

Trends in brain cancer incidence and survival in the United States: Surveillance, Epidemiology, and End Results Program, 1973 to 2001

SUNDEEP DEORAH, M.A., CHARLES F. LYNCH, M.D., PH.D., ZITA A. SIBENALLER, PH.D., AND TIMOTHY C. RYKEN, M.D.

Department of Epidemiology, College of Public Health; and Departments of Neurosurgery and Radiation Oncology, College of Medicine, University of Iowa Hospitals and Clinics, Iowa City, Iowa

Object. An increasing incidence of brain cancer has been reported for the last three decades. In this study of brain cancer incidence and patient survival in the US, the authors attempt to update information on trends by examining data provided by the Surveillance, Epidemiology, and End Results (SEER) Program.

Methods. Population-based data from the SEER Program were used to calculate the incidence of and survival rates for people with brain cancer. The approximate Poisson method was used to calculate relative risks for brain cancer and to determine a 95% confidence interval. Annual age-standardized incidence rates were calculated, and time-trend analysis was conducted using joinpoint regression analysis.

The relative risks of brain cancer were 1.48 for men compared with women, 3.18 for elderly persons compared with young adults, 1.86 for Caucasian patients compared with African-American patients, and 1.35 for those in metropolitan counties compared with those in nonmetropolitan counties. The incidence of brain cancer increased until 1987, when the annual percentage of change reversed direction, decreasing from 1.68 to -0.44% . The elderly experienced an increase until 1985, but their rates were stable thereafter. Rising trends were noticed for glioblastoma multiforme (GBM), oligodendroglioma, anaplastic astrocytoma, medulloblastoma, and mixed glioma, and falling trends were observed for astrocytoma not otherwise specified and malignant glioma. The survival rate for patients with GBM has not shown improvement in the last two decades.

Conclusions. Increased risk of brain cancer is associated with being male, Caucasian, elderly, and residing in a metropolitan county. The incidence rate of brain cancer in the US is gradually declining, but the rising trend of GBM combined with its poor survival rate is disconcerting and needs further exploration.

KEY WORDS • brain neoplasm • tumor incidence • tumor registry

P RIMARY brain cancers have attracted increased attention in recent decades because, although the survival rate continues to remain poor, there are several reports suggesting an increasing trend in incidence rates.^{8,10,11,13,15} The bulk of this increase is reportedly due to rising incidence rates among the elderly and children.^{6,8,11,13} Although the exact reasons behind this trend are debatable, one reason could be that our ability to diagnose intracranial neoplasms improved dramatically after the introduction of CT in the 1970s and MR imaging in the early 1980s.⁴ The use of stereotactic brain biopsy procedures and a more aggressive approach toward the diagnosis of elderly persons with

neurological symptoms have likewise made their own contributions to the observed trend.¹³ It is not known whether these technological advances are entirely responsible for the increasing trend or if environmental and lifestyle risk factors or the increase in life expectancy are driving the incidence rates. Recently, several epidemiological studies attempting to link the use of cellular phones with the occurrence of brain tumors have renewed concern about brain cancer incidence.^{7,14}

An evaluation of the trend of increased brain cancer cases has important implications, both from clinical and public health standpoints, because it may lead to the improvement of diagnostic methods or the identification of a potential new risk factor. Accurate estimates of incidence rates help clinicians select an appropriate sample size for their clinical studies. Public health officials base their resource allocations and functions on such accurate estimates of disease burden in the community. Furthermore, histology-specific trends could suggest possible explanations for the rate of disease incidence, including etiological risk factors.

In this descriptive study, we examine the incidence of

Abbreviations used in this paper: APC = annual percentage of change; CBTRUS = Central Brain Tumor Registry of the United States; CI = confidence interval; CNS = central nervous system; CT = computerized tomography; EAPC = estimated APC; GBM = glioblastoma multiforme; ICD = International Classification of Diseases; ICD-O = ICD for Oncology; MR = magnetic resonance; NOS = not otherwise specified; SEER = Surveillance, Epidemiology, and End Results.

brain cancer in the US using the SEER database during a period encompassing the introduction of CT and MR imaging and the widespread use of cellular phones. We also provide population-based survival rates for patients with brain cancer. Both tumor incidence and patient survival are described by the patient's race, sex, place of residence, and duration of survival.

