Increased Incidence Rates but No Space-Time Clustering of Childhood Astrocytoma in Sweden, 1973–1992

A Population-Based Study of Pediatric Brain Tumors

Ulf Hjalmars, M.D.1
Martin Kulldorff, Ph.D.2
Yngve Wahlqvist, M.D.3
Birgitta Lannering, MD, Ph.D. 4

1 Department of Pediatrics, Östersunds Hospital, Östersund, Sweden.
2 Biometry Branch, Department of Cancer Prevention, National Cancer Institute, Bethesda, Maryland.
3 Pediatric Cancer Unit, Karolinska Hospital, Stockholm, Sweden.
4 Department of Pediatrics, University of Göteborg, Göteborg, Sweden.

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Address for reprints: Ulf Hjalmars, M.D., Department of Pediatrics, Östersunds Hospital, S-831 83 Östersund, Sweden.

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BACKGROUND. Incidence patterns, trends, and spatial and/or temporal clustering of childhood brain tumors were analyzed in the population-based national cancer registry of Sweden.

METHODS. Temporal trends were analyzed by a logistic regression procedure in which the average annual percentages of change in incidence rates and the corresponding 95% confidence intervals (CIs) were calculated. Spatial and/or temporal clustering were investigated by using a geographic information system and analyzed with a modified version of the Knox test and a spatial scan statistic.

RESULTS. Primary brain tumors in 1223 children ages 0–15 years were registered during 1973–1992. In 80% of cases, the tumor was classified as malignant. Conclusive histopathology was classified in 1142 cases. The age-adjusted incidence rate for all subtypes of brain tumors was 35.9 cases per million children, and for malignant brain tumors 28.6. A statistically significant increasing temporal trend was observed for the group of malignant brain tumors as a whole (P = 0.0001) and the astrocytoma subgroup (P = 0.0001). The annual average increases were 2.6% (95% CI = 1.5–3.8) and 3.0%, respectively (95% CI = 1.6–4.4). The increase in astrocytoma cases was significantly larger for girls than for boys (P = 0.021) and was most striking for girls ages 6–15 years, with an annual average increase of 4.7%. Rates had not increased for the primitive neuroectodermal tumor (PNET)/medulloblastoma or ependymoma subgroups. The geographic distribution of astrocytomas was homogenous. No statistically significant space-time interaction or local clusters in space and/or time were found for astrocytomas only or when astrocytomas were grouped with PNETs/medulloblastomas and ependymomas.

CONCLUSIONS. The results show statistically increased incidence rates of childhood astroglial tumors, predominantly for girls, in Sweden during the period 1973–1992, but no clustering in space or time. Cancer 1999;85:2077–90.

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KEYWORDS: childhood brain tumors, astrocytoma, primitive neuroectodermal tumor/medulloblastoma, ependymoma, epidemiology, incidence trends, cluster analysis, geographic information systems, spatial scan statistic, Knox test.

Brain tumors are, next to leukemia, the most common malignancy in childhood and constitute approximately 20% of all cancers in children younger than 15 years.1 In comparison with other pediatric cancers, progress in improving survival has been slow, although some decrease in mortality rates has occurred during the last decades due to improvements in neurosurgical techniques, radiation therapy, and
chemotherapy. The overall 5-year survival rate is approximately 60%. Children who do survive often experience severe sequelae.

Annual incidence rates for childhood brain tumors vary considerably among countries in international surveys. Astrocytomas and primitive neuroectodermal tumor (PNET)/medulloblastomas, comprising about 50% and 20%, respectively, of primary brain tumors, are the most common histologic subtypes in a majority of published studies.1

Several international registries have shown rising incidence rates for childhood astrocytoma.2–5 The cause of this trend is not known. Improvements and changes in diagnostic methods are often considered the most likely explanation. Enhanced exposure to carcinogenic environmental factors in modern society may have contributed to the increasing rate, although the exact nature of such environmental factors has not been established.

