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HIGHLIGHTS

Incidence

- The CNS malignancies represented 16.6% of all malignancies during childhood (including adolescence). CNS cancer as a group was the second most frequent malignancy of childhood and the most common of the solid tumors. In the US approximately 2,200 children younger than 20 years of age are diagnosed annually with invasive CNS tumors.
- Astrocytomas accounted for 52% of CNS malignancies, PNET comprised 21%, other gliomas 15% and ependymomas an additional 9% (Figure III.1).
- Unlike adults and older children, young children have a relatively high occurrence of malignancies in the cerebellum and the brain stem. In fact, in children younger than 10 years of age, brain stem malignancies were nearly as common as cerebral malignancies, and cerebellum malignancies were far more common than cerebral malignancies (Figure III.2).
- The incidence of invasive CNS tumors was higher in males than females and higher among white children than black children (Figure III.5).
- The average annual incidence of CNS cancer varied only slightly by age of diagnosis from infancy (36.2 per million) through age 7 years (35.2 per million). From age 7 to 10, a 40% drop in the incidence rate (to 21.0 per million) was observed. CNS cancer rates were fairly consistent among children aged 11 through 17 years, until another substantial decrease occurred at age 18 (Figure III.6).
- The increase in CNS cancer rates in the past two decades has been the subject of numerous reports. One concern is that changes in environmental exposures may be responsible for the increasing incidence rates, although epidemiologic evidence to support this hypothesis currently is lacking. An alternative explanation is that improvements in diagnostic technology and case ascertainment may be contributing to the increasing trend.

Survival

- In general, children with CNS cancer do not share the favorable prognosis of those with many other common pediatric neoplasms.
- Very young children with CNS cancer, especially infants with ependymoma or PNET, had low survival rates (Table III.2).

Risk factors

- There is no specific risk factor that explains a substantial proportion of brain tumor occurrence, but there are a couple of factors that explain a small proportion (Table III.3).

INTRODUCTION

Since most of the neoplasms described in this chapter are in the central nervous system, the abbreviation CNS will be used to refer to neoplasms that originate in the brain, other intracranial sites such as the pituitary or pineal glands, and the spinal cord. In the US, approximately 2,200 children and adolescents younger than 20 years of age are diagnosed with malignant central nervous system tumors each year. Over 90 percent of primary CNS malignancies in children are located within the

brain. This report only includes malignant CNS tumors.

Classification system

CNS tumors are heterogeneous in regards to histology and clinical course. Because of the many relatively similar histopathological types and their rarity, it is necessary for epidemiologic purposes to group CNS tumors into rather broad histologic categories. There are several classification systems that are used for describing CNS tumors and no system has yet emerged as the definitive gold standard [1,2]. For most of this monograph, malignancies are grouped according to the International Classification of Childhood Cancer (ICCC) system [3]. There are a few minor discrepancies within the ICCC system for CNS tumors, however, that somewhat compromise accurate comparisons with other published work. Most notable, intracranial neuroblastoma and pineoblastoma, which, along with medulloblastoma are generally considered primitive neuroectodermal tumors (PNET), are not included with the PNET category of the ICCC for CNS. For the descriptive analysis that follows, we modified the ICCC groupings for CNS tumors in the following manner: "Other specified intracranial and intraspinal neoplasms excluding pineoblastoma (IIIe)" and "Unspecified intracranial and intraspinal neoplasms (IIIf)" were combined into one category, called 'other CNS'; the "Ependymoma (IIIa)" category was not changed; the "PNET (IIIc)" category was expanded to include intracranial neuroblastoma (these were also reported with ICCC IV) and pineoblastoma. Finally, the ICCC system places intracranial and intraspinal germ cell malignancies within the germ cell category, rather than the CNS tumor category. We chose to follow the ICCC system for CNS germ cell tumors, thus we did not include intracranial and intraspinal germ cell tumors in this chapter (see ICCC group X). The average annual incidence rates for the CNS germ cell malignancies from 1990-95 were 0.2 per million children younger than 15 years of age, and 1.9 per million children younger than 20 years of age. Fifty-three additional tumors were excluded because they occurred outside the brain, intracranium and spinal cord.

It also should be noted that data reported here are comprised solely of CNS tumors that are classified as primary and malignant. Primary CNS neoplasms are tumors that originated in the central nervous system. Thus, they exclude cancer that developed in some other location in the body and then spread to the CNS. Likewise, CNS tumors classified as benign or with uncertain behavior (nonmalignancies) are not routinely collected by SEER areas, and thus are not included in this report. The pathological distinction between malignant and nonmalignant tumors of the CNS is not always consistent with clinical behavior, particularly for intracranial tumors. Depending on the location and the size of the tumor, some intracranial tumors that are classified as benign can have a destructive clinical course (eg. craniopharyngioma). In contrast, some tumors classified as malignant may require no treatment and have little clinical significance (eg. pilocytic astrocytomas of the optic pathway). Although all central registries will include malignant neoplasms in their case ascertainment, when comparing CNS incidence rates across cancer surveillance systems it is necessary to determine whether a given registry also includes nonmalignant tumors. An analysis of data from the Central Brain Tumor Registry of the United States (a compilation of data from population-based registries that include case ascertainment of nonmalignant CNS tumors) showed that the incidence of only malignant CNS tumors underestimates the incidence of both malignant and nonmalignant CNS tumors by approximately 28% [4].

