

Brain and Other Central Nervous System Cancers: Recent Trends in Incidence and Mortality

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Background: During the 1980s, the incidence of primary malignant brain and other central nervous system tumors (hereafter called brain cancer) was reported to be increasing among all age groups in the United States, while mortality was declining for persons younger than 65 years. We analyzed these data to provide updates on incidence and mortality trends for brain cancer in the United States and to examine these patterns in search of their causes. **Methods:** Data on incidence, overall and according to histology and anatomic site, and on relative survival were obtained from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute for 1975 through 1995. Mortality data were obtained from the National Center for Health Statistics. Medicare procedure claims from the National Cancer Institute's SEER-Medicare database were used for imaging trends. Statistically significant changes in incidence trends were identified, and annual percent changes were computed for log linear models. **Results/Conclusions:** Rates stabilized for all age groups during the most recent period for which SEER data were available, except for the group containing individuals 85 years of age or older. Mortality trends continued to decline for the younger age groups, and the steep increases in mortality seen in the past for the elderly slowed substantially. Patterns differed by age group according to the site and grade of tumors between younger and older patients. During the last decade, use of computed tomography scans was relatively stable for those 65-74 years old but increased among those 85 years old or older. **Implications:** Improvements in diagnosis and changes in the diagnosis and treatment of elderly patients provide likely explanations for the observed patterns in brain cancer trends. [J Natl Cancer Inst 1999;91:1382-90]

Projections for 1999 estimated that 16 800 new cases (9500 in males and 7300 in females) of primary brain and other cancers of the central nervous system (hereafter called brain cancer) would be diagnosed in the United States and that 13 100 patients (7200 males and 5900 females) would die of brain cancer (1). Because causes of brain cancer are poorly understood, there is considerable interest in examining incidence patterns to identify potential etiologic clues. Using the latest data available from the Surveillance, Epidemiology, and End Results (SEER) Program¹ at the National Cancer Institute, we update reports of increasing brain cancer incidence published earlier this decade (2-10) by presenting the most recent age-specific incidence trends that indicate that brain cancer incidence is leveling off in nearly every age group. The introduction of magnetic resonance imaging (MRI) in the mid-1980s coincided with a modest jump in childhood brain cancer incidence (11); however, similar abrupt increases in incidence were not observed for persons diagnosed when older than 15 years of age. We also examined age-specific

trends in mortality and in gliomas by grade and site, which helped to elucidate the potential impact of MRI and computed tomography (CT) on incidence for each age group. Another commonly posited explanation for increasing rates among the elderly is increasing physician willingness to pursue a diagnosis for older patients (6,12,13). Therefore, we explored detailed assessments of brain cancer incidence and mortality patterns in subgroups of elderly patients. To assess medical practice patterns with respect to diagnosing the elderly, we ascertained recent age-specific utilization trends for CT, MRI, and stereotactic biopsy procedures for the same subgroups in the population and thereby updated past reports (14). We briefly summarize the potential role of known and suspected exogenous risk factors in explaining the observed trends.

SUBJECTS AND METHODS

Sources of Data

Brain cancer incidence data (for malignant tumors only, the SEER Program does not require reporting benign brain tumors) were derived from the SEER Program's nine long-standing population-based registries throughout the United States, which represent approximately 10% of the total U.S. population, including the states of Connecticut, Iowa, New Mexico, Utah, and Hawaii and the metropolitan areas of Atlanta (GA), Detroit (MI), San Francisco (CA), and Seattle (WA). The data begin in 1975, when all of these areas were reporting (15). U.S. mortality data were from the National Center for Health Statistics, Hyattsville, MD. Imaging and stereotactic biopsy procedure data for the elderly were obtained from Medicare claims from physicians and hospital outpatient departments for persons 65 years old or older who were eligible for Medicare and who resided in any of the SEER areas from 1986 through 1994. The Medicare data evaluated were restricted to fee-for-service coverage among participants eligible for part B. This dataset has been described in detail elsewhere (16).

Classification

Incident cancers diagnosed from 1973 through 1976 and reported in SEER Program registries were classified according to the *Manual of Tumor Nomenclature and Coding* (17). Those cancers diagnosed during the period from 1977 through 1991 were classified according to the International Classification of Diseases for Oncology (ICD-O) (18), and those diagnosed in 1992 or later were classified according to the International Classification of Diseases for Oncology, 2nd edition (ICD-O-2) (19). After publication of ICD-O-2, all incident cancer cases diagnosed and reported in the SEER Program before 1992 were recoded to ICD-O-2 criteria by use of a standardized computer algorithm. Because the level of histologic detail included in the *Manual of Tumor Nomenclature and Coding* codes was sometimes insufficient to recode to the more specific codes in ICD-O, our analyses by histologic category were restricted to the period from 1977

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See "Notes" following "References."

through 1995, which encompasses the years in which tumors were coded according to either the first or the second edition of ICD-O. Because of relatively small numbers of brain cancer cases in many histologic categories of gliomas, we combined subtypes into two major groups: high-grade gliomas (ICD-O-2 codes = 9380, 9381, 9401, 9422, 9423, 9430, 9440, 9441, 9442, 9443, and 9481) and low-grade gliomas (ICD-O-2 codes = 9383, 9384, 9400, 9410, 9411, 9420, 9421, and 9424) [see Prados et al. (20) for a comprehensive summary of issues related to classification].

