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G.R. Bunin
(Ph.D. Thesis)

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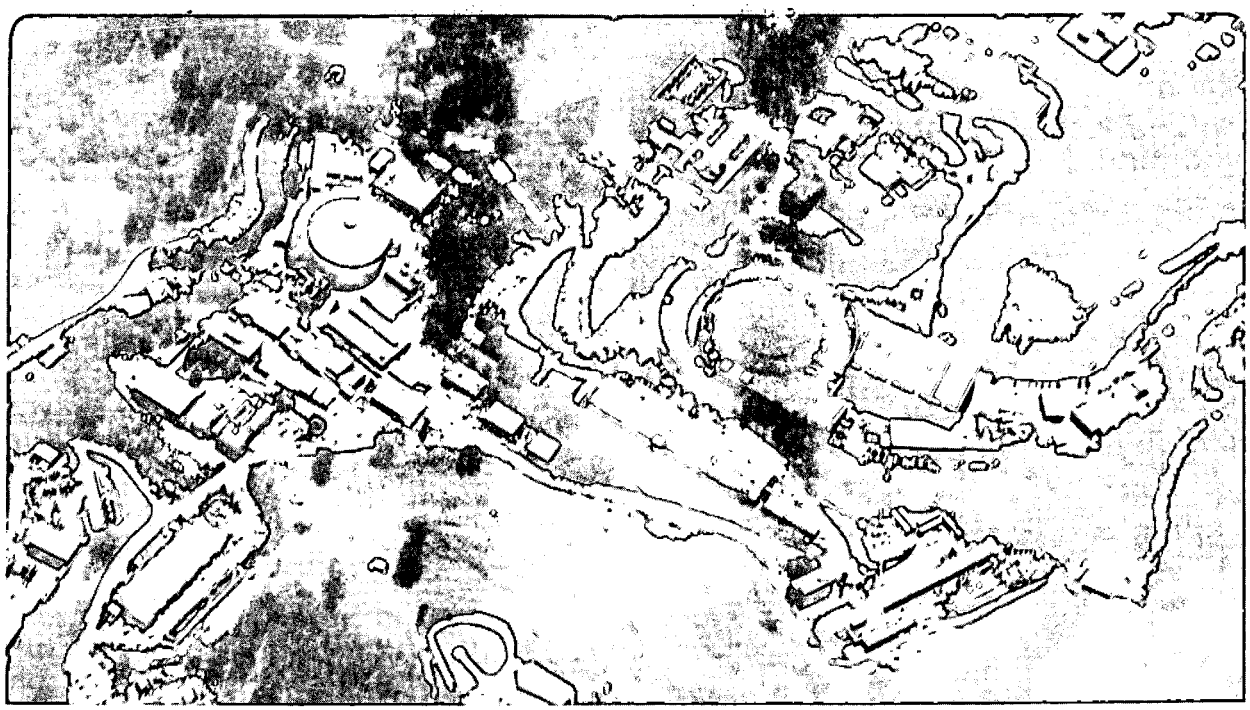

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Descriptive Epidemiology and Geographic Variation of Childhood Brain Cancer in the U.S.

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Descriptive epidemiology and geographic variation

in childhood brain cancer in the U.S.

by

Greta Renee Bunin

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Glossary of Abbreviations

AGL	Acute granulocytic leukemia
ALL	Acute lymphocytic leukemia
ALNOS	Acute leukemia, not otherwise specified
CNS	Central nervous system
CT	Computed tomography
DNA	Deoxyribonucleic acid
ICD	International Classification of Diseases
ICD-O	International Classification of Diseases for Oncology
MOTNAC	Manual of Tumor Nomenclature and Classification
NCI	National Cancer Institute
NOS	Not otherwise specified
OR	Odds ratio
PMR	Proportionate mortality ratio
RNA	Ribonucleic acid
SEER	Surveillance, Epidemiology, and End Results
SES	Socioeconomic status
SFO	San Francisco - Oakland
SMR	Standardized mortality ratio
SMSA	Standard metropolitan statistical area
STF2	Summary tape file 2
STF3	Summary tape file 3
SV40	Simian vacuolating virus 40
TNCS	Third National Cancer Survey
WHO	World Health Organization

CHAPTER 1

Literature Review

Introduction

This chapter reviews the literature on childhood brain cancer including studies of its descriptive epidemiology and of possible risk factors. Studies of brain cancer at all ages combined are cited for comparison with data on children or when no data on children alone exist. The dearth of known risk factors for childhood brain cancer and unanswered descriptive questions justified the present study. The descriptive and geographic analyses may generate new etiologic hypotheses.

Cancer kills more children after the first year of life and before the sixteenth year than any other cause except accidents. Brain cancers account for about 20% of these cancers; only leukemia accounts for more cases. According to the most recent figures, 50% of children diagnosed with brain cancer survive at least five years (1). Many patients who do survive have permanent disabilities, including emotional problems, cranial nerve palsies, and impaired growth, vision, hearing, motor ability, and intelligence (2). Despite the prominence of brain cancer as a cause of childhood morbidity and mortality, relatively little is known about its etiology.

Methodological issues

Several methodologic problems arise in the epidemiologic study of brain cancers. Some are more relevant to the study of these cancers in children than others. The first problem is the difficulty of histologic diagnosis. For 10 to 20% of biopsied tumors, the pathologist has difficulty in establishing a single, predominant cell type (3). Part of the difficulty arises because cancerous

cells of one type in the brain may promote the malignant transformation of neighboring cells of other types (4). In addition, some brain tumors are not even biopsied for histologic diagnosis because the location of the tumor makes a biopsy a life-threatening procedure. Brain stem tumors, which are more common in children than adults, fall into this category and are usually not biopsied.

Another problem arises from differences among studies of the anatomic sites included as "brain." The most restrictive definition (and the one used in this study) includes the brain (International Classification of Diseases for Oncology (5) (ICD-O) 191) but not the meninges, the covering of the brain. Also excluded are tumors of the spinal cord and its meninges. Another aggregation, central nervous system (CNS) tumors, includes the brain, the spinal cord and the meninges of both. Spinal cord tumors account for 10-15% of all CNS tumors (6-8). The same cell types occur in the spinal cord as in the brain, although the relative proportions differ. No bias would result from studying CNS tumors instead of brain tumors if cell types had the same etiology regardless of location. The effect of including meningiomas in the CNS grouping should be small, since they account for only 5% of childhood CNS tumors (9, 10). A third grouping, intracranial tumors, excludes the spinal cord and includes the brain, its meninges, the pituitary gland, and the pineal body. About 12% of childhood intracranial tumors occur in the pituitary, pineal, or meninges (10). The dilution of brain tumors with these other tumors is worse in adults; about 26% of intracranial tumors are of the meninges, pituitary, and pineal (10).

Mortality statistics use yet another grouping--brain and other nervous system, i.e., the entire nervous system. Unfortunately, an important tumor of childhood, neuroblastoma, occurs in the sympathetic nervous system. Tumors of this part of the nervous system account for 25-30% of all nervous system tumors in children (7, 8). Obviously, the results of studies of nervous system

cancers may be inaccurate with regard to brain tumors. The separation of tumors of the sympathetic nervous system (and other parts of the nervous system) from those of the brain is possible using the subdivisions of the International Classification of Diseases (ICD) codes (11-14), but few mortality studies do so.

The difficulty of distinguishing between benign and malignant tumors presents another problem and source of inconsistency among studies. Benign and malignant tumors of the brain may have similar clinical courses. Benign as well as malignant tumors may produce death by pressure on vital centers in the brain. Malignant brain tumors seldom metastasize. Histologic examination can distinguish benign from malignant tumors, but, as already noted, a substantial proportion of tumors are not biopsied. The proportion of cases diagnosed histologically varies geographically and temporally. Inclusion of both benign and malignant tumors in comparing rates across time and place, for example, would eliminate bias introduced by variation in the proportion histologically diagnosed. However, such a practice would dilute any findings if benign and malignant tumors had different etiologies.

A final problem involves the distinction between primary and metastatic brain tumors. Obviously, an epidemiologist would like to include only primary brain tumors in studies of etiology. However, the proportion of cases not histologically diagnosed may include some metastatic tumors. Metastatic tumors are not a problem in studies of childhood brain tumors because few brain metastases occur in children. In adults, on the other hand, the brain is a frequent site of metastasis.

In summary, several of the methodological problems that affect studies of brain cancer and their interpretation are of particular importance to childhood brain cancer. A substantial proportion of childhood tumors are not

biopsied or are difficult to diagnose accurately. Because that proportion is likely to vary nonrandomly, bias may result. The anatomic groupings of tumors used often include unrelated tumors with brain tumors. About 30% of nervous system cancers of childhood and about 12% of intracranial cancers are not brain tumors. Using these groupings, especially nervous system, could dilute findings. On the other hand, bias caused by using the CNS grouping is probably slight, as most of the nonbrain tumors are of types found in the brain as well. Distinguishing benign from malignant tumors is also difficult and could lead to bias if the two types had different causes. Comparison of rates would also be problematic if the proportion histologically examined or the distinguishing criteria varied.

Histologic types

Gliomas, including astrocytomas, medulloblastomas, ependymomas, and oligodendrogliomas, account for about 83% of primary brain tumors of childhood in the U.S. and about 90% of brain tumors in adults (10). Gliomas arise from one of the several types of glial cells or neuroglia, which support and protect the nerve cells or neurons, and participate in neural activity, neural nutrition, and the defense processes of the central nervous system (15). The classification of gliomas is based on the predominant cell type, as many contain mixtures of different neoplastic cells (3).

Childhood and adult gliomas differ in cell type distribution and in anatomic location. Medulloblastomas and ependymomas occur proportionally more frequently in children than in adults, while the opposite is true of glioblastomas (10). Table 1 shows the distribution of histologic types of gliomas among children and among adults. Location of tumors also differs with age, partly as a result of cell type distribution. About 65% of childhood brain tumors arise infratentorially, that is, in the cerebellum, brain stem, and fourth ventricle (4, 9, 16). In adults, most tumors are supratentorial, occurring in the cerebrum (4).

Table 1.

Comparison of childhood and adult distribution of gliomas:
Histologically confirmed brain tumors
Connecticut 1935-1964*

Children 0-14 yr			Adult 15 yr and older		
Type	No.	%	Type	No.	%
Medulloblastoma	74	33	Glioblastoma	1105	79
Astrocytoma	63	29	Astrocytoma	214	15
Glioblastoma	62	28	Medulloblastoma	27	2
Ependymoma	20	9	Ependymoma	27	2
Oligodendroglioma	2	1	Oligodendroglioma	22	2
Total	221	100	Total	1395	100

* adapted from Schoenberg et al. (10)

Astrocytoma

Astrocytomas originate from astrocytes, which are the largest of the neuroglia and possess numerous long processes. Many of their processes have expanded pedicles at their ends which attach to the walls of blood capillaries (15). There are two types of astrocytes and about seven types of astrocytoma in the World Health Organization (WHO) classification (3). The cells of the astrocytomas differ in size, shape, the presence and location of intracytoplasmic fibrils, as well as other characteristics. Epidemiologically, astrocytomas exhibit a bimodal age distribution with a low broad peak between ages 0 and 10 and a much larger peak centered at about age 55 (17). They often grow slowly, with symptoms and survival dependent on their location (18). In children many astrocytomas occur in the cerebellum and of these, most are slow growing, well circumscribed, and of low-grade malignancy (16). Neurosurgeons can excise totally about 65% of cerebellar astrocytomas eliminating in many cases the need for radiation treatment (16). Children with cerebellar astrocytomas survive far longer than those with any other brain tumor; the five-year survival rate is 89% (19). Childhood astrocytomas also occur in the cerebrum with a less favorable

survival rate of 30 to 40% after five years (19). Most adult astrocytomas occur in the cerebrum with a worse prognosis (16).

Glioblastoma

Glioblastoma is a highly malignant tumor and has characteristics of such tumors. It is anaplastic and highly cellular, with poorly differentiated cells. Necrosis, hemorrhage, and invasive growth are usually prominent features. Some glioblastomas show no evidence of a more differentiated tumor, while others contain areas of recognizable astrocytoma, less commonly oligodendroglioma, or, exceptionally, ependymoma (3). Any of these gliomas may terminate as a glioblastoma (3). Glioblastomas account for about 75% of adult brain tumors (10) but only 5 to 20% of childhood tumors (10, 16). They usually occur in the cerebrum. Glioblastoma, like astrocytoma, shows two peaks of incidence--a small one between ages 5 and 9 and a much larger one centered at about age 55 (17). Generally, less than 10% of patients survive five years (19).

Brain stem tumor

Brain stem tumors are often considered a separate category of brain tumors. They occur most frequently in children, accounting for 10% of intracranial neoplasms, with peak incidence between 4 and 8 years of age (16). Virtually all such tumors are astrocytomas and glioblastomas (16). Because of the location of these tumors, surgery is risky and serves mostly a diagnostic purpose. The prognosis is worse than for other childhood brain tumors. Only 16% of patients with brain stem tumors are alive after five years; the median survival is about nine months (19). The mainstay of treatment is radiation, which results in improvement in most cases (16).

Medulloblastoma

Medulloblastomas are thought to arise from primitive cells, medulloblasts, which can differentiate into both neuronal and glial cells. However, the medulloblast has never been satisfactorily identified as a normally occurring cell (19). The tumor cells are poorly differentiated and tend to form what are called Homer-Wright rosettes ("pseudorosettes") (3). Medulloblastomas account for 20-25% of childhood brain tumors and occur almost exclusively in the cerebellum or roof of the fourth ventricle (3). The incidence decreases sharply with age; 80% of medulloblastomas occur in children under age 15 (16). Males are affected 1.5 to 2.0 times as often as females (20-23). In spite of the radiosensitivity of the tumor, the rapid growth and high invasiveness results in an only fair prognosis, most recently estimated at 37% (19). However, five-year survival rates of 70% have been reported, for example, at university cancer centers in Connecticut (19, 24).

Ependymoma

Ependymal cells line the cavities of the brain and spinal cord and are bathed by the cerebrospinal fluid which fills these cavities (15). Derivatives of these cells sometimes form ependymomas. Ependymomas consist predominantly of uniform ependymal cells forming rosettes, canals, and perivascular rosettes (3). The ependymal rosettes are diagnositic for ependymoma. Ependymomas, like medulloblastomas, are more common in childhood than later in life. Fifty to 60% of all intracranial ependymomas (i.e., excluding those of the spinal cord) occur under age 15 (16). The age distribution is bimodal; the incidence rate decreases through childhood to a low at age 25 and then increases and peaks at about age 55 (17). The peak incidence rate of childhood slightly exceeds that of later life. About two-thirds of intracranial ependymomas of childhood arise from the fourth ventricle (19). Overall five-year survival is about

30% but is highly dependent on grade of the tumor (19).

Oligodendroglioma

Oligodendrocytes, the derivative cells of oligodendrogliomas, are much smaller and possess fewer and shorter processes than astrocytes (15). Focal calcifications are often found within oligodendrogliomas and at their peripheries (3). Oligodendrogliomas occur rarely in adults and children, accounting for about 1% of brain tumors in both (10). Incidence peaks between ages 30 and 50 (25, 26). In children, males are reportedly affected twice as often as females (27). Oligodendrogliomas are usually located in the cerebrum and often grow slowly (19), but survival varies greatly. In one series of 12 childhood cases, the mean survival was close to nine years and ranged from less than one month to more than ten years (27). A mixed oligo-astrocytoma is recognized (3).

Summary

The histologic types of gliomas that occur in children vary in location, age-incidence curves, sex ratio, and survival. Some of the information is summarized below in Table 2. Fig. 1 shows the incidence curves for the different gliomas and for all brain cancer.

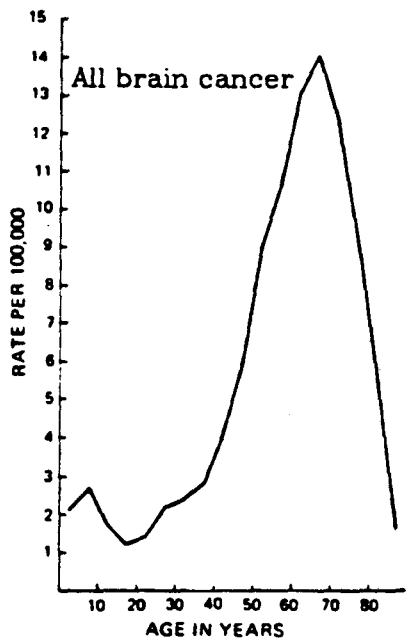
Table 2.
Epidemiological characteristics of childhood gliomas

	Peak of incidence	M/F ratio in children	5-year survival in children	Location in children
Astrocytoma	Adult	0.9-1.1	30-90%	Cerebellum
Glioblastoma	Adult	1.2	<10%	Cerebrum
Medulloblastoma	Childhood	1.5-2.0	37%	Cerebellum
Ependymoma	Childhood	1.0-1.5	30%	Fourth ventricle
Oligodendroglioma	Adult	2.0	70%	Cerebrum

Figure 1.

