Background: The reported incidence of primary malignant brain tumors among children in the United States increased by 35% during the period from 1973 through 1994. The purpose of our study was twofold: 1) to determine whether the reported incidence rates for this period are better represented by a linear increase over the entire period ("linear model") or, alternatively, by a step function, with a lower rate in the years preceding 1984–1985 and a constant higher rate afterward ("jump model"); and 2) to identify the specific brain regions and histologic subtypes that have increased in incidence. Methods: Incidence data from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute for the period from 1973 through 1994 for primary malignant brain tumors in children were used to model the number of cases in a year as a random variable from a Poisson distribution by use of either a linear model or a jump model. Results/Conclusions: The increase in reported incidence of childhood primary malignant brain tumors is best explained by the jump model, with a step increase in incidence occurring in the mid-1980s. The brain stem and the cerebrum are the primary sites for which an increase in tumor incidence has been reported. The increase in reported incidence of low-grade gliomas in the cerebrum and the brain stem (unaccompanied by an increase in mortality for these sites) supports the substantial contribution of low-grade gliomas to the overall increase in reported incidence for childhood brain tumors. Implications: The significantly better fit of the data to a jump model supports the hypothesis that the observed increase in incidence somehow resulted from changes in detection and/or reporting of childhood primary malignant brain tumors during the mid-1980s. [J Natl Cancer Inst 1998;90:1269–77]
In examining the reported incidence of childhood primary malignant brain tumors, we were struck by the apparent difference in rates for the years preceding 1985 compared with the years subsequent to 1985 (Fig. 1). That 1985 appeared to be the dividing point between periods of lower and higher reported incidence seemed noteworthy, since the years around 1985 were a period when the availability of MRI sharply increased in the United States. MRI was not commonly used before 1984, but it has been applied much more widely from 1986 to the present. Evidence supporting these years as a watershed time for MRI utilization includes the following:

- In 1982, there were only 10 MRI units installed in the United States. By 1984, the number had increased to 108; by the end of 1985, there were 371 installed units (7,8). For comparison, diffusion of CT-imaging technology in the United States occurred in the mid-1970s, with the number of CT scanners increasing from eight in 1973 to 921 in 1977 (7).
- The initial publications describing the potential superiority of MRI for central nervous system (CNS) imaging for childhood brain tumors appeared in 1984 (9).
- By 1985, MRI was no longer restricted to research institutions and was becoming available at many non-research tertiary care centers (10).
- For the elderly population, a dramatic expansion in the use of MRI occurred between 1985 and 1987, increasing from 0.05 per 1000 eligible Medicare recipients to 4.31 per 1000 eligible Medicare recipients (11). Since children with serious conditions such as cancer are more likely to be evaluated at tertiary care centers than elderly adults (12), the transition for children likely occurred earlier.
- Third-party reimbursement for MRI was quite limited through 1985 (7). For example, in July 1985, only 14 of 70 local Blue Cross plans were reimbursing providers for MRI (7). In November 1985, Medicare approved coverage for MRI, indicating the changing attitudes of third-party payers toward this technology during this time period (8).

Visual inspection of Fig. 1, showing childhood brain tumor incidence during the period from 1973 through 1994, indicates two distinctive alternatives to explain the temporal pattern for the increase during this period. In the first alternative, the incidence of childhood primary malignant brain tumors increases at a constant rate throughout the period from 1973 through 1994; in the second alternative, the incidence is a step function with a constant lower rate in the years preceding 1984–1985 and with a constant higher rate afterward. The distinction between these two alternatives is important, since, if the step function model fit the reported incidence data significantly better than the linear increase model, this would support the hypothesis that the observed increase somehow resulted from changes in detection and/or reporting of childhood brain tumors during the mid-1980s (e.g., changes in diagnostic imaging utilization). In the analyses that follow, we demonstrate that the observed incidence data are described significantly better by a step function model (henceforth termed the “jump model”) than by a Poisson regression model (henceforth termed the “linear model”). We also describe total incidence rates and incidence rates for specific histologic subtypes for the brain sites for which the increase in reported incidence was most pronounced.

Methods

Incidence and Mortality Data

Incidence data for the period from 1973 through 1994 for childhood primary malignant brain tumors are from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI), which since 1973 has coordinated a network of population-based cancer incidence registries located in selected areas of the country and covering about 10% of the U.S. population (1,13). By the end of 1994, the database contained information on more than 2 million cancer cases diagnosed since 1973, with more than 150,000 new cases accessioned yearly. SEER incidence rates are per 100,000 person-years and are age-adjusted to the 1970 U.S. standard population.