Primary brain cancer incidence trends were also delineated with respect to anatomic site, including cerebrum (ICD-O-2 codes C71.0–C71.4), cerebellum (code C71.6), brain stem (code C71.7), and other anatomic sites (codes C70.0–C70.9, C71.5, C71.8, C71.9, and C72.0–C72.9). Excluded from our analyses were lymphomas arising in the brain, tumors of the pituitary and pineal glands, and any brain and other central nervous system tumors designated as benign. The ninth revision of the International Classification of Diseases, Injuries, and Causes of Death (21) (ICD-9 codes = 191.0–191.9, 192.0–192.3, and 192.8–192.9) was used to define brain and other central nervous system cancers as the underlying causes of death.

Role of Diagnostic Technologies

To evaluate how changing medical practice and technical improvements in the diagnosis and treatment of elderly patients may have affected brain cancer incidence trends, we examined imaging and stereotactic biopsy procedure trends in the elderly population at large, not just among those with brain cancer. Age-specific rates for head and other central nervous system MRI (CPT [Common Procedural Terminology] codes 70551–70553) and CT (CPT codes 70450, 70460, and 70470; American Medical Association's *Physicians' Current Procedural Terminology*, 4th edition (22) [CPT-4]), obtained from Medicare data, were computed separately for the elderly age subgroups (65–74 years old, 75–84 years old, and ≥ 85 years old). Comparable data are not available for those under 65 years old because persons of that age are not generally eligible for Medicare. In addition, age-specific stereotactic biopsy rates were examined as a proxy for physician willingness to pursue an aggressive line of treatment for the same subgroups and years. A recent thorough description of diagnostic neuroimaging has been provided by Prados et al. (20).

Statistical Methods

Age-specific incidence rates of brain cancer were computed for the period from 1975 through 1995 by use of data from the SEER Program (23). Like all of the rates reported herein, U.S. mortality rates were calculated per 100 000 person-years, where a person-year represents one person surviving an entire year. Both the incidence and mortality rates were age adjusted to the 1970 U.S. standard million population. We examined age-specific incidence at diagnosis during the earliest (1975 through 1979) and the most recently available (1991 through 1995) 5-year periods. Lower and upper 95% confidence intervals for individual rates are reported for selected age groups. The age at diagnosis is particularly important in characterizing brain cancer; therefore, throughout this article, we analyzed trends by using four broad age groups (ages 0–14 years, 15–44 years, 45–64 years, and ≥ 65 years). To describe trends in incidence and mortality over time, we fit segment-wise linear models to the logarithms of the rates by using several permutation tests to identify the number of changes in the trend and those years (referred to as “join points”) when the linear trends in the logarithm of the rates changed. Each *P* value was found by use of Monte Carlo methods, and a Bonferroni correction is used to maintain the overall asymptotic significance level [for more detail on this method, see Kim et al. (24)]; all *P* values are two-sided. The model that we considered requires that there are no abrupt jumps or discontinuities in the trend. For time periods between join points, we computed the estimated annual percent changes by using the estimated slopes of the segments. The estimated annual percent changes in the last time interval were then tested to determine whether there was evidence of a trend upward or downward in the most recent years. In those cases where no change in the trend was identified throughout the 21-year study period, we also calculated the estimated annual percent changes for the last decade of the study (1986 through 1995) to provide a sense of recent trend patterns. All of the estimated annual percent changes were tested for equality to zero by use of the corresponding standard errors. Because of the higher incidence of brain tumors in older patients, there were sufficient numbers of patients in older age groups to allow a similar analysis of incidence trends for an even finer gradation of the elderly, i.e., those 65–74 years old, those 75–84 years old, and those 85 years old or older.

Join points and recent estimated annual percent changes were also computed for analyses of trends by grade for the broader age groups (0–14 years old, 15–44 years old, 45–64 years old, and ≥ 65 years old) as described above. In addition, we evaluated trends in the proportion of brain cancers microscopically confirmed and in incidence by anatomic site for 3-year intervals from 1975 through 1995 for these same age groups because small numbers of patients precluded the use of annual rates for these breakdowns. We also calculated 5-year relative survival rates (25), i.e., the ratio of the observed survival rate to the expected survival rate, for a patient cohort diagnosed from 1975 through 1985 and from 1986 through 1995 according to age group. Cases where the only source of a brain cancer diagnosis was a death certificate or autopsy report were excluded from the survival analysis.

RESULTS

In the SEER areas, brain cancer ranked second only to leukemia in incidence for children 0–14 years old from 1991 through 1995. During that period, more than 23% of incident childhood cancers arose in the brain, with an annual age-adjusted incidence of 3.3 cases per 100 000 children. More than 26% of childhood cancer deaths were attributed to brain cancer. Brain cancer accounted for approximately 1% of all adult cancers, with an annual age-adjusted incidence of 7.2 cases per 100 000 persons 15 years old or older in 1991 through 1995. More than 2% of all adult cancer deaths were attributed to brain cancer, placing the brain among the top 10 sites with respect to adult cancer mortality. The age-adjusted brain cancer incidence rate among all African-Americans from 1991 through 1995 was 3.6 per 100 000 African-American individuals versus 6.6 per 100 000 white individuals of all ages. The age-adjusted mortality rates showed a similar relationship, with 2.5 deaths per 100 000 African-Americans and 4.5 deaths per 100 000 whites from 1991 through 1995. Age-adjusted incidence rates by sex were 7.3 cases per 100 000 males and 5.0 cases per 100 000 females from 1991 through 1995. Overall, trends were similar for males and females. Small numbers of African-Americans in the various subgroups precluded the separate analysis of African-Americans and whites. Thus, for the remainder of this article, we combined males and females and all races, but we performed separate analyses for specific age groups.