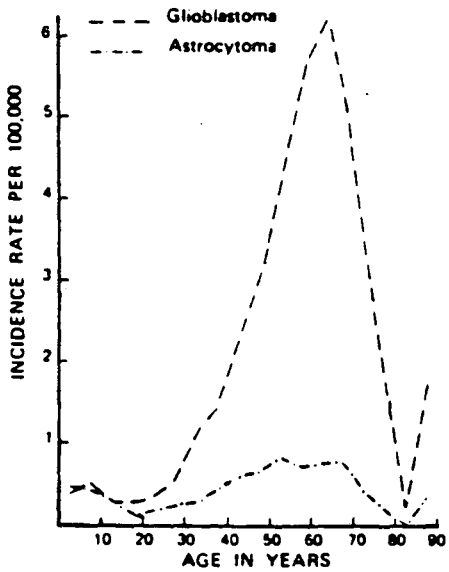
Age-incidence curves of brain cancer

All types and selected cell types



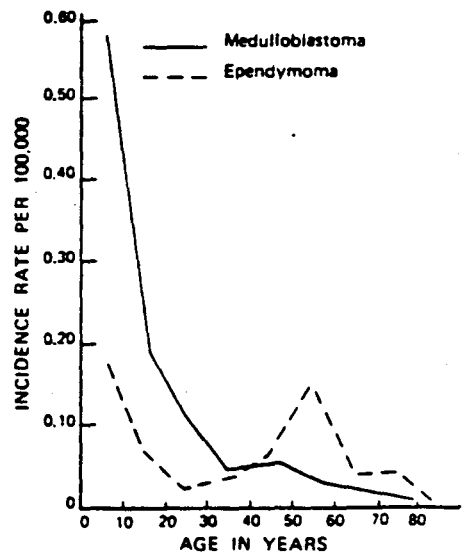
Average annual age-specific incidence rates for brain tumors, United States 1969–1971

Source: Cutler and Young (1975)



Average annual age-specific incidence rates for selected neoplasms of the brain, Connecticut, 1935–1984

Source: Schoenberg et al (1976)



Average annual age-specific incidence rates for selected neoplasms of the brain, Connecticut, 1935–1984

Source: Schoenberg et al (1976)

Sex and race

Investigators usually find a slightly higher incidence of childhood brain cancer in males than females with male-female rate ratios of 1.0 to 1.2 (6, 9, 28-31). Medulloblastoma shows the greatest discrepancy between the sexes; males experience a rate 1.5 to 2.0 times higher than females (20-23). Sex ratios of ependymoma tend to be the next highest, between 1.1 and 1.5 in incidence studies (6, 9, 32). Astrocytomas affect males and females equally with recent rate ratios of 0.9 to 1.1 (9, 32). The largest population-based series, with 2072 intracranial and spinal cord tumors, gave the following sex ratios: medulloblastoma--1.7, ependymoma--1.5, astrocytic glioma--1.1, glioma not-otherwise-specified (NOS)--1.0, and pontine glioma--1.1 (9). Ependymomas and astrocytomas account for most of the spinal cord tumors; 8-10% of ependymomas (6, 33) and 7% of astrocytic gliomas (6) occur in the spinal cord. Inclusion of spinal cord tumors would be likely to change the sex ratios only if tumors in the spinal cord had dramatically different occurrence by sex than the same cell type located in the brain. Two reports on the sex ratio for spinal cord ependymomas differed, but together reported seven male and four female cases. (6, 33).

The sex ratio for all childhood brain tumors in whites first increases with age until about age ten. It then drops to about one or below around puberty and finally increases (7, 30, 34, 35). In Baltimore, the sex ratio of incidence rates of intracranial tumors in children declined during the period 1960-74 (30). However, each sex- ,time- specific rate was based on an average of only 20-25 cases. A sex ratio that changes with age or year could reflect a trend for one or more cell types or could result indirectly from changing cell type distributions. However, no investigators have reported on changes in sex ratios for specific cell types.

Generally, rates of childhood brain cancer in whites are reported to

exceed those of nonwhites. Ederer et al. reported the largest white excess, a white-nonwhite ratio of 1.45, in mortality from nervous system neoplasms for 1950-59 in the U.S. (36). In the Third National Cancer Survey (TNCS) data, however, white and black children experienced identical incidence rates (31). A decade's experience of a pediatric tumor registry in the northeast U.S. observed white-black rate ratios of about 1.0 for glioma NOS and medulloblastoma, and ratios of 1.2 for ependymoma, 1.3 for astrocytoma, and 1.1 for all gliomas combined (32). In a mortality study of the whole U.S. for 1960-68, Miller and Dalager observed higher childhood rates of ependymoma and medulloblastoma but lower rates of glioma NOS in whites compared to nonwhites (37). White and nonwhites experienced about equal mortality rates for astrocytoma.

Time trends

Mortality rates from malignant neoplasms of the brain and other parts of the nervous system increased about sevenfold in white and nonwhite children aged 0-14 in the U.S. between 1930 and 1961 (38, 39). Investigators suggested that improved ascertainment accounted for at least some of the increase (40). The observed increase occurred before 1959; between 1950 and 1961, the rates did not change. In a similar study, Greenberg analyzed mortality rates from childhood nervous system cancer in the U.S. for 1950-75 (41). Little change occurred in rates in children under 10 and females under 20, but rates for males aged 10-19 increased between 1950 and 1960. Between 1965 and 1975, all age-, sex- specific mortality rates for whites declined. For nonwhites, the rates were more variable but did not appear to be declining.

In contrast to childhood rates of mortality from nervous system cancer which on the whole did not increase after 1950, the rates in adults continued to rise through the 1950s and 1960s (38, 39). The age-adjusted rates appeared to level off around 1970, but only one time point after 1970 was included (40). The

cessation of rate increases in children but not adults may reflect such factors as a more rapid rise to complete ascertainment in children, one or more environmental factors affecting only adults, or improved survival in children only.

Some incidence data exist but may not reflect trends in the entire U.S. In Rochester, Minnesota, a community with excellent medical care, little heavy industry, and a 70% autopsy rate, the age-adjusted incidence rates of gliomas and meningiomas (which together account for 80-90% of CNS cancers) did not change between the first and second halves of the period 1950-1977 (42). During the same period, U.S. mortality rates from nervous system cancers increased. This observation can be explained equally well by more complete ascertainment in Rochester, or by rising ascertainment or changing environmental exposures in the rest of the U.S. but not in Rochester, Minnesota.

The incidence of childhood CNS tumors increased significantly in both sexes in Finland in 1953-70 (43) and Sweden in 1958-64 (44). In Sweden, the incidence rates increased 4% per year for males and 1% for females, on average. The actual change in rates is not presented in the Finnish study. However, the significance of the trend and the number of age groups affected is greater for males, suggesting a greater increase among males. The Swedish researchers suggested that if environmental factors were causing the increase, no sex difference in trends should have occurred. In both countries, the largest increases occurred under age five, although the Swedish study presented this analysis only for all nervous system cancers combined. The Swedish investigators studied mortality as well as incidence rates; the mortality rates included all parts of the nervous system. (The incidence of neuroblastoma, the predominant tumor outside the central nervous sytem, increased slightly more than the incidence of CNS tumors did.) Mortality rates changed less than incidence rates; male mortality rates increased, while female mortality rates hardly changed. A

recent study in Baltimore, based on small numbers, observed a decrease in incidence rate of intracranial neoplasms in white males under age 20 from 1960 to 1974; the rate in white females changed very little over the same time period (30).

The possibilities of increased ascertainment and international differences make time trends in mortality and incidence rates difficult to interpret. In addition, differences may exist between the etiologies of childhood and adult brain cancers. Possible changes in survival rates further complicate the interpretation of trends in mortality rates. However, the results from Finland and Sweden suggest that incidence rates for children may have increased. As both countries have accessible medical care, and as the increases occured after increases in the U.S. had ceased, the trends are not likely to be due to better ascertainment. In addition, if improved ascertainment caused the increases, males and females should have experienced similar trends. The Swedish study also presented evidence that recent mortality rates for children may not accurately reflect incidence.

Social class

The data on the association of social class with childhood brain cancer conflict. Cases of childhood brain cancer in Finland and intracranial tumors in Denmark did not differ from controls in social class distribution (29, 45). Stewart et al. made the same observation for childhood cancer deaths in England and Wales (46). In contrast, MacMahon, using pay status to define socioeconomic status, observed a 50% higher death rate from CNS cancer for private patients than for clinic patients (47). The report did not give the statistical significance of the result. However, the difference in rates was significant for all cancer deaths combined and the effect of pay status was greatest for the CNS category. In a more recent study, Sanders et al. observed a significantly

increased proportionate mortality ratio (PMR) for childhood cancer among children of professional fathers (48); the analysis of only brain cancers showed the same association. However, the high PMR might have resulted from lower death rates from other causes among children of professional fathers. Chance, international differences, and/or different effects by cell type may explain the conflicting data on social class.

Religion

Several investigators observed a higher death rate from brain cancer at all ages combined among Jews compared to people of other religions. MacMahon reported the same trend for CNS cancer deaths among children, although only 14 such deaths occurred among Jewish children and the significance of the 60% difference in rates is not given (47). However, in their case-control study of childhood brain tumors, Gold et al. observed a protective effect of being Jewish (49). The odds ratio (OR) was small, 0.17, but not significant; seven pairs were discordant for religion and in six of those, the control was Jewish. The two studies that investigated religion conflict and both results are based on small numbers. Therefore, the effect of being Jewish on the risk of childhood cancer remains unknown.

Geographic variation

International differences

About ten-fold international variation in incidence rates of childhood brain cancer has been observed (50). Nigeria and India reported low rates while Israeli Jews, regardless of continent of birth, experienced rates about ten times higher. The U.S., Denmark, Colombia, and Japan experienced intermediate rates. In Israel, the rate for Jews was almost twice that for Arabs. The Japanese and U.S. whites experienced similar rates, which were about one-third the rate of Israeli Jews. These incidence data generally include benign, malignant, and

unspecified neoplasms of the brain and other parts of the nervous system. In a study including only malignant tumors, Virag and Modan presented data that question the high rate in Israeli Jews and the difference in rates between Jews and Arabs (51). They observed rates for Arabs and Jews that were similar to each other and to rates in other developed countries.

Adult mortality rates generally follow the same pattern as childhood incidence rates. A study of age-adjusted mortality rates in 28 countries from neoplasms (benign, malignant, and unspecified) of the brain and other parts of the nervous system observed the lowest rates in Mexico, Chile, and Japan (0.7-2.3/100,000) (52). Israel reported the highest rate, 6.8/100,000; the rates in all other countries varied between 3.4/100,000 (U.S. nonwhites) and 5.6/100,000 (Denmark). Iceland and three Scandinavian countries--Denmark, Norway, and Sweden--had the highest rates except for Israel; Finland had a lower rate. The investigators attributed part of the geographic variation of rates to differences in the ascertainment of cases, completeness of reporting, and death certificate coding practices. Incidence rates show the same international pattern as mortality rates (53), making death certificate coding practices an unlikely explanation. Differences in ascertainment may explain the low rates in developing countries such as Chile and Mexico, but not those in Japan.

Two studies of migrants suggest that environmental rather than genetic factors may explain some of the observed variation in rates. Japanese migrants to the U.S. had mortality rates which approached those of U.S. whites (54). Chinese children in Shanghai experienced higher incidence rates of brain cancer than Chinese children in Singapore (55).

Dohrmann and Farwell compared the distribution of histologic types of childhood intracranial neoplasms among six case series from four continents (56). Differences in ascertainment are unlikely to affect these comparisons, but

variation in histological diagnosis could. After combining astrocytomas and glioblastomas and excluding the nonbrain intracranial tumors and the unclassified tumors, the proportion of astrocytoma-glioblastoma, medulloblastoma, and ependymoma varied among series. The proportion of cases diagnosed as astrocytoma or glioblastoma ranged from 41% in Japan and 42% in India to 59% in Africa. Chance may explain the high proportion in the African series of only 61 cases. After the African series, the highest proportion was 52% in Austria. The proportion of cases diagnosed as medulloblastoma ranged from 18% in Africa to 33% in Connecticut. Again, the smallest series gave an extreme value; however, the value for India, 22%, was close to that of Africa. The proportion of ependymoma varied two-fold from 12% in Connecticut to 24% in India.

U.S. regional differences

Rate differences within a country may provide etiologic clues and are less likely to result from diagnostic, coding, and medical care differences than are international comparisons. Investigators have observed similar geographic patterns for childhood and for all nervous system cancer mortality.

In a study of childhood cancer deaths in the 1950s, Ederer et al. observed significantly higher mortality rates of nervous system tumors in the Pacific States (SMR=113) than in the U.S. as a whole. The Southern and Mountain States had significantly lower rates (SMRs 85-93). Kurtzke investigated the geographic differences in mortality rates for all nervous system tumors including benign and unspecified tumors in U.S. whites for 1951-53 and for 1961-63 (57). In both time periods, the Pacific States, Nevada, and some of the southern New England and Mid-Atlantic States (Connecticut, New York, Massachusetts, and New Jersey) reported rates higher than the national average. The rest of the country, except Nebraska and Florida, generally reported low rates. As the mortality rate from nervous system tumors covaried significantly with the

distribution of physicians, the author attributed the geographic variation to differences in completeness of ascertainment. In the studies of both Kurtzke and Ederer et al., the geographic variation observed was small. For all ages, the mortality rates varied from 70% to 120% of the national rate; for children from 85% to 113%. Similar geographic patterns were seen for childhood and age-adjusted mortality rates; rates were high in the Pacific States and low in the Mountain and Southern States.

No striking geographic pattern in the U.S. occurred in county mortality rates (1950-69) for cancer of the nervous system (58). Counties of high and low incidence were scattered across the country. Some correspondence existed between the patterns for males and females.

Urban-rural differences

Choi and his associates studied the death certificates of all Minnesota residents who died with primary central nervous system neoplasms between 1958 and 1962 (59). They compared the distribution of residence (urban place, rural nonfarm, rural farm) of cases of all ages to that of the Minnesota population. A higher proportion of the cases lived on farms compared to the state's population. This association was significant for unspecified brain tumors, gliomas, and all brain tumors in males and for unspecified brain tumors in females. According to the authors, the number of significant findings for males was unlikely to occur by chance, but the association for females might be due to chance. In their report, Choi et al. cited supporting, unpublished data from the Norwegian Cancer Registry. Although urban areas in Norway experienced higher total incidence rates than rural areas (about 40% for both sexes), higher rates in rural areas were observed in both sexes under age 20. Males and females under age 20 living in rural Norway experienced higher rates of medulloblastoma than their urban counterparts. Astrocytoma rates under age 20 were higher in rural

areas for males, but in urban areas for females. These findings emphasize the possible irrelevancy of rates for all ages to childhood brain tumors.

In Iowa in 1950, as in the Norwegian data, urban areas experienced incidence rates of primary brain tumors about 1.5 times that of rural areas (60). However, the small number of childhood cases did not permit separate analysis.

Greenberg compared rural and urban mortality rates from nervous system cancer in white children aged 0-19, 1950-69 (41). He defined urban residents as those persons living in a county in which at least 75% of the population lived in towns of 2500 or more inhabitants in 1970. The most urbanized counties had higher child and teenage cancer mortality rates than the entire U.S. The difference was most marked, though small, for nervous system cancers in both sexes. The urban excess was 7% for males and 9% for females ($p<0.05$). Greenberg also investigated time trends in urban-rural differences. Between 1950 and 1975, urban-rural differences in total white cancer mortality rates decreased. The urban excess in children decreased by half between the two periods.

Part of the discrepancy between higher urban brain cancer rates and overrepresentation of farm residents among cases may result from the definitions of residence used. Choi et al. observed similar proportions of rural residents among the cases and among the general population (59). Only when rural residence was classified as farm or nonfarm was the higher proportion of rural farm residents observed. High rates among rural farm residents but very low rates among rural nonfarm residents might explain the overall low rates for rural areas.

Birth characteristics

Researchers have investigated possible associations of birth characteristics with childhood brain cancer. In a study of childhood cancer deaths

between 1947 and 1958 in the northeastern U.S., MacMahon and Newill observed increasing nervous system cancer mortality rates with increasing maternal age (61). Gold et al. in a case-control study of brain cancer found no effect of maternal age (49), while Choi et al. observed more mothers of cases under age 30 at the birth of the child than mothers of controls (80% vs 55%) (62). The last observation was derived from only 20 glioma deaths and 20 controls and was not significant.

The same researchers and others investigated the effect of birth order. Choi et al. found more first-born cases than matched controls in the categories of all gliomas, astrocytomas and medulloblastomas (62). Forty-five percent of the cases under age 20 with gliomas were first-born compared to 15% of the controls; the finding was of borderline significance. Similarly, in the study of Gold and her associates, the cases were more likely to be first-born than their matched normal controls (not significant). However, the cases did not differ from their matched controls with other malignancies (49). MacMahon and Newill reported no association with birth order in their study of deaths from nervous system cancers (61). Neither did Preston-Martin et al. in their study of tumors of the brain and its meninges (63).

The data on the association of birthweight and childhood brain cancer conflict. Cases (and their controls with other malignancies) were significantly more likely to have a birthweight of over 8 lbs than their normal controls (49). The observed association may have underestimated the effect as the children with brain tumors tended to have lower birth orders than normal children and first births tend to be of lower birth weight than subsequent births. Choi et al. observed a mean birthweight of children with brain tumors slightly higher than that of controls, but not significantly so (62). MacMahon and Newill observed a very small difference of .09 lbs in birthweights between children dying of brain

cancer and comparison births which consisted of the next birth certificate in file following that of the child who died (61). They suggested that the difference resulted from the inclusion of low birthweight premature births many of whom died before reaching the age of cancer risk. Preston-Martin et al. observed no association with birthweight (63).

The studies mentioned also investigated a miscellany of other factors. Among the 20 cases of glioma under age 20 in the case-control study of Choi et al., mothers of nine cases and three controls had experienced complications of delivery (p=.07) (62). The case mothers had had seven spontaneous abortions before the relevant pregnancy compared to one among the controls (p=.02). There were no differences in stillbirths and malformations. Preston-Martin et al., in their recent case-control study with 209 pairs, did not confirm the results on delivery and abortion (63). They found no association with prolonged labor, delivery by caesarean section, inhalation of gas during labor, use of forceps, or history of spontaneous abortion prior to the index pregnancy.

