Prevalence estimates for primary brain tumors in the United States by behavior and major histology groups[1]

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Prevalence rates are used to supplement descriptions of disease and are unavailable for all primary brain tumors in the United States. Data from two population-based tumor registries were obtained from the Central Brain Tumor Registry of the United States and used to compute age-specific incidence rates (1985-1994) and survival curves for further use in a statistical model to estimate prevalence rates. Prevalence rates were then used to estimate the number of individuals living with a brain tumor diagnosis in the U.S. population for the year 2000. The overall incidence rate in these regions is 13.8 per 100,000 with 2-, 5-, and 10-year survival rates of 58%, 49%, and 38%, respectively. The prevalence rate for all primary brain tumors is 130.8 per 100,000 with approximately 350,000 individuals estimated to be living with this diagnosis in the United States in 2000. The prevalence rate for malignant tumors, 29.5 per 100,000, is similar to previous reports. The prevalence rate for benign tumors, 97.5 per 100,000, is new. Unlike incidence data, the proportion (and expected number) of existing benign tumors (75%, 267,000) is considerably greater than that for malignant tumors (23%, 81,000), reflecting the better prognosis of benign tumors diagnosed in individuals younger than 60 years old. These data underscore the impact of primary brain tumors in the U.S. health care system and emphasize the need for quality-of-life considerations, particularly for those long-term survivors of benign tumors. *Neuro-Oncology 3, 152–158, 2001 (Posted to Neuro-Oncology [serial online], Doc. 00-056, June 5, 2001. URL <neuro-oncology.mc.duke.edu>)*

Cancer statistics routinely include incidence, mortality, and survival rate estimates. Although useful for many reasons, these estimates do not provide a complete understanding of the burden of disease (Adami et al., 1989; Feldman et al., 1986). Prevalence rate estimates can be used to supplement the description of disease by measuring the proportion of a population that is affected by disease (new patients and former patients who are survivors) at a given point in time. Prevalence estimates reflect the combined patterns of incidence, survival, and population aging. Prevalence rates for cancer have only recently become available in the United States (http://www-dccps.ims.nci.nih.gov/SRAB/Prevalence) and are useful for health care planning purposes.

Prevalence estimates available for brain tumors reflect the portion of tumors that are malignant. Just as routine incidence statistics from cancer registries underrepresent the full spectrum of primary brain tumor cases (Davis et al., 1999), the omission of nonmalignant tumors in prevalence estimates falsely minimizes the impact of this disease in a population. This is particularly important because the nonmalignant cases with a better prognosis contribute far more to prevalence estimates than malignant cases with a poorer prognosis (Hakama et al., 1975). This underestimation may influence the health care preparedness for continued surveillance and treatment of patients and may discourage researchers, funding

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[3]Abbreviations used are as follows: CBTRUS, Central Brain Tumor Registry of the United States; SEER, Surveillance, Epidemiology and End Results.

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agencies, and the biotechnology industry from undertaking the development of new therapeutic approaches for recurrent disease. For chronic diseases such as brain tumors, the number of prevalent cases may define a subgroup with specific clinical and social support needs. The objective of this report is to provide preliminary prevalence estimates as a starting point toward better understanding of the health care impact from all primary brain tumors.

Methods

Prevalence is one of several measures of the overall burden of disease in a population and is influenced by the rate at which new cases develop, the length of time individuals survive with disease, and whether or not individuals become disease free. Prevalence estimates for cancer generally assume the diagnosis is irreversible. Once diagnosed, a case becomes prevalent for life. Statistical models have been developed to estimate prevalence rates, as it would be extremely expensive to measure these rates directly in a population. Applying these models requires information on incidence rates, survival rates, the population's age distribution, and death rates.

CBTRUS[3] has compiled state cancer registry data to describe the incidence of malignant and nonmalignant primary brain tumors located in the brain, spinal cord, cranial nerves, and in all other CNS tumors, plus those in the pituitary and pineal glands (Surawicz et al., 1999). Two SEER regions, Connecticut and Utah, provided CBTRUS with incidence data on all primary brain tumors for the years 1985-1994 and survival data up to 1997. Population data from these states were obtained from the SEER-National Cancer Institute Web site. General U.S. population death rates for use in computing expected survival values were obtained from National Center for Health Statistics. Data were compiled and estimates were programmed using the Statistical Analysis System (SAS^R, 1992).