Incidence by Age

Fig. 1 compares the age-specific incidence for the earliest 5-year period (1975 through 1979) with the most recently available 5-year period (1991 through 1995). For persons under age 70 years, the age-specific rates were similar in both periods. Among children 0–14 years old, rates were highest for children 0–4 years old and declined throughout the remaining years of childhood. Adolescents (15–19 years old) had the lowest rates of all age groups, with approximately two cases per 100 000 individuals. Incidence rates increased slowly, but steadily, with age from young adulthood. After age 45 years, rates accelerated more rapidly. For both periods, rates dropped from the group aged 70–74 years old to the group aged 75–79 years old and continued to decline for each successively older age group thereafter.

For children and the elderly, incidence was uniformly higher in the most recent period than in the earlier period; however, for those 45–70 years old, the rates were lower or the same during the two periods. While the rates among those who were 65–69 years old were nearly identical in the two periods, the peak among those who were 70–74 years old in 1991 through 1995 was notably higher than their counterparts in the earlier time

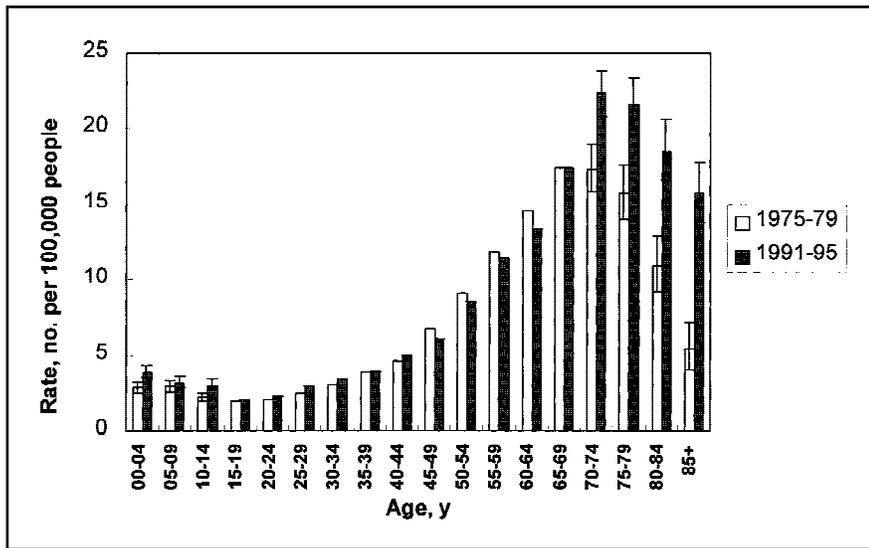


Fig. 1. Age-specific incidence for brain and other central nervous system cancers, Surveillance, Epidemiology, and End Results Program, 1975–1979 versus 1991–1995; 95% confidence intervals are shown for selected age groups.

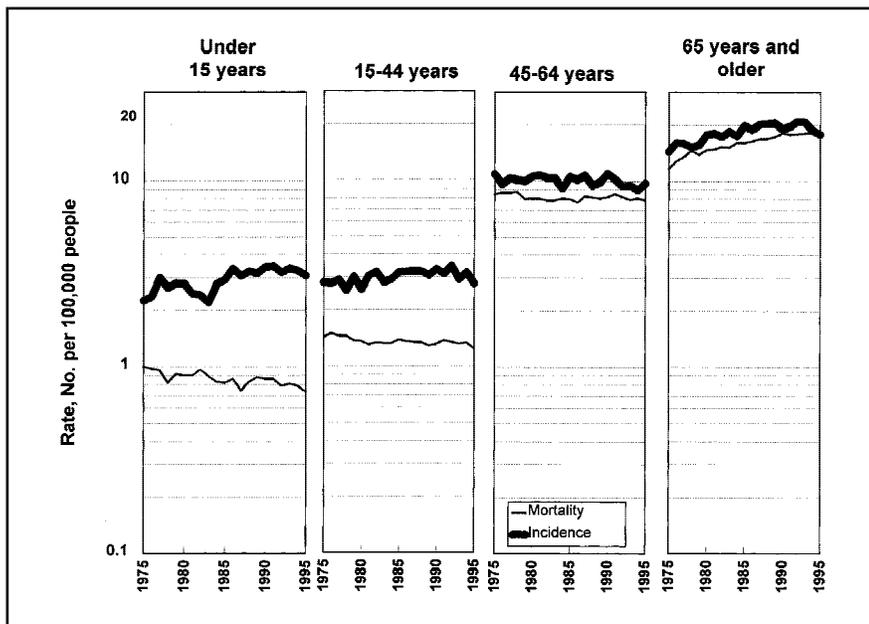


Fig. 2. Trends in incidence (Surveillance, Epidemiology, and End Results Program, 1975–1995) and mortality (United States, 1975–1995) for malignant brain tumors and other central nervous system cancers by age.

period. Particularly striking was the nearly threefold higher incidence among persons 85 years old or older in 1991 through 1995 (15.7 cases of cancer per 100 000 individuals) in contrast to the incidence in this age group in 1975 through 1979 (5.4 cases of cancer per 100 000 individuals).