Mortality data are from a public use tape containing information on all deaths occurring in the United States by calendar year obtained from the National Center for Health Statistics, Hyattsville, MD (1). Information on each death includes the subject’s age at death, sex, geographic area of residence, and underlying and contributing causes of death. Only the underlying cause of death was used to calculate mortality rates. The ninth revision of the International Classification of Diseases, Injuries, and Causes of Death was used for tumor classification for mortality, with the following codes used to define “brain and other nervous system” tumors as underlying causes of death: 191.0–191.9, 192.0–192.3, and 192.8–192.9 (1). Mortality rates are per 100,000 person-years and are age-adjusted to the 1970 U.S. standard population.

Definition of Incident Brain Tumor Cases, Brain Tumor Sites, and Brain Tumor Histologies

The SEER Program codes site and histology by the International Classification of Diseases for Oncology, 2nd ed. (ICD-O-2) (14). All cases diagnosed before 1992 were machine converted to ICD-O-2. Analyses by histology are restricted to the period from 1977 through 1994, which encompasses the years in which tumors were coded according to either the first or the second edition of the International Classification of Diseases for Oncology.

The definition of incident brain tumor cases was that of the SEER Program
and employs ICD-O-2 site codes C70.0–C72.9 (1). All histologies with a behavior code of 3 (i.e., malignant, invasive) were included with the exception of lymphomas. The SEER Program analyzes CNS lymphomas with other lymphomas rather than with brain tumors. Only 12 CNS lymphomas were counted among children for SEER cases from 1973 through 1994 (compared with 3396 cases of brain tumors among children <15 years old). In a similar manner, tumors of the pituitary gland and pineal gland were analyzed with the endocrine tumors rather than with brain tumors. During the period from 1973 through 1994, there were only 11 pituitary tumors and 80 pineal gland tumors for SEER cases among children younger than 15 years. Inclusion of both CNS lymphoma cases and pituitary and pineal gland cases would have increased the overall incidence of brain tumors for the years 1986–1994 by only 3% (from 3.3 to 3.4 per 10^5 person-years); thus, conclusions based on the SEER definition of incident cases are likely to apply for other definitions of brain tumors that include one or more of these groups. Specific brain site locations were defined as follows: cerebrum (including lobes) = C71.0–C71.4; cerebellum = C71.6; brain stem = C71.7; and other = C70.0–C70.9, C71.5, C71.8, C71.9, and C72.0–C72.9. Except where otherwise noted, all analyses are for the population less than 15 years of age.

Because the numbers of cases for individual ICD-O-2 diagnoses are not adequate for analysis of incidence trends over time, we grouped these diagnoses into four histologic categories: high-grade glioma, low-grade glioma, medulloblastoma/PNET, or other.

High-grade glioma is defined by the following codes: 9380/3 (glioma, malignant), 9381/3 (gliomatosis cerebri), 9401/3 (astrocytoma, anaplastic), 9422/3 (spongioblastoma, not otherwise specified [NOS]), 9423/3 (spongioblastoma polare), 9430/3 (astroblastoma), 9440/3 (glioblastoma, NOS), 9441/3 (gliosarcoma), 9442/3 (gliosarcoma), 9443/3 (primitive polar spongioblastoma), and 9481/3 (monstrocellular sarcoma).

Low-grade glioma is defined by the following codes: 9383/3 (subependymal glioma), 9384/3 (subependymal giant cell astrocytoma), 9400/3 (astrocytoma, NOS), 9410/3 (astrocytoma, protoplasmic), 9411/3 (astrocytoma, gemistocytic), 9420/3 (astrocytoma, fibrillary), 9421/3 (astrocytoma, pilocytic), and 9424/3 (pleomorphic xanthoastrocytoma).

Medulloblastoma/PNET is defined by the following codes: 9470/3 (medulloblastoma, NOS), 9471/3 (medulloblastoma, desmoplastic), 9472/3 (medulloblastoma, NOS), and 9473/3 (primitive neuroectodermal tumor).

The “other” category includes all other histologies.

In comparing incidence rates according to the four histologic categories for individual brain sites, we utilized 4- or 5-year time periods because of the small number of cases within any individual histologic category in a brain region in a single year. The year 1977 was chosen as the initial year for presenting incidence data by histologic subtype (see above), and the year groupings were selected to evenly divide the years before and after 1985 as follows: 1977–1981, 1982–1985, 1986–1989, and 1990–1994.