INCIDENCE

Unless otherwise indicated, the discussion on incidence that follows will pertain to children younger than 20 years of age and only malignant tumors. For the 21-year period of 1975-95, there were 4,945 primary malignant tumors of the CNS diagnosed among children in SEER areas. This represented 16.6% of all malignancies during childhood (including adolescence). CNS cancer as a group was the second most frequent malignancy of childhood and the most common of the solid tumors. Astrocytomas accounted for 52% of CNS malignancies, PNET comprised 21%, other gliomas 15%, and ependymomas an additional 9% (Figure III.1).

The incidence rates by location within the brain and other CNS sites as a function of age are shown in Figure III.2. Unlike adults and older children, who have higher rates in the cerebrum, young children have a relatively high occurrence of malignancies in the cerebellum and the brain stem. In fact, in children between the ages of 5 and 9, brain stem malignancies were nearly as common as cerebral malignancies, and cerebellum malignancies were far more common than cerebral malignancies. The pattern shifted among children between the ages of 10-19, in that the incidence of both brain stem and cerebellar cancers decreased while cerebral malignancies increased slightly. The "other" brain site group included the ventricles, where ependymomas generally develop, and malignancies with brain sites not otherwise specified. The "Other CNS" category includes malignancies of the meninges, cranial nerves and spinal cord.

Figure III.1: Percent distribution of malignant CNS tumors by age and histologic group, all races both sexes, SEER, 1975-95

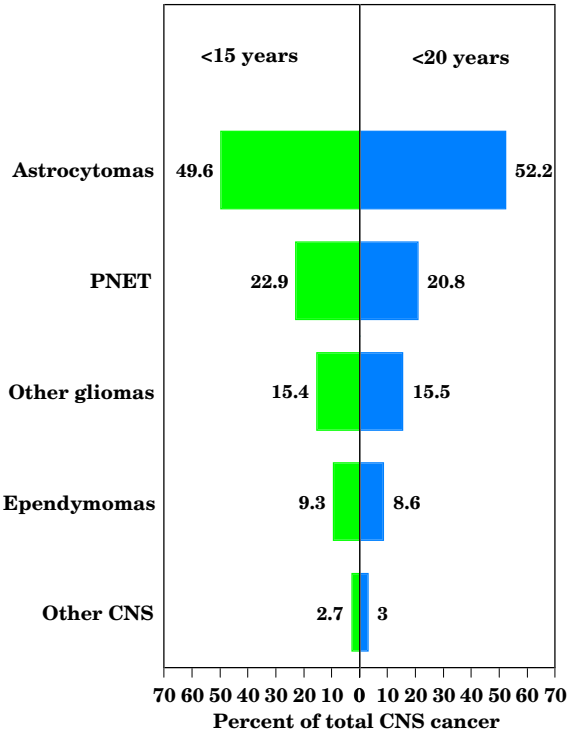


Figure III.2: Malignant CNS tumor age-specific incidence rates by anatomic site and age all races, both sexes, SEER, 1975-95

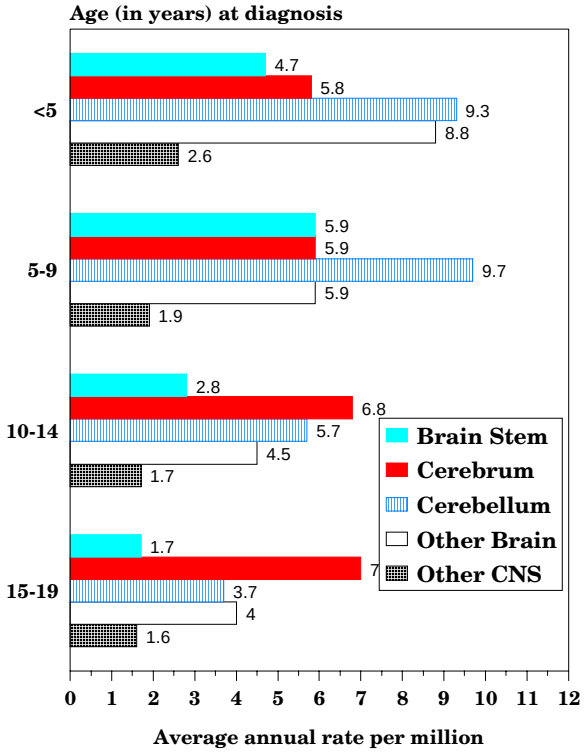
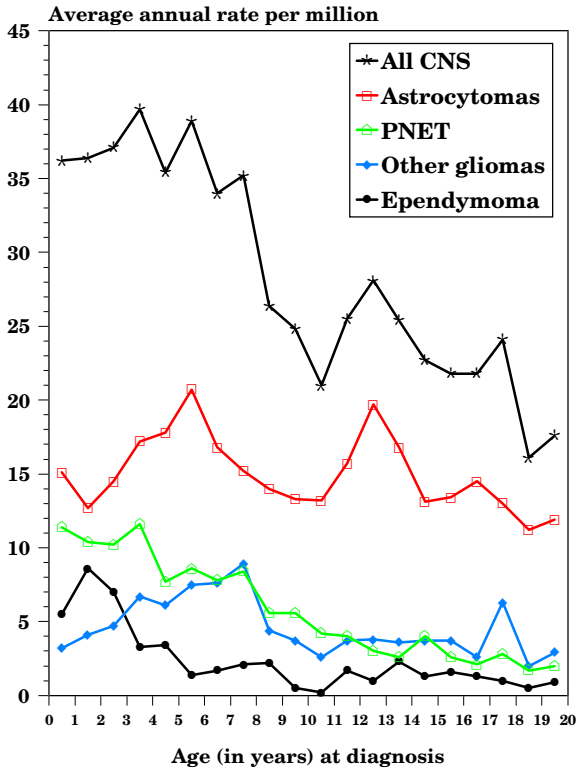