Crude incidence rates were computed grouping 1985-1994 cases from these 2 regions. Age-specific incidence rates, stratified by age at diagnosis in 5-year intervals, were computed and used in making the prevalence estimates.

Survival rates were computed using standard life table procedures (Collett, 1994). Estimates of survival up to the age of diagnosis were based on general population death rates. Estimates of survival after diagnosis were complicated because the postdiagnosis period for these data is rather short (maximum of 12 years), so 2 assumptions were made to compute survival curves beyond this point. Assumption 1 asserted that the conditional survival after the observed follow-up (beyond 10 years) was the same as the population survival (estimated from death rates obtained from the U.S. census). This assumption was used to estimate prevalence for the benign tumors and tumors of the meninges. Assumption 2 asserted that conditional survival drops to zero after the observed follow-up (beyond 10 years) and was used to estimate those survival curves underlying the computation of prevalence rates for malignant tumors and tumors of uncertain behavior. Prevalence estimates under both assumptions presume a steady-state situation with respect to incidence and survival rates, and estimates based on both assumptions are reported for all primary brain tumors to allow the reader a sense of the variability associated with each assumption.

The statistical model used to estimate age-specific prevalence is based on the conditional probability of having ever been diagnosed, given that one is currently still alive.[4] The formulas used were as follows:

- Age-specific prevalence:

$$\Pr(D \le k | T > k) = \frac{\Pr(D \le k \text{ and } T > k)}{\Pr(T > k)} = \frac{\sum_{i=1}^{k} \Pr(D = i)\ \Pr(T \ge i | D > i)\ \Pr(T > k | T \ge i, D = i)}{S(k)}$$

D = age at diagnosis
T = age at death
$S(k)$ = conditional survival in the population (at age k)

- Estimation formula:

$$\Pr(D \ge k / T > k) = \frac{\sum_{i=1}^{k} \left\{ \prod_{j=1}^{j=i} [1 - l(j)] \right\} l(i) S^*(i-1) S^{**}(i, k)}{S(k)}$$

Age-specific incidence:

$$I(k) = \Pr(D = k | D \ge k)$$

Prediagnosis survival:

$$S^*(k) = \Pr(T > k | D > k)$$

Postdiagnosis survival:

$$S^{**}(k,t) = \Pr(T > k + t | D = k)$$

Population survival:

$$S(t) = \Pr(T > t)$$

Briefly, incidence and postdiagnosis survival were estimated within 5-year age groups, beginning with 0-4 and ending with 85+. Age-specific prevalence (at age k) is defined as the sum of probabilities of having been diagnosed at each age up to and including age k (incidence rates), surviving up to age at diagnosis, and subsequent survival up to age k, given that one was still alive at age k. Overall prevalence estimates are then a weighted average of the age-specific prevalence rates. Although estimates of the variability in the prevalence rate estimates would be optimal, they have not yet been derived. Variability for the incidence and survival rates underlying the prevalence estimates is shown as 95% confidence intervals, and the resulting prevalence estimates should be considered quite crude.

Prevalence estimates for several groups (not necessarily mutually exclusive groups) were computed using this model and by applying the underlying survival assumptions as noted. These estimates were computed for all primary brain tumors and for several subgroups: malignant

Table 1. Distribution of histologic categories by behavior of selected primary brain tumors, Connecticut and Utah, 1985-1994

	Malignant		Benign		Uncertain		Total	
Tumor category	*n*	%	*n*	%	*n*	%	*n*	%
Neuroepithelial								
Diffuse astrocytoma	53	100.0	0	0.0	0	0.0	53	1.6
Anaplastic astrocytoma	289	100.0	0	0.0	0	0.0	289	8.8
Glioblastoma	1543	99.9	1	0.1	0	0.0	1544	47.3
Pilocytic astrocytoma	95	100.0	0	0.0	0	0.0	95	2.8
Oligodendroglioma	121	100.0	0	0.0	0	0.0	121	3.7
Ependymoma/anaplastic ependymoma	90	96.8	0	0.0	3	3.2	93	2.9
Mixed glioma	62	100.0	0	0.0	0	0.0	62	1.9
Astrocytoma, not otherwise specified	534	99.8	1	0.2	0	0.0	535	16.4
Glioma malignant, not otherwise specified	185	99.5	1	0.5	0	0.0	186	5.7
Benign and malignant neuronal/glial, neuronal and mixed	17	21.2	10	12.5	53	66.3	80	2.5
Embryonal/primitive/neuroblastoma	99	100.0	0	0.0	0	0.0	99	3.0
Other	37	33.6	18	16.4	55	50.0	110	3.4
Total	3125	95.6	31	1.0	111	3.4	3267	100.0
Meningeal	63	3.4	1690	92.3	78	4.3	1831	100.0
Pediatric	521	77.6	81	12.1	69	10.3	671	100.0