Incidence and Mortality Trends

Fig. 2 contrasts the incidence and mortality trends over time for four broad age groups by use of a logarithmic scale to facilitate comparisons of changes in rates over time. Only the youngest and oldest age groups experience significant changes in the incidence trend over the study period (1975 through 1995), with statistically significant changes² in the trend occurring at 1977, 1983, and 1986 for those under 15 years of age and

at 1988 for those 65 years old or older. Data for patients under 15 years of age showed statistically significant changes in the trend in 1986 (from increasing to stabilizing), and data for patients 65 years old or older showed statistically significant changes in the trend in 1988 (from increasing to stabilizing). During the last period (1986 through 1995 for those 0–14 year olds and 1988 through 1995 for those ≥ 65 years old), neither age group exhibited substantial increases or decreases in incidence. There were no statistically significant join points for the young adults (15–44 years old) or middle-aged persons (45–64 years old), and neither of these age groups exhibited a statistically significant trend upward or downward over the entire 21-year study period.

Mortality was lower and demonstrated sustained improvement among the young, whereas mortality was higher and more closely paralleled incidence trends among those patients 45 years old or older (Fig. 2). Mortality trends exhibited steady decreases throughout the study period (1975 through 1995) for young people (estimated annual percent changes of -1.1% [$P < .001$] and -0.5% [$P < .001$] for the groups 0–14 years old and 15–44 years old, respectively). After a decline in mortality from 1975 through 1982, mortality rates for patients diagnosed between age 45 years and age 64 years leveled off (estimated annual percent change before 1982 is -1.3% [$P = .023$] and from 1982 through 1995 is 0.2% [not statistically significantly different from zero]). Steep increases in mortality rates for the elderly (≥ 65 years old) seen early in the study period slowed incrementally, first at 1977 and again at 1990, and then stabilized thereafter (estimated annual percent change from 1990 through 1995 is 0.2% [not statistically significantly different from zero]).

A closer examination of patterns among subgroups of the elderly revealed some distinctions between three elderly age groups (65–74 years old, 75–84 years old, and ≥ 85 years old; Fig. 3). Incidence trends for the older age groups appeared similar to, but lagged behind, those in the younger elderly subgroups. For patients 65–74 years old, incidence increased at approximately 1.5% per year from 1975 to 1987 ($P < .001$) and then remained steady (estimated annual percent change from 1987 through 1995 is -0.8% [not statistically significantly different from zero]). Mortality increased slowly, but steadily, for this age group throughout the study period (estimated annual percent change from 1975 through 1995 is 0.9% [$P < .001$]). For those aged 75–84 years, incidence rates began at a lower level, and the trend rose at a faster rate (3.9% per year from 1975 through 1989 [$P < .001$]) and then slowed down 2 years after the slowdown for the group 65–74 years old (trend change at 1989, estimated annual percent change from 1989 through 1995 is -3.1% [not

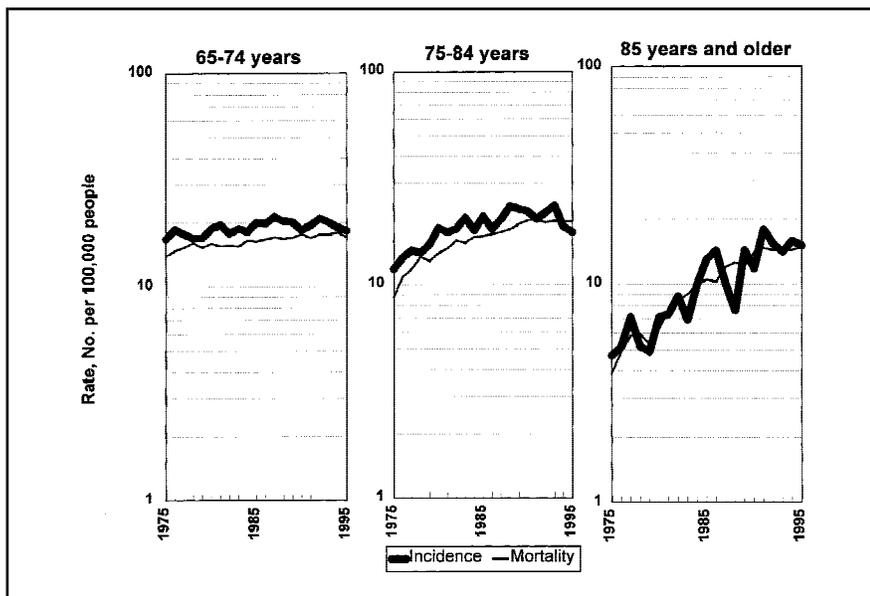


Fig. 3. Trends in incidence (Surveillance, Epidemiology, and End Results Program, 1975–1995) and mortality (United States, 1975–1995) for malignant brain tumors and other central nervous system cancers in the elderly by age group.

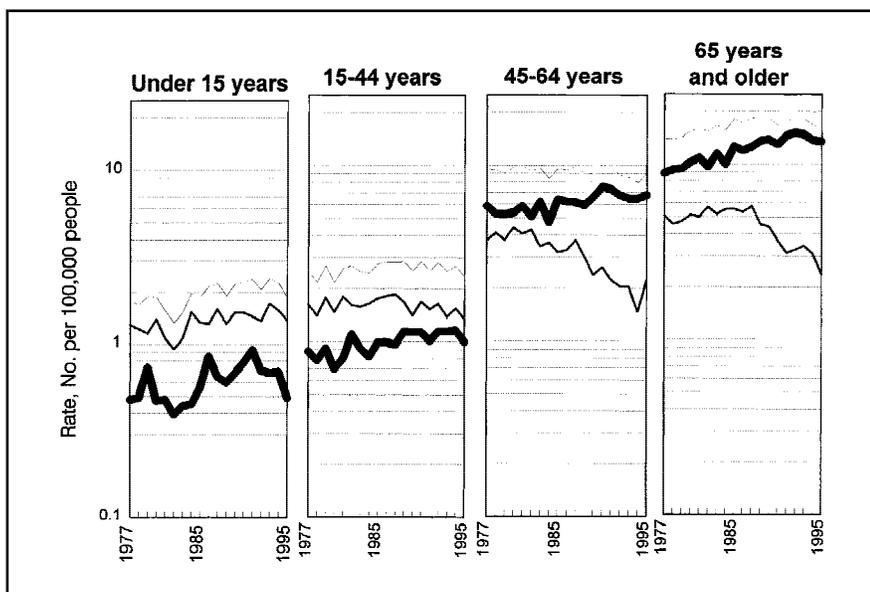


Fig. 4. Trends in the incidence for gliomas according to grade and age (Surveillance, Epidemiology, and End Results Program, 1977–1995). **Light line** = high + low grade; **solid line** = low grade; **thick line** = high grade.