Thus, birth characteristics are unlikely to be risk factors for childhood brain cancer. The data conflict enough to suggest that no strong associations exist with birthweight, maternal age, previous spontaneous abortions, or complications of delivery.

Genetic factors, familial aggregation, and associations with other conditions

Researchers interested in genetic factors as possible risk factors for childhood brain cancer have studied the distribution of ABO blood types of patients with brain tumors, familial aggregation of brain tumors, and the occurrence of brain tumors in children with known genetic disorders. Gold in her review of the epidemiology of brain cancer (64) provides more information than will be discussed here.

Studies of the distribution of ABO blood types of patients with brain

tumors have yielded conflicting results. Yates et al. found a reduction of blood group O in children under age 15 diagnosed with astrocytoma after 1945 compared to earlier cases and controls (65). A study of patients of all ages with astrocytomas replicated the finding, which also seemed present in the small number of childhood cases (66). Several studies (62,67-69) observed no differences between cases and controls.

Two studies reported the familial aggregation of childhood brain tumors by comparing the observed and expected number of sibling pairs affected. After excluding twins and pairs in which one or both children had genetic diseases associated with brain tumors, Draper et al. observed eight pairs of siblings with brain tumors compared to about three expected (70). Miller observed eight sibling pairs, both of whom died in the U.S. between 1960 and 1967, with about one expected (71). Both studies also reported an excess of sibling pairs in which one had a brain tumor and the other had a cancer at a site other than the brain; the association of brain tumors and bone cancers in siblings was observed in both studies.

Findings of Gold et al. suggest that some childhood brain tumors may be part of a familial constellation of neurologic disorders (49). Children with brain tumors were more likely than normal controls (but no more likely than controls with other cancers) to have siblings with epilepsy or seizures. In addition, two mothers of cases had had epilepsy and three had had strokes relatively early in life. No mothers of controls reported these conditions.

Anecdotal case reports and a few small studies suggest associations between brain tumors and several genetic diseases and birth defects. Neurofibromatosis or von Recklinghausen's disease (autosomal dominant) has been associated with all types of gliomas, acoustic neuromas, and meningiomas by case reports (see 64). In addition, of nine adults with confirmed

neurofibromatosis who were identified through autopsy files, three had astrocytomas (72). A study of 48 cases of meningiomas in children and adolescents observed that 23% of the cases had neurofibromatosis (73). Anecdotal reports (see 64) and one study link another autosomal dominant disease, tuberous sclerosis, with intracranial tumors. In the study, of 48 patients with tuberous sclerosis, seven, all children, had intracranial tumors (74). Studies of the occurrence of brain tumors with Down's syndrome and spina bifida in the same individual or family suggest no association or a weak association (see 64).

Familial factors, then, may cause a small proportion of childhood brain cancers. These factors include genetic diseases, such as neurofibromatosis and tuberous sclerosis, as well as undefined genetic or environmental factors causing occurrence in pairs of siblings.

Environmental factors

Infections

1. Viral infections

A. Animal data

Certain DNA and RNA viruses induce CNS tumors in animals by intracerebral inoculation. Eight DNA-containing viruses (four papovaviruses and four adenoviruses) and four RNA-containing retroviruses, including avian sarcoma virus, have such capabilities (see 75). All the major cell types of childhood brain cancer can be induced by at least one of these viruses. The tumors have been induced in rats, hamsters, monkeys, and other animals, although not all viruses have been shown to have neuro-oncogenic properties in all animals (see 75).

B. Epidemiological studies

Some evidence links papova viruses to human brain tumors. The epidemiological evidence comes from studies of the effect of Salk polio vaccine during pregnancy. Some batches of the vaccine were contaminated with live,

infectious simian vacuolating virus 40 (SV40), a papova virus that was unknown at the time (see 75). The Salk vaccine was prepared by growing poliovirus in rhesus monkey cells. SV40, endogenous (integrated into the host DNA) to the rhesus monkey, resisted the treatment used to kill the poliovirus. SV40 isolated from some batches of the vaccine induced brain tumors in hamsters.

Heinonen et al. studied the outcome of 50,897 pregnancies that occurred between 1959 and 1966 (76). Of 18,342 children whose mothers had been vaccinated with Salk vaccine during pregnancy, 14 developed malignancies before age one or died of a malignancy before age four, for a rate of 7.6 per 10,000. The corresponding rate for the 32,555 children of mothers not vaccinated during pregnancy was 3.1 per 10,000 based on ten cases. The rates differed significantly ($p<.05$). If only those children exposed during the first four months of pregnancy were considered, the rate was 13.2 per 10,000. Seven of the 14 tumors in exposed children occurred in the CNS (although only two in the brain as defined in the present study) compared to one of the ten tumors in nonimmunized children. The authors did not discuss the likelihood that contaminated vaccine was used in the years of the study.

Another study compared a random sample of CNS cancer cases aged 0 to 19 to birth certificate controls. The cases had been reported to the Connecticut Tumor Registry and were born between 1956 and 1962. Farwell et al. observed that 37% of the cases (19/52) and 21% of the controls (8/38) had been exposed to the contaminated vaccine (77). The difference is suggestive but not significant ($p=.15$). However, 50% of the tumors in SV40-exposed children were medulloblastomas compared to 25% of all childhood CNS cancer cases reported to the tumor registry in the same period ($p<.01$). The small numbers and large degree of nonresponse complicate interpretation of the results.

Postnatal exposure to SV40 has, in general, not been associated with

increased cancer risk. Innis compared children hospitalized between 1958 and 1963 for a malignancy with a hospital control group (78). The cases and controls did not differ in the proportion immunized against polio. However, 88% of the cases over one year of age had been exposed to the vaccine compared to 81% of the matched controls ($p<.001$). Innis did not state which children were given the SV40-contaminated vaccine nor the types of malignancies that the children developed. Stewart and Hewitt, in a similar study, found no association between immunization against polio and childhood cancer (79). Mortimer et al. studied children vaccinated as neonates (80). None died of cancer in the 17 to 19 years following vaccination, but only one such death was expected.

If papova viruses cause brain tumors, then researchers should be able to isolate virus from, and/or detect viral antigens in human tumors as in induced animal tumors. So far, only 36 of 336 human intracranial tumors studied have been positive for a papova virus antigen called large T antigen (see 75). However, data exist suggesting that the insufficient sensitivity of the assay, the production of structurally abnormal T-antigen by tumors, and/or tumor interference with antigen production may account for the apparent lack of antigen. Two reports claim the isolation of papova viruses themselves from human intracranial tumors--a reticulum cell sarcoma and a glioblastoma (81).

A few investigators have reported associations of childhood cancer with other maternal viral infections during pregnancy. Stewart et al. observed ten viral infections during the relevant pregnancy in the mothers of children who died of cancer but only one such infection in the mothers of controls (46). The distribution of the ten cases by site did not differ from the usual distribution of childhood cancers. A later report used data from the same survey but, by the early 1970s, data on 9000 case-control pairs had been collected and analyzed compared to 1400 in the earlier paper. Using the 9000 pairs, Bithell et al.

observed a significantly increased risk associated with influenza and chickenpox, and an almost significant increase associated with rubella infection during pregnancy (82). The distribution of the cases associated with influenza and, presumably, those associated with rubella were distributed by site as were all childhood cancers. However, two or three (one diagnosis was ambiguous) of the seven chickenpox-associated cases were medulloblastoma; less than one medulloblastoma was expected among the seven cases. The authors point out that varicella virus tends to persist in nervous tissue. They considered unlikely the possibility that recall bias explained the results; the accuracy of the mothers' reports which could be verified did not differ between cases and controls, nor did the reported frequency of common conditions of pregnancy.

Other studies found no excess of cancers or an excess of only leukemias after maternal viral infections. Fedrick and Alberman observed an increased risk of death from cancer associated with maternal influenza, but only leukemia occurred in excess (83). Adelstein and Donovan reported an excess of leukemia but not other cancers associated with chickenpox; however, the cohort of exposed mothers was only 270 (84). Leck and Steward did not observe an increase in the incidence of leukemia or other neoplasms in children born after influenza epidemics in the 1950s and 1960s (85).

2. Other infections

A few studies report on the association of brain cancer with certain previous infections in the patient. Ward and his associates found that 22% of adult patients with gliomas but only 7% of hospital controls had had tuberculosis ($p<.01$) (86). The authors suggested that development of both gliomas and tuberculosis may result from an impaired immune system. Another study, however, used three times as many cases and controls (300 cases, 300 controls) and found no association (87). The two studies differed in the control group used.

The latter study used patients seen for spinal conditions, intracranial lesions, and peripheral neurological lesions, while the first used patients admitted to general medical units.

Schuman and colleagues tested the sera of 126 patients of all ages with histologically verified CNS tumors and hospital controls for toxoplasma antibodies (88). They observed that 56% of the cases and 41% of the controls tested positive, a significant difference (p=.02). The largest difference occurred in the astrocytoma group; 60% of the cases and 31% of the controls had toxoplasma antibodies (p=.02). The difference existed for all age groups, including ages 0-19. Toxoplasma is a protozoa often infecting humans but seldom causing recognizable disease. Contact with chickens (Kimball), other domesticated fowl (89), cats (90), and raw and undercooked meat (90) increased the probability of human infection. In addition, glioma-like tumors have occurred in chickens spontaneously and experimentally infected with toxoplasma (91).

Associations of childhood cancers with animal contact support infectious agent hypotheses. Gold et al. found that more of the children with brain tumors (and of those with other malignancies) reported exposure to farm animals (OR=4, p=.04) and to sick pets (OR=4.5, p=.07) (49). Of the recent studies that investigated the association of childhood cancers with parental occupation, one found no excess of fathers who were farmers (92), while two others found suggestive, rather weak associations (48, 93). In one (93), the OR for all malignancies was 1.2 and was significant at the .05 level; the OR for brain cancer was similar but not significant.

3. Summary

The evidence to date, then, suggests papova virus, chickenpox, and infections associated with animal contact as possible risk factors for childhood brain cancer. Although the epidemiological evidence on prenatal exposure to

polio vaccine contaminated with SV40 is not convincing, it is supported by animal data and the recent isolation of SV40 and a related virus from human brain tumors. Some evidence also suggests that maternal chickenpox infection may be a risk factor for childhood brain cancer. This association based on only three cases may be spurious or indirect, of course. If it is causal, the attributable risk would be small since only three of about 450 medulloblastomas occurred in association with chickenpox. Infections associated with animal contact may also be risk factors. Associations with toxoplasma antibodies, exposure to farm animals, and farm residence support a zoonotic hypothesis.

Radiation

Since radiation causes cancer in animals and humans, epidemiologists have studied the relationship of radiation exposure and childhood brain cancer. Follow-up studies of children whose scalps were irradiated for tinea capitis (ringworm of the scalp, a fungal disease) provide evidence of the ability of x-rays to cause brain cancer. Modan et al., using a retrospective cohort design, followed about 11,000 irradiated children and their matched controls for 13 to 24 years (94). Eight malignant and eight benign brain tumors ocurred in the irradiated group compared to 2 brain tumors in the control group. The authors did not give the statistical significance of this result but the increase for all head and neck neoplasms was significant ($p<.01$ for malignant and $<.05$ for benign). Another study followed about 2200 children irradiated for tinea capitis and 1400 controls treated for the same disease during the same time period without x-ray therapy (95). Six brain tumors occurred in the irradiated group but none among controls ($p=.07$). In both studies, the exposed and control groups experienced the same incidence of neoplasms outside the head and neck area.

Prenatal exposure to x-rays may also contribute to the etiology of childhood brain cancers. Stewart et al. observed an odds ratio of 1.9 ($p<.001$)

for abdominal x-ray examinations during pregnancy in a case-control study of all childhood cancer deaths before age 10 (46). The association held for cancers of most sites including the central nervous system. MacMahon confirmed the results in a study using objective evidence of intrauterine x-ray exposure rather than recall of the mother (47). Children exposed *in utero* had a risk of leukemia, CNS, and other cancers 30-40% higher than unexposed children, after correction for possible confounders such as birth order and demographic variables. The excess risk appeared to be exhausted by age 8 in this study but not in that of Stewart et al. (46). Salonen and Saxen found an association of pelvimetry with leukemia (not significant) but not brain cancer (96). The sample size was twice that but the prevalence of fetal x-ray about half that in MacMahon's study. Thus, the power of the two studies was similar. Preston-Martin et al. in their case-control study of brain tumors (including meningiomas) occurring before age 25, observed a nonsignificant OR of 1.3 associated with pelvic x-ray during pregnancy (63).

Radiation treatment during childhood appears to be a risk factor for childhood brain cancer. The data on prenatal radiation are for the most part convincing although not entirely consistent. Differences in x-ray dose and practices between time periods and countries might explain the inconsistent findings. For example, the two large studies with positive findings used cases dying in the late 1940s and 1950s, while the cases in the large study that observed no effect occurred in 1959-68.

Chemical Agents

1. Animal data

The information on neuro-oncogenesis in experimental animals was obtained from a review by Kleihues, unless otherwise noted (97). Researchers have demonstrated that more than 40 compounds cause tumors in experimental

animals if administered during fetal or early postnatal development. These developmental carcinogens induce tumors at sites that vary among species. In rats, malignant gliomas of the CNS, malignant neurinomas of the peripheral nervous system and, less commonly, nephroblastomas occur most frequently. Mice, on the other hand, respond with an increased incidence of benign tumors of the respiratory tract (adenomas) and the liver (hepatomas). Researchers have demonstrated transplacental carcinogenesis of the nervous system in rats, mice, hamsters, and rabbits and early postnatal carcinogenesis in rats, gerbils, and opposums.

Humans have widespread exposure to one class of developmental carcinogens that act on the nervous system, the N-nitroso compounds. These compounds exist in cigarette smoke, food, beer, makeup, and other commonly encountered substances (98). In addition, nitrosamines and nitrosamides, two types of N-nitroso compounds, can form in the body from their chemical precursors, amines and nitrites.

Neurogenic carcinogenicity in fetuses and newborns differs from the process in adult animals. While only repeated administration of carcinogens will produce a high incidence of neurogenic tumors in adults, a single dose given perinatally suffices to induce tumors in 90-100% of experimental animals. Fetuses also show a greatly increased susceptibility to many carcinogens. The neuro-oncogenic chemicals exert their effects at concentrations which have little effect in the pregnant female. This is particularly true for ethylnitrosourea, an N-nitroso compound that induces neural tumors transplacentally in half of the experimental animals at a level 1/50 of that required for the same effect in adults. The latency period is decreased as well. Thirty day old rats develop nervous system tumors after a latency period 2.5 times longer than newborn rats given a similar dose. The organs in which tumors occur after exposure to a

particular chemical differ in adults and fetuses. DMBA induces predominantly neurogenic and renal neoplasms transplacentally, but causes mammary tumors in young female rats.

The sensitivity of the nervous system to transplacental carcinogens varies with the time of exposure. For example, transplacental carcinogens induce neurogenic tumors only when exposure occurs after day 11 of gestation, even though carcinogens do penetrate into fetal tissues before that. The susceptibility of the nervous system increases after day 11 and peaks during the final period of intrauterine development. After one month of age, young rats respond to neuro-oncogenic agents as adults do.

The organ in which tumors occur also can vary with the stage of gestation during which exposure occurs. In rabbits, exposure of fetuses to ethylnitrosourea induces neurogenic tumors with exposure during the early stages of gestation and renal neoplasms with exposure at later stages.

These animal data have implications for the etiology of childhood brain cancer in humans. First, exposure to carcinogens during gestation could cause childhood brain tumors, especially as, in animals, the fetal nervous system is more susceptible to carcinogens than the nervous system in adults. According to one researcher, the same is probably also true of the human nervous system, as the animal data are very consistent across species (99). Most other organ systems do not exhibit this increased prenatal susceptibility. Second, brain tumors in children and adults may have different etiologies. A chemical that causes nervous system tumors in anmals after prenatal exposure often causes tumors of a different system or organ with postnatal expposure. Finally, carcinogens that induce tumors other than those in the nervous system are still potential nervous system carcinogens in humans, as a chemical may cause nervous system tumors in one species but other tumors in a second species.

2. Epidemiological studies

A. Parental occupation

Transplacental exposure to carcinogens could occur through the occupational exposure of the parents--either through the mother's exposure on the job or through substances brought home on the father's skin or clothing. That indirect exposure through a parent's clothing can cause illness has been documented in several cases (100).

Researchers have investigated parental occupation as a possible route of exposure to transplacental carcinogens. Several methodologic problems exist in these studies. Parental occupation only measures exposure in a very crude way. The chemicals to which the parent (and fetus) are exposed are surmised but not known. The level of exposure is also not known since that depends on the circumstances of each person's job. The validity of occupational information from birth certificates, which is used in some studies, may not be high. All the studies suffer from the large number of occupations leading to groupings of different occupations or odds ratios based on small numbers. The large number of occupations also leads to the problem of multiple comparisons and chance associations.

Fabia and Thuy observed that 386 children who died of cancer under age 5 were more likely than controls to have fathers in hydrocarbon-related occupations (92). The association, however, was only slight for nervous system cancers, but pronounced for leukemia and all other malignancies. Fabia and Thuy's study motivated a spate of case-control studies which sought to replicate and expand the findings. The studies differed in size, source of occupational information, and use of incident or death cerficate cases. All but one include children up to age 15 or 16, while Fabia and Thuy used only the youngest cases. Zack et al. with 296 (52 nervous system) cases (101), Sanders et al. with 6920

(1921 brain) cases (48), Kwa and Fine with 692 (132 CNS) cases (102), and Hakulinen with 852 (219 brain) cases (103) observed no association with hydrocarbon-related occupations. Hakulinen analyzed the youngest cases separately as well as with the other cases.