Figure III.3: Malignant CNS tumor age-specific incidence rates, all races, both sexes SEER, 1986-94



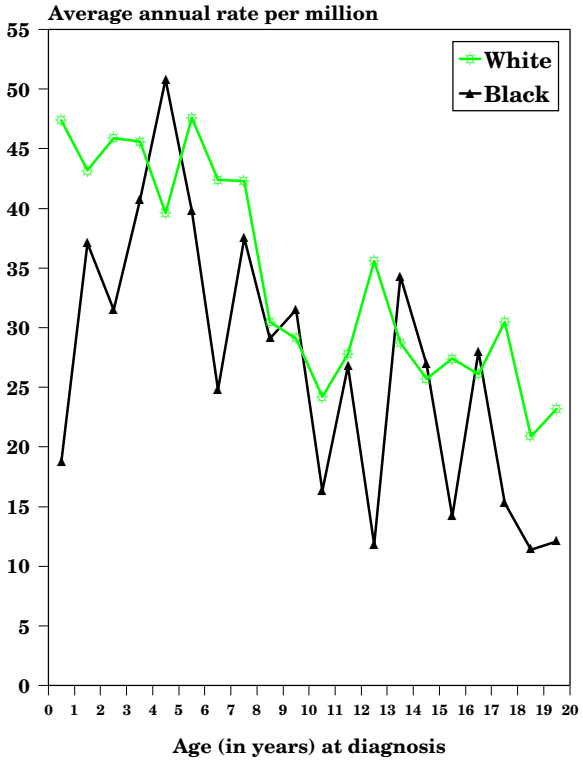
Age-specific incidence

Incidence rates by single year of age are presented in Figure III.3.[1] The average annual incidence of CNS cancer varied only slightly by age of diagnosis from infancy (36.2 per million) through age 7 years (35.2 per million). From age 7 to 10, a 40% drop in the incidence rate (to 21.0 per million) was observed. CNS cancer rates were fairly consistent among children aged 11 through 17 years, until another substantial decrease occurred at age 18.

The incidence of astrocytomas peaked at age 5 (20.7 per million) and a second peak occurred at age 13 (19.7 per million). PNET rates were fairly steady from infancy through age 3 years (ranging from 11.6 to 10.2 per million) and then steadily declined thereafter. Rates of ependymomas were highest through age 3 years, with the age of peak incidence occurring during the second year of life (8.6 per million). Among children aged 5-14, ependymomas are very rare, averaging only 1.4 per million.

Although in our data the age-specific rates for black children were fairly unstable because of small numbers of cases (295 cases from 1986-94), the greatest difference in rates between whites and blacks was observed during the first year of life (47.8 vs. 18.7 per million, respectively) (Figure III.4). In the second year of life, rates among whites decreased from the first year,

Figure III.4: Malignant CNS tumor age-specific incidence rates by race, both sexes SEER, 1986-94



[1] Enumeration of the population at risk by single years of age was available only for the census years 1980 and 1990. The US Bureau of the Census provides intercensal population estimates by 5-year age groups, but not by single years of age. Therefore, the population estimates for 1980 were used in rate calculations for cases diagnosed from 1976-84 and the 1990 estimates were used for cases diagnosed from 1986-94.

while rates in blacks increased substantially. To a degree, this could suggest a pattern in which whites were diagnosed earlier than blacks (on average) for the CNS malignancies that occur early in life, although we are aware of no other evidence that supports this speculation.