statistically significantly different from zero]). Escalating mortality for this group slowed at 1978 and again at 1989, after which mortality stabilized (estimated annual percent change from 1990 through 1995 is -0.04% [not statistically significantly different from zero]). In contrast, among those 85 years old or older, incidence rates started out considerably lower than for persons 65–74 years old, with sharper increases (estimated annual percent change is 5.5% [$P < .001$]) sustained throughout the study period (1975 through 1995, no statistically significant change in trend). Mortality rate increases of 8.5% ($P < .001$) per year slowed at 1988, increasing at only 2.1% ($P = .021$) per year from 1988 through 1995. By 1995, incidence rates in the

youngest elderly age groups were very similar (16.1 and 16.7 cases of cancer per 100 000 individuals aged 65–74 years and 75–84 years, respectively), and rates among those 85 years old or older were considerably closer to these two age groups than they were at the start of the study period (13.6 cases per 100 000 individuals in 1995).

Trends in Grade

Our classification of high-grade and low-grade gliomas included close to 90% of incident brain cancers for persons 45 years old or older at diagnosis, whereas this group of gliomas represented 80%–85% of those patients 15–44 years old at diagnosis and less than 70% of those under 15 years of age at diagnosis. These percentages remained consistent over the time of this study. The proportion of cases identified as high-grade gliomas increased with age. For children, high-grade gliomas represented only 21% of brain cancers and low-grade gliomas represented approximately 44% of brain cancers (1991 through 1995 SEER data). For those 15–44 years old, 37% and 48% were high grade and low grade, respectively. In contrast, among those aged 45–64 years, high-grade gliomas represented 71% and low-grade gliomas represented 21% of cases of brain cancers, which was similar to the percentages observed for those 65 years old or older (73% and 15%, respectively).

Trends in the incidence of gliomas by grade for the different age groups are shown in Fig. 4 with a logarithmic scale. Although the estimated annual percent changes computed for the 19 years of available data (1977 through 1995) suggest steady increases in childhood glial tumors (estimated annual percent changes of 2.1% [$P = .034$] for high-grade gliomas and 1.5% [$P = .002$] for low-grade gliomas), in the last decade of our study, there were no statistically significant increases in the rates for high-grade or low-grade gliomas among children aged 0–14 years (estimated annual percent changes from 1986 through 1995 are -2.2% [not statistically significantly different from zero] for high grade and 0.8% [not statistically significantly different from zero] for low grade). For those 15–44 years old, high-grade and low-grade glioma rates converged over the study period (1977 through 1995), with rates for high-grade gliomas stabilizing in the last decade (estimated annual percent change from 1986 through 1995 is 0.9% [not statistically significantly different from zero]) and low-grade incidence declining statistically significantly (estimated annual percent change from 1986 through 1995 is -2.9% [$P < .001$]). In contrast to the fairly constant difference between low-grade and high-grade tumors in the very young and the near convergence of the two among young adults, incidence rates for high-grade and low-grade gliomas diverged over time for both of the older age groups (45–64 years old and ≥ 65 years old). Low-grade glioma

incidence trends began to decline after 1981 for those 45–64 years old (estimated annual percent change from 1981 through 1995 is -5.6% [$P < .001$]) and after 1986 for those 65 years old or older (estimated annual percent change from 1986 through 1995 is -8.3% [$P < .001$]). High-grade glioma rates continued to rise throughout the study period among those 45–64 years old (estimated annual percent change = 1.6% [$P < .001$]), whereas increases subsided among those in the oldest age group (≥ 65 years old) by 1992 (estimated annual percent change from 1992 through 1995 is -3.6% [not statistically significantly different from zero]).

When the high-grade and low-grade gliomas were combined, the rates increased an average of 1.8% ($P < .001$) per year for those under 15 years of age from 1977 through 1995 but declined an average of 0.2% (estimated annual percent change) per year during the last decade. In fact, all age groups experienced a drop in the incidence of the high-grade and low-grade gliomas combined from 1986 through 1995 (estimated annual percent changes of -1.4% [$P = .019$] for age group 15–44 years, -1.4% [not statistically significantly different from zero] for age group 45–64 years, and -0.7% [not statistically significantly different from zero] for age group ≥ 65 years).