Hemminki et al. found paternal occupation as a motor vehicle driver or painter to be significantly associated with childhood cancers (93). For brain tumors, paternal occupations of painter or machine repairman (but not motor vehicle driver) showed significant or borderline associations. Another study also offered some support of Fabia and Thuy's findings. Peters et al. observed a significant association of paternal exposure to solvents, especially paints, with brain cancer in children under age ten (104). They also observed an excess of fathers working in the aircraft industry, an association of high statistical significance.

Other findings from these studies include associations with paternal employment as a paper or pulp mill worker (102), paternal occupation as a professional (48), maternal exposure to chemicals (104), maternal occupation as a baker, factory worker or pharmacist (93), and maternal employment the year before pregnancy (104). The associations mentioned were significant for brain tumors or significant for all cancers and present for brain tumors to a similar degree.

The finding of Fabia and Thuy that paternal hydrocarbon-related occupation was associated with childhood cancer has not been replicated. However, other associations with parental occupation have been observed that should motivate further study. Of particular interest is the association, observed in two studies, with parental exposure to paints.

B. Other chemical factors

Two recent matched case-control studies of childhood brain cancers

have investigated a variety of chemical factors (49, 63). Maternal smoking during pregnancy and child's residence in a home treated by an exterminator showed no significant association in either study. Preston-Martin et al. (63) solicited information on exposure to N-nitroso-compound-containing substances, as these compounds cause nervous system cancers in animals, particularly when the exposure is transplacental. Beer, cigarette smoke, incense smoke, and cosmetics contain nitrosamines. Maternal smoking as mentioned above and beer consumption were not associated with brain cancer. However, the investigators observed significant associations (p-values .005 to .02) with living with a smoker, burning incense, and using makeup frequently during pregnancy. Meats cured with sodium nitrite contain nitrosamines and the precursors of nitrosamines. Consumption of cured meats by either the mother during pregnancy or the child was significantly higher in the cases than the controls. The odds ratio for high compared to low consumption was 2.3 (test for trend p=.008 maternal, p=.01 child). No association was observed with consumption of high nitrate vegetables.

The same study by Preston-Martin et al. also reported significant associations with antihistamines, diuretics, and general anesthesia during pregnancy. Kinnier-Wilson and associates studied the use of drugs during pregnancy and childhood cancer deaths (105). They found significant associations of all drugs, sedatives, and other and unspecified drugs with ORs of 1.4 to 2.6 when controlled for prenatal x-rays. The ORs for exposure to these drugs along with x-rays ranged from 1.8 to 3.4. No effect of hormones was observed. Comparisons with the study of Preston-Martin et al. are difficult since Kinnier-Wilson did not report results for brain cancers separately. Preston-Martin et al. observed no association with the use of sedatives.

Barbituates present a more complicated picture, as one of their

common uses is treatment of epilepsy or seizures, often an early symptom of a brain tumor. Preston-Martin et al. observed an association with drugs used to control seizures, but not with other barbituates, and, thus, attributed the association to epilepsy as an early symptom of brain cancer (63). Gold et al. observed a nonsignificant OR of 2.5 for use of barbituates prior to diagnosis in a very small study (106). They also observed associations, based on small numbers, with maternal use of barbituates during pregnancy.

Conclusion and study rationale

In spite of substantial research, little is known of the etiology of childhood brain cancer. The studies of brain tumors in individuals receiving radiation to the scalp as children present perhaps the most convincing evidence of a causal environmental factor. Prenatal x-ray exposure probably also causes brain cancer, but the evidence is not altogether consistent. The genetic diseases--neurofibromatosis and tuberous sclerosis--and unknown familial genetic and/or environmental factors also predispose to brain tumors. The evidence linking childhood brain tumors and prenatal or postnatal infections is not convincing but suggestive. The evidence consists of associations with toxoplasma antibodies, exposure to farm animals and sick pets, and *in utero* exposure to chickenpox and contaminated polio vaccine. The observation of a higher proportion of farm residents among young brain cancer deaths also contributes to the evidence. Weak associations of having a father who is a farmer occurred in two of three studies. The evidence on the relationship between birth characteristics is so contradictory that it suggests that these are not risk factors. More recent findings on parental occupation and exposure to N-nitroso compounds and drugs are preliminary.

The most convincing evidence exists for factors which would explain only a small proportion of childhood brain cancers because of low relative risks

and/or the rarity of the exposure. Thus, most childhood brain tumors remain unexplained. The general lack of consistent associations suggests the need for a thorough study of the descriptive epidemiology and geographic variation by cell type. Although the age-incidence curves and sex-ratios differ for the major cell types and, thus, suggest distinct diseases, very few studies have investigated the cell types separately. Most of the studies that did separate the cell types reported results based on very small numbers. Thus, a study of the descriptive epidemiology and geographic variation of childhood brain cancer by cell type in a large data set would provide useful information and, it is hoped, generate new etiologic hypotheses. For each cell type, the present study indicates time trends, sex ratios, geographic variation, racial differences, urban-rural differences, and socioeconomic differences. ws, in animals, one virus or chemical often causes tumors at several sites, the sex, race, age and SES of childhood brain cancer cases was compared to the epidemiologic profile of childhood leukemias, the most common childhood malignancies. Similar epidemiological profiles would imply similar etiologies.

CHAPTER 2

Methods

Introduction

This chapter describes the source of case and population data from which rates by geographic area, race, sex, cell type, and combinations of these were calculated. The case data alone were used for comparing the distributions of demographic variables among cell types, and the distributions of cell types between blacks and whites, and males and females. The methods for analyzing urban-rural and population density differences in rates are described, as are other analyses using adult brain cancer rates, leukemia cases, median census tract income, and physician concentration. The statistical methods for testing the significance of the results of analyses are also presented.

Case data

This study used case data from the population-based registries of the Third National Cancer Survey (TNCS) and the Surveillance, Epidemiology, and End Results (SEER) programs of the National Cancer Institute (NCI). The TNCS program reported all cases of cancer diagnosed in 1969-71 in the states of Colorado and Iowa and in the standard metropolitan statistical areas (SMSAs) of San Francisco - Oakland, Atlanta, Birmingham, Detroit, Minneapolis, Pittsburgh, and Dallas - Fort Worth. The ongoing SEER program began in 1973 and covers the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah; the SMSAs of San Francisco - Oakland, Atlanta, New Orleans and Detroit; and the Puget Sound region of Washington, including the SMSAs of Seattle and Tacoma and several rural counties. Puget Sound did not begin surveillance until 1974 and Atlanta not until 1975. NCI user tapes supplied the TNCS data and the SEER data of

1973-80.

This study included childhood brain cancer cases reported by TNCS and SEER registries in the years 1969-71 and 1973-80, respectively. Childhood brain cancers were defined as those occurring under age 15 in the brain (ICD-0 site code 191). Cases occurring in the spinal cord or in an unspecified part of the nervous system were not included. Cases from the registries reporting 20 or fewer white cases--Hawaii, New Orleans, and Birmingham--were excluded since unstable cell type-specific rates would result. The other 12 TNCS and SEER registries reported a total of 1210 brain cancers in children under age 15; of these, 1053 occurred in whites and 140 in blacks. The TNCS (1969-71) registries reported 384 cases and the SEER (1973-80) registries reported 826 cases.

When this work began, SEER data beyond 1977 was not available. John Horm of NCI supplied partial data on the 1978-80 cases, which were used in early analyses before the new SEER user tape was available. The new user tape with 1973-80 data contained four more cases than the combination of the original SEER data (1973-77) and the supplemental data (1978-80) from John Horm. Because of this discrepancy of four cases, numbers of cases may differ slightly among analyses.

Only 1.5% of the cases were first diagnosed at autopsy. These cases were included as it is likely that a brain tumor found at autopsy in a child would be the cause of death and not an incidental finding. In addition, these cases were few and evenly distributed among the histologic groups (Table 3), and thus, would hardly affect the results. However, a higher proportion of black than white cases were first diagnosed at autopsy.

Table 3.

Percent (and number) of cases of childhood brain cancer first diagnosed at autopsy
By histologic group
12 TNCS and SEER registries

Cell type	Whites		Blacks	
	Percent	No.	Percent	No.
Astrocytoma	1	7	5	3
Medulloblastoma	1	2	3	1
Ependymoma	3	2	25	2
Oligodendroglioma	0	0	0	0
Glioma NOS	0	0	0	0
Cancer NOS	0	0	0	0
Other	0	0	0	0
Total	1	11	4	6

Histologic diagnosis was microscopically confirmed for 89% of the white cases and 84% of the black cases. The majority of the unconfirmed cases occurred in the glioma NOS group. Only small proportions of astrocytomas, medulloblastomas, ependymomas, and oligodendrogliomas were not confirmed (Table 4). As expected, a large proportion, about 50%, of the glioma NOS and cancer NOS cases were not histologically confirmed. To make the cell type groupings as precise as possible, unconfirmed cases of astrocytoma, medulloblastoma, ependymoma, and oligodendroglioma were excluded from histologically specific groups and placed in the glioma NOS group. These decisions on autopsy diagnosed and unconfirmed cases are unlikely to have affected the analyses that follow because of the small numbers and the fairly even distribution of these cases among geographic area, sex, and race subgroups.

Table 4.

Microscopically unconfirmed cases of childhood brain cancer by histologic group and race
12 TNCS and SEER registries

Histologic type	Whites	Blacks
Astrocytoma	11	0
Medulloblastoma	2	0
Ependymoma	0	0
Oligodendroglioma	1	1
Glioma NOS	84	20
Cancer NOS	15	2
Other	0	0
Total	113	23
% of all cases	11%	16%

As the data were used for analyses of geographic variation, one would like to assess the geographic variation of the completeness of case reporting. The TNCS and SEER programs used the percent of cases with information only from a death certificate as one measure of completeness of reporting. (The registries gather information from the signing physician on cases initially identified by death certificate. If the physician provides no further information, the registry considers the case a "death certificate-only" case.) The proportion of death certificate-only cases measures completeness of reporting in that the registry did not find these cases through its surveillance activities. However, other cases also evaded the surveillance system—those initially identified by death certificate but for which the signing physician provided more information and those cases which the registry did not find but who did not die. If the number of these two kinds of cases is proportional to the number of death certificate-only cases, we can use the latter quantity to assess the completeness of reporting.

The proportion of brain cancer cases ascertained by death certificate only was 1.9% for all SEER areas combined, 1973-77, and ranged from 0% in

Atlanta to 4.3% in New Mexico (8). For the TNCS areas, the same figure was 2.5%; it varied from 0.4% in Minneapolis to 5.1% in Pittsburgh (7). Since only 15 death certificate-only cases occurred in children under age 15 in 12 areas, it was not possible to calculate meaningful percentages for children.

Population estimates

Midyear population estimates were calculated for the years 1970 and 1973-80 by linear interpolation of 1970 and 1980 census population figures. State or county level figures were used for statewide and metropolitan registries, respectively. Midyear estimates were summed to obtain population estimates for 1973-76 and 1977-80. Three times the 1970 midyear population figure was used as the total population figure for the years 1969-71; extending the line between 1970 and 1980 back to 1969 and summing the 1969, 1970, and 1971 estimates would give the same estimate for the three year period. Adding the 1969-71, 1973-76, and 1977-80 estimates provided an estimate for the entire period of 1969-80, excluding 1972 and some years in some registries during which no data were collected.

Population data for whites came from the revised counts by age and sex from the 1970 Census. The Census Bureau revised the original 1970 counts in order to compensate for errrors in the census tabulation of centenarians and of nonspecified races and to provide estimated age-race-sex distributions for corrections that changed a county total (107). The 1980 Census of the Population and Housing, Summary Tape File 2 (STF2) provided the 1980 counts for whites. Linear interpolations provided population estimates for the 0-4, 5-9, and 10-14 age groups by sex. For adult population estimates, interpolations were calculated for ten-year age groups. Population estimates for nonwhites (used in only one analysis) were calculated exactly as were those for whites.

Black population counts by age and sex for 1980 were not available to

me at the time this work was done. Instead, this study used the estimates for blacks based on sample data from the 1980 Census Summary Tape File 3 (STF3). Actual population counts for blacks were, however, available by age but only for both sexes combined. The accuracy of the sample data relative to the actual counts was estimated by comparing the populaton figures from the two sources for both sexes combined. Comparisons were only possible and relevant for the under age five group. The differences between the actual counts and the sample estimates ranged from 0.04% (five persons) in Pittsburgh to 4.6% (46 persons) in Utah. For the combined 12 TNCS and SEER registries used in the analyses, the sample data gave an estimate 0.12% higher than the actual count. Thus, the sample data differed little from the population counts for blacks under five years of age. Only two age groups under age 15 were available from the sample data. Interpolation provided estimates for the 0-4 and 5-14 year age groups for males and females.

For analyses done on the county level (e.g., the urban-rural analysis), the same interpolation was done using the population counts of individual counties. Three counties in Colorado changed boundaries between 1970 and 1980, making the interpolation inaccurate. For these counties (Adams, Arapahoe, and Denver), which are all in the Denver area, three times the 1970 count, rather than the midyear 1970 estimate, was used for the 1969-71 period. The difference between the 1970 count and the 1970 midyear population is the difference in the population size between mid-April when the census is taken and July 1 and is, presumably, small. Since Colorado participated in the TNCS but not the SEER program, no other population estimates were required.

Rates

Average annual incidence rates were calculated using, as the numerator, all cases diagnosed in the specified time period and population subgroup

and, as the denominator, the sum of the midyear population estimates for the specified years. Rates were calculated for many subgroups including geographic area, cell type, sex, race, and residence (urban or rural). Unless otherwise specified, reported rates are crude incidence rates per million per year. When rates were age-adjusted, the 1970 U.S. white population was used as the standard. Age-adjusted and crude rates hardly differed in analyses for children under age 15.

Leukemia cases

Childhood leukemia cases were compared to childhood brain cancer cases by cell type to investigate differences in the distribution of demographic variables. Data on childhood leukemia cases under age 15 were extracted from the TNCS and SEER tapes and processed identically to the brain cancer cases. The exclusions used for the brain cancer cases were applied to the leukemia cases. The two major childhood leukemias, acute lymphocytic leukemia (ALL) and acute granulocytic leukemia (AGL) accounted for 67% and 14% of the white cases under age 15, respectively. A sizeable proportion of cases, 10%, was diagnosed as acute leukemia NOS (ALNOS), and would be likely to include some ALL and AGL cases. The other NOS categories in which ALL and AGL cases could fall (lymphoid leukemia NOS, granulocytic leukemia NOS and leukemia NOS) together accounted for only 2.4% of the cases. The proportion of cases diagnosed as ALNOS varied greatly among registries, from 0% in Colorado and Minneapolis to about 30% in Detroit. In addition, the ALNOS rate declined over the time period, while the rate of ALL increased and that of AGL remained the same (Table 5). If the ALNOS cases had a similar distribution of cell types as acute leukemias with specified diagnoses, most ALNOS cases actually would have been ALL cases and few would have been AGL. Therefore, analyses involving ALL cases had to be adjusted for the geographic and temporal variation in ALNOS rates. To

do so, comparisons of ALL with a type of childhood brain cancer were done in two ways, with only the ALL cases and with the ALL and ALNOS cases combined.

Table 5.

Time trends in childhood leukemia incidence, 1969-80
SFO, Detroit, and Iowa combined
Whites, age 0-14
Rates per million per year
(Number of cases)

	1969-71	1973-76	1977-80
ALL	24.6 (178)	27.5 (228)	36.8 (262)
AML	6.4 (46)	7.5 (62)	5.6 (40)
ALNOS	10.0 (72)	8.6 (71)	2.4 (17)

Adult brain cancer rates

To investigate geographic correlation with childhood rates, adult brain cancer rates by cell type were calculated for the 12 TNCS and SEER registries using cases aged 25 and over and interpolated population figures for ten-year age groups. The rates were age-adjusted by ten-year age groups to the 1970 U.S. white population.

Urban-rural analyses

Urban-rural differences were investigated using data from the five registries which covered entire states. These states were Connecticut, Iowa, Colorado, Utah, and New Mexico. Iowa was studied separately because of its geographic distance from the other three states and because the numbers of cases permitted such an analysis. Utah, Colorado, and New Mexico were combined because of their geographic proximity and the small number of cases in any one of these states. Analyses of urban-rural differences were generally not done for Connecticut because its division into only eight large counties precluded any precise categorization of urban and rural. However, ependymoma rates were

studied, since only Connecticut had enough cases to permit investigation of possible urban-rural differences.

For urban-rural analyses, counties with similar levels of urbanization were grouped together and rates calculated for each level. This study divided the counties of Iowa and the three southwestern states into urban and rural categories in two ways. In the first analysis (Method I), counties were divided into low, moderate, and high levels of urbanization based on the census variable, percent of population living in places of 2500 or more inhabitants. Counties with less than 50% of their population urban by this definition were classified as not urbanized, counties with between 50% and 75% of their population urban as moderately urbanized, and counties with more than 75% of their population urban, as highly urbanized. Counties which would have been placed in different categories based on the 1970 and 1980 values of the variable were categorized by the following scheme: counties in TNCS-only registries were categorized based on 1970 values; counties in SEER-only registries, on 1980 values; and counties in registries that participated in both TNCS and SEER, by the mean of 1970 and 1980 values.

For the second analysis (Method II), counties were classified by a different variable, percent of the population living in urbanized areas. In 1980, the Census Bureau defined an urbanized area as an incorporated place and adjacent densely settled surrounding area that together have a minimum population of 50,000. Counties were divided into those with less than 10% of their population living in urbanized areas and those with 70% or more of their population living in such areas. Only five counties (one in Iowa, one in Colorado, and three in New Mexico) had between 10% and 70% of their population living in urbanized areas. The number of cases in these counties did not permit analysis of this intermediate level of urbanization. Several Iowa counties with high levels of

urbanization by Method II were of only moderate urbanization by Method I, as between 70% and 74.9% of their inhabitants lived in cities of 50,000 or more. The same scheme described above for Method I was used to allocate counties in which the percent of the population living in urbanized areas changed dramatically between 1970 and 1980.