Geographic clustering has been reported for other childhood malignancies, such as leukemia and lymphoma.5–7 Several earlier studies have addressed the question of geographic clustering of pediatric brain tumors. Some investigations have shown regional differences in incidence rates and spatial clustering of childhood brain tumors, i.e., occurrence of cases close to other cases independent of where in the study area they occur.8–11 Looking at the geographic distribution is as important a part of disease surveillance as temporal trend analysis. However, disease cluster analyses often occur in response to media or community concerns. By chance there will often be some area in a region with a higher-than-average disease rate; and if all high rate areas are chosen for detailed study, a lot of random noise will be investigated. A better approach is to integrate the geographic analysis as part of surveillance efforts, analyzing the data while making the necessary statistical adjustments to account for the inherent multiple testing procedures.

The aim of the current study was to investigate incidence rates, temporal trends, and spatial and space–time clustering of primary brain tumors among Swedish children younger than 16 years during the 20-year period 1973–1992.

**MATERIALS AND METHODS**

Based on reports from all relevant Swedish hospitals and physicians, neoplastic diseases are registered for the entire population by the Swedish Cancer Registry. The registry is updated yearly with a few years’ delay. Furthermore, every neoplasm diagnosed by a pathologist or cytologist is also reported to the registry. Thus, every case of a diagnosed tumor is separately reported by two sources, resulting in a high rate of case ascertainment.

The current study covers all registered primary intracranial tumors diagnosed and reported in Sweden during the years 1973–1992 for children younger than 16 years, the age group for which treatment was performed in pediatric cancer centers during the years in question. Analyses were also conducted separately for the age groups 0–5, 6–10, and 11–15 years.

There were 1223 primary pediatric brain tumors. Of these, 975 were classified as malignant. The remaining tumors, including the craniopharyngiomas, were classified as benign. Cases with malignant tumors were further analyzed. A number of disease variables were recorded for each case. In the current study, age, histopathology, date of diagnosis, and residential parish at diagnosis were used. Parish codes were known for all cases except three (two astrocytomas and one PNET/medulloblastoma).

Histopathology was determined for 1142 children, 93% of all cases. Brain tumors comprise a heterogeneous group consisting of a number of histologically different types, here classified into 23 groups. The dominating classification system used during the study period was that proposed by Kernohan and Sayres.12 However, during the later part of the study the revised World Health Organization (WHO) classification system was also used. The WHO classification was proposed in 1979 to standardize the nomenclature for most human tumors and was revised in 1985, when it was especially designed for pediatric tumors.13 Not until the last decade did the WHO pediatric classification system become more widely adopted among Swedish neuropathologists. The numeric grades were assigned solely based on the microscopic appearance of the tumor. The difference between the two classification systems used in our study is small and not likely to bias the results. The accuracy of the histopathologic diagnosis for pediatric brain tumors in the Swedish cancer registry has previously been shown to be very good, especially for astrocytoma patients in this age group. A sample of 198 patients from the registry comprising all children diagnosed with brain tumors within the geographic area of West Sweden during 1970–1984 had their histopathologic slides reevaluated by neuropathologists. Only 3 of 67 astrocytoma cases in this sample were reclassified as belonging to other diagnostic groups.14 The grading of astrocytomas in this study makes a distinction between Grade 1–2 and 3–4, although both groups are classified as malignant tumors. All ependymomas were classified into one group. As there are no obvious reasons to assume a common etiology for different histopathologic types of brain tumors, detailed analyses...
were performed for the three most common subgroups: astrocytomas, PNET/medulloblastomas, and ependymomas.

For the background population, comprehensive databases from Statistics Sweden (SCB) covering the entire Swedish childhood population were used. Precise estimates of person-years at risk were obtained by annual age-stratified data from all 284 municipalities in Sweden. Over the years, the average child population ages 0–15 years was 1.7 million.