Anatomic Site

The proportion of tumors at various anatomic sites differed by age. Among children younger than 15 years during the period from 1993 through 1995, tumors of the brain stem and cerebellum accounted for 43% of brain cancer, whereas malignancies at these sites accounted for only 13% of neoplasms among young adults and only 5% of tumors among persons 45 years old or older. In contrast, tumors of the cerebrum accounted for only one third of the brain cancer among children but represented more than 60% of total brain cancer for persons 15 years old or older

in this most recently available 3-year period. The age-specific incidence trends by anatomic site are presented for 3-year periods on a logarithmic scale in Fig. 5. Among children, there was a marked increase in rates of brain stem cancer as well as a smaller increase in the rate of tumors arising in the cerebrum. The brain stem was the only site for which young and middle-aged adults demonstrated any increase in rates during the study period. Elderly adults also experienced increases in the rates of tumors of the brain stem, as well as tumors of the cerebellum and cerebrum. However, for all age groups beyond childhood, the incidence of brain stem tumors was low, and only a small fraction of brain cancers arose in this location. Brain not otherwise specified constitutes approximately one third of the “other brain” category for any one age group and represents from 6.5% (age group 15–44 years old) to 12.7% (age group ≥ 65 years old) of total incidence. Because these “other brain” rate series are fairly flat in each age group, it is unlikely that the patterns for the identified sites changed as a result of increasingly precise specification, but this situation cannot be categorically ruled out.

Histologic Confirmation

The proportion of cases microscopically confirmed was considerably lower among the elderly than among the younger age groups. Throughout the study period (1975 through 1995), approximately 90% of tumors among people under age 65 years were microscopically confirmed, whereas the proportions were closer to 80% for those aged 65–74 years and dropped below 70% and 60% for those aged 75–84 years and 85 years or older, respectively. The proportion of microscopically confirmed cases increased over time for persons diagnosed at ages 65–84 years; however, for those 85 years old or older at diagnosis, the proportion of cases with microscopic confirmation actually declined from 53% in 1975 through 1977 to 35% in 1993 through 1995.

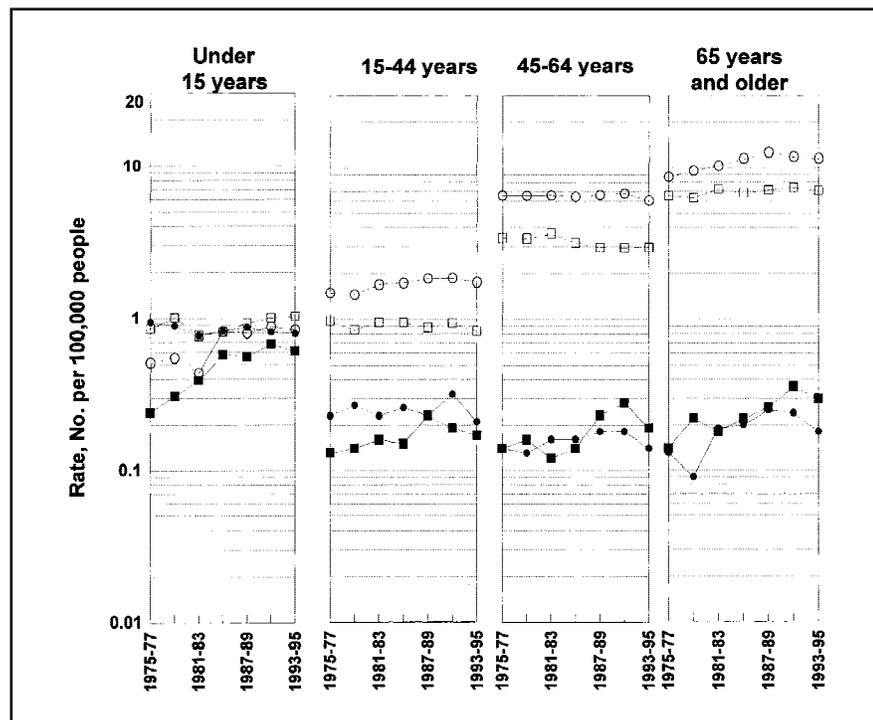


Fig. 5. Trends in the incidence for malignant brain tumors by anatomic site and age group for 3-year intervals from 1975–1977 through 1993–1995. ■ = brain stem; □ = other brain/central nervous system; ● = cerebellum; ○ = cerebrum/lobes.

Relative Survival

Survival remained poor for the elderly compared with the survival among younger brain cancer patients. Between the periods from 1975 through 1985 and from 1986 through 1995, the 5-year relative survival increased modestly for children (0–14 years old) from 58% to nearly 63%, for young adults (ages 15–44 years) from 48% to 55%, and for middle-aged adults (ages 45–64 years) from 12% to 16% (Fig. 6). There was little change in relative survival for the elderly (≥ 65 years old)—from 4% to 5%.

Radiologic Imaging and Stereotactic Biopsy Procedure Data

In Fig. 7, we turn from analyses of brain cancer patients to an examination of imaging procedure data for all part B-eligible Medicare participants in the SEER areas. From 1986 through 1994, no increases in head and/or central nervous system CT scan procedure rates were evident for persons aged 65–74 years, whereas the population-based rates for CT scans increased from 1986 through 1988 and were stable thereafter among persons

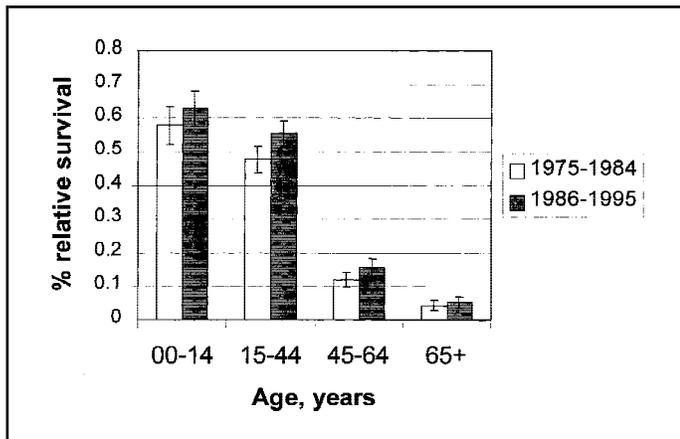


Fig. 6. Five-year relative survival for persons with malignant brain tumors by age for 1975-1985 and 1986-1995.