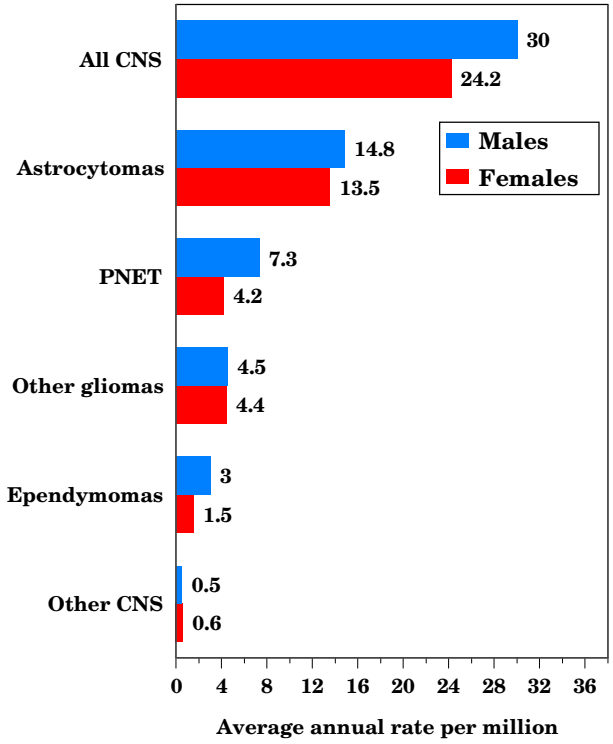
Sex-specific incidence

As will be discussed below, brain cancer incidence rates in children have increased in SEER areas over the past 2 decades. For this reason, the following CNS cancer incidence rates are reported for the time period 1990-95, rather than 1975-95, to reflect recent patterns. The rates that follow were adjusted to the 1970 US standard million population. The incidence rate of primary CNS malignancies was 27.2 per million children younger than 20 years of age (if intracranial germ cell malignancies are included, the rate was 29.1 per million). Males (30.0 per million) had a 24% higher incidence rate relative to females (24.2 per million). Figures III.5 and III.6 illustrate the sex-specific rates by histologic groups of children younger than 20 years of age and younger than 15 years of age, respectively. A clear male preponderance for both PNET and ependymomas was evident, but rates for males and females were similar for the other histologic groups.

Black-white differences in incidence

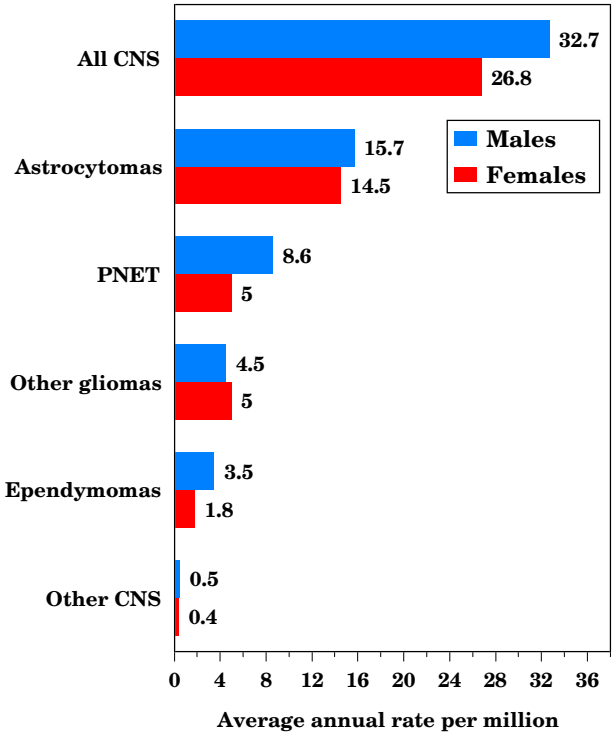
White children (28.5 per million) had an 18% higher average CNS incidence rate compared with black children (24.2 per million). Figure III.7 depicts overall inci-

Figure III.5: Malignant CNS tumor age-adjusted* incidence rates by histologic group and sex age <20, all races, SEER, 1990-95



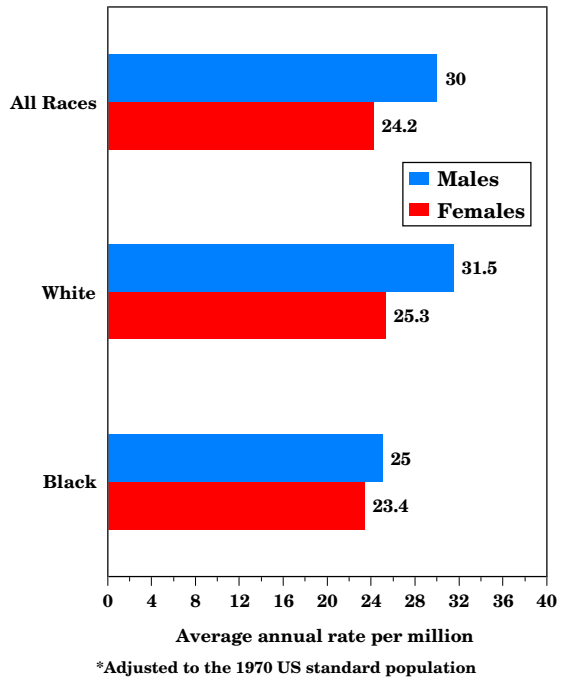
*Adjusted to the 1970 US standard population

Figure III.6: Malignant CNS tumor age-adjusted* incidence rates by histologic group and sex age <15, all races, SEER, 1990-95



*Adjusted to the 1970 US standard population

Figure III.7: Malignant CNS tumor age-adjusted* incidence rates by race and sex age <20, all races, SEER, 1990-95