Analytic Method for Comparison of Linear Model Versus Jump Model for the Incidence of Childhood Primary Malignant Brain Tumors

We modeled the number of cases in a year as a random variable from a Poisson distribution. The Poisson distribution is a one-parameter distribution. That is

\[ P \sim \text{Poisson}(\lambda) \]

where \(\lambda\) is the mean of the Poisson distribution. The Poisson distribution is a one-parameter distribution. That is

\[ \lambda = \alpha + \beta t + \log(n) \]

for \(t = 0, 1, 2, \ldots, 21\), respectively, and \(n\) denotes the number of children at risk during year \(t\). The parameters \(\alpha\) and \(\beta\) were fit to the data to maximize the Poisson likelihood function using the SAS GENMOD procedure (SAS Institute, Inc., Cary, NC). The significance of the slopes to the models was tested with the use of the Wald chi-squared statistic.

The 1984–1985 jump model had the Poisson parameter constant for the pre-1984 years, except for its dependence on size of the at-risk population. The parameter was also considered constant, except for population size changes, for the years following 1985. That is

\[ \log(\lambda) = \alpha_1 + \log(n) \text{ for } t \leq 1984 \]

\[ \log(\lambda) = \alpha_2 + \log(n) \text{ for } t > 1984 \]

This is also a two-parameter model, and the values of \(\alpha_1\) and \(\alpha_2\) were determined to maximize the Poisson likelihood for the years excluding 1984 and 1985. Call this value of the likelihood \(L_{\text{jump}}\). The jump model is not defined for the transition years 1984 and 1985. To compare the fit of the jump model to that of the linear model, we computed the Poisson likelihood \(L_{\text{linear}}\) for the years other than 1984–1985 using the parameters obtained from fitting the linear model to the complete dataset. We then calculated a ratio \(R = L_{\text{linear}} / L_{\text{jump}}\) to measure whether and to what extent the jump model provided a better fit to the data than did the linear model.

To evaluate the statistical significance of the \(R\) value obtained, we used the following “bootstrap” procedure. \(\alpha_0\) and \(\beta_0\) denoted the parameters for the linear model obtained from the complete dataset. Using these values, we generated new data according to the linear model:

\[ \log(\lambda_i) = \alpha_0 + \beta_0 t + \log(n) \]

That is, using the \(\lambda_i\) values, we generated from the Poisson distribution new incidence figures for the years 1973–1994. Using these new data, we fit a linear model and jump model and computed the likelihood ratio \(R\) as described above for the true data. For the first set of synthetic data randomly generated, the likelihood ratio obtained was called \(R_0\). We used the subscript notation because we repeated this entire procedure 10 000 times (generating 10 000 sets of synthetic data, fitting a linear and a jump model to each set of data, and computing a likelihood ratio \(R_1, R_2, \ldots, R_{10000}\). The proportion of these 10 000 ratios that exceeded the \(R\) value computed from the true data is the statistical significance level. This is because the 10 000 sets of synthetic data were generated from the linear model (equation 3).

Results

Comparison of Linear Model and Jump Model

The incidence of childhood primary malignant brain tumors in the United States in the period from 1973 through 1994 was fit to both a linear model and a jump model, as described in the “Methods” section. The ratio of the Poisson likelihood function for the jump model to the linear model was 49.2, indicating that the jump model provided a substantially better fit for the incidence data. By use of the “bootstrap” procedure described in the “Methods” section, the statistical significance value obtained for the comparison was \(P = .002\).

To avoid bias based on preselection of the change point at 1984–1985, we also fit an optimal change-point model with the
year of the change point determined to maximize the Poisson likelihood. The optimal change point found for the data was 1984. The ratio of the Poisson likelihoods of the optimal change-point and linear models was 14.8, favoring the optimal change-point model. The statistical significance level determined for this comparison was .041. It is not surprising that the significance level is increased compared with the jump model, in part because the optimal change-point model does not provide for a gradual transition in incidence during the transition years 1984–1985. Furthermore, it is more likely that data generated from a linear model will be better fit by a change-point model with unspecified change point than by a change-point model with a prespecified change point. Nevertheless, the likelihood ratio value for the optimal change-point model achieves the conventional level of statistical significance.