Clinical Material and Methods

Brain Tumor Databases

There are two centralized population-based brain tumor databases in the US: the CBTRUS and the National Cancer Institute's SEER Program.¹ We selected the SEER database for our study because it provides population-based incidence data beginning in 1973 as well as patient survival data. The SEER Program collects data on malignant brain tumors through several population-based cancer registries across the US. Five states (Connecticut, Hawaii, Iowa, New Mexico, and Utah) and four metropolitan areas with diverse population subgroups (Atlanta, Detroit, San Francisco–Oakland, and Seattle–Puget Sound) began participating in the SEER Program as early as 1973. Together they represent 9.5% of the US population.¹⁶ The data collected in the SEER database are known to be of high quality because the program has set a high standard for the collection of cancer data, which are used extensively for research. We requested and received permission to use the SEER data set.

Data Extraction

For this study, SEER*Stat software (version 5.3.0) was used to calculate incidence rates, using the US population for the year 2000 as the standard. A total of 38,453 patients diagnosed with malignant brain tumor in the period between 1973 and 2001 were included. For patient survival analyses, only microscopically confirmed and actively followed cases were included. Patients with multiple primary tumors were excluded from these analyses because including them would have led to underestimation of actual survival rates. Relative survival rates were calculated using a table showing the expected rate of tumors for 1970, 1980, and 1990 for Caucasians, African-Americans, and members of other racial groups.

Data Grouping

The study population was divided into children (< 20 years old at diagnosis), young/middle-aged adults (20–65 years old), and elderly adults (> 65 years old). Counties were classified into metropolitan and nonmetropolitan areas, based on a report by the US Office of Management and Budget, to act as surrogates for urban and rural counties, respectively. Determined from 1990 decennial census data, these definitions were announced by the Office of Management and Budget in 1996. A total of 32,659 cases occurred in people living in metropolitan counties, and the remaining 5794 cases occurred among those living in nonmetropolitan counties. Brain tumors were classified by grouping ICD-O (second edition) four-digit histology codes into broad histology subgroups based on CBTRUS and CNS histology groupings (2002 revision): GBM, ICD-O codes 9440–9442, 9481; oligodendroglioma, ICD-O code

9450; anaplastic astrocytoma, ICD-O codes 9401, 9411; mixed glioma, ICD-O code 9382; medulloblastoma, ICD-O codes 8963, 9363, 9364, 9470–9473, 9501–9503; astrocytoma NOS, ICD-O code 9400; and malignant glioma, ICD-O code 9380.

Statistical Analysis

We used SEER*Stat software to obtain age-standardized incidence rates adjusted to the 2000 US population by age, sex, race, and other user-defined variables. The relative risk, defined as the ratio of incidence rates of brain cancer for one value of a variable divided by another, was calculated for race, age, sex, and place of residence. The approximate Poisson method was used to calculate a 95% CI regarding the relative risk, and any interval not including the value zero was regarded as statistically significant. Age-standardized incidence rates were calculated for all years from 1973 to 2001, and time-trend analysis was performed using the Joinpoint regression analysis software (version 2.7) available through SEER*Stat. Joinpoint is statistical software for the analysis of trends by using joinpoint models, wherein several different lines are connected together at the “joinpoints.” The software takes trend data (for example, cancer rates) and fits them to the simplest joinpoint model that the data allow. The user determines the minimum and maximum number of joinpoints. The program starts with the minimum number of joinpoints (for example, zero joinpoints, which is a straight line) and tests whether other joinpoints are statistically significant and must be added to the model (up to the maximum number). This enables the user to test whether an apparent change in trend is statistically significant. The software's tests of significance use a Monte Carlo permutation method.

Because GBM is the most frequently occurring brain cancer and is associated with a poor prognosis, we investigated its trend in greater detail, using the Joinpoint regression program. We also evaluated the survival rate of patients with GBM in three different decades to detect any significant changes in the survival rates over time. All comparisons were made using two-tailed tests, and results with a probability value less than 0.05 were reported as statistically significant.