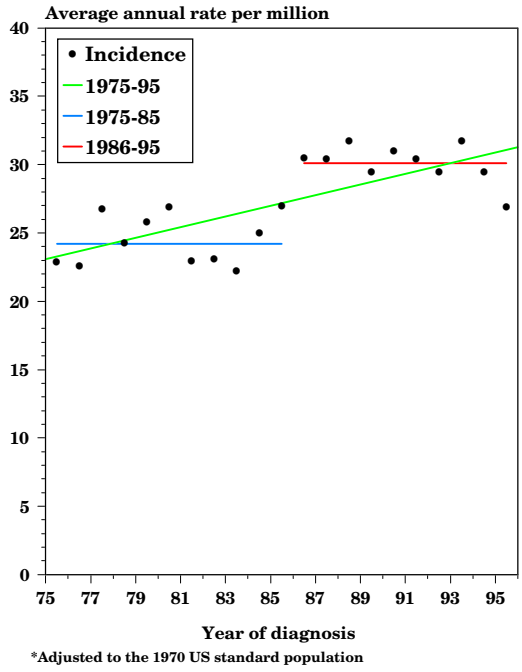
dence rates by sex for white children, black children, and all children combined. It is evident that the racial difference in CNS rates was primarily concentrated among males. There was only a slightly higher CNS cancer incidence rate among white compared with black females (8%), while the racial difference in rates for males was somewhat more pronounced (26%).

TRENDS

The observation that CNS cancer incidence in children appears to have increased in the past two decades has been the subject of numerous previous reports [5-8]. There is considerable debate regarding the possible reasons for the apparent trend. One concern is that changes in environmental exposures may be responsible for the increasing incidence, although epidemiologic evidence to support this hypothesis currently is lacking [9]. An alternative explanation is that changes in reporting due to improvements in diagnostic technology and case ascertainment may be contributing to the increasing trend.

Figure III.8 illustrates the increase in incidence rates of CNS cancer for the years 1975-95 for children younger than 15 years of age. Based on a model using a constant rate of increase in incidence over this period, the estimated annual percentage change (EAPC) was +1.5% (continuous green line in Figure III.8). Smith et al [5] recently evaluated CNS trends for children in the United States from SEER data using a more sophisticated statistical modeling technique. They demonstrated that the incidence of CNS malignancies did not increase steadily from 1973 to 1994, but rather "jumped" to a steady, but higher rate after 1984-85. When the same methodology was applied to the younger than 15 year old age group described in this chapter for the years 1975 to 1995, this "jump model", with the optimal change point from lower to higher incidence occurring after 1985, produced a significantly better fit than the model using a constant linear rate

Figure III.8: Temporal trends in malignant CNS tumor age-adjusted* incidence rates, age <15 all races, both sexes, SEER, 1975-95



of increase (p = 0.003). The EAPC from 1975-84 was –0.1% (blue line in Figure III.8) and for 1986-95 the EAPC was also –0.1% (red line in Figure III.8). The timing of the jump in incidence is coincident with the wide-scale availability of magnetic resonance imaging (MRI) in the United States [5]. This observation, combined with the absence of any jump in CNS cancer mortality during the same period, lends support to the contention that improved diagnosis and reporting during the 1980's is largely responsible for the temporal trends in CNS incidence rates that have been observed since the 1970s. Whether the relatively stable rates of childhood CNS cancer observed over the past decade in the US will continue, however, remains to be seen.

SURVIVAL

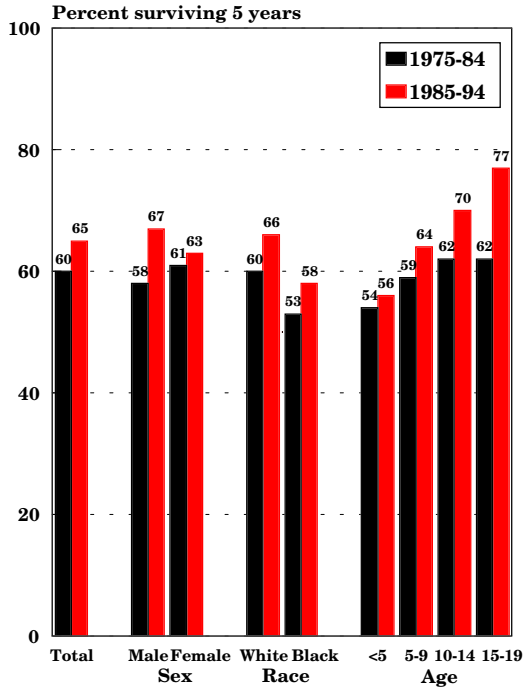
Although survival differs by histology, behavior, size and location of the malignancy, in general children with CNS cancer do not share the favorable prognosis of those with many other common pediatric neoplasms, such as acute lymphoblastic leukemia. Additionally, for children who do survive CNS cancer, long term morbidity can be substantial. Table III.1 provides 5-year relative survival probabilities by histologic group within 2 time periods.

Table III.1: 5-year relative survival rates for CNS by type and time period age <20, all races, both sexes SEER 1975-84 and 1985-94

ICCC Group	1975-84	1985-94
All CNS Cancer	60%	65%
Astrocytoma	70	74
Other Glioma	47	57
Ependymoma	39	56
PNET	52	55

Survival probability improved somewhat over the two time periods. Nevertheless, other than astrocytomas, many of which were low grade malignancies such as

Figure III.9: Total malignant CNS tumor 5-year relative survival rates by sex, race, age and time period SEER (9 areas), 1975-84 and 1985-94



juvenile pilocytic astrocytomas, survival probability was less than 60%. While there were only minimal differences in survival of CNS cancer by sex and race, age was an important factor. Table III.2 provides 5-year relative survival for 1986-94 according to age and histologic groups.