For the cluster analyses, we used weighted population counts for the total population ages 0–15 years enumerated in 1976, 1982, 1988, and 1994 for all Swedish parishes. As there have been minor changes in the geographic borders of Sweden’s parishes, the spatial and space–time cluster analyses were based on 2507 geographically constant “standard” parishes. The geometric midpoint at each parish, the centroid, was used in the spatial analyses. The parishes had an average population count for the analyzed age groups of 659, varying from 0 to 13,197.

The geographic information system (GIS) ARC/INFO was used for parts of the spatial analyses. A GIS can be described as a computer-assisted information management system for geographic data, including automated systems for the capture, storage, retrieval, analysis, and display of spatial data.

**Statistical Methods**

**Temporal trend analyses**

Temporal trends were estimated by fitting a logistic regression model with disease status as the dependent variable and year as the independent variable. By fitting a linear term on the log scale, an estimate of the proportional increase or decrease per year is obtained, together with a 95% confidence interval. The test for linear trend is done by testing whether the regression parameter for year is significantly different from zero.

**Cluster analyses**

The notion of disease clustering is not a uniquely defined phenomenon. It may be a localized excess in a specific area, or it may occur globally throughout the study region so that cases tend to occur close to other cases. Moreover, clustering may be defined in space, in time, or in both space and time. Most commonly, “clustering” refers to phenomena leading to spatial, temporal, or spatio-temporal variation that is greater than what would be expected by chance alone after adjustment for the spatial distribution of the population at risk and for known confounders, such as age. The most commonly used statistical method for disease clustering is the Knox test for space–time interaction, which is based on computation of all pairwise distances of cases in space and time. The test statistic is the number of cases that are close in both space and time, as defined by some critical distances. If the value of the test statistic is large, so that cases that are close in space are also close in time, and vice versa, then there is space–time interaction. The Knox test only looks at the interaction effect, and it adjusts for any purely spatial or purely temporal clustering. Moreover, if there are population shifts, so that the population growth is not the same in all parts of the study region, the test is biased in that the reported P values are smaller than the true ones. For this study, we used a recently developed unbiased version of the Knox test that adjusts for such population shifts. The analyses were performed for a set of multiple critical distances, while adjusting for the multiple testing inherent in such a procedure. As critical distances, we used all pairwise combinations of 0, 2, 5, 10, 20, 50, and 100 kilometers and 0, 3, 6, 12, and 24 months.

In addition to space–time interaction, we have also looked at local clusters, simultaneously detecting their location and testing their statistical significance. This was done using the spatial scan statistic, which we have previously applied to childhood leukemia in Sweden. A circular window moves across the map, defining a set of zones containing different parishes with different numbers of cases and population sizes. The center of the circular zones are at each of the parish centroids in turn, whereas the radius of the circle varies continuously from zero to an upper limit so that at most 10% of the total population at risk is included. According to the null hypothesis, cases are generated as Poisson random variables with intensity proportional to the confounder-adjusted population size.

A space–time version of the scan statistic looks for clusters that are localized in both space and time. The window is now a cylinder, and for every spatial coordinate and radius the window is flexible in terms of start and end year, in turn taking any possible time interval of consecutive years.

For statistical inference, 999 Monte Carlo replications were performed for the space–time statistic, and 9999 were performed for the purely spatial scan statistic and the Knox analyses. Calculations for the spatial and space–time scan statistics were done using the SaTScan software. Cluster analyses were performed on the astrocytoma Grade 1–4 and the combined subgroups of PNET/medulloblastoma, ependymoma, and astrocytoma Grade 1–4. The space–time cluster analyses were adjusted for the increasing temporal incidence trends. Because the counts of PNET/medulloblastomas and ependymomas were relatively few,
separate cluster analyses for each of these subgroups would give statistical power too low to be meaningful.

RESULTS
Incidence Patterns, Age, and Gender Distribution
The total number of childhood primary brain tumors and numbers of histopathologic subgroups are listed in Table 1.