Results

Incidence of Brain Tumor

Between 1973 and 2001, 38,453 cases of malignant brain tumor were reported by the nine registries to the SEER database, giving an overall age-adjusted incidence rate of 6.1 cases per 100,000 person-years. The most common histologically confirmed tumor type reported was GBM, which accounted for 16,797 cases, corresponding to an incidence rate of 2.8 cases per 100,000 person-years. The next most common tumor type occurring during the study period was astrocytoma NOS, with an incidence rate of 1.2 cases per 100,000 person-years. The incidence rates of GBM and astrocytoma NOS in 2001 were 3 and 0.3 per 100,000 person-years, respectively.

Figure 1 shows that the age-specific incidence rates of brain cancer during the study period were bimodal, with a small peak in early childhood and a more pronounced peak in the elderly. Incidence rates among children, young adults,

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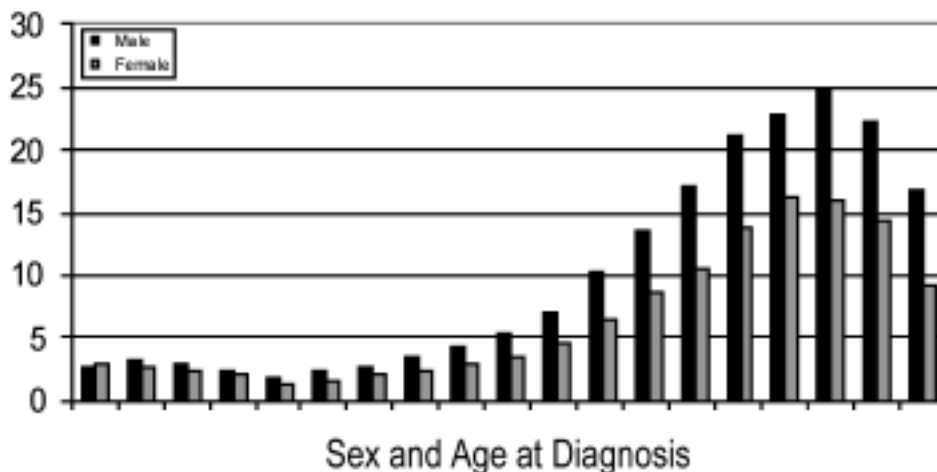


FIG. 1. Bar graph showing brain cancer incidence per 100,000; population based on data from the nine standard SEER registries (1973–2001) depicted by sex and age.

and the elderly were 2.5, 5.5, and 17.5 per 100,000 person-years, respectively. The relative risk of brain cancer among the elderly compared with young adults was 3.18 (95% CI 3.09–3.22; Fig. 2). The age-adjusted incidence rate for men was significantly higher than the rate for women (7.4 compared with 5.0 per 100,000), corresponding to a relative risk of 1.48 (95% CI 1.45–1.51). Examination of incidence by race showed that Caucasians were at significantly higher risk for brain cancer than African-Americans (6.7 compared with 3.6 per 100,000); the corresponding relative risk was 1.86 (95% CI 1.78–1.94). Brain cancer was found to occur more frequently among residents of metropolitan counties compared with nonmetropolitan counties (6.5 compared with 4.89 per 100,000). The relative risk of 1.35 (95% CI 1.31–1.38) for metropolitan counties was statistically significant.

Brain Cancer Trends

The age-adjusted incidence rates of brain cancer by the year of diagnosis from 1973 to 2001 are demonstrated in Fig. 3. With Joinpoint regression analysis, two distinct trends were observed for this period. The incidence

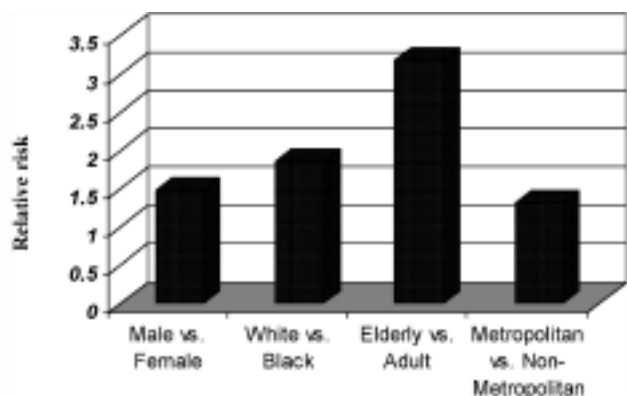


FIG. 2. Bar graph showing relative risks of brain cancer according to sex, age, race, and rurality, based on data from the nine standard SEER registries (1973–2001).