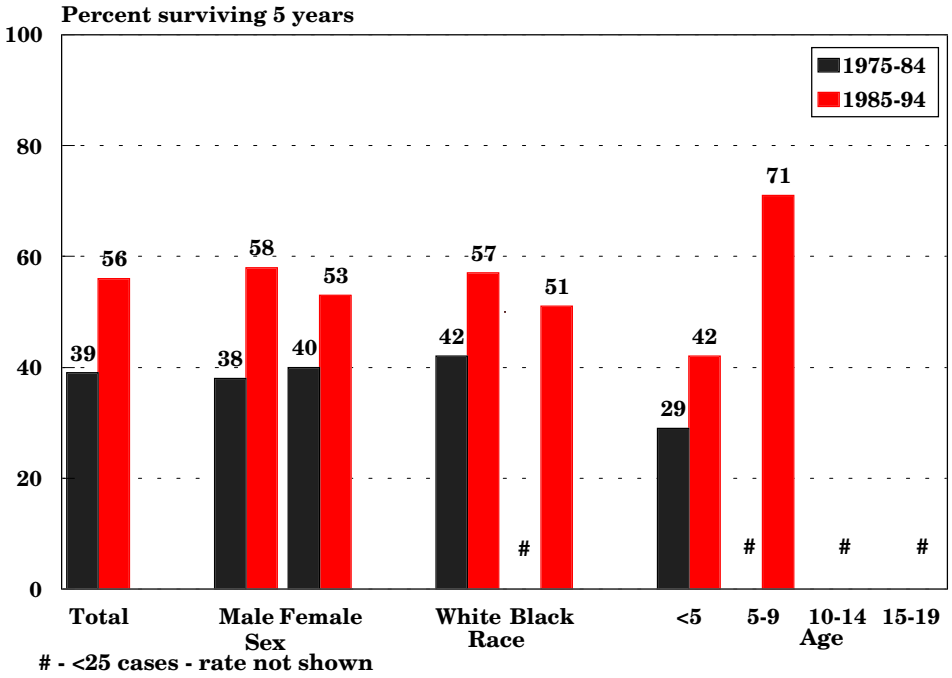
For all CNS cancer combined, survival probability increased with increasing age. Very young children with CNS cancer, especially infants with ependymoma or PNET, were at particularly high risk of

Table III.2: 5-year relative survival rates for CNS cancer by type and age group all races, both sexes, SEER, 1986-94

ICCC Group	<1	1-4	5-9	10-14	15-19
All CNS Cancer	45%	59%	64%	70%	77%
Astrocytoma	69	79	70	75	75
Other Glioma	*	51	43	64	79
Ependymoma	25	46	71	76	*
PNET	19	46	69	57	75

* less than 20 cases.

Figure III.10: Ependymoma 5-year relative survival rates by sex, race, age and time period, SEER (9 areas), 1975-84 and 1985-94



- <25 cases - rate not shown

Figure III.11: Astrocytoma 5-year relative survival rates by sex, race, age and time period, SEER (9 areas) 1975-84 and 1985-94

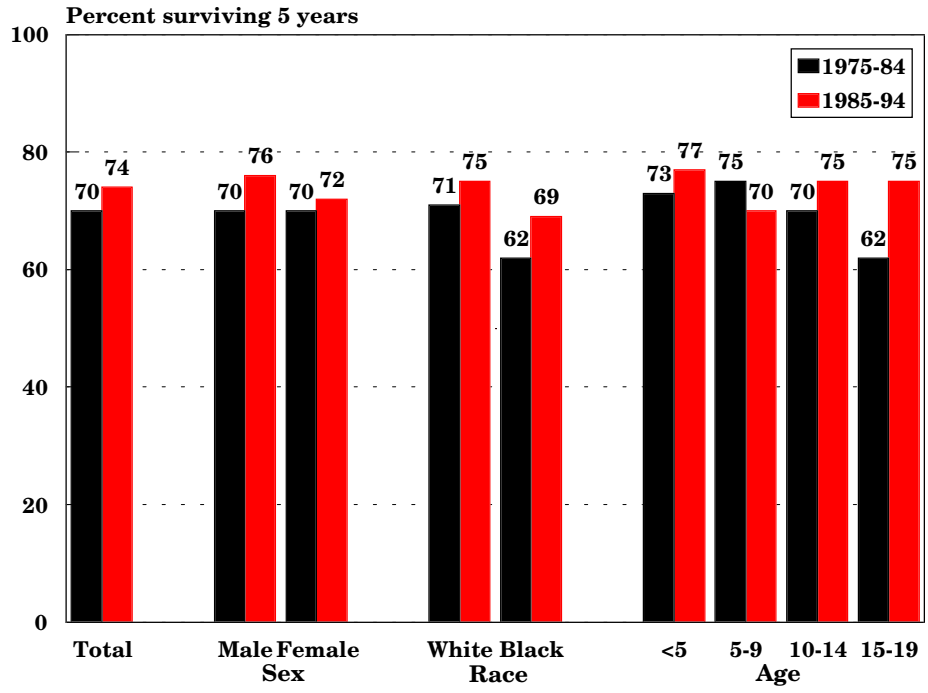


Figure III.12: PNET 5-year relative survival rates by sex, race, age and time period, SEER (9 areas), 1975-84 and 1985-94