(behavior code 3 regardless of the histologic diagnosis); benign (behavior code 0); uncertain behavior (behavior code 1); neuroepithelial (histologic grouping regardless of behavior); meningeal (histologic grouping); pediatric (tumors diagnosed before age 20); and malignant pediatric (behavior code 3). Data were too sparse to allow stable estimates of less frequent tumor categories; however, tumor subgroups and their frequencies are reported to assist the reader in the interpretation of these broader groupings (Table 1).

To explore the impact of the conservative assumption (assumption 2) underlying the survival curves for malignant tumors, our prevalence estimates were compared with those published from the Connecticut SEER registry, which used long-term survival data (SRAB/NCI, 2000). As the prevalence estimates for nonmalignant tumors were quite different based on which survival assumption was used, we elected to test our choice of the first assumption by comparing our estimated survival curve for meningiomas to an observed survival curve based on 20 years of data (1953-1984) from a Finnish population–based registry (Sankila et al., 1992). Although the time periods that these data cover are quite different, the tumors are still primarily surgically managed tumors, making this crude comparison seem reasonable. Our survival curve was estimated using weighted averages of the survival rate for each age group and year, with the weights based on the age distribution of the cases at diagnosis. For each age group, observed rates were used for as many years as available (between 10 and 12 years), and conditional general population survival estimates were used for yearly estimates up to 20 years.

To provide crude estimates of the expected number of cases living with primary brain tumors in the United States, we applied calculated category-specific prevalence rates to the U.S. population census estimates for the year 2000. To compute for all primary brain tumors an expected number that incorporates the most appropriate survival curve assumptions, we summed the expected numbers for malignant, uncertain, and benign tumors.

Results

To allow for a better understanding of the estimates that follow, we show the tumor groupings in Table 1 and report the frequencies by behavior and major histology groupings. The neuroepithelial category is a very broad one that includes most of the malignant brain tumors for both pediatric and adult patient populations. It is important to note that, although 95.7% of the neuroepithelial group is malignant, we applied the most conservative survival assumption (assumption 2) for estimating prevalence rates in this category and, although 3.4% of the meningiomas were malignant, we applied the least conservative survival assumption (assumption 1) to this predominantly benign category. As such, the resulting prevalence estimates are relatively crude.

The incidence and survival rates observed for the 6908 brain and CNS cancer cases in Connecticut and Utah between 1985 and 1994 are summarized in Table 2. About 52.5% of these tumors were malignant, primarily neuroepithelial (90% of malignant tumors), and 42.2% were benign. Over half of the benign tumors are tumors of the meninges (62.8%). As a group, neuroepithelial tumors had an incidence rate of 6.5 per 100,000 and meningiomas a rate of 3.7 per 100,000. There were 671 (9.7%) cases diagnosed before the age of 20, and most of those were coded as malignant (77.6%). As pilocytic tumors are coded as malignant in cancer registries, this percentage may be artificially high. The overall incidence rate was 13.8 per 100,000, and the incidence rate for pediatric tumors was much lower (0.71 per 100,000). The 5- and 10-year survival rates for all malignant

Table 2. Incidence and survival rates by selected primary brain tumor subgroups, Connecticut and Utah, 1985-1994