of brain cancer increased from 1973 to 1987 (APC 1.68%; 95% CI 1.22–2.13), followed by a decline thereafter (APC –0.44%; 95% CI –0.84 to –0.03). The results of Joinpoint regression analyses of brain cancer trends by age, sex, race, and rurality are summarized in Table 1. The incidence rates of brain cancer decreased among men and women after the years 1986 and 1987, respectively. Although the decline was statistically significant among the women, it did not reach significant levels among the men. Analysis by age revealed that the elderly had the steepest rise in incidence rates until 1985, and the rates have been stable since then. The incidence rates among young adults show a statistically significant decline after 1987. Currently, Caucasians and African-Americans are experiencing falling and rising trends, respectively, both of which are not statistically significant. Although the annual incidence rates are declining in metropolitan counties, they are on the rise in nonmetropolitan counties. Histological diagnoses that have demonstrated rising trends are GBM, oligodendroglioma, anaplastic astrocytoma, medulloblastoma, and mixed glioma; those with falling trends are astrocytoma NOS and malignant glioma (Figs. 4 and 5). Time-trend analysis of GBM revealed that its incidence declined until 1979 (APC –5.58%; 95% CI –8.91 to –2.12), followed by a significant rise until 1991 (APC 2.88%; 95% CI 1.47–4.30; Fig. 4). After 1991, there has been a gradual rising trend that has not reached statistical significance (APC 0.321%; 95% CI –1.00 to 1.66).

Survival Rates

Table 2 summarizes the five-year relative survival rates for patients with brain cancer. Statistically significant differences in survival rates are noted by sex, race, age, and rurality. The five-year survival rates showed improvement over the study period (21% in the 1970s, 27% in the 1980s, and 31% in the 1990s, $p < 0.001$). However, for GBM, 1-year relative survival rates showed improvement from only the 1970s to the 1980s (28% compared with 32%, $p < 0.001$). There is no statistically significant improvement in the survival rate for GBM after the 1980s.