Two reasons motivated the use of more than one definition of urban. First, the small numbers of cases used in these analyses resulted in unstable rates. Thus, an urban-rural difference observed by both methods would increase one's confidence in the finding. In addition, the two methods emphasize different aspects of urbanization. If farm residence were a risk factor, one would expect to see a larger urban-rural difference by Method I, since by Method II counties whose residents lived in small cities of less than 50,000 would be classified as rural and would dilute the effect of farm residence. By similar logic, Method II would show a larger urban-rural difference if the risk factor were associated with large cities. Counties with many small towns would be classified as highly urbanized by Method I and would dilute the effect of city life.

Urban-rural differences in ependymoma rates were studied only in Connecticut where the number of cases permitted such analysis. The large size of the counties in that state necessitated a different urban-rural classification from that used for Iowa and the southwestern states. The scheme used relied on the urban definition of Method II, percent of population living in urbanized places of 50,000 or more inhabitants. The use of Method I would have resulted in a similar division of counties. The three counties with 25% or less of their populations in urbanized areas were classified as of low urbanization. Three counties were classified as highly urbanized as more than 85% of their populations lived in urbanized areas. In the remaining two counties, 42% and 62% of the people lived in urbanized areas. These counties made up the stratum of moderate

urbanization.

Population density

This study investigated whether childhood brain cancer rates in urban areas varied with the population density. Only counties with more than 70% of their population living in cities of 50,000 or more in 1980 were included. Since the 1980 value of the urbanization variable was used, all TNCS (1969-71) cases were excluded and only the SEER (1973-80) cases used. The 1980 population density was calculated for all counties in SEER registries using the area of the county in square kilometers and the 1980 total population.

The counties were divided into four strata of population density--fewer than 100, 100-350, 351-700, and more than 1500 persons per square kilometer. No counties had between 700 and 1500 persons/sq. km. Rates were calculated for each stratum.

Physician concentration

The concentration of physicians was calculated from data published in the 1977 County and City Data Book (108). The number of professionally active, non-Federal physicians and the concentration per 100,000 population in 1975 is given for each county. These data were used to calculate denominators and then, by combining counties, the concentration for each TNCS and SEER area.

Socioeconomic status

As an indicator of socioeconomic status, each white case with a valid census tract number was assigned the median family income for whites in that census tract, as reported in the 1970 census. Since census tracts change rapidly in socioeconomic character, 1970 median income would not be accurate for cases diagnosed in the late 1970s. Thus, analyses using these data included only the TNCS (1969-71) cases. Only six TNCS cases residing in counties within metropolitan areas (SMSAs) lacked valid census tract numbers and had to be

excluded from the analyses.

A mean for the general population was calculated by weighting the median income of the 4362 census tracts by the tracts' white population under 15 years of age. Census tracts with suppressed income data were excluded, resulting in the exclusion of about 130 children out of about 4.4 million. Also excluded were census tracts in counties outside SMSAs, as census tract numbers for cases in these tracts were not reported in the TNCS data.

Statistical tests

Distributions of sex, age, cell type, race, and other variables were compared among groups using χ^2 tests. In the analyses of geographic variation, the proportions of cases and noncases were compared across areas and tested for significance using the χ^2 statistic. Either the student t-test or analysis of variance was used to test the significance of differences between two means of age or income, and analysis of variance for differences among three or more means. The difference in mean income between cases and the general population was tested using a weighted t-test. Pairs of rates were compared by the Z-test for proportions. Changes in rates with time were tested using the χ^2 test for trend of quantitatively ordered proportions (109). For trends in rates across strata of population density and degree of urbanization, the same test, but for qualitatively ordered proportions was used (109). Spearman's rank correlation coefficients were calculated for brain cancer rates and another rate or variable to assess covariation across geographic areas.

CHAPTER 3

Histologic Classification

Introduction

This chapter explains the development of the groupings of histologic diagnoses used in this study. Many clinical and epidemiological researchers have observed astrocytoma, medulloblastoma, glioblastoma, and ependymoma to be the most common cell types of brain cancers in children. Astrocytoma and glioblastoma were combined into a single histologic group for epidemiological and biological reasons. This combined group, medulloblastoma, and ependymoma became the three specific glioma groups for which analyses are reported throughout this study. Gliomas NOS were numerically important and, because of their potential to affect rates of specific cell types, epidemiologically important. In addition to the four histologic groups mentioned, three minor histologic groupings were used. The last section discusses the possibility of bias caused by nonspecific diagnoses and the method used in this study to avoid such bias.

Grouping of histologic diagnoses

The TNCS program classified cancers by the Manual of Tumor Nomenclature and Classification (MOTNAC) (110), while the SEER program used the International Classification of Diseases for Oncology (ICD-O) (5). The more recent ICD-O scheme separates many MOTNAC histologic diagnoses into two or more diagnoses. The childhood brain cancer cases represented approximately 30 different histologic types in the ICD-O classification. Table 6 shows the histologic types and notes those not included in the MOTNAC classification. This study required a classification scheme that would meet the usual epidemiologic requirements, i.e., one that would include reasonably large numbers of cases in

each category without lumping together etiologically different tumors. The validity and power of the data analysis obviously depended on the classification used.

The development of the histologic groups was based on the analysis of time trends by cell type. Table 7 shows the incidence by histologic diagnosis for the combined three registries which reported data for all 11 years of the study period. Dramatic changes in the incidence of some cell types suggested that changes in diagnosis had occurred. In such circumstances, an epidemiologically sound histologic group would contain more than one cell type. Cell types with unchanging rates over time were considered to be single disease entities.

Table 6.

Childhood brain cancer cases by detailed histologic diagnosis
Whites and Blacks
12 TNCS and SEER registries

Histology	Whites	Blacks
Glioma NOS	145	28
*Mixed glioma	8	1
Choroid plexus papilloma	2	1
Ependymoma	75	7
*Ependymoma, anaplastic type	6	1
Astrocytoma NOS	275	26
*Astrocytoma, anaplastic type	2	1
Protoplasmic astrocytoma	4	0
Fibrillary astrocytoma	22	2
*Pilocytic astrocytoma	25	2
Astroblastoma	75	14
*Spongioblastoma NOS	1	0
Glioblastoma	90	15
*Giant cell glioblastoma	2	0
Oligodendroglioma NOS	15	4
Medulloblastoma NOS	244	30
*Desmoplastic medulloblastoma	1	0
*Medullomyoblastoma	0	1
Cerebellar sarcoma	0	1
Malignant melanoma	1	0
Sarcoma NOS	3	0
Fibrosarcoma NOS	1	0
Rhabdomyosarcoma NOS	1	0
Germinoma	1	0
Embryonal carcinoma	1	0
Hemangiopericytoma	1	1
Teratoma	5	0
Chordoma	0	1
Ganglioneuroblastoma	1	0
Neuroblastoma NOS	13	0
Neuroepithelioma NOS	1	0
Malignant neoplasm NOS	29	3
*Malignant tumor, small cell type	2	1
Code not decipherable	1	0
Total	1053	140

*ICD-O code with no MOTNAC equivalent. Under MOTNAC, these cases would be included in the category listed directly above.

Astrocytic glioma

The rates of astrocytoma, astroblastoma, and glioblastoma changed dramatically between 1969 and 1980. The rate of astrocytoma more than tripled, while the rates of astroblastoma and glioblastoma plummeted (Table 7, Fig. 2). These trends were highly significant. As a disease rarely disappears in an 11-year period as astroblastoma appeared to have done, changes in diagnostic practices may have caused the trends in cell type occurrence. Astroblastoma apparently represents a more malignant stage of astrocytoma, although some neuropathologists disagree (4). In the MOTNAC classification, astrocytoma grade II is classified as astroblastoma. These two facts suggested the grouping of astrocytoma and astroblastoma into one category. Combining astrocytoma and astroblastoma decreased but did not eliminate the change in occurrence over time; the rate approximately doubled over the 11 years.

Table 7.

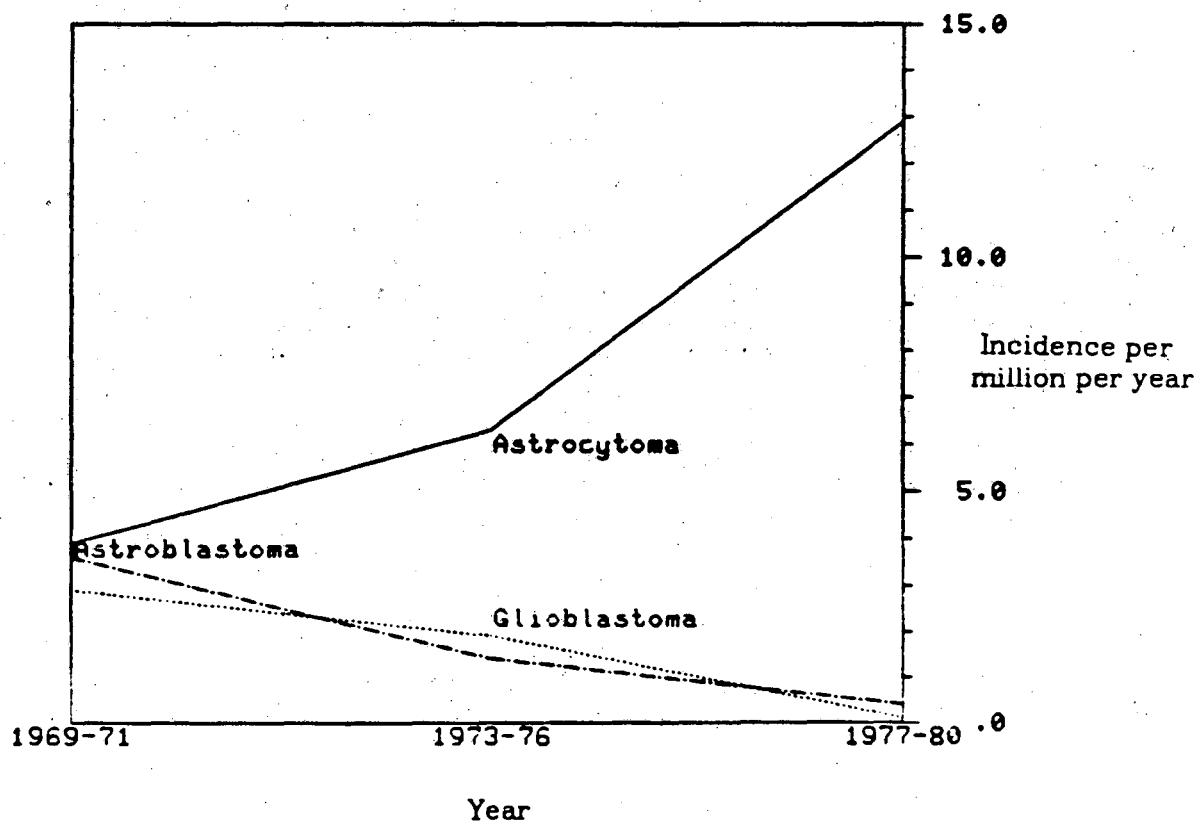
Time trends in childhood brain cancer incidence
by histologic type, 1969-80
San Francisco - Oakland, Detroit, and Iowa combined
Whites age 0-14
Rates per million per year
(Numbers of cases)

Histologic type	1969-71	1973-76	1977-80
Astrocytoma*	3.9 (28)	6.3 (52)	13.1 (93)
Astroblastoma**	2.9 (21)	1.9 (16)	0.1 (1)
Glioblastoma***	3.6 (26)	1.4 (12)	0.6 (4)
Medulloblastoma	5.0 (36)	4.9 (41)	5.9 (42)
Ependymoma	1.3 (9)	1.1 (9)	1.7 (12)
All types	23.4 (169)	20.2 (168)	26.7 (192)

* $\chi^2_{trend}=373$, $p<.001$
** $\chi^2_{trend}=16.5$, $p<.001$
*** $\chi^2_{trend}=20.6$, $p<.001$

Figure 2.

Time trends in the incidence of astrocytic gliomas
by specific diagnosis
Whites, age 0-14
SFO, Detroit, and Iowa combined



The doubling in rate could have represented a real change in the incidence of these cell types. However, as glioblastoma, the other cell type whose incidence declined dramatically, and astrocytoma are related tumor types, changing diagnostic practices again might have explained the increase. Adding glioblastoma to the astrocytoma-astroblastoma category resulted in relatively stable rates over the three study periods. Thus, considering the three histologic types as one group seemed epidemiologically sound.

Was the grouping biologically sound? In other words, are all glioblastomas of astrocytic origin? Many glioblastomas are known to be of astrocytic origin as they contain areas of recognizable astrocytoma. Smaller numbers of glioblastomas, however, include regions of oligodendroglioma or ependymoma (3). To further complicate the issue, many glioblastomas show no evidence of a more differentiated glioma (4). It is controversial but accepted by many pathologists that these latter glioblastomas also result from pre-existing gliomas by a rapid anaplastic course that obliterates all traces of ancestry (4). If this view is true, all glioblastomas are gliomas. However, not all are of astrocytic origin. Thus, combining glioblastomas with astrocytomas would misclassify nonastrocytic gliomas that had progressed to glioblastomas.

Assuming that all glioblastomas evolve from gliomas and using two facts, we can estimate the proportion of nonastrocytoma cases included in the astrocytoma-astroblastoma-glioblastoma group. First, 20% of gliomas that were more specifically categorized were not astrocytomas or astroblastomas. Second, 20% of the cases in the inclusive astrocytoma-astroblastoma-glioblastoma group were originally classified as glioblastoma. Thus, the proportion of nonastrocytic gliomas in the aggregated category was probably about .20 (proportion of gliomas that were not astrocytomas) multiplied by .20 (proportion of glioblastomas in the aggregated group), or 4%. That is, because

oligodendrogliomas and ependymomas, as well as astrocytomas, can progress to glioblastomas, about 4% of the cases in the aggregated group were not astrocyte-derived tumors and belonged in another histologic category.

This calculation assumed that all gliomas were equally likely to progress to the glioblastoma stage. As most gliomas were astrocytomas, most glioblastomas were assumed to be of astrocytic origin. Pathologic experience supports that assumption, as those glioblastomas with areas of differentiation most often contain recognizable astrocytes. The advantages of combining glioblastomas with the astrocytoma-astroblastoma group outweighed the probably small proportion of misclassified cases. The aggregated group of astrocytomas, astroblastomas, and glioblastomas will be referred to as astrocytomas.

Medulloblastoma

The incidence of medulloblastoma showed no consistent time trend. Because of the stability of the incidence rate and the tumor's pathological distinctiveness, medulloblastoma was studied as its own histologic group.

Ependymoma

Like medulloblastoma, ependymomas showed no convincing time trend in incidence and are histologically distinct from other gliomas. Thus, ependymoma was studied as a separate histologic group.

Glioma NOS

Gliomas not otherwise specified constituted a significant proportion of the cases. In this study, mixed gliomas, also known as oligo-astrocytomas, were included with gliomas NOS. The MOTNAC scheme (used in the TNCS data) classified mixed gliomas as gliomas NOS, while the ICD-O scheme separated mixed gliomas as a distinct tumor type. In order to create a scheme that would be consistent over the time period, mixed gliomas had to be included with gliomas NOS. In the SEER data, nine of the 109 gliomas NOS were actually mixed

gliomas. If the same proportion of gliomas NOS were mixed gliomas in both the SEER and TNCS data, then about 8% of the gliomas NOS in this study were probably mixed gliomas and may have belonged in another category. The WHO classification scheme, for example, includes mixed gliomas in the oligodendroglioma category (3).

Minor histologic groups

1. Oligodendrogliomas were considered a separate category of gliomas, but were seldom included in analyses because so few occurred.

2. A small proportion of cases were not gliomas and for the purposes of this study were grouped in the "other" category. The three choroid plexus papillomas among the SEER cases were classified as nongliomas and placed in the "other" category. The MOTNAC scheme, however, classified choroid plexus papillomas of the TNCS period as benign ependymomas. Presumably, then, none of the malignant ependymomas that occurred during the TNCS years were choroid plexus papillomas. Any bias that may have occurred by grouping choroid plexus papillomas of the TNCS but not the SEER years as ependymomas must be small, as only three of these tumors occurred in the eight SEER years compared to 70 ependymomas.

3. The few remaining cases had only the nonspecific diagnosis, malignant neoplasm NOS.

Summary

In summary, four major histologic groupings were used throughout this study. They were astrocytic glioma (referred to as astrocytoma), medulloblastoma, ependymoma, and glioma NOS. Astrocytomas, astroblastomas, and glioblastomas were considered as one histologic group because of their dramatic and complementary time trends. The inclusion of glioblastoma probably resulted in a low misclassification rate. A small amount of misclassification might have also

occurred by the inclusion of mixed gliomas as gliomas NOS. The minor groupings were oligodendrogliomas, cancer NOS, and other. Table 8 shows the distribution of cases by histologic group.

Table 8.

Distribution of childhood brain cancer cases by histologic group
12 TNCS and SEER registries
All races

Histologic group	Number	Percent
Astrocytoma	550	46
Medulloblastoma	276	23
Ependymoma	91	8
Oligodendroglioma	17	1
Glioma NOS	199	16
Cancer NOS	38	3
Other	39	3
Total	1210	100

Bias and NOS diagnoses

Cases may have been diagnosed no more specifically than glioma NOS because of lack of access to high quality medical care or inaccessibility of the tumor. Differences in such factors could result in artefactual differences in rates of glioma NOS. As all gliomas NOS presumably belong in a more specific histologic group, the rates of the major cell types would also be affected. In fact, the proportion of cases diagnosed as glioma NOS did vary between blacks and whites, and among geographic areas. Although the variation was not significant, it could cause misleading results in some analyses. Table 9 shows the distribution of white cases by histologic group and site. Most gliomas NOS occurred in the brain stem (few brain stem tumors are biopsied) and almost all brain stem tumors that were histologically confirmed were astrocytomas. It seemed logical then that most gliomas NOS in the brain stem were astrocytomas. The gliomas NOS could be distributed among the specified glioma types

according to the site-cell type distribution of the specified cases (Table 9). Doing so resulted in the consideration of 77% of the gliomas NOS as astrocytomas.