**Changes in Reported Tumor Incidence Over Time for Specific Brain Sites**

Fig. 2 shows that the reported incidence of childhood primary malignant brain tumors increased from 2.76 per 10^5 person-years in 1977–1981 to 3.34 per 10^5 in 1990–1994. To determine whether this increase occurred uniformly for all areas of the brain or was confined to specific locations, we compared incidence rates over time for the cerebellum, cerebrum, brain stem, and ‘‘other’’ sites (Fig. 2). From 1977–1981 to 1990–1994, incidence rates for the cerebellum decreased (0.94 to 0.80 per 10^5 person-years), and there was a small increase for ‘‘other’’ sites (0.95 to 1.01 per 10^5). For the cerebrum and for the brain stem, there were substantial increases in incidence during the same period. The reported incidence for tumors of the brain stem more than doubled from 0.31 per 10^5 in the years 1977–1981 to 0.67 per 10^5 in the years 1990–1994. For tumors of the cerebrum, the incidence increased by over 50% from 0.56 to 0.86 per 10^5. The increases in incidence for the cerebrum and the brain stem are sufficient to account for virtually all of the overall increase in reported incidence of childhood primary malignant brain tumors during this period.

We examined the incidence data for the brain stem region by whether the tumor diagnosis was microscopically confirmed or not. This distinction is important, since the diagnosis of diffuse intrinsic brain stem glioma in children is generally made on the basis of radiographic findings and without microscopic confirmation (as a result of the morbidity associated with biopsy and the characteristic radiographic appearance of diffuse brain stem gliomas) (15). Fig. 3 demonstrates that the increase in the reported incidence of brain stem tumors is the result of a striking increase beginning in the early 1980s in cancer of the brain stem with microscopic confirmation of diagnosis. Fig. 4 shows the incidence by histology over time for the microscopically confirmed brain stem tumors. An increase in the incidence of low-grade gliomas occurring in the early 1980s (0.07 to 0.20 per 10^5 person-years) and a more slowly appearing increase in the incidence of high-grade tumors (0.06 to 0.14 per 10^5) account for much of the overall increase. The appearance of some cases of medulloblastoma/PNET after 1985 and a small increase in ‘‘other’’ diagnoses account for the remainder of the increase.

Fig. 5 shows the incidence by histology over time for the cerebrum. The increase in incidence in the cerebrum occurred in the mid-1980s, and higher constant rates occurred subsequently. Approximately 50% of the increase in incidence that occurred in the mid-1980s is accounted for by an increase in the incidence of low-grade gliomas. The remainder of the increase is accounted for by a numerically smaller increase in rate for high-
changes in the period from the mid-1970s (approximately 1.0 per 10^5 person-years) to the early 1990s (approximately 0.8 per 10^5) (Fig. 1). Mortality rates by individual brain region for 1979–1994 show significant decreases for the cerebrum, cerebellum, and “other” category (Fig. 7), with no significant change in mortality rates for the brain stem and brain NOS categories.

**Discussion**

We have demonstrated that the increase in the reported incidence of childhood primary malignant brain tumors observed by the SEER Program is better described by a jump model than by a linear model and that the significantly better performance of the jump model is not dependent on *a priori* assumptions about the timing of the transition from lower to higher incidence rates. The most important contribution of this observation is in focusing attention to the years around 1984–1985 in attempting to understand the increase in reported incidence of childhood primary malignant brain tumors. As described in the introduction, our impetus for conducting this analysis was the hypothesis that the increasing incidence of childhood brain tumors was somehow associated with expanding MRI utilization for the diagnosis of CNS conditions in children. Reports describing the ability of MRI to detect tumors not detectable by CT imaging support this explanation (16–19). However, other hypotheses could explain these data, including the following:

- Changes in histologic classification of brain tumors that occurred in the years around 1984–1985 (20), under the assumption that these changes somehow resulted in pathologists labeling entities as malignant brain tumors that previously had been considered “benign.” Since the SEER Program collects incidence data only for malignant tumors, brain tumors labeled as “benign” are not included among SEER cases. As an example, the convention of describing low-grade gliomas of the brain stem and other anatomic sites as “benign” lesions may have contributed to an underreporting of some cases of low-grade gliomas (18,21,22).
- Changes in neurosurgical practices (e.g., stereotactic biopsies) in the mid-1980s (18,21,22) that might have led to increased diagnosis and reporting of childhood brain tumors (21,23).
- A true increasing incidence in childhood primary malignant brain tumors that occurred over this brief period of time.