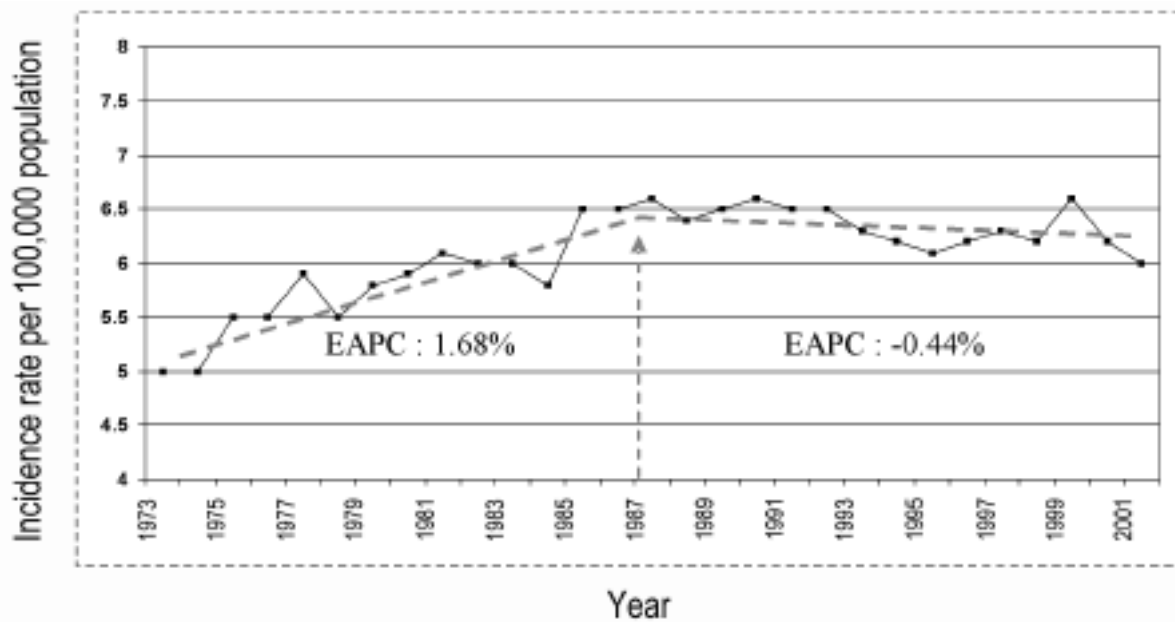


FIG. 3. Graph showing results of SEER*Stat Joinpoint analysis of brain cancer incidence in the US by year, based on data from the nine standard SEER registries (1973–2001). The arrow indicates the year in which the trend significantly changed; the dashed line indicates the trend.

Discussion

Incidence of Brain Tumors

Our review of 38,453 cases of malignant brain tumor reported to the SEER registry from 1973 to 2001 involves one of the largest collections of data on these patients. Using the US population in the year 2000 as a reference for standardization, we report an overall incidence rate of 6.1 cases per 100,000 person-years. The SEER data include only malignant CNS tumors (that is, those with an ICD-O behavior code of 3) and exclude nonmalignant CNS tumors (behavior codes of 0 and 1), despite their potential for causing death or significant morbidity. A more recently established centralized database, CBTRUS, collects data on all primary CNS tumors. An annual incidence of 14.1 cases per 100,000 person-years (based on the 2000 population standard) for all primary CNS tumors was noted in the CBTRUS statistical report for 2004. Meningiomas, pituitary tumors, and nerve sheath tumors accounted for approximately 24, 8, and 6.5%, respectively, of all CNS tumors, thus largely explaining the differences in incidence rates produced by the two registries.¹⁸

In accordance with previous studies, we found that very young adults have the lowest risk of brain cancer and that the risk continues to rise with age. Higher incidence for those in older age groups suggests a possible role for bioaccumulation from environmental toxic exposure in the cause of malignant brain tumor. Our results also confirm previous observations of a higher incidence of brain cancer in men compared with women. Although some investigators have suggested that female sex hormones have a protective effect against brain cancer, others have suggested innate differences in the susceptibility of X and Y chromosomes to tumorigenic stimuli.¹¹

There have been several reports on the association between race and the incidence of malignant brain tumor. In

our study, Caucasians had a relative risk of 1.86 compared with African-Americans for malignant brain tumor. This is less than that reported by Robertson, et al.,¹⁷ who found the relative risk for African-Americans to be 6.2 for GBM, 3.5 for astrocytoma, and 4.3 for oligodendroglioma. Others have reported that Caucasians have a relative risk of 2.3 to 2.5 compared with African-Americans for GBM.^{5,12} At least a portion of this difference is related to socioeconomic differences and better access to health care for Caucasians

TABLE 1
Joinpoint regression analyses of brain cancer trends*

Parameter	EAPC of Trend Plot (95% CI)		Yr of Trend Change
	Segment 1	Segment 2	
sex			
M	1.75 (0.99 to 2.52)	-0.31 (-0.80 to 0.18)	1986
F	1.92 (1.34 to 2.50)	-0.75 (-1.26 to -0.23)	1987
age†			
children	1.91 (0.72 to 3.12)	0.22 (-1.25 to 1.73)	1989
young/middle-aged adults	0.62 (0.00 to 1.24)	-0.98 (-1.57 to -0.38)	1987
elderly adults	3.87 (2.58 to 5.19)	0.08 (-0.50 to 0.68)	1985
race			
Caucasian	1.87 (1.35 to 2.40)	-0.37 (-0.82 to 0.08)	1987
African-American	0.14 (-0.56 to 0.85)	NA‡	NA‡
other	1.05 (0.32 to 1.78)	NA‡	NA‡
rurality			
MA	1.64 (1.09 to 2.20)	-0.53 (-1.03 to -0.04)	1987
non-MA	0.65 (0.28 to 1.01)	NA‡	NA‡

* Based on data from the nine standard SEER registries (1973–2001). Abbreviations: MA = metropolitan area; NA = not applicable.