Table 2 shows the number of cases and the incidence rates by gender and age groups for all primary malignant brain tumors and the 5 subgroups analyzed: 3 groups of astrocytomas (Grade 1–4, 1–2, and 3–4), PNET/medulloblastomas, and ependymomas. In Figure 1 the distribution by 1-year age specific and gender specific incidence rates is shown for all malignant brain tumors and the three most common histopathologic subtypes: astrocytomas, PNET/medulloblastomas, and ependymomas.

All primary brain tumors
Incidence rates for childhood brain tumors in Sweden were high during the study period. The overall rate for all primary pediatric brain tumors was 35.9 cases per million children. Sex distribution was essentially even. Of a total of 1223 children ages 0–15 years, 975 (80%) were classified as having malignant tumors and 248 (20%) were classified as having benign tumors. Conclusive histopathology was achieved in 1142 cases (Table 1). The 3 dominating diagnostic groups, constituting 77% of all primary brain tumors, were astrocytomas in 628 cases (51%), PNET/medulloblastomas in 210 cases (17%), and ependymomas in 100 cases (8%). All other diagnostic subgroups represented less than 5% each.

For malignant brain tumors, the average annual incidence rate was 28.6 per million children. The rates were highest in the age group 0–5 years for both genders. Approximately 40% were younger than 6 years. Gender distribution was even.

**Astrocytoma Grade 1–4**
For astrocytomas, incidence rates were high overall (considerably higher in Grade 1–2 than in Grade 3–4) and in both subgroups were higher for girls than for boys.

For all astrocytoma cases, Grade 1–4 combined, a slight female predominance was found, with a male-to-female ratio of 0.9 (95% CI = 0.87–0.92) and with an overall incidence rate of 18.4 cases per million. For boys the rate was 17.0 and for girls 19.0. In the astrocytoma Grade 1–2 group, the age and gender specific rates were highest for females in both groups: in the Grade 1–2 group for patients ages 0–5 and 6–10 years (15.2 cases per million) and in the Grade 3–4 group for patients ages 6–10 years (9.8 cases per million).

When the two astrocytoma subgroups were analyzed, Grade 1–2 and 3–4, separately, the former group showed a considerably higher incidence rate: 14.1 cases per million compared with 4.4 for the latter group. Rates were slightly higher among girls than among boys in both groups. The gender ratio was 0.92 (95% CI = 0.90–0.95) for Grade 1–2 tumors and 0.8 (95% CI = 0.75–0.88) for the Grade 3–4 subgroup. Gender and age specific incidence rates were significantly different in both groups. The highest incidence rates were found for females in both groups: in the Grade 1–2 group for patients ages 0–5 and 6–10 years (15.2 cases per million) and in the Grade 3–4 group for patients ages 6–10 years (9.8 cases per million) (Table 2).

**PNET/medulloblastoma**
The PNET/medulloblastoma group was the second most frequent group of brain tumors after the astrocytomas and had a high incidence, predominantly among young males.

The incidence rates were 6.2 cases per million overall, 7.1 for boys and 5.2 for girls. There was thus a clear male predominance, with a male-to-female ratio...
of 1.4 (95% CI = 1.38–1.50). The age and gender specific rates were highest for children younger than 6 years and most prominent for boys (Table 1, Fig. 1).

**Ependymoma**

The third most common type of brain tumor in this study was ependymoma. However, incidence rates were not particularly high in an international comparison. The overall incidence rate was 2.9 cases per million, 3.0 for boys and 2.9 for girls. The rates were highest among the youngest children and slightly higher for males, with a male-to-female ratio of 1.1 (95% CI = 1.03–1.14). Approximately 50% of the children were younger than 6 years at diagnosis (Table 2).

**Time Trends**

The results of the time trend analyses (logistic regression analyses) are shown in Table 3 and Figure 2.

**Malignant brain tumors**

Over the 20 years studied, the incidence for the whole group of malignant brain tumors rose at a statistically strongly significant average annual rate of 2.6% (P < 0.0001, 95% CI = 1.5–3.8). Thus, an increase of greater than 50% occurred during the entire study period.