Tumor category	*n*	Incidence per 100,000	2-yr survival (95% CI)	5-yr survival (95% CI)	10-yr survival (95% CI)
Primary brain	6905	13.8 (13.5-14.1)	0.58 (0.57-0.59)	0.49 (0.48-0.50)	0.38 (0.37-0.40)
Malignant	3625	7.2 (7.0-7.5)	0.34 (0.32-0.35)	0.25 (0.23-0.26)	0.19 (0.17-0.20)
Benign	2914	5.8 (5.6-6.0)	0.88 (0.87-0.89)	0.78 (0.77-0.80)	0.62 (0.60-0.65)
Uncertain	366	0.7 (0.6-0.8)	0.71 (0.66-0.76)	0.63 (0.58-0.68)	0.49 (0.42-0.56)
Neuroepithelial	3264	6.5 (6.3-6.8)	0.35 (0.33-0.37)	0.27 (0.26-0.29)	0.21 (0.20-0.23)
Meningeal	1831	3.7 (3.5-3.8)	0.84 (0.82-0.86)	0.73 (0.71-0.75)	0.55 (0.52-0.59)
Pediatric	671	4.3 (4.0-4.7)	0.77 (0.74-0.81)	0.71 (0.67-0.75)	0.68 (0.64-0.72)
Malignant pediatric	521	3.4 (3.1-3.7)	0.73 (0.69-0.77)	0.65 (0.61-0.70)	0.62 (0.58-0.67)

Abbreviation: CI, confidence interval.

tumors were 25% and 19%, respectively, primarily reflecting the largest subgroup of neuroepithelial tumors with rates of 27% and 21%, respectively. Similarly, the 5- and 10-year rates for benign tumors were 78% and 62%, respectively, similar to rates of 73% and 55% for the largest subset of meningiomas. The overall survival rates for pediatric tumors were 71% at 5 years and 68% at 10 years. When considering pediatric malignant tumors alone, the survival rates remained relatively high, with 65% at 5 years and 62% at 10 years.

As expected, observed survival rates differed greatly between malignant and benign tumors (Fig. 1). For malignant tumors, survival dropped rapidly during the first 2 years after diagnosis and stabilized after that initial period. The same pattern is observed at all ages, having a steeper drop in survival with increasing age at diagnosis. For benign tumors, this drop was apparent only at 60 years old or older; for younger groups, the survival rate decreased at a constant low rate with a much better overall prognosis than malignant tumors.

To explore the impact of our assumption underlying the survival curves for nonmalignant tumors, we computed age-specific prevalence rates using both assumptions, as shown in Fig. 2. Although it is likely that the true prevalence rates will be between the extremes shown, the greater than 2-fold differences in rates at older ages underlies the importance of choosing the most appropriate assumption based on empirical evidence. Fig. 3 shows survival curves for meningiomas; our estimate from Connecticut and Utah data, using the general population assumption for rates beyond 10 years, is similar to survival observed in a Finnish population with 20 years of follow-up (Sankila et al., 1992). This subjective comparison supports the decision to estimate prevalence rates for nonmalignant tumors by using the first assumption for survival curve estimation for data beyond the 10 years of available follow-up.

The final estimated prevalence rates and expected numbers of cases are summarized in Table 3. The estimated prevalence for benign tumors is much higher than for malignant tumors (97.5 per 100,000 and 29.5 per 100,000, respectively), reflecting the higher long-term survival rates for benign tumors. If these relatively crude estimates are used, benign tumors make up 74.6% (expected n > 260,000) of prevalent cases and malignant tumors 22.6% (expected n > 80,000), with 2.9% (expected n > 10,000) being of uncertain behavior. The overall prevalence rate, estimated using the expected numbers for