The observation that the higher level in reported incidence subsequent to 1985 appears to have been maintained for all age cohorts less than 25 years of age (see Fig. 6) is consistent with a change in tumor diagnosis and/or reporting that occurred during this period and that has subsequently been maintained. Alternatively, new imaging capabilities and/or neurosurgical procedures available since 1984–1985 might have led to the diagnosis of brain tumors that were previously not detected. A specific example of this is the detection by MRI (but not by CT) of low-grade gliomas of the midbrain in patients who might previously have been diagnosed as having idiopathic late-onset aqueductal stenosis (16–18). A third explanation consistent with the persistently higher rates since 1985 is the diagnosis of tumors that occurred rarely before 1984–1985 but that have occurred at
a higher constant rate in the years after 1985. A biologic explanation for this possibility is not readily apparent. A fourth explanation, that the higher incidence rates since 1985 were the result of earlier detection of tumors (e.g., through increased MRI utilization) that would have eventually been detected, requires the corollary prediction that there eventually would be a decrease in reported incidence to pre-1985 levels. Since this appears not to have occurred, either this explanation is not applicable or the tumors accounting for the increase have a very long latent period between early detection and clinical presentation. As an example of brain tumors with long latent periods, entities such as the low-grade gliomas of chronic epilepsy may be associated with years of symptoms that in retrospect are identified as relating to a brain tumor diagnosis (24). These low-grade gliomas associated with epilepsy rarely exhibit tumor recurrence or anaplastic transformation and rarely result in tumor-related death (24).

The U.S. mortality data provide some clues that are helpful in understanding the increasing reported incidence rate. From 1973 through 1994, there has been a small, but significant, decline in mortality associated with brain tumors in children (Fig. 1). Importantly, in the years immediately following 1984–1985, there was no increase in mortality for brain sites in spite of the significant increase in brain tumor incidence that occurred during this period. Since there were no dramatic breakthroughs in the identification of curative therapies for childhood brain tumors in the 1980s with 5-year survival rates remaining at 61%–62% throughout the decade (19,25), this lack of an increase in mortality effectively rules out several specific diagnoses with particularly poor outcome as substantially contributing to the increase in reported brain tumor incidence. For example, diffuse intrinsic brain stem gliomas and glioblastoma multiforme of the cerebrum are associated with survival rates of 25% or less at 2–3 years (26,27). A substantial increase in either of these diagnoses would likely have contributed to an overall increase in total brain tumor mortality rates and to an increase in mortality rates for the brain stem site and the cerebrum site. The fact that increases at these sites were not observed (Fig. 7) reduces the likelihood that these tumor types contributed substantially to the increase in incidence. Furthermore, children with medulloblastoma of the cerebellum have had 5-year survival rates of 50%–70% with little improvement in outcome during the decade of the 1980s (19,25,28,29). Substantial increases in the true incidence of medulloblastoma should have been reflected by increasing, rather than by decreasing, mortality rates for the cerebellum (Fig. 7). In interpreting U.S. mortality data by brain anatomic site, it is important to note that approximately 45% of childhood deaths from brain tumors are reported for the ‘‘brain NOS’’ category and not for a specific brain region (see Figs. 1 and 7). The relatively constant mortality rate for ‘‘brain NOS’’ from 1979 through 1994 makes it less likely that a substantial increase in deaths associated with a specific brain site...
might have been missed because of reporting in the ‘‘brain NOS’’ category.

The major category of childhood brain tumors that has 5-year survival rates well above 50% is the group of low-grade gliomas (25,30,31). Given the absence of an increase in mortality rates, the low-grade gliomas are the most likely diagnostic category to account for the increasing incidence rates observed by the SEER Program. This category is also the category for which MRI is most contributory, since MRI is more sensitive than CT in detecting low-grade glial lesions (17,19,32,33). However, in the interpretation of changes over time in reported incidence of different histologic types, it is important to use caution, since there have been changes in histologic classification systems and practices over time (20). Furthermore, the grade of some cases of pediatric gliomas can be very difficult to assign, and even experienced neuropathologists reach different conclusions concerning characteristics associated with high versus low grade (34).

The increase in reported incidence of brain stem tumors warrants additional comment. Diffuse intrinsic brain stem gliomas
are all commonly of low grade and are associated with a favorable outcome. Diffuse brain stem enlargement or progression, even in the absence of treatment, this finding in NF1 patients is often not associated with disease. Important for future study will be careful evaluation of available records of the cases of gliomas of the brain stem and cerebrum reported to the SEER registry (particularly those diagnosed after 1985), with the goal of better characterizing these tumors that account for much of the increase in incidence of childhood primary malignant brain tumors.

### References


Notes

1Editor's note: SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the NCI. Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

2Authors' note: Subsequent to the analyses performed for this study and submission of the article, 1995 incidence data for childhood brain tumor cases have become available through the SEER Program. These computer tapes are then edited by the NCI and made available for analysis.

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