence rates of CNS tumors can reveal changes in the prevalence of environmental risk factors and provide new hypotheses for their etiology. If exposures to environmental risk factors during pregnancy or in the early neonatal period are changing, we would have expected a birth cohort effect, but the incidence of CNS tumors by birth cohort was relatively stable during the study period. Nevertheless, the number of birth years studied was limited.

In summary, the age-standardized incidence rates of childhood CNS tumors in the Nordic countries have been stable over the past 22 years. It is therefore unlikely that major changes in environmental risk factors have occurred during this period.

ACKNOWLEDGMENTS

This work was supported by grants from the Danish Cancer Society, the Danish Strategic Research Council and the Danish Childhood Cancer Foundation. We thank Henrik Schröder, Finn Wessenberg, and Mikko Perkkiö for providing data from the Nordic Society of Paediatric Haematology and Oncology registry.

REFERENCES

1. Parkin DM, Kramarova E, Draper GJ. International incidence of childhood cancer. IARC Scientific Publications no. 1, 1998.
2. Johannesen TB, Ngell-Andersen E, Tretli S, et al. Trends in incidence of brain and central nervous system tumors in Norway, 1970–1999. Neuroepidemiology 2004;23:101–109.
3. Lannering B, Sandstrom PE, Holm S, et al. Classification, incidence and survival analyses of children with CNS tumours diagnosed in Sweden 1984–2005. Acta Paediatr 2009;98:1620–1627.
4. Peris-Bonet R, Martinez-Garcia C, Lacour B, et al. Childhood central nervous system tumours-incidence and survival in Europe (1978–1997): Report from Automated Childhood Cancer Information System project. Eur J Cancer 2006;42:2064–2080.
5. Raaschou-Nielsen O, Sorensen M, Carstensen H, et al. Increasing incidence of childhood tumours of the central nervous system in Denmark, 1980–1996. Br J Cancer 2006;95:416–422.
6. McNally RJ, Kelsey AM, Cairns DP, et al. Temporal increases in the incidence of childhood solid tumors seen in Northwest England (1954–1998) are likely to be real. Cancer 2001;92:1967–1976.
7. McWhirter WR, Dobson C, Ring I. Childhood cancer incidence in Australia, 1982–1991. Int J Cancer 1996;65:34–38.
8. Smith MA, Freidlin B, Ries LA, et al. Trends in reported incidence of primary malignant brain tumors in children in the United States. J Natl Cancer Inst 1998;90:1269–1277.
9. Spix C, Eletr D, Blettner M, et al. Temporal trends in the incidence rate of childhood cancer in Germany 1987–2004. Int J Cancer 2008;122:1859–1867.
10. Hjalmars U, Kulldorff M, Wahlqvist Y, et al. Increased incidence rates but no space-time clustering of childhood astrocytoma in Sweden, 1973–1992: A population-based study of pediatric brain tumors. Cancer 1999;85:2077–2090.
11. Bao PP, Zheng Y, Wang CF, et al. Time trends and characteristics of childhood cancer among children age 0–14 in Shanghai. Pediatr Blood Cancer 2009;53:13–16.
12. Legler JM, Ries LA, Smith MA, et al. Cancer surveillance series [corrected]: Brain and other central nervous system cancers: Recent trends in incidence and mortality. J Natl Cancer Inst 1999;91:1382–1390.
13. Linabery AM, Ross JA. Trends in childhood cancer incidence in the U.S. (1992–2004). Cancer 2008;112:416–432.

14. Linet MS, Ries LA, Smith MA, et al. Cancer surveillance series: Recent trends in childhood cancer incidence and mortality in the United States. J Natl Cancer Inst 1999;91:1051–1058.
15. Houben MP, Aben KK, Teepen JL, et al. Stable incidence of childhood and adult glioma in The Netherlands, 1989–2003. Acta Oncol 2006;45:272–279.
16. Jakab Z, Balogh E, Kiss C, et al. Epidemiologic studies in a population-based childhood cancer registry in Northeast Hungary. Med Pediatr Oncol 2002;38:338–344.
17. Gurney JG, Wall DA, Jukich PJ, et al. The contribution of nonmalignant tumors to CNS tumor incidence rates among children in the United States. Cancer Causes Control 1999;10:101–105.
18. McKinney PA, Ironside JW, Harkness EF, et al. Registration quality and descriptive epidemiology of childhood brain tumours in Scotland 1975–90. Br J Cancer 1994;70:973–979.
19. McCarthy BJ, Propp JM, Davis FG, et al. Time trends in oligodendroglial and astrocytic tumor incidence. Neuroepidemiology 2008;30:34–44.
20. Desmeules M, Mikkelsen T, Mao Y. Increasing incidence of primary malignant brain tumors: Influence of diagnostic methods. J Natl Cancer Inst 1992;84:442–445.
21. Steliarova-Foucher E, Stiller C, Lacour B, et al. International Classification of Childhood Cancer, third edition. Cancer 2005;103:1457–1467.
22. Tulinius H, Storm HH, Pukkala E, et al. Cancer in the Nordic countries, 1981–86. A joint publication of the five Nordic Cancer Registries. APMIS Suppl 1992;31:1–194.
23. Kim HJ, Fay MP, Feuer EJ, et al. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000;19:335–351.
24. Arora RS, Alston RD, Eden TO, et al. Age-incidence patterns of primary CNS tumors in children, adolescents, and adults in England. Neuro Oncol 2009;11:403–413.
25. Parkin DM, Bray F. Evaluation of data quality in the cancer registry: Principles and methods Part II. Completeness. Eur J Cancer 2009;45:756–764.
26. McCarthy BJ, Surawicz T, Bruner JM, et al. Consensus Conference on Brain Tumor Definition for registration. November 10, 2000. Neuro Oncol 2002;4:134–145.
27. Birch JM, Marsden HB. A classification scheme for childhood cancer. Int J Cancer 1987;40:620–624.
28. Fouladi M, Hunt DL, Pollack IF, et al. Outcome of children with centrally reviewed low-grade gliomas treated with chemotherapy with or without radiotherapy on Children's Cancer Group high-grade glioma study CCG-945. Cancer 2003;98:1243–1252.
29. Elger CE, Schmidt D. Modern management of epilepsy: A practical approach. Epilepsy Behav 2008;12:501–539.