The increase was predominantly confined to girls, as shown by analyses of gender specific subgroups (Table 3). For boys ages 0–15 years, the annual increase was 1.4%, and for girls it was 4.0%. The difference in temporal trends between the genders was statistically significant (P = 0.021).

**Astrocytomas**

Time trend analysis showed a striking increase of incidence rates for the whole group of astrocytomas Grade 1–4. The increase was strongly statistically significant (P < 0.0001, average annual change 3.0%, 95% CI = 1.6–4.4). Analyses of the gender subgroups indicated a very strong increase for females of 3.9% (P = 0.0001, 95% CI = 2.0–5.8), most pronounced in the age groups older than 6 years. For girls ages 6–10 years the average change was 5.0% (P = 0.003, 95% CI = 1.7–8.5), and for girls ages 6–15 years the average change was 4.7% (P = 0.0002, 95% CI = 2.2–7.2).

The two chosen histopathologic subgroups of astrocytomas were analyzed separately for incidence trends.

For tumors Grade 1–2, a statistically significant increase was found for ages 0–15 years in both genders combined as well as for boys and girls separately.

For the group of astrocytomas Grade 3–4, the increase for ages 0–15 years, for both genders combined, was statistically significant (P = 0.005, average change 4.1%, 95% CI = 1.3–7.1). The increase was strongest for females (P = 0.0003, average change 7.4, 95% CI = 3.3–11.7) and was confined mainly to girls in the age groups 6–10 years and 11–15 years, with an average change of 6.8% and 10.2%, respectively (P =

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**TABLE 2**

Malignant Brain Tumors in Sweden, 1973–1992: Number of Cases and Average Annual Incidence Rates per Million Children for the Age Groups 0–5, 6–9, and 10–15 Years

<table>
<thead>
<tr>
<th>Age group</th>
<th>No. of cases</th>
<th>Incidence rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Male</td>
</tr>
<tr>
<td>Primary malignant brain tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–5</td>
<td>401</td>
<td>207</td>
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<tr>
<td>6–10</td>
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<td>138</td>
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<td>11–15</td>
<td>295</td>
<td>148</td>
</tr>
<tr>
<td>Astrocytoma Grade 1–4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–5</td>
<td>238</td>
<td>108</td>
</tr>
<tr>
<td>6–10</td>
<td>189</td>
<td>78</td>
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<tr>
<td>11–15</td>
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<tr>
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<tr>
<td>6–10</td>
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<tr>
<td>11–15</td>
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<tr>
<td>6–10</td>
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<td>11–15</td>
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<tr>
<td>11–15</td>
<td>23</td>
<td>10</td>
</tr>
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</table>
0.04 and 0.02, 95% CI = 0.5–13.6 and 18.8–19.3, respectively) (Table 3).

**PNET/medulloblastomas**
No significant rising incidence trends were found for PNET/medulloblastoma. The average changes for boys were –0.1% (P = 0.97, 95% CI = –3.0 to 13.0), for girls 3.1% (P = 0.1, 95% CI = –0.16 to +7.0), and for both genders combined 1.2% (P = 0.30, 95% CI = –1.1 to +3.6) (Table 3).

**Ependymomas**
The incidence pattern for ependymomas did not show statistically significant increasing trends for all cases combined or for males and females separately. The average change for both genders combined was 2.5% (P = 0.15, 95% CI = –0.9 to +6.1), for boys 0.4% (P = 0.86, 95% CI = –4.2 to +5.2), and for girls 4.9% (P = 0.06, 95% CI = –0.2 to +1.2) (Table 3).