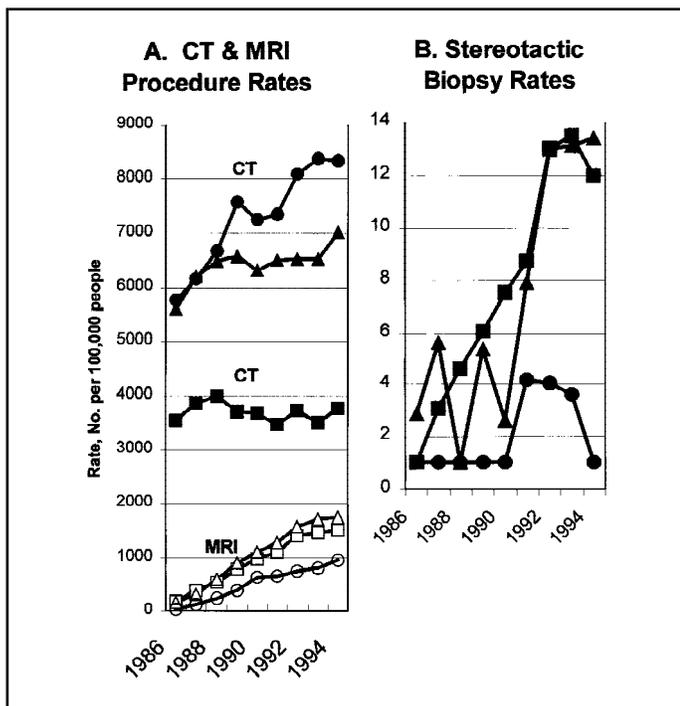


Fig. 7. Rate of computed tomography (CT) and magnetic resonance imaging (MRI) of the head and central nervous system (A) and stereotactic biopsy use (B) per 100,000 Medicare beneficiaries 65 years old or older residing in the Surveillance, Epidemiology, and End Results areas, 1986-1994. ■, □ = 65-74 years old; ▲, △ = 75-85 years old; ●, ○ = older than 85 years.

aged 75-84 years. In contrast, there was an increase in CT scan procedures throughout the period (1986 through 1994) among persons 85 years old or older. The rates for MRI were substantially lower than those for CT scans throughout the period from 1986 through 1994 and showed steady increases for each age group throughout the period, with similar rates for the groups aged 65-74 years and 75-84 years and lower rates for the group older than 85 years. The increased use of stereotactic biopsy during the same period was notable for persons aged 65-74 years and for those aged 75-84 years. The rates for persons 85 years old or older were somewhat unstable as a result of the small number of procedures performed in this age group. Nonetheless, the volume of activity in the last half of the study period was larger than that early in the study period.

DISCUSSION

In contrast to earlier reports of increasing incidence (2-4,6,9,12,26-28), this population-based study found that the most recent data available indicated that trends in incidence rates for total brain cancer have been level or declined slightly in all but the most elderly persons (i.e., those ≥ 85 years old). To provide perspective and to follow-up on these earlier evaluations, we analyzed age-specific incidence and mortality patterns covering a large geographic area of the United States over the longest period for which data were available by comparing trends in four major age groups but focusing on a detailed study of the elderly. This more extensive assessment of the elderly involved a comparison of trends for age-specific brain cancer incidence with the most recent age-specific utilization trends for CT and MRI imaging procedures and stereotactic biopsy procedures, updating previous reports using Medicare data (14). In addition, we have used newly developed statistical methods to identify years at which trends changed (24,29), and we have examined trends for statistically significant increases or decreases in the most recent time period for which data were available. Accompanying analyses of age-specific trends in mortality, incidence of gliomas by grade, incidence by anatomic site, relative survival, and the proportion of histologically confirmed tumors suggest that the timing and impact of factors affecting incidence and mortality trends differ markedly among age groups.

Although clearly affected by some common factors, the age-specific incidence patterns are distinctive, and our more thorough examination of the elderly revealed further distinctions. An abrupt rise in brain cancer incidence among children from 1984 through 1986 was followed by a decade of stable rates. Among the elderly, brain cancer incidence reached a plateau for the group 65-74 years old in 1987 and for the group 75-84 years old in 1989. Steadily increasing rates were observed for those 85 years old or older, with rates now approaching those observed for the age groups 65-74 years old and 75-84 years old. In contrast to the changing patterns of incidence for children and for the elderly, brain cancer incidence has been essentially constant for the population 15-64 years old during the years 1975 through 1995.

Smith et al. (11) have persuasively linked the rapid, although relatively small, rise in brain cancer incidence among children in this time period to the increased availability of MRI (30,31). MRI provides superior visualization of low-grade glial neoplasms compared with CT imaging (32-36). Other possible explanations for the sudden increase in incidence of childhood brain tumors include changes in histologic classification of brain tumors that occurred during the years from 1984 through 1985 (37). In addition, changes in neurosurgical practices (e.g., stereotactic biopsies) that occurred in the mid-1980s might have led to increased diagnosis and reporting of childhood brain tumors (38,39). The continuous, although modest, decline in mortality during the period from 1975 through 1995 supports the interpretation that the abrupt rise in incidence during the mid-1980s is due to diagnostic and reporting improvements rather than to other factors.