Combining astrocytomas and gliomas NOS should have reduced any bias due to differences in the proportion of gliomas NOS. As an estimate of the true number of astrocytomas, the combined group erred by misclassifying 23% of the gliomas NOS. However, those cases constituted only 6% of the combined group. When glioma NOS rates varied among comparison groups, the combined astrocytoma-glioma NOS category was used as a better estimate of the true astrocytoma incidence. For most analyses, this study reports results for astrocytoma alone and for astrocytoma and glioma NOS combined.

A similar argument can be made for cancers NOS. They, too, actually belong in other categories and thus, could bias results. However, the small number of cancers NOS (3% of all cases) made the introduction of bias unlikely. Some analyses considered the possibility of such a bias by adding cancers NOS to the combined astrocytoma-glioma NOS group. Assuming that all cancers NOS and gliomas NOS were actually astrocytomas gave a worst case estimate of this possible diagnostic bias.

Table 9.

Distribution of childhood glioma cases
by histologic group and site
Whites, age 0-14
12 TNCS and SEER registries

SITE	COUNT / ROW PCT / COL PCT	1 ASTROCYTOMA	2 MEDULLOBLASTOMA	3 EPENDYMOMA	4 OLIGODENDROGLIOMA	5 GLIOMA NOS	ROW TOTAL
910 CEREBRUM NOS		153	6	17	7	33	216
		70.8	2.8	7.9	3.2	15.3	21.8
		31.5	2.5	21.0	50.0	19.8	
915 VENTRICLE		38	27	31	0	11	107
		35.5	25.2	29.0	0.0	10.3	10.8
		7.8	11.1	38.3	0.0	6.6	
916 CEREBELLUM NOS		148	195	8	1	11	363
		40.8	53.7	2.2	0.3	3.0	36.7
		30.5	80.2	9.9	7.1	6.6	
917 BRAIN STEM		31	2	3	0	78	114
		27.2	1.8	2.6	0.0	68.4	11.5
		6.4	0.8	3.7	0.0	46.7	
918 OTHER PARTS		16	1	3	1	4	25
		64.0	4.0	12.0	4.0	16.0	2.5
		3.3	0.4	3.7	7.1	2.4	
919 BRAIN NOS		99	12	19	5	30	165
		60.0	7.3	11.5	3.0	18.2	16.7
		20.4	4.9	23.5	35.7	18.0	
COLUMN TOTAL		485	243	81	14	167	990
		49.0	24.5	8.2	1.4	16.9	100.0

CHAPTER 4

Results

Introduction

This chapter reports the results of descriptive and ecological analyses of childhood brain cancer by cell type. Results for all childhood brain cancer and for the two most common histologic types, astrocytoma and medulloblastoma, are presented for most analyses. Ependymomas are discussed when the number of cases permitted analysis. The nonspecific histologic categories of glioma NOS and cancer NOS are often included, because most of these cases probably belonged in one of the major histologic groups and thus could affect those results. In particular, analyses of astrocytoma alone and of astrocytoma and glioma NOS combined are compared to assess bias due to differing frequencies of nonspecific diagnosis.

The analyses fall into four categories:

Descriptive epidemiology

Time trends in rates, time and age trends in sex ratios, and comparisons of rates and case distributions of demographic variables by race and sex are presented. The socioeconomic status of cases is compared among cell types and to the socioeconomic status of the general population. Astrocytoma cases occurring at different sites within the brain are compared to assess whether at different sites, these tumors represent epidemiologically distinct diseases.

Ecological analyses

The effect of urbanization and population density on childhood brain cancer rates by cell types is investigated.

Geographic analyses

Geographic variation in childhood brain cancer rates by cell type is described. Analysis of the correlation of childhood brain cancer rates with physician concentration investigates one possible explanation of the observed variation. The covariation between rates of the major cell types is described.

Comparisons with selected cancers

Two analyses are described that assess the likelihood that childhood brain cancer has an etiology similar to that of adult brain cancer or that of childhood leukemias. The epidemiological profiles of childhood brain cancers and leukemias by cell type are compared. The correlation of adult and childhood brain cancer rates is described.

DESCRIPTIVE EPIDEMIOLOGY

Description of cases

The two sources of cases, TNCS (1969-71) and SEER (1973-80), contributed 384 and 826 cases, or 32% and 68%, respectively. The cases were 53% male and 47% female. Whites constituted 87% of the cases, blacks 12%, and other races 0.9%; 0.5% of the cases were of unknown race. The cases were almost equally distributed among the three age groups; 32% were aged 0-4, 37% were aged 5-9 and 31% were aged 10-14 at diagnosis. Table 10 shows the distribution of cases by registry; three registries--Iowa, Detroit, and San Francisco - Oakland--reported 50% of the cases. The distribution of cell type in each geographic area is shown in Table 11.

Table 10.

Distribution of childhood brain cancer cases by registry
Whites and Blacks

Registry	Years	Whites		Blacks	
		Number	Percent	Number	Percent
SF-Oakland	69-71, 73-80	170	16.1	28	20.0
Colorado	69-71	33	3.1	2	1.4
Connecticut	73-80	118	11.2	12	8.6
Atlanta	69-71, 75-80	58	5.5	19	13.6
Iowa	69-71, 73-80	174	16.5	2	1.4
Detroit	69-71, 73-80	185	17.6	55	39.3
Minneapolis	69-71	29	2.8	0	0.0
New Mexico	73-80	35	3.3	3	2.1
Pittsburgh	69-71	39	3.7	6	4.3
Dallas-Ft Worth	69-71	41	3.9	11	7.9
Utah	73-80	77	7.3	0	0.0
Puget Sound	74-80	94	8.9	2	1.4
All areas		1053	100	140	100

Table 11.

Distribution of cases of childhood brain cancer

by registry and histologic group

Whites, age 0-14

REGISTRY	COUNT / ROW PCT / COL PCT	TYPE: 1 ASTROCYTOMA	2 MEDULLOBLASTOMA	3 EPENDYMOMA	4 OLIGODENDROGLIOMA	5 GLIOMAS	6 N CANCER OS	7 N OTHER OS	ROW TOTAL
6 SAN FRAN-OAKLAND		78	45	6	3	31	2	5	170
		45.9	26.5	3.5	1.8	18.2	1.2	2.9	16.1
		16.1	18.5	7.4	21.4	18.6	6.5	15.6	
8 COLORADO		20	9	1	0	3	0	0	33
		60.6	27.3	3.0	0.0	9.1	0.0	0.0	3.1
		4.1	3.7	1.2	0.0	1.8	0.0	0.0	
9 CONN		51	25	20	2	12	1	7	118
		43.2	21.2	16.9	1.7	10.2	0.8	5.9	11.2
		10.5	10.3	24.7	14.3	7.2	3.2	21.9	
13 ATLANTA		16	20	8	0	9	2	1	56
		31.0	34.5	13.8	0.0	15.5	3.4	1.7	5.5
		3.7	8.2	9.9	0.0	5.4	6.5	3.1	
19 IOWA		88	33	13	1	21	12	6	174
		50.6	19.0	7.5	0.6	12.1	6.9	3.4	16.5
		18.1	13.6	16.0	7.1	12.6	38.7	18.8	
26 DETROIT		87	41	11	3	36	3	4	185
		47.0	22.2	5.9	1.6	19.5	1.6	2.2	17.6
		17.9	16.9	13.6	21.4	21.6	9.7	12.5	
27 MINNEAPOLIS		13	7	2	0	7	0	0	29
		44.8	24.1	6.9	0.0	24.1	0.0	0.0	2.8
		2.7	2.9	2.5	0.0	4.2	0.0	0.0	
35 NEW MEXICO		11	10	1	3	5	4	1	35
		31.4	28.6	2.9	8.6	14.3	11.4	2.9	3.3
		2.3	4.1	1.2	21.4	3.0	12.9	3.1	
42 PITTSBURGH		17	9	1	0	9	2	1	39
		43.6	23.1	2.6	0.0	23.1	5.1	2.6	3.7
		3.5	3.7	1.2	0.0	5.4	6.5	3.1	
48 DALLAS-FORT WORT		22	6	1	0	10	0	2	41
		53.7	14.6	2.4	0.0	24.4	0.0	4.9	3.9
		4.5	2.5	1.2	0.0	6.0	0.0	6.3	
49 UTAH		38	18	5	1	9	4	2	77
		49.4	23.4	6.5	1.3	11.7	5.2	2.6	7.3
		7.8	7.4	6.2	7.1	5.4	12.9	6.3	
53 PUGET SOUND		42	20	12	1	15	1	3	94
		44.7	21.3	12.8	1.1	16.0	1.1	3.2	8.9
		8.7	8.2	14.8	7.1	9.0	3.2	9.4	
COLUMN TOTAL		485	243	81	14	167	31	32	1053
		46.1	23.1	7.7	1.3	15.9	2.9	3.0	100.0

Race and sex

Introduction

This section reports analyses on the effect of race and sex on childhood brain cancer as a whole and by cell type. The cell type distributions, age distributions, incidence rates, and mean ages at diagnosis of blacks and whites and of white males and white females were compared. The small numbers of black cases of all cell types did not permit reliable comparisons between males and females.

Although analyses of the minor cell types are not discussed, they are generally included in the tables for completeness. Tables containing rates by race, rates by sex, and mean age at diagnosis by sex and race are referred to throughout the section and are located at the end of the section (Tables 19-21).

All cell types combined

1. Race

Black and white cases showed similar distributions of cell types (Table 12), although more black than white cases were diagnosed as gliomas NOS. However, the difference in cell type distribution was not statistically significant.

Table 12.

Distribution of histologic groups for whites and blacks*
Ages 0-14
12 TNCS and SEER registries

Histologic group	Whites		Blacks	
	Number	Percent	Number	Percent
Astrocytic gliomas	485	46	60	43
Medulloblastoma	243	23	32	23
Ependymoma	81	8	8	6
Oligodendroglioma	14	1	3	2
Glioma NOS	167	16	30	21
Other	32	3	3	2
Cancer NOS	31	3	4	3
Total	1053	100	140	100

* χ^2=3.0, df=4, p=.68

Ependymomas and oligodendrogliomas were combined and cancer NOS and other were combined for the χ^2 test so that all expected values would be greater than five.

The incidence rate in whites slightly exceeded that in blacks (Table 19). Black and white cases differed significantly in age distribution. A higher proportion of black than white cases occurred in the middle age (Table 13). The mean ages, 7.0 for whites and 6.7 for blacks, did not differ significantly (T=.69, p=.49).

Table 13.

Age distribution of childhood brain cancer cases
In whites and blacks*
12 TNCS and SEER registries

Age	White		Black	
	No.	%	No.	%
0-4	335	32	37	26
5-9	378	36	71	51
10-14	340	32	32	23
Total	1053	100	140	100

*χ^2=11.9, df=2, p=.003

2. Sex

White male cases differed significantly from white female cases in cell type distribution (Table 14), due to proportionally more medulloblastomas among males. The incidence rate in males slightly exceeded that in white females (Table 20).

Table 14.

Childhood brain cancer cases:
Frequency of cell type by sex
Whites, age 0-14

Histologic group	Whites			
	Males		Females	
	%	No.	%	No.
Astrocytoma	44	251	48	234
Medulloblastoma	27	154	18	89
Ependymoma	8	43	8	38
Oligodendroglioma	1	6	2	8
Glioma NOS	15	83	17	84
Other	2	16	4	15
Cancer NOS	3	14	3	
Total	100	567	100	486

χ^2=13.0, df=6, p=.04

Astrocytoma and glioma NOS

1. Race

Whites and blacks experienced similar combined astrocytoma-glioma NOS rates (Table 19). The similar combined rates resulted from higher astrocytoma rates but lower glioma NOS rates in whites than in blacks. The analyses in this section are reported for astrocytomas and gliomas NOS combined, although the results were similar for astrocytoma alone.

As for all cell types combined, black astrocytomas-gliomas NOS occurred more frequently in the 5-9 year age group than did white cases (Table 15). A χ^2 test showed the difference to be highly significant. The difference in age distribution occurred in males (χ^2=8.5, df=2, p=.01) and females (χ^2=12.5, df=2, p=.002). The mean age in whites was slightly higher than that in blacks (7.8 vs 7.1), but not significantly so (F=1.6, p=.21).

Table 15.

Age distribution of childhood astrocytoma and glioma NOS cases
Whites and Blacks*
12 TNCS and SEER registries

Age	White		Black	
	No.	%	No.	%
0-4	178	27	17	19
5-9	235	36	54	60
10-14	239	37	19	21
Total	652	100	90	100

* χ^2=19.3, df=2, p<.001

If the difference in age distribution and incidence curves were due to delay of diagnosis among blacks, the largest difference between blacks and whites might occur as children entered school, i.e., at age 4-5. In order to see if this were so, the age distribution by single years was investigated (Table 16).

The black excess was limited to ages five, six, and seven with the largest excess by far at age six.

Table 16.

Age distribution (single years)
of childhood astrocytoma and glioma NOS cases
Whites and Blacks
12 TNCS and SEER registries

Age	Whites		Blacks	
	No.	%	No.	%
0	32	5	2	2
1	34	5	4	4
2	30	5	4	4
3	36	6	3	3
4	46	7	4	4
5	50	8	10	11
6	49	8	20	22
7	42	6	9	10
8	51	8	7	8
9	43	7	8	9
10	39	6	2	2
11	55	8	5	6
12	54	8	6	7
13	49	8	1	1
14	42	6	5	6
Total	652	100	90	100

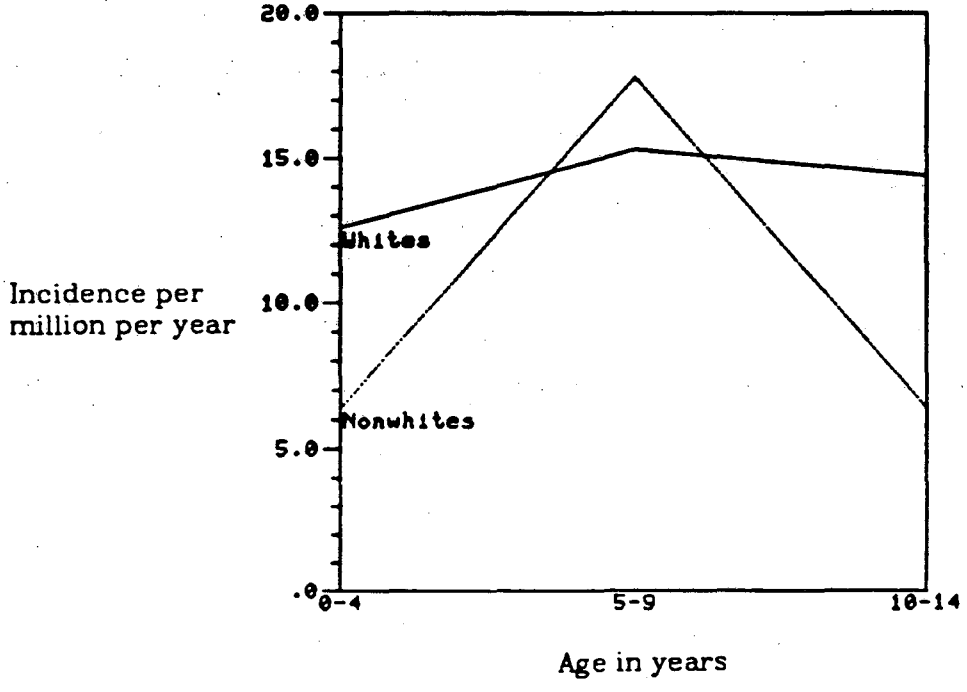
To further investigate the age difference, nonwhite and white rates were calculated by age. (The available census data did not permit calculation of rates for blacks by five-year age groups.) Since the large majority of the nonwhite cases were black, the results should reflect black rates. For age groups 0-4 and 10-14, the white rate was twice the nonwhite rate. Nonwhite and white rates were similar in the middle age group (Table 17, Fig. 3).

Table 17.

Age-specific incidence of astrocytoma-glioma NOS
Nonwhites and whites
Rates per million per year
12 TNCS and SEER registries

Age	Whites		Nonwhites	
	Rate	No.	Rate	No.
0-4	12.6	178	6.4	19
5-9	15.3	235	17.8	55
10-14	14.4	239	6.4	20
0-14	14.2	652	10.2	94

Figure 3.
Age-specific incidence of astrocytoma-glioma NOS
Nonwhites and whites
Rates per million per year
12 TNCS and SEER registries



2. Sex

White males and females had identical rates of astrocytoma and glioma NOS combined. The mean age at diagnosis was about 0.5 years higher among females than males (p=.10).

Medulloblastoma

1. Race

The white rate of medulloblastoma exceeded that of blacks (Table 19). Unlike astrocytoma cases, similar proportions of black and white medulloblastoma cases occurred at ages 5-9 (Table 18). The mean age at diagnosis did not differ significantly between blacks and whites (p=.31) (Table 21).

Table 18.