**Cluster Analyses**
No evidence of clustering was found for the childhood brain tumors in Sweden. Analyses by the modified Knox test showed no statistically significant space–time interaction of astrocytoma Grade 1–4 (P = 0.98) or PNET/medulloblastoma and ependymoma combined with astrocytoma Grade 1–4 cases (P = 0.69) (Table 4).
Scan statistics were used for both purely spatial and space–time analysis. Analyses of astrocytoma Grade 1–4 did not reveal statistically significant local spatial or space–time clusters ($P = 0.27$ and 0.48, respectively). Similarly, results of the tests for the combined group of the 3 most common tumor subgroups showed no statistically significant clusters ($P = 0.32$ and 0.76, respectively) (Table 5).

**Variation among Geographic Regions**

A chi-square test of the distribution of childhood astrocytomas among the six different regions of Sweden showed no statistically significant difference (data not shown).

**Variation among Municipalities with Different Degrees of Urbanization**

Incidence rates for different types of municipalities were analyzed. A chi-square analysis of incidence rates among urban, semiurban, and rural municipalities did not show statistically significant differences for the entire group of primary brain tumors; the subgroups of astrocytomas, PNET/medulloblastomas, and ependymomas together; or the astrocytoma group alone (data not shown).
DISCUSSION
The study of changes in cancer incidence is important for several reasons. An increase or decrease in incidence rates over time may lead to hypotheses concerning factors of etiologic importance. Identification of such factors is in turn important in reducing exposure to hazardous agents and thereby the risk of developing childhood cancer.

The age-adjusted incidence rates for brain tumors vary considerably among countries. An international
comparison of brain and spinal tumors based on data coordinated by the International Agency for Research on Cancer essentially covered the decade 1970–1979. In that study, the four Nordic countries Sweden, Norway, Denmark, and Finland together showed the highest incidence rate in the world, at 31.4 cases per million children ages 0–14 years; Sweden was the highest of these, at 33.7. The incidence rates in other Western populations were lower. In Italy and France, the rates were 27.1 and 26.9, respectively. In the U.S., the reported rate was 26.4 for white children. England and Wales had a rate of 24.4, and the lowest reported rate in Europe was found in Germany, with 18.2 cases per million per year.

Necessary prerequisites in studies of incidence patterns include accurate diagnosis and high case ascertainment, which must be consistent for the period under study. These prerequisites were fulfilled in the current investigation.

Significantly rising trends of tumors in the central nervous system have been reported from other parts of the world. Some earlier studies have reported gender differences for children with astrocytoma, although the patterns have not been consistent. In a study of temporal trends in cancer incidence in children younger than 15 years in the U.S., astroglial tumors showed a stronger increase for girls than boys among children ages 2–6 years. For the age group 10–14 years, the increase was mainly confined to boys, 3.8% annually. A report from the Greater Delaware Valley Pediatric Tumor Registry in the U.S. showed an overall annual increase of central nervous system tumor incidence of 2.7%. For glioma, the rising trend was strongest for white females ages 0–4 years, a 6.2% annual increase. In England a significant increase in juvenile astrocytoma was found for males, with a quinquennial increase of 15%.

Etiology of the vast majority of childhood brain tumors remains unknown. Brain tumors in children cannot be considered a single entity. The relative frequencies of different histologic types vary considerably between children and adults. This may be the consequence of different etiologic factors in different age groups. A number of possible casual factors have been suggested and investigated. The only established causes of primary central nervous tumors are heritable syndromes, which account for less than 5% of all cases, and ionizing radiation. High dose radiation by cranial irradiation has been consistently associated with increased risk. Among other factors that have been suggested for the etiology of astroglial tumors are electromagnetic fields, head trauma, maternal medications given during pregnancy, and maternal and child exposure to N-nitroso compounds; however, the results are as yet inconclusive. The relative contributions of genetic and environmental factors remain unclear. In children, brain tumors may be the result of exposure to carcinogens before conception, during pregnancy, or after birth. Familial and other parental factors may imply genetic susceptibility and new germline mutations. The human brain forms over a long period of time compared with many other organs and is vulnerable to many factors. Proliferation and migration of neurons continue for a considerable time postnatally, as do the development of receptor and transmitter systems. The blood-brain barrier is not fully developed until the middle of the first year of life.