† Age categories are divided as follows: children (< 20 years old at diagnosis); young/middle-aged adults (20–65 years old); and elderly adults (> 65 years old).

‡ Linear model without a Joinpoint best describes the trend.

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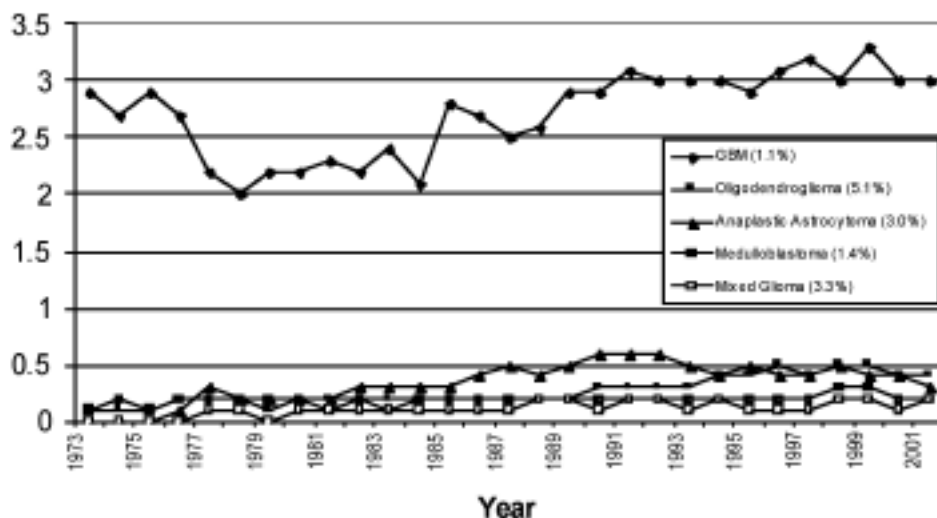


FIG. 4. Graph showing the histological types of brain cancer that demonstrated a rise in annual incidence rates based on data from the nine standard SEER registries. Values in parentheses represent the EAPC.

rather than a difference in genetic susceptibility. Residents of metropolitan counties (used as surrogates for urban residence) were 1.35 times at higher risk of malignant brain tumor compared with residents of nonmetropolitan counties (used as surrogates for rural residence). Although farming and pesticide exposure have been suggested as potential risk factors, either their effects are small or there are larger risk factors operating in urban areas. Differences in access to medical care may also be a reason for this discrepancy between urban and rural incidence rates. At the same time, there is a possibility of nondifferential misclassification of exposure (for example, residence) due to mobility of the study population, because SEER obtains information on the patient's residence at the time of diagnosis but does not collect data on prior residences.

Incidence Trend

Several studies have addressed the issue of the incidence trend for primary malignant brain tumor in recent decades. Although they generally concur that the incidence of primary malignant brain tumor has been rising, some are based on a relatively small number of cases, and others have used statistical sampling methods to arrive at this conclusion. We have used a population-based approach to calculate incidence trend, and we report that the incidence of malignant brain tumor is decreasing in the US. By using regression analysis, we found that the incidence rate increased until 1987, and has been declining, albeit modestly, since then.

During the period of rising incidence rate, from 1973 to 1987, the elderly population experienced the greatest increase (EAPC 3.87%). This period also corresponds to the