Age distribution of childhood medulloblastoma cases
Whites and Blacks
12 TNCS and SEER registries

Age	Whites		Blacks	
	No.	%	No.	%
0-4	81	33	14	44
5-9	99	41	12	38
10-14	63	26	6	19
Total	243	100	32	100

2. Sex

The medulloblastoma rate differed significantly between white males and females (Table 20); males had a rate 65% higher than females ($Z=3.8$, $p<.001$). Females had a lower mean age at diagnosis than males ($p=.09$) (Table 21).

Ependymoma

Too few cases occurred to compare black and white rates. White males and females experienced similar rates and had similar mean ages at diagnosis (Tables 20 and 21).

Summary

The white rate of childhood brain cancer slightly exceeded the black rate. Whites experienced higher rates of astrocytoma and medulloblastoma but lower rates of glioma NOS than blacks. The combined rate of astrocytoma and glioma NOS was similar for both races.

White male and female rates were similar overall and for astrocytoma and glioma NOS combined, but males had significantly higher rates of medulloblastoma.

A higher proportion of black than white cases of astrocytoma-glioma NOS were aged 5-9. The greatest racial difference occurred at age six. The age-

specific rates showed a different pattern for whites and nonwhites. Whites had fairly constant rates for the three 5-year age groups, while nonwhite rates peaked in the middle age group.

Table 19.

Incidence of childhood brain cancer by cell type and race
Ages 0-14
Rates per million per year
12 TNCS and SEER registries

	Astro-cytoma	Medullo-blastoma	Ependy-moma	Glioma NOS	Combined*	Other
Whites	10.4	5.3	1.8	3.6	14.0	1.7
Blacks	9.1	4.8	1.2	4.5	13.6	1.6

*includes astrocytoma and glioma NOS

Table 20.

Incidence of childhood brain cancer by sex and histologic group
Whites, ages 0-14
Rates per million per year
12 TNCS and SEER areas

	Astro-cytoma	Medullo-blastoma	Ependy-moma	Oligodendro-glioma	Glioma NOS	Cancer NOS	Other	All brain
Males	10.6	6.5	1.8	0.25	3.5	0.7	0.6	23.9
Females	10.4	4.0	1.7	0.36	3.7	0.7	0.8	21.5
Rate ratio	1.0	1.7	1.1	0.7	0.9	1.0	0.7	1.1

Table 21.

Mean age at diagnosis by sex, histologic group, and race
Ages 0-14
12 TNCS and SEER registries

Type	Whites			Blacks		
	Both sexes	Male	Female	Both sexes	Male	Female
Astrocytoma	7.8	7.5	8.1	7.1	7.4	6.8
Medulloblastoma	6.6	6.9	6.0	5.8	4.4	7.3
Ependymoma	5.0	4.8	5.3	6.0*	9.7*	3.8*
Oligodendroglioma	8.7	9.7*	8.0*	10.0*	-	10.0*
Glioma NOS	6.6	6.3	6.9	6.7	7.0	6.4
Cancer NOS	6.8	7.1	6.6	3.3*	3.0*	3.5*
Other	4.8	3.5	5.7	12.7*	12.5*	13.0*

* based on less than 10 cases

Trends in the sex ratio

Changes with age

Researchers have observed and speculated upon a decline in the sex ratio of brain cancer at puberty. Such a decline could result from changes in the sex ratio of one or more cell types or a change in the distribution of cell types with age. For example, the decline might result if cell types with high sex ratios occurred less frequently at older ages. As medulloblastoma had a sex ratio greater than one, a decline in the proportion of cases diagnosed as medulloblastoma would lower the overall sex ratio. The other major cell types had sex ratios close to one and changes in the frequency of these cell types would not affect the overall sex ratio. If a change in the distribution of histologic types explained the decrease in sex ratio, then one would expect the sex ratios for each type to be the same at all ages.

The expected decline in sex ratio with age was observed in these data (Table 22). The distribution of cell types also changed (Table 23), but the decrease in the proportion of medulloblastoma was small and explained only part of the sex ratio decline. Therefore, the sex ratios of the major cell types, astrocytoma and medulloblastoma, were investigated using first, five-year age groups and then, two- to three-year age groups. Results are presented for both astrocytoma alone and for astrocytoma and glioma NOS combined. Results for astrocytoma alone would be biased if males and females had different probabilities of obtaining specific diagnoses. Although it seems unlikely that males and females had unequal access to specialized medical care, the location of tumors and therefore the probability of biopsy might differ by sex. In fact, the results for astrocytoma and astrocytoma-glioma NOS differed only slightly.

Table 22.

Incidence by sex and sex ratio of childhood brain cancer by age
Whites
12 TNCS and SEER registries

	0-4	5-9	10-14
Males	25.5 (184)	26.6 (209)	20.5 (174)
Females	22.0 (151)	22.5 (169)	20.4 (166)
Sex Ratio	1.16	1.18	1.00

Table 23.

Childhood brain cancer:
Distribution of cell types by age*
Whites
12 TNCS and SEER registries

	0-4		5-9		10-14	
	%	No.	%	No.	%	No.
Astrocytoma	36	119	46	174	57	192
Medulloblastoma	24	81	26	99	19	63
Ependymoma	14	46	5	18	5	17
Oligodendroglioma	0.6	2	1	5	2	7
Glioma NOS	18	59	16	61	14	47
Cancer NOS	3	9	3	13	3	9
Other	6	19	2	8	2	5
Total	100	335	100	378	100	340

* χ^2=60.4, df=12, p<.001

The sex ratio for astrocytoma declined slightly while that for medulloblastoma increased from the 0-4 to the 10-14 (Table 24). Neither trend in the proportion of male cases was significant.

Table 24

Sex ratio by age:
Childhood astrocytoma and medulloblastoma
12 TNCS and SEER registries
Whites

Age	Astrocytoma**	Combined*	Medulloblastoma***
0-4	1.3	1.1	1.3
5-9	1.0	1.1	1.7
10-14	0.9	0.8	2.0
0-14	1.0	1.0	1.7

* Includes astrocytoma and glioma NOS
** χ^2_{trend}=2.53, p=.11
*** χ^2_{trend}=1.66, p=.20

To investigate these trends in narrower age groups, male to female case ratios were used, as the population figures for these age groups were not available. Male-female case ratios accurately approximate rate ratios in this age range because the male to female ratio of the population is close to 1 (1.04). More importantly, the male-female ratio of the population hardly changes in this age range. Therefore, trends over age in the case ratio should not differ from trends in the rate ratios.

As shown in Table 25, the case ratio for astrocytoma decreased with age. The trends for astrocytoma alone and for astrocytoma-glioma NOS differed slightly. For astrocytoma alone, the increase in the proportion of females among the cases began in the very young age groups and appeared to end by age 11. For astrocytoma-glioma NOS, the sex ratio was fairly constant and greater than one before age nine and after that, less than one. Both trends approached statistical significance.

Although the sex ratios for medulloblastoma increased with age when three age groups were used, no such trend occurred in the case ratio using narrower age groups. The lack of trend using narrower age groups could have

resulted from the smaller number of cases in each age group. For medulloblastoma, the number of cases in each age group varied from 27-49; for astrocytoma, the number was larger varying from 58-80.

Table 25.

Male-female case ratios for childhood brain cancer
by age and histologic group
Whites
12 TNCS and SEER registries

Age	Astrocytoma*		Combined**		Medulloblastoma	
	Ratio	No.	Ratio	No.	Ratio	No.
0-2	1.4	61	1.2	96	0.9	47
3-4	1.3	58	1.1	82	2.8	34
5-6	1.2	73	1.3	99	1.9	35
7-8	1.0	71	1.2	93	1.9	49
9-10	0.8	62	0.8	82	1.4	31
11-12	1.1	82	0.9	109	4.4	27
13-14	0.9	78	0.9	91	1.5	20
Total	1.1	485	1.1	652	1.7	243

* χ^2_{trend}=3.0, p=.08
** χ^2_{trend}=2.43, p=.12

In summary, the sex ratio for childhood brain cancer declined with age. The decreased proportion of medulloblastoma with its male predominance explained only a small part of the decline. The sex ratio for astrocytoma decreased with age. Although the decline in the proportion of astrocytomas occurring in males was not significant, the change explained much of the decrease in the sex ratio for all childhood brain cancer.

Time trends

Gold and Gordis reported that the sex ratio for childhood brain cancer declined between 1960 and 1974 in Baltimore (30). In the present study, the sex ratio for all childhood brain tumors did not change between 1969 and 1980. The sex ratio of astrocytomas increased (Table 26), but the corresponding increase in the proportion of male cases was not statistically significant (χ^2_{trend}=.82, p=.37). Moreover, when astrocytomas and gliomas NOS were considered together, no change occurred in the case ratio. Table 26 shows the time trends in sex ratios of the major cell types.

Table 26.

Time trends in the sex ratio of childhood brain cancer, 1969-80
By histologic group
SFO, Detroit, Iowa combined
Whites, age 0-14

Type	1969-71		1973-76		1977-80	
	Ratio	No.	Ratio	No.	Ratio	No.
All brain	1.02	169	1.03	168	1.03	192
Astrocytoma	.94	75	.96	80	1.22	98
Combined*	.95	106	.93	107	.95	128
Medulloblastoma	2.19	36	1.11	41	1.57	42

*includes astrocytoma and glioma NOS

Socioeconomic status

The median census tract income was used to investigate possible differences in socioeconomic status among cell types, and between each cell type and the general population. The mean of the white median income of the census tract of residence is given for each cell type in Table 27. Table 27 also gives the mean for all census tracts in SMSA counties, weighted by the white population under age 15.

Table 27.

Childhood brain cancer:
Mean income by histologic group, 1969-71
Whites, age 0-14

Cell type	No.	Mean income ($)
Astrocytoma	133	12662
Glioma NOS	56	12498
Astrocytoma and glioma NOS	189	12613
Medulloblastoma	63	11449
Ependymoma	12	11425
All types	281	12263
General population	4355769	12013

When all types of childhood brain cancer were included, the mean income did not differ from that of the general population (p=.26). The mean income of the astrocytoma cases was slightly greater than the general population mean (p=.09). When gliomas NOS were included with the astrocytomas, the difference reached significance (p=.05). The mean income of the medulloblastoma cases was less than the general population mean (p=.06). The mean of the ependymoma cases was nearly the same as that of the medulloblastoma cases. However, the analysis included only 12 ependymoma cases and the difference was not significant.

Comparisons among cell types showed that the mean income of astrocytoma and medulloblastoma cases differed significantly (p=.04). Including gliomas NOS with the astrocytomas did not change the result (p=.03). No other differences among cell types were observed.

Site

Are astrocytomas at different sites within the brain distinct entities requiring separate study? To answer this question, the age, sex, race, and geographic distributions of astrocytoma cases at three sites--the cerebrum, cerebellum, and brain stem--were compared. In addition, the geographic variation in incidence by site was investigated. Different descriptive epidemiologies would suggest that astrocytomas should be studied separately by site.

Gliomas NOS were included with astrocytomas for brain stem cases, but not with those at the other two sites. The large majority of the brain stem gliomas NOS were inferred to be astrocytomas by the site-type distribution of specifically diagnosed gliomas (see Table 9). The inclusion of gliomas NOS with cerebellar and cerebral astrocytomas would misclassify some nonastrocytomas among the gliomas NOS. As few cerebellar and cerebral glioma NOS cases occurred, the results did not change with their inclusion. Although the proportion of astrocytoma cases with brain NOS as the site varied significantly by geographic area (χ^2=12.7, df=5, p=.03 for the six largest areas), investigating only cases with a specified site would not introduce bias if the distribution of brain NOS astrocytomas were the same as that of the specified cases.

Differences in age and geographic distribution were noted between cerebral astrocytomas and astrocytomas at the other two sites. Only cerebellar astrocytomas showed significant variation in incidence across geographic areas.

Brain stem and cerebellar cases were younger than cerebral cases. The mean age at diagnosis did not differ significantly, but the distributions by five-year age groups did (Table 28).

Table 28.

Age distribution of childhood astrocytomas by site*
Whites, ages 0-14
12 TNCS and SEER registries

Site	0-4	5-9	10-14	age 0-14	Mean age**
Cerebrum	37 (24%)	45 (29%)	71 (46%)	153 (100%)	8.2
Cerebellum	37 (25%)	61 (41%)	50 (34%)	148 (100%)	7.7
Brain stem	28 (26%)	51 (47%)	30 (28%)	109 (100%)	7.1
All three sites	102 (25%)	157 (38%)	151 (37%)	410 (100%)	7.7

* Distribution χ^2=12.3, df=4, p=.02
** Mean age F=2.2, df=2, df=407, p=.11

Astrocytomas at the three sites did not differ significantly in race distribution, although more brain stem and fewer cerebral cases occurred in blacks than in whites (Table 29). Among whites, the sex distribution of astrocytomas did not differ significantly by site (Table 30).

Table 29.

Race distribution of childhood astrocytomas by site*
Ages 0-14
12 TNCS and SEER registries

Site	White	Black
Cerebrum	153 (37%)	16 (28%)
Cerebellum	148 (36%)	19 (33%)
Brain stem	109 (27%)	22 (39%)
All three sites	410 (100%)	57 (100%)

* χ^2=3.9, df=2, p=.14

Table 30.

Sex distribution of childhood astrocytomas by site*
Whites, ages 0-14
12 TNCS and SEER registries

Site	Male	Female	Total
Cerebrum	82 (54%)	71 (46%)	153 (100%)
Cerebellum	72 (49%)	76 (51%)	148 (100%)
Brain stem	52 (48%)	57 (52%)	109 (100%)
All three sites	206 (50%)	204 (50%)	410 (100%)

* χ^2=1.1, df=2, p=.57

As discussed earlier, blacks showed a significantly different age distribution of astrocytoma cases than whites (p<.001). Similar differences between blacks and whites in age distribution were observed for cerebellar, cerebral, and brain stem astrocytomas (Table 31). The small numbers of black cases precluded tests for significance.

Table 31.

Age distribution of childhood astrocytomas by site
Whites and blacks
12 TNCS and SEER registries

Site	0-4	5-9	10-14	Total (0-14)
All sites				
Whites	119 (25%)	174 (36%)	192 (40%)	485 (100%)
Blacks	10 (17%)	38 (63%)	12 (20%)	60 (100%)
Cerebrum				
Whites	37 (24%)	45 (29%)	71 (46%)	153 (100%)
Blacks	3 (19%)	8 (50%)	5 (31%)	16 (100%)
Cerebellum				
Whites	37 (25%)	61 (41%)	50 (34%)	148 (100%)
Blacks	3 (16%)	12 (63%)	4 (21%)	19 (100%)
Brain stem*				
Whites	28 (26%)	51 (47%)	30 (28%)	109 (100%)
Blacks	4 (18%)	16 (73%)	2 (9%)	22 (100%)

*includes gliomas NOS

The geographic distributions across the six largest areas did not differ significantly by site (Table 32).

Cerebellar astrocytoma rates showed significant geographic variation across the six areas, but the rates at the other two sites did not. SFO and Puget Sound experienced high rates of cerebellar astrocytoma, while Connecticut had a low rate. The ratio of the highest to the lowest rate was similar for brain stem and cerebellar astrocytomas and lower for cerebral tumors. Rates of brain stem astrocytomas were high in SFO and fairly constant in the other five areas. The highest rate of cerebral astrocytoma occurred in Iowa and the lowest in SFO. Table 33 summarizes the geographic variation by site.

Table 32.

Distribution of astrocytomas by site and registry
Whites, ages 0-14

	SITE			
COUNT / ROW PCT / COL PCT	CEREBRUM NOS 910	CEREBELLUM NOS 916	BRAIN ST EM* 917	ROW TOTAL
SAN FRAN-OAKLAND	6 13 21.7 10.9	27 45.0 23.1	20 33.3 27.4	60 19.4
CONN	9 18 47.4 15.1	11 28.9 9.4	9 23.7 12.3	38 12.3
IOWA	19 32 46.4 26.9	24 34.8 20.5	13 18.8 17.8	69 22.3
DETROIT	26 31 40.8 26.1	25 32.9 21.4	20 26.3 27.4	76 24.6
UTAH	49 12 44.4 10.1	10 37.0 8.5	5 18.5 6.8	27 8.7
PUGET SOUND	53 13 33.3 10.9	20 51.3 17.1	6 15.4 8.2	39 12.6
COLUMN TOTAL	119 38.5	117 37.9	73 23.6	309 100.0

* includes gliomas NOS

Table 33.

Geographic variation of childhood astrocytoma incidence by site
Six TNCS and SEER registries
Whites, ages 0-14

Site	Lowest	Highest	High/Low	p-value	# cases
Cerebrum	SFO	Iowa	1.7	.71	119
Cerebellum	Conn	Puget Sound	2.4	.05	117
Brain stem	Utah	SFO	2.3	.15	73

In summary, astrocytomas at the three sites showed epidemiological similarities and differences. Astrocytomas at all three sites had similar race and sex distributions. In addition, at all three locations, a higher proportion of black than white cases were diagnosed at ages 5-9. Cerebellar and brain stem astrocytomas resembled each other but differed significantly from cerebral astrocytomas in age distribution. Cerebral astrocytomas were diagnosed more frequently in older children than astrocytomas at the other two sites. Astrocytomas at the three sites showed nonsignificant differences in geographic distribution. Cerebral astrocytomas accounted for a smaller proportion of cases in SFO and Puget Sound than in the other four areas. The rates of only cerebellar astrocytomas, and not astrocytomas at the other two locations, showed more than random variation across geographic areas.

Time trends

Introduction

Registries in SFO, Iowa, and Detroit participated in both the TNCS and SEER programs, thus providing data from 1969-80 (excluding 1972) and permitting analysis of time trends. Time trends were investigated for these three areas combined. An increase in astrocytoma rates occurred, with Iowa accounting for most of the change. The remaining analyses described the time trend in age group, sex, location in Iowa, and anatomic site within the brain.