The increasing incidence trends of astrocytomas in Sweden for the last 2 decades in this study is only partly consistent with the incidence trends in other European countries and the U.S. The rise may have several explanations. One hypothesis is that the increasing rates are attributable to improvements in diagnostic procedures. In the current study, age and gender distribution revealed that the increase was essentially confined to females. This finding, shown by a statistically significant difference between the trends for boys and girls (P = 0.021), makes diagnostic bias unlikely. Against diagnostic bias there is also the finding that the tumors were not diagnosed at a younger age, as the increase of incidence was greatest among girls ages 6–15 years. The increase was also linear over the entire study period and no step function was found, with a constant higher rate after a particular time during the study period. Furthermore, it seems unlikely that earlier detection by improved diagnostics would be confined mainly to astrocytomas but not to PNET/medulloblastomas or ependymomas, despite the different prediagnostic clinical courses among the different histopathologic groups.

One may theorize as to whether the difference between genders in endocrine function can possibly play a role in the risk for childhood brain tumors. There are some indications that estrogen-related antigens may play a role in the growth and angiogenesis of astrocytoma. Attention has also been drawn to the fact that certain chemical pollutants, known as xenestrogens, mimic the effect of estrogen both in vitro and in vivo. Existing information is as yet insufficient to resolve whether there is an association between astrocytoma and estrogenlike agents, and the need for further research is obvious.

If environmental factors that are geographically concentrated to restricted areas (such as polluting factors, pesticides in agriculture, and others) are of etiologic importance, then spatial clusters would be expected. Spatial–geographic analyses of the Swedish
FIGURE 2. The following rates per million children ages 0–15 years (log linear regression) are given: (a) annual incidence rates of primary brain tumors, both genders; (b) annual incidence rates of malignant brain tumors, both genders; (c) annual incidence rates of astrocytoma Grade 1–4, both genders; (d) annual incidence rates of astrocytoma Grade 1–4, boys; (e) annual incidence rates of astrocytoma Grade 1–4, girls; (f) annual incidence rates of astrocytoma Grade 1–2, both genders; (g) annual incidence rates of astrocytoma Grade 3–4, both genders; (h) annual incidence rates of medulloblastoma, both genders; (i) annual incidence rates of ependymoma, both genders.
data revealed no evidence of such local geographic clusters. Note that in this analysis we would only have seen a significant geographic cluster if the rate had been so high that it was not likely to occur by chance anywhere in the study region. That is, we adjusted for the fact that clusters would occur somewhere in the study region.

It is thus unclear why the incidence rates for childhood brain tumors are increasing and why the increase is mainly confined to astrocytomas and, in that group, girls ages 6–15 years. It may be that some environmental factor(s) of etiologic importance have changed over time, but there is no direct evidence to support this hypothesis.

The rising incidence trends found in this study, which were most pronounced for childhood astrocytomas in girls, thus warrant further investigation.

REFERENCES


### TABLE 4

Unbiased $P$ Values from the Knox Analysis for Childhood Astrocytoma, Medulloblastoma, and Ependymoma in Sweden, 1973–1992

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</table>

Combined $P$ value = 0.688.

### TABLE 5


<table>
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<tr>
<th>Tumor type</th>
<th>Most likely clusters</th>
<th>Parish cluster center</th>
<th>No. of cases</th>
<th>Expected no. of cases</th>
<th>Population</th>
<th>Annual incidence</th>
<th>Time frame</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure spatial analyses</td>
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<tr>
<td>Astrocytoma I–IV + ependymoma +</td>
<td></td>
<td>Faringe</td>
<td>14</td>
<td>3.9</td>
<td>7067</td>
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<td>Skeda</td>
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<tr>
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<td>12,833</td>
<td>1986–1986</td>
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<td>12,833</td>
<td>1986–1986</td>
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In increased incidence of childhood astrocytoma/Hjalmars et al. 2089