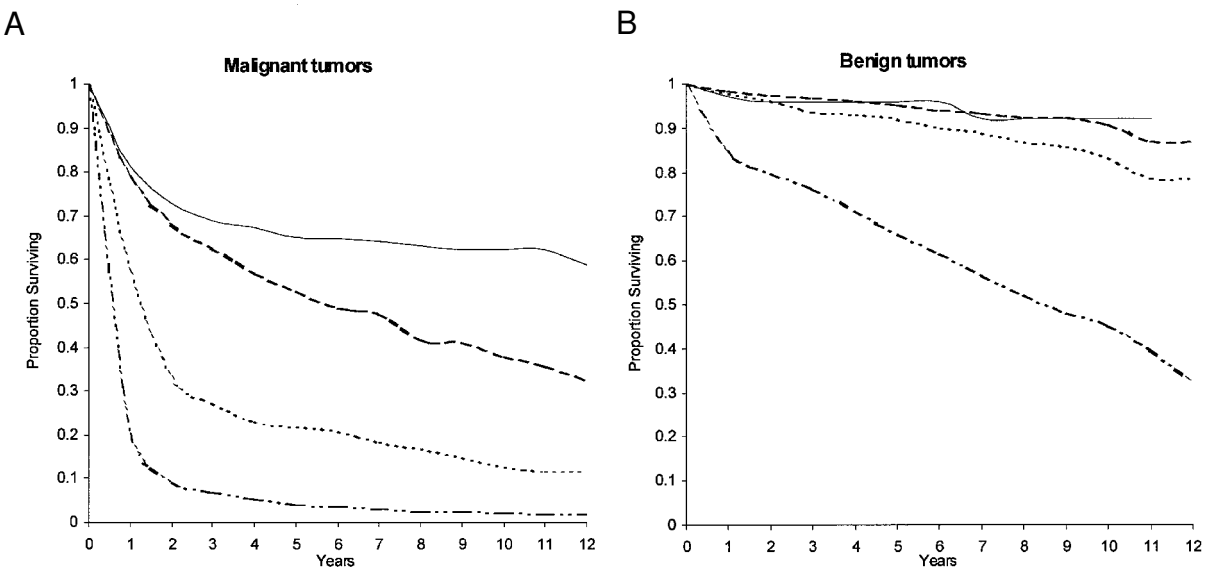

Fig. 1. Observed survival by age for malignant brain tumors (A) and benign (B) brain tumors. — Ages 0–19; – – ages 20–39; ··· ages 40–59; –·– age 60+.

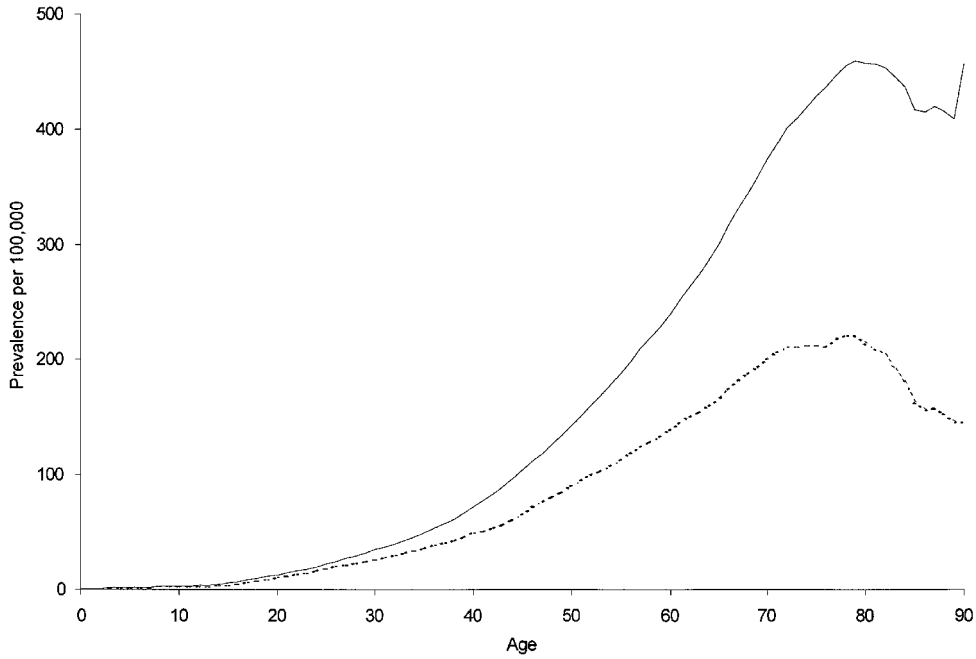

Fig. 2. Prevalence estimates for benign brain tumors using different assumptions. Postdiagnosis survival assumes population survival after last observation (—); postdiagnosis survival assumes zero after last observation (···). The former assumption was used for final prevalence estimates for benign tumors.

malignant, uncertain, and benign tumors, is 130.8 per 100,000. The expected number of all living cases with a previous diagnosis of brain and CNS tumors is approximately 350,000. About 7.3% (expected n > 26,000) of prevalent cases are aged 20 years or younger at diagnosis.