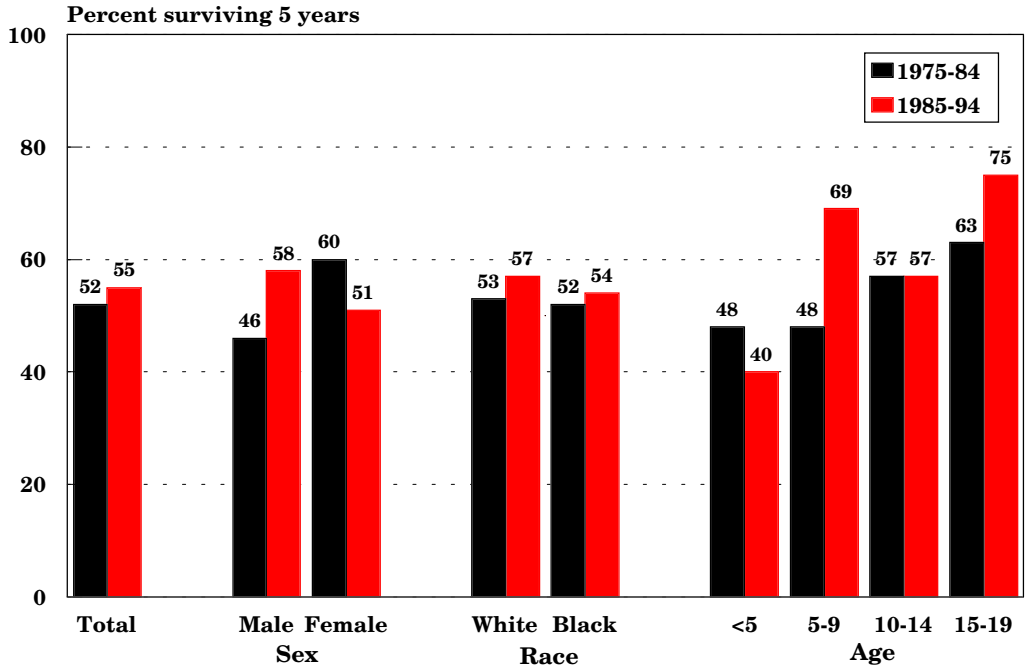


Figure III.13: Other gliomas 5-year relative survival rates by sex, race, age and time period, SEER (9 areas), 1975-84 and 1985-94