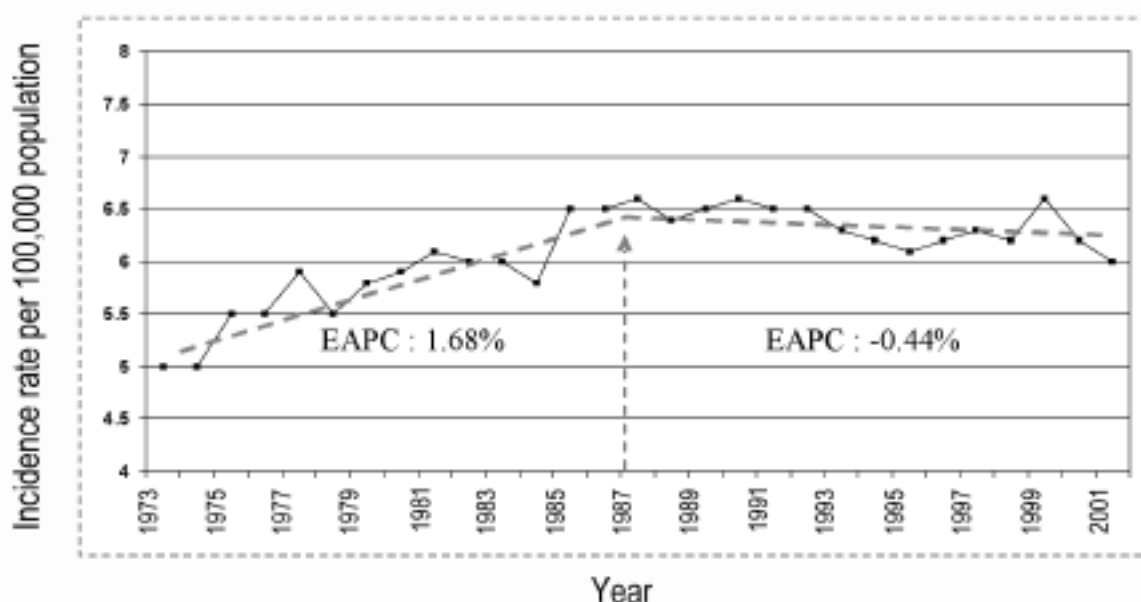


FIG. 5. Graph showing the histological types of brain cancer that demonstrated a decline in annual incidence rates based on data from the nine standard SEER registries.

TABLE 2

*Five-year relative survival rates in patients with brain tumors**

Parameter	5-Yr Relative Survival Rate (%)	95% CI	p Value
sex			
M	26.7	26 to 27.4	<0.001
F	28.8	28 to 29.6	
age†			
children	66.1	64.6 to 67.6	<0.001
young/middle-aged adults	27.8	27.1 to 28.5	
elderly adults	2.7	2.3 to 3.1	
race			
Caucasian	26.8	26.2 to 27.4	<0.001
African-American	32.8	30.3 to 35.3	
other	36.9	33.8 to 40.0	
rurality			
MA	28.0	27.4 to 28.6	<0.001
non-MA	25.6	24.2 to 27.0	<0.001

* Based on data from the nine standard SEER registries (1973–2001).

† Age categories are divided as follows: children (< 20 years old at diagnosis); young/middle-aged adults (20–65 years old); and elderly adults (> 65 years old).

period of the introduction and widespread use of CT and MR imaging, which increased the sensitivity of brain cancer diagnosis. However, some investigators believe that the increased incidence of brain cancer in this time period was not entirely due to an artifact of increased case identification. By retrospective review of medical records, Desmeules, et al.,² determined that approximately 20% of CNS tumors remained undiagnosed without the use of CT or MR imaging studies. Therefore, they argued that CT or MR imaging should account for only a 20% increase in the incidence among the elderly. Because the increase was much larger, there were reasons to believe that factors besides CT and MR imaging were important in creating the observed increase in the incidence rate of brain tumor. Technological advances related to stereotactic brain biopsy procedures and the increased understanding and knowledge of physicians could also have affected the incidence trend during this period.¹³ Because the rising trend was seen across both sexes and all ages, races, and places of residence, it appears less plausible that a specific risk factor was operating in that time period that affected everyone alike.

A notable finding in this study is the falling incidence trend of malignant brain tumor in the US after 1987. Using SEER data, Gurney and Kadan-Lottick³ reported that incidence rates for CNS cancer had stabilized after 1991 in all age groups, including the very elderly. However, concerns over changes in environmental toxicants, such as radiofrequency exposure, pesticides, N-nitroso compounds, and ionizing radiation, as well as several epidemiological studies linking them to brain tumor, have continued to fuel interest in the close monitoring of incidence trends for brain cancer. Cellular phones were introduced in the 1980s and became widespread by the early 1990s. There is growing concern among the public that exposure to radiofrequency fields from cellular phones might increase the risk of brain cancer.⁹ Recently, investigators have reported in large case-control studies that there is no association between cellular phone use and risk of brain cancer.^{7,14} Likewise, our results do not support the hypothesis relating cellular phone use

and brain cancer at the population level. If anything, the incidence of brain cancer declined during the period of cellular phone use. Of particular interest is the observation that the incidence rates are declining in the urban counties, which are expected to contain heavy users of cellular phones. However, being a population-based observation study, our study suffers from ecological fallacy, and consequently it contributes only modestly to causality. In addition, concerns, including potentially long induction periods, persist for long-term, heavy users of cellular phones.