Discussion

The prevalence rate for all primary brain tumors is 130.8 per 100,000 with over 350,000 cases estimated to be living in the United States in the year 2000. The prevalence rate for malignant tumors, 29.5 per 100,000, is similar to that reported by the National Cancer Institute (30.2 per 100,000 for females and 37.1 per 100,000 for males) (SRAB/NCI, 2000). The prevalence rate for benign tumors, 97.5 per 100,000, has not been reported previously in the United States. Although the proportion of incident malignant tumors (53%) is greater than that for benign tumors (42%), the proportion of prevalent cases with benign tumors (75%) is considerably greater than that for malignant tumors (23%), reflecting the better prognosis of benign tumors diagnosed in patients younger than 60 years. These data underscore the impact

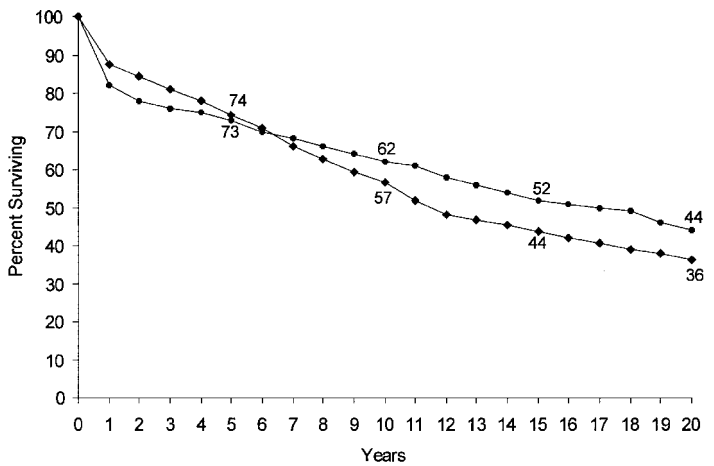

Fig. 3. Meningioma survival assuming postdiagnosis survival is equal to the population survival after last observed follow-up in Connecticut and Utah (1985-1994) (◆) compared with observed survival in Finland (1953-1994) (●). Observed follow-up for Connecticut and Utah was up to 12 years.

Table 3. Estimated prevalence rates and expected numbers of cases in year 2000 for different categories of primary brain tumors

Tumor category	Prevalence rate per 100,000[a]	Expected *n*
Primary brain	130.8[b]	359,194[b]
Malignant	29.5[c]	81,017
Benign	97.5[d]	267,851
Uncertain	3.8[c]	10,326
Neuroepithelial	28.5[c]	78,161
Meningeal	50.4[d]	138,388
Pediatric	9.5[c]	26,200
Malignant pediatric	7.9[c]	21,696

[a]Rates assume a steady state for incidence and survival.

[b]Estimated using expected values for malignant, benign, and uncertain tumors.

[c]Postdiagnosis survival assumed to drop to zero after last observed follow-up.

[d]Postdiagnosis survival assumed to follow population conditional survival after last observed follow-up.

of primary brain tumors in the U.S. health care system and emphasize the need for standardized follow-up programs and quality of life, social support, and family functioning considerations (Kazak et al., 1997).

Recent estimates for prevalence for all primary brain and CNS tumors are unavailable in the literature. Prevalence rates for 1984 have been reported from Sweden (68 and 93 per 100,000 in males and females, respectively) based on incidence and survival data from 1958 to 1984 (Adami et al., 1989). Because incidence and survival rates changed during this period and demographics of the population changed since this time period, one would expect current prevalence rates to be substantially higher, as observed in our overall estimate of 130 per 100,000. The current estimate of prevalence for malignant tumors (25.9 per 100,000 for females and 32.7 per 100,000 for males) is slightly less than recent estimates from Connecticut data (30.2 per 100,000 for females and 37.1 per 100,000 for males) (SRAB/NCI, 2000). Because incomplete follow-up was present in our data, it was pragmatic to use a conservative assumption for survival beyond 10 years. The similarity in prevalence rates from these 2 sources supports the reasonableness of our model for overall malignant tumors. However, because pediatric patients with malignant brain tumors have a substantially better survival rate than older patients, the prevalence estimate for this subset may be considerably underestimated. As the prevalence rate for nonmalignant brain tumors is not reported in the literature, it is difficult to know if the rate of 97.5 per 100,000 estimated here is reasonable. To provide a test of reasonableness for the nonmalignant brain tumor estimates, we looked at the ratio of prevalence rates for all primary brain tumors (Adami et al., 1989) to malignant brain tumors (Feldman et al., 1986) from 2 earlier reports. This ratio was approximately 3.0 for males and 5.0 for females (for an average of 4.0) and compared favorably with the ratio of 4.4 from the current estimates.