The relationship between the pattern of incidence increases among subsets of the elderly population and trends in central nervous system imaging is inherently different from that for children. In contrast to the low-grade glial tumors that predominate in children, the high-grade gliomas of adults are easily detected by CT scans, whereas MRI does not provide an appre-

cial gain in diagnostic sensitivity. Therefore, unlike Smith et al. (11) who used equipment diffusion data and Modan et al. (6) who looked at trends in all diagnostic head imaging procedures combined for patients 65 years old or older, we examined trends in the use of CT, MRI, and stereotactic biopsy procedures separately for the elderly subgroups in the population. In spite of the widespread availability of CT scanners since the late 1970s (30), we observed increasing use of CT for the older elderly subgroups from 1986 through 1994, with only the age group 65–74 years old having fairly stable use during this period. The increasing use of CT among older subgroups, despite its long availability, likely reflects more aggressive diagnostic testing by physicians for older elderly persons presenting with neurologic symptoms. The increasing use of stereotactic biopsy procedures for the elderly subgroups indicates that physicians are applying more aggressive procedures to older patients throughout this time period. The increase in the number of imaging studies requested by physicians cannot be explained by an increasing frequency of brain cancers because the incidence of brain cancers among the older elderly population makes up less than 1% of brain imaging for this population. Thus, increases in imaging and stereotactic biopsy procedures among the elderly are consistent with a more widespread tendency of physicians to aggressively pursue diagnoses in older patients. Notably, these trends in imaging and stereotactic biopsy procedure rates are similar to the pattern of brain cancer incidence among the elderly subgroups for the same period.

Trends in brain cancer histology during the period from 1977 through 1995 are notable for the declining incidence of low-grade gliomas for all adult age groups. The decline appeared to begin in the early 1980s for the group aged 45–64 years and in the mid-1980s for the group 65 years old or older. Given the absence of a statistically significant change in incidence for high- and low-grade gliomas combined from 1985 through 1995 for the population 15 years old or older, the changing incidence pattern for low- and high-grade gliomas seems most consistent with changes in diagnostic classification. A less likely explanation is that exogenous factors have simultaneously caused a decline in low-grade and an increase in high-grade glial malignancies. The poor reproducibility among neuropathologists for diagnosis of high- versus low-grade gliomas in children has been documented; while it may have increased the variability in these series, it is unlikely to have produced the sustained trends that were observed (40).

Throughout the study period, mortality declined among patients with brain cancer who were under 65 years of age. Improvements in various components of brain cancer treatment (e.g., neurosurgical technique and delivery of radiation therapy) likely contributed to this decline. For the group 65 years old or older, mortality paralleled incidence trends, with initial increasing rates during earlier years followed by subsequent stabilization of mortality rates. Improvements in survival rates were decidedly modest for all age groups, and survival remained especially poor among brain cancer patients 45 years old or older. These observed age-specific patterns in mortality and survival rates are consistent with our analysis of glial tumors by grade and age. Low-grade gliomas, which are associated with favorable outcome, predominate among children and young adults, whereas high-grade gliomas, which have a very poor prognosis, predominate among middle-aged and elderly adults. Although advances in brain cancer therapy over the last decade

have been modest at best, several important treatment initiatives provide a reason to anticipate treatment advances in the near-to-intermediate term. These include improvements in neurosurgical and radiation therapy techniques (41–43), development of new treatment approaches to circumvent resistance to conventional chemotherapy agents (44,45), and evaluations of novel therapeutic strategies such as inhibition of angiogenesis (46) and inhibition of signal transduction pathways involved in cell survival and growth (47). Important new clinical research infrastructures are being established to implement new treatment initiatives and include adult and pediatric brain tumor clinical trial consortia.

The only known risk factors for brain tumors in humans are high doses of ionizing radiation and selected congenital and genetic disorders (48). These factors explain only a small proportion of primary brain cancers and have not changed over time in such a way as to account for the observed incidence trends described above. Little is known about the factors responsible for the majority of primary brain cancers, although some data (48,49) have suggested that occupational exposures to organic solvents or pesticides may be linked. Early studies (50,51) suggested an association between electromagnetic fields and brain cancers, but more recent studies (52–60) have suggested that the risk, if present at all, is small. Diet, tobacco smoking, and alcohol consumption have not been strongly associated with increased risks or protective effects for brain cancer in adults (48). Limited evidence (49,53,61,62) inconsistently suggests associations between maternal diet and brain tumors in children. Overall, recent changes in lifestyle factors that play a major role in other cancers do not appear to have strongly affected or to be consistently linked with observed trends in brain cancer incidence.

In summary, brain cancer incidence has stabilized over the past decade for all major age groups with distinctive age-specific patterns. Auxiliary analyses are consistent with differential effects of potential explanatory factors such as imaging and classification. The continuing increase in incidence for the oldest subset of the elderly population (those ≥ 85 years old) may be related to more aggressive diagnostic testing for this population, as evidenced by similar patterns of increase in CT imaging rates and age-specific brain cancer incidence trends in the elderly subgroups. Careful monitoring of brain cancer incidence for all age groups needs to continue, and analytical studies to identify causes and risk factors for brain cancers should be prioritized.

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NOTES

¹*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

²A series of hypotheses tests led to the selection of the model with three join points for those diagnosed before their 15th birthday. Null versus alternative models with zero versus three join points ($P = .004$), one versus three join points ($P = .002$), and two versus three join points ($P = .003$) led to the selection of the three-join-point model. For those patients 65 years old or older at diagnosis, models with zero versus three join points ($P = .002$), one versus three join points ($P = .135$), and one versus two join points ($P = .100$) led to the choice of a model with a single join point at 1988.

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