Several findings specific to certain tumor types are noted in the study. Of particular concern is the continued rising incidence of GBM. Although its increase in the 1970s and 1980s can be explained on the basis of increased case identification due to improved imaging techniques, its rising trend in the late 1980s and 1990s can, in part, be explained by a falling trend for astrocytoma NOS. A shift between diagnostic categories may not reflect a real change in the incidence, but rather, changes in pathologic diagnostic practice, such as better techniques to obtain and store biopsy specimens and the expertise of neuropathologists in making a specific diagnosis.

Survival Rates

Consistent with earlier reports, survival for patients with brain cancer has improved over the last three decades. The population-based data suggest that either cases are being diagnosed at an earlier stage or that improvements in treatment have, at least partially, been transferred to the general population. As reported earlier, the 5-year relative survival rate differs only minimally by sex, race, and place of residence. As in several clinical and population-based studies, we noted a pattern of decreasing survival rates corresponding with increasing age of the patients. Responses to both radiotherapy and chemotherapy have been correlated with the age of patients and are thought, at least partially, to explain the importance of age in the prognosis of patients with brain tumor. Unlike those for patients with malignant brain tumor in general, survival rates for patients with GBM have not shown any improvement after the 1980s. There is a need to develop more innovative and effective therapies to deal with this lethal cancer.

The statistics reported in this study reflect the experience of approximately 10% of the US population, which has been oversampled for ethnic and rural population. Because SEER maintains very high standards in terms of data collection and the study includes a very large number of cases, the incidence rates and survival estimates reported in this study are robust for several categories, including relatively small population or histologic subgroups. By having a large number of cases in each year of diagnosis after 1973, we had meaningful trend data to test the effect of changes in environmental risk factors on brain cancer risk at the population level. However, being a population-based study, the results contribute only in a limited manner to causal inference. In addition, there is no uniform microscopic review; cases reported to the registries are based upon diagnoses rendered by multiple pathologists with varying levels of expertise. Another limitation of our study is that we included only malignant brain tumors. Because several brain tumor subtypes may have benign and malignant entities or may progress from benign to malignant, this limits our un-

derstanding of etiologic factors of tumor subtypes and their trends over time.

The advantage of using SEER data for calculating patient survival rate is that it is a population-based estimate and it reflects the end results of research, clinical trials, and diffusion of therapy to the general population. The individual case series and clinical trials have motivated patients and physicians, and the survival experiences shown by them are generally larger than what is finally seen at the population level. However, by excluding benign CNS tumors, which show better survival rates, SEER data underestimate survival rates for patients with brain tumors.

Conclusions

People in population subgroups at higher risk for brain cancer are the elderly, Caucasians, men, and those living in metropolitan counties. Despite raised concerns related to the risk of brain cancer from using cellular phones, our study fails to find support for this hypothesis at the population level. After 1987, the incidence of brain cancer in the US decreased at the rate of 0.44% per year. The cause for this decline is unclear because of the paucity of definitive knowledge on the risk factors of brain cancer, but solace can be taken from the fact that brain cancers are not rising in this era of increasing environmental toxic exposures. However, the rising trend of GBM, combined with poor survival rates for people with GBM, is disconcerting and needs further exploration. Despite their limitations, high-quality registry data continue to be an important source of incidence and survival information about these rare tumors. Efforts should be made to link registry data to individual patient information, such as demographics, occupation, social class, and clinical and treatment data to help researchers study etiologic risk factors and determine the effect of therapeutic advances on patient survival.

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Address reprint requests to: Timothy C. Ryken, M.D., Departments of Neurosurgery and Radiation Oncology, University of Iowa Hospitals and Clinics, Iowa City, Iowa 52242. email: timothy-ryken@uiowa.edu.