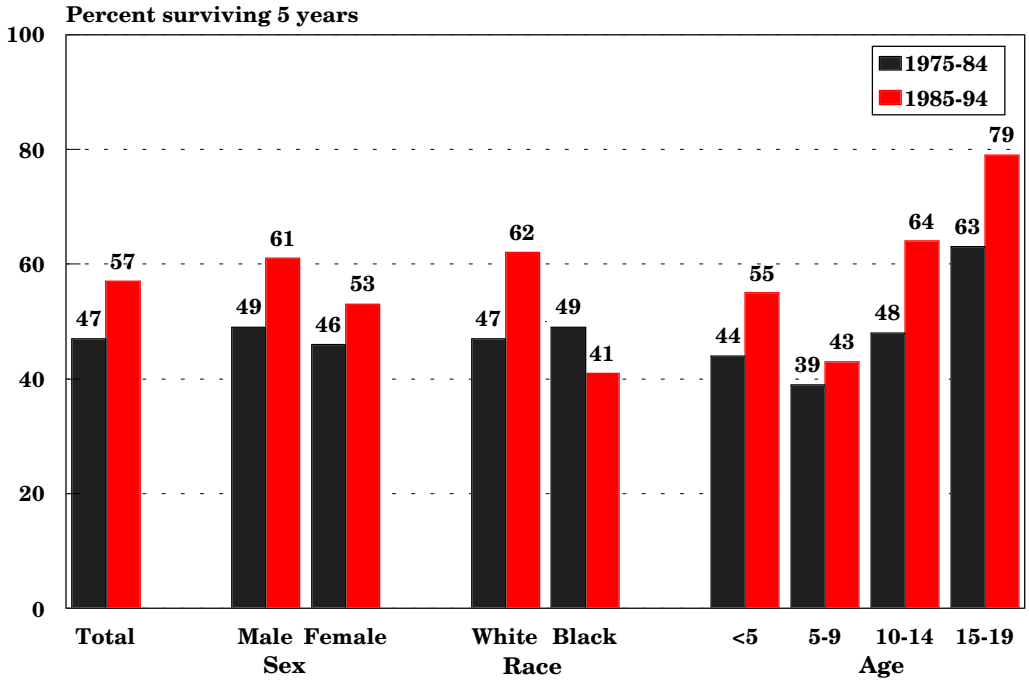


Table III.3: Current knowledge on causes of childhood brain tumors

Exposure or Characteristic	Comments	References
Known risk factors		
Sex	Incidence of medulloblastoma and ependymomas in males is higher than in females. For other types of brain tumors, there is little difference between males and females.	10
Therapeutic doses of ionizing radiation to head	Children treated for tinea capitis experienced 2.5-6-fold increased risk. Currently, those at risk are children treated with radiation to the head for leukemia or a previous brain tumor.	11,12
Neurofibromatosis, tuberous sclerosis, nevoid basal cell syndrome, Turcot syndrome, Li-Fraumeni syndrome	Children with these genetic conditions have a greatly increased risk of brain tumors, for example, 50-fold for neurofibromatosis and 70-fold for tuberous sclerosis. Together, these conditions account for less than 5% of all childhood brain tumors.	10,13,14,28
Factors for which evidence is suggestive but not conclusive		
Maternal diet during pregnancy	Frequent cured meat consumption has been consistently associated with a 1.5-2.0 fold increased risk. However, it is unclear whether cured meats or another dietary factor are responsible, since most aspects of diet have not yet been studied.	10,13,15-17
Parent or sibling with brain tumor	Having a sibling or parent with a brain tumor has usually been associated with a 3-9 fold increased risk. It may be that the excess risk is explained completely by the specific genetic conditions listed above.	10,13,17,18
Family history of bone cancer, leukemia or lymphoma.	The increased risk seen in some studies may be explained by the Li-Fraumeni syndrome.	10,13,22,23, 24
Factors for which evidence is inconsistent or limited		
Electromagnetic fields	A small increase in risk has been observed in some studies, but not most.	10,13,19,29, 30
Products containing N-nitroso compounds: beer, incense, make-up, antihistamines, diuretics, rubber baby bottle and pacifier nipples	The data are inconsistent; associations seen in one study have generally not been reported in later studies.	10,13,21
Father's occupation and related exposures	Many associations have been reported, but few have been replicated: aircraft industry, agriculture, electronics mfg., petroleum industry, painter, paper or pulp mill worker, printer, metal-related occupation, exposure to paint, ionizing radiation, solvents, electromagnetic fields.	10,13,25
Pesticides	There has been little focused research on this topic. Two small studies suggest an association with use of no-pest strips.	10,13,20,31
History of head injury	This is difficult to study because of the rarity of serious head injury and the possibility that mothers of children with brain tumors are more likely than control mothers to recall minor head injuries.	10,13,26
Family history of epilepsy or seizures	The data are inconsistent. One study suggests that the effect of family history of seizures may differ by type of brain tumor and/or type and circumstances of seizures.	13,18,27
Family history of mental retardation	Increased risk observed in one study of adults and one of children.	13

Note that the majority of these risk factors have been reviewed recently in references 10 and 13; only selected references are presented for additional reading.

mortality. Relative to younger children, adolescents with CNS cancer tended to fare well (Figures III.9-III.13).

RISK FACTORS

Table III.3 presents a general summary of the current knowledge on causes of brain cancer in children. To date, there is no specific risk factor known to explain a substantial proportion of brain tumor occurrence. Some hereditary conditions that are clearly associated with increased susceptibility to CNS cancer in children include neurofibromatosis type 1, nevoid basal cell syndrome, and tuberous sclerosis. These diseases are rare, however, and not all children with genetic predispositions go on to acquire cancer. Although a somewhat increased risk has been observed when a sibling or parent has had a brain tumor, the association with family history is not strong or consistent. Thus, from a population perspective, known inherited genetic factors explain only a small percentage of childhood CNS cancer incidence. The same can be said for many other exposures that have been studied. While therapeutic doses of ionizing radiation to the head are definitively known to increase the risk of brain tumors in children, this exposure is largely historical in nature because therapeutic head x-rays are now used very sparingly and with much greater caution than in the past. There is some evidence that certain dietary components during pregnancy may either raise or lower risk, but the relevant aspects have not yet been clarified. For exposures with inconsistent or limited data that are listed in the table, it is not yet possible to say whether they influence risk. We know a few factors that do not appear to increase a child's risk of developing a brain tumor, including passive cigarette smoke exposure, electric blanket use, and ultrasound testing during pregnancy. The difficulty in identifying CNS cancer risk factors may stem in part from studying all childhood brain tumors as a single entity when many different histologic subtypes occur. The rarity of any specific histologic type makes it very difficult to accrue enough cases for epidemiologic study.

SUMMARY

Cancer of the brain and central nervous system comprises nearly 17% of malignancies in children younger than 20 years of age. As a group, CNS cancer is the most common solid tumor and the second most common malignancy of childhood. The overall annual incidence in the United States is about 27 per million children younger than 20 years of age (29 per million with intracranial germ cell malignancies included). The incidence of CNS cancer is higher in children younger than 8 years of age than in older children or adolescents. This difference is largely attributable to cerebellar PNET (medulloblastoma), brain stem gliomas and ependymomas, which all occur primarily before the age of 10 years. CNS cancer incidence is slightly higher in males than in females, largely due to the male predominance of PNET and ependymomas. Rates are higher in white children than in black children, although the differences are seen primarily in males and in young children. Survival, which is dependent on the type and location of the CNS malignancy, tends to be worse in very young children than in older children. CNS cancer incidence rates remained essentially stable from 1986-95. Unfortunately, the causes of CNS cancer remain largely undetermined. The few definitive risk factors that are known explain only a small proportion of the total case population.

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