Because the most uncertainty in the prevalence estimates for nonmalignant tumors resides with the assumption used to estimate survival beyond 10 years, we searched for empirical evidence to test assumption 1. Because population-based data for nonmalignant brain tumors as a group is limited, we focused on meningiomas, which comprise the largest proportion of nonmalignant tumors. Crude observed survival estimates at 5 years from Connecticut and Utah (1985-1994) and Finland (1953-1984) were similar to ours at 73%. Our 10-year observed survival rate (55%) appears somewhat lower than that from Finland (63%) (Sankila et al., 1992). Although time and regional differences make this an imperfect comparison, the similarity of these survival curves lends some credence to the assumption used in the prevalence model for nonmalignant tumors.

The method used to obtain prevalence estimates is an elaboration on the concept that prevalence is a function of incidence and duration of the disease, accounting more accurately for age by estimating age-specific prevalence rates within 5-year categories.[4] This model assumes that the disease is rare and that once diagnosed, a case is prevalent for life (the disease is not curable). Incidence rates are assumed to be constant from 1985 to 1994. Recent time-trend analysis suggests that, if incidence rates for these tumors are increasing, it is at a modest rate, so this assumption appears to be appropriate (Jukich et al., 2000; Legler et al., 1999). This clustering of years allows for more robust age-specific estimates of incidence and survival, allowing age-appropriate prevalence estimates to be computed for a rare disease.

We estimate approximately 350,000 individuals are now living after a diagnosis of brain and CNS tumors. This estimate reflects the year 2000 population distribution and will be a reasonable approximation of prevalence for the next decade unless one of the underlying parameters changes significantly (incidence or survival). The expected number of prevalent cases, had we used the most conservative survival assumption for both malignant and nonmalignant tumors, would have been 248,461. The above comparison of survival curves for meningiomas suggests that this would be a conservative number.

As underreporting of nonmalignant tumors is likely in tumor registries, estimated incidence rates can be lower than what they would be in reality, resulting in corresponding lower estimates of prevalence rates. The age-adjusted incidence rate (13.1 per 100,000) from the 2 SEER regions reported here is similar to the age-adjusted rate reported for all CBTRUS regions (12.8 per 100,000) (Surawicz et al., 1999). This suggests that case ascertainment is similar in Connecticut and Utah compared with the other registries included in CBTRUS, and use of these data provides a conservative prevalence estimate. For the estimates of the number of prevalent cases in the United States to be reasonable, one must also assume that the incidence and survival rates for brain tumors from these 2 regions are representative of the U.S. population.

Several assumptions in the prevalence model may affect the accuracy of the resulting prevalence estimates as applied to brain tumors. First, the assumption "once a case always a case" seems more appropriate for malignant than nonmalignant tumors. However, as neurologic and other complications from treating a nonmalignant brain tumor are likely present, prevalent cases may have long-term quality of life issues to address, even if the tumor has been successfully removed and does not recur

(or is essentially cured). Second, without complete survival data, patients who were diagnosed before the time period included in a model may still be living at the prevalence time point but not be included in the prevalence estimate. Feldman et al. (1986) estimated that overall cancer prevalence would be underestimated by 16% with 17 years follow-up. More recently, Capocaccia and De Angelis (1997) estimated the completeness of prevalence rates based on varying follow-up time periods and age groups. Their analysis suggested that prevalence rates for brain cancer would be 68%, 59%, 52%, 46%, and 42% complete for ages 40, 50, 60, 70, and 80, respectively, with 10 years of follow-up data. Finally, this model also presumes a steady-state situation with respect to incidence and survival rates. If either underlying measure increases (or decreases), these prevalence rate estimates will underestimate (or overestimate) true rates. Taken together, the prevalence estimates reported here seem to be quite conservative.

In the future, it would be helpful to have long-term observed survival rates that would make the assumptions and the resulting imprecision in the current estimates unnecessary. Until such time, these prevalence estimates provide a conservative basis on which to plan health care services and to develop programmatic strategies for surviving brain tumor patients and their families.

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