Time trends by cell type

Table 34 and Fig. 3 show the rates for whites by cell type and time period for San Francisco-Oakland, Detroit, and Iowa combined. The incidence of brain cancer in white children under age 15 increased slightly, although the lowest rate occurred in the middle time period. The rates of astrocytoma, medulloblastoma, and ependymoma rose during the period; those of glioma NOS and other types remained the same, and that of cancer NOS declined.

Table 34.

Childhood brain cancer incidence, 1969-80
SFO, Detroit, Iowa combined
Whites, ages 0-14
Age adjusted rates per million
(Numbers of cases)

Histologic group	1969-71	1973-76	1977-80
Astrocytoma*	10.3 (75)	9.6 (80)	13.5 (98)
Medulloblastoma	5.0 (36)	5.0 (41)	5.9 (42)
Glioma, NOS	4.3 (31)	3.3 (27)	4.2 (30)
Ependymoma	1.3 (9)	1.1 (9)	1.7 (12)
Oligodendroglioma	0.6 (4)	0.0 (0)	0.4 (3)
Other, specified	0.7 (5)	0.6 (5)	0.6 (5)
Cancer, NOS	1.2 (9)	0.7 (6)	0.3 (2)
Total**	23.3 (169)	20.2 (168)	26.6 (192)

* $\chi^2_{trend}=3.66$, p=.06
** $\chi^2_{trend}=1.35$, p=.24

The increase in the astrocytoma rate for this period approached statistical significance. If changes in diagnosis contributed to the increase, the rates of two groups which would probably have included unbiopsied astrocytomas--gliomas NOS and cancers NOS--should have decreased. In fact, the glioma NOS rate hardly changed. The decline in the cancer NOS rate, however, could have contributed to the observed increase in astrocytoma.

Iowa accounted for most of the increase with a 70% higher rate in 1978-80 than in 1969-71 (p=.03) (Table 35). In SFO, the astrocytoma rate hardly changed. The rate of astrocytoma increased 20% in Detroit. Thus, only in Iowa did astrocytoma rates increase significantly.

Figure 4.

Time trends in childhood brain cancer
by histologic group
Whites, age 0-14
Age-adjusted rates per million per year
SFO, Detroit, and Iowa combined

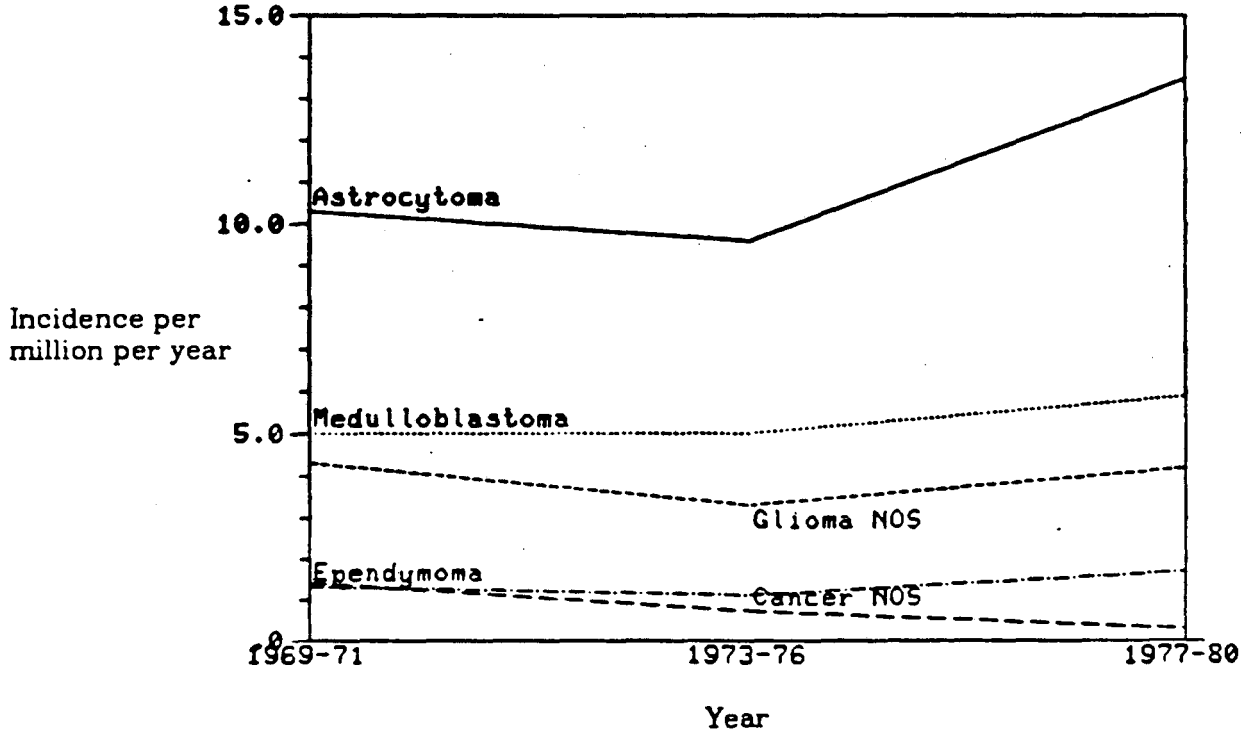


Table 35.

Time trends in incidence of childhood astrocytoma, 1969-80
SFO, Iowa, and Detroit
Whites, ages 0-14
Rates per million per year
(Numbers of cases)

Registry	1969-71	1973-76	1977-80
SFO	13.0 (24)	15.1 (31)	13.9 (23)
Iowa*	9.3 (22)	8.3 (24)	15.9 (42)
Detroit	9.5 (29)	7.3 (25)	11.7 (33)
Total	10.4 (75)	9.6 (80)	13.8 (98)

* χ^2_{trend}=4.84, p=.03

Most of the increase in the rate of medulloblastoma occurred in San Francisco - Oakland; The rate increase was about 50% and was limited to children aged 5-9 (Table 36).

Table 36.

Time trends in incidence of childhood medulloblastoma 1969-80
San Francisco - Oakland
Whites, ages 0-14
Rates per million per year

Age	1969-71		1973-76		1977-80	
	Rate	No.	Rate	No.	Rate	No.
0-4	9.2	5	14.8	9	9.9	5
5-9	6.3	4	7.4	5	15.2	8
10-14	4.5	3	4.0	3	4.8	3
Total	6.6	12	8.5	17	9.8	16

In summary, incidence rates generally changed little over the 11-year period in the three registries combined. Astrocytoma rates, however, rose significantly in Iowa.

Astrocytoma trends in Iowa

Within Iowa, rates rose significantly in children under age ten but hardly changed in the 10-14 group (Table 37). Both males and females exhibited the pattern of increasing rates in children under age ten, but not in those aged 10-14 (Table 38).

Table 37.

Time trends in incidence of childhood astrocytoma, 1969-80
Iowa whites, ages 0-14
Rates per million per year

Age	1969-71		1973-76		1977-80	
	Rate	No.	Rate	No.	Rate	No.
0-4*	2.9	2	4.5	4	12.8	11
5-9**	9.8	8	8.3	8	22.4	19
10-14	13.9	12	11.6	12	12.9	12
Total	9.3	22	8.3	24	15.9	42

*χ^2_{trend}=5.50, p=.02
**χ^2_{trend}=4.78, p=.03

Table 38.

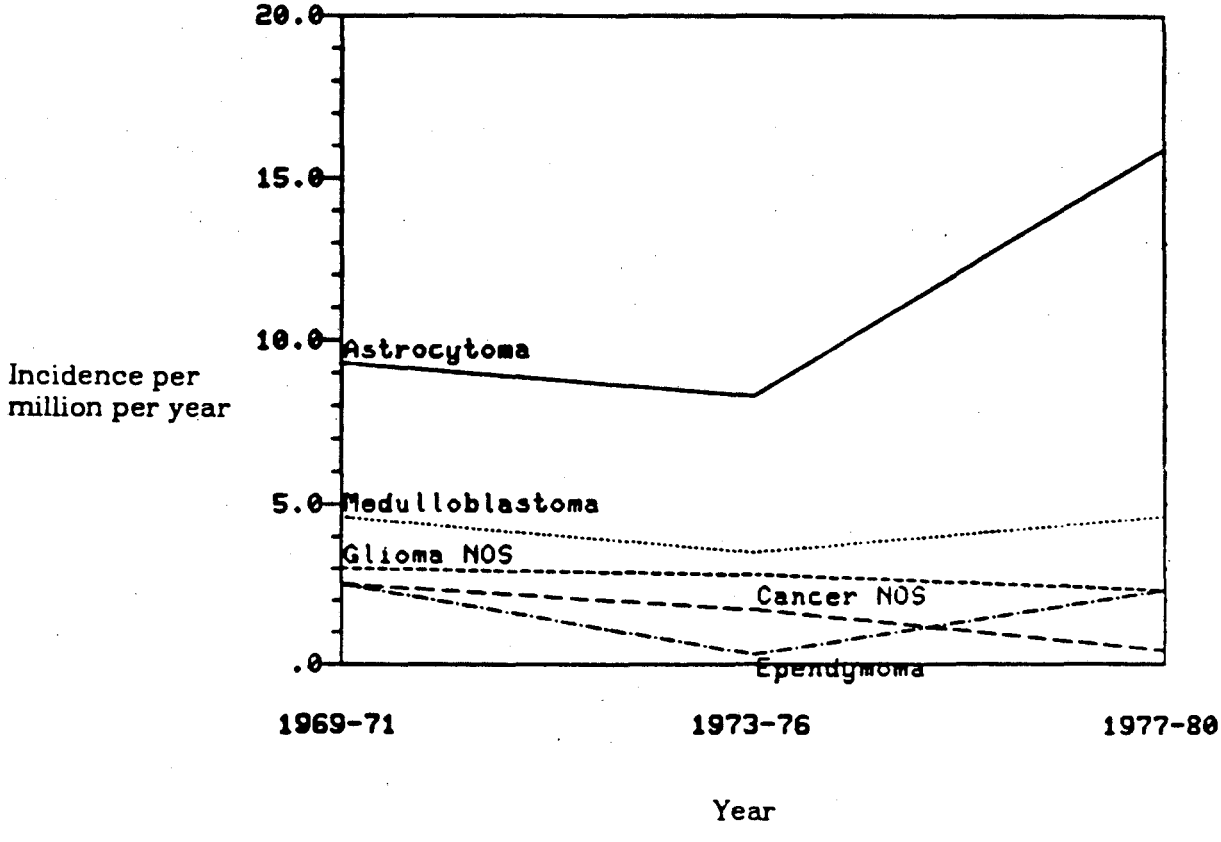
Time trends in incidence of childhood astrocytoma 1969-80
By age and sex
Iowa whites
Rates per million per year

Age	1969-71		1973-76		1977-80	
	Rate	No.	Rate	No.	Rate	No.
0-4						
Male	0.0	0	6.6	3	13.7	6
Female	6.0	2	2.3	1	11.9	5
5-9						
Male	9.6	4	12.2	6	25.4	11
Female	10.0	4	4.2	2	19.3	8
10-14						
Male	13.6	6	9.5	5	10.5	5
Female	14.2	6	13.9	7	15.5	7
0-14						
Male	8.3	10	9.5	14	16.3	22
Female	10.4	12	7.1	10	15.5	20

If the increase in the rate of astrocytoma resulted from more accurate diagnosis, one would expect the rate of glioma NOS and cancer NOS to have decreased, as most of these tumors were probably astrocytomas. In Iowa, the glioma NOS rate decreased slightly (Fig. 5), but not enough to explain any substantial portion of the increase in astrocytoma incidence. The cancer NOS rate, however, declined sharply. Although the rates were low, the decline could explain part of the increase in astrocytoma incidence. Table 39 shows the effect on the astrocytoma increase if gliomas NOS and cancers NOS were considered to be misclassified astrocytomas. Combining astrocytomas and gliomas NOS resulted in an rate increase of about 50%, a trend of borderline significance (Table 39). If all gliomas NOS and cancers NOS were actually astrocytomas, the rate of astrocytoma would have increased by 26% (not significant) instead of the observed 72% (Table 39). When the analysis was limited to children under ten,

Figure 5.

Time trends in childhood brain cancer incidence
by histologic group
Iowa whites, age 0-14
Rates per million per year



the group in which the trend was observed, somewhat larger increases remained when gliomas NOS and cancers NOS were included. The original 2.7-fold increase fell to 50% when both NOS categories were included (Table 39). More accurate diagnosis, then, could explain part of the observed increase, although assuming that all NOS cases were astrocytomas probably overestimated the effect.

Table 39.

Time trends in incidence of childhood astrocytoma and related cell types, 1969-80
Iowa whites
Rates per million per year
(Numbers of cases)

Cell type	1969-71	1973-76	1977-80	p-value
Under 15				
Astrocytoma	9.3 (22)	8.3 (24)	15.9 (42)	.03
and glioma NOS	12.3 (29)	11.1 (32)	18.2 (48)	.08
and cancer NOS	14.8 (35)	12.8 (37)	18.6 (49)	.28
Under 10				
Astrocytoma	6.6 (10)	6.5 (12)	17.6 (30)	.002
and glioma NOS	10.6 (16)	8.7 (16)	19.9 (34)	.02
and cancer NOS	14.0 (21)	9.7 (18)	20.5 (35)	.13

If a real increase in the incidence of astrocytoma occurred without any changes in the incidence of other cell types, the total childhood brain cancer rate would have increased. A slight increase in the rate of childhood brain cancer occurred (p=.58), but a very low rate occurred in the middle time period. The trend for children under ten was similar and not significant. Table 40 gives these results.

Table 40.

Time trends in incidence of childhood brain cancer, 1969-80
Iowa whites
Rates per million per year
(Numbers of cases)

Age	1969-71	1973-77	1978-80
0-14	23.7 (56)	17.0 (49)	26.2 (69)
0-9	26.7 (40)	14.1 (26)	29.9 (51)

In summary, the declines in NOS rates explained most of the increase in astrocytoma incidence. If all NOS cases were assumed to be astrocytomas, rate increases of about 25% and 50% remained for children under age 15 and under age ten, respectively. The trend for all childhood brain cancer suggests that the remaining increase in astrocytoma incidence occurred by chance.

Urban/Rural Time Trends

1. Introduction

Time trends in astrocytoma incidence were further investigated by urban-rural analyses. Under the assumption that urban residents have greater access to specialized medical care, the analyses helped distinguish between three possible explanations of the increase in astrocytoma incidence. The three possibilities were:

1. An increase due to a shift of cases from the nonspecific glioma NOS and cancer NOS groups to the astrocytoma group. This possibility predicted a greater increase in rural than urban areas and a rural increase that was largely explained by declines in NOS rates.

2. An increase due to improved ascertainment of childhood brain tumors. This explanation predicted a greater increase in rural than urban areas. The rural increase would not be completely explained by declines in NOS rates.

3. An actual increase in either urban or rural Iowa. As the decline in NOS rates did not explain the entire increase in Iowa, analyses might locate an actual increase in either rural or urban Iowa.

The second and third possibilities would be indistinguishable if the increase occurred in rural areas.

Counties were divided by degree of urbanization in two ways. Method I used the census variable, proportion of population living in places with 2500 or more inhabitants. Method II used another census variable, proportion of population living in cities of 50,000 or more. Both methods are explained in chapter two.

2. Astrocytoma

Astrocytoma rates rose more in rural than urban Iowa, especially by Method I and for children under age ten (Tables 41 and 42). When either urban definition was used, the trend was significant in rural areas for both children under age 15 and children under age ten. Rural trends were greater using Method I, while urban trends were affected less. In summary, the increase in astrocytoma rate appeared greater in rural areas, especially for children under age ten.

Table 41.

Urban and rural time trends in the incidence of childhood astrocytoma 1969-80
Iowa whites, ages 0-14
Rates per million per year
(Numbers of cases)

Method I Urbanization	1969-71	1973-76	1977-80	Ratio 1977-80/1969-71
Low*	10.1 (10)	7.4 (9)	21.4 (24)	2.1
Moderate	4.7 (3)	11.7 (9)	10.0 (7)	2.1
High	12.2 (9)	6.7 (6)	13.5 (11)	1.1
Method II				
Low**	9.0 (13)	9.1 (16)	17.3 (28)	1.9
High	10.3 (9)	7.6 (8)	14.7 (14)	1.4

*χ^2_{trend}=5.1, p=.02
**χ^2_{trend}=4.3, p=.04

Table 42.

Urban and rural time trends in the incidence of childhood astrocytoma 1969-80
Iowa whites, under age 10
Rates per million per year
(Numbers of cases)

Method I Urbanization	1969-71	1973-76	1977-80	Ratio 1977-80/1969-71
Low*	4.9 (3)	5.2 (4)	24.9 (18)	5.1
Moderate	4.9 (2)	8.0 (4)	8.8 (4)	1.8
High	10.4 (5)	6.9 (4)	15.1 (8)	1.5
Method II				
Low**	5.5 (5)	6.2 (7)	20.0 (21)	3.6
High	8.8 (5)	7.3 (5)	14.5 (9)	1.6

*χ^2_{trend}=11.4, p<.001
**χ^2_{trend}=9.6, p=.002

3. Astrocytoma and glioma NOS combined

As rural areas experienced a higher glioma NOS rate than urban areas, the increasing astrocytoma rates in rural areas might have resulted from the shift over time of cases from the glioma NOS to the astrocytoma group.

Combining astrocytoma and glioma NOS substantially reduced the rural increase and therefore the urban-rural discrepancy in rate increase (Tables 43 and 44). The rural trends remained significant for children under age ten but not for children under age 15. Rural rate increases were less twice the urban increases, and in one analysis, rural and urban rates increased by the same amount. As for astrocytoma alone, the analysis using Method I for children under age ten gave the largest urban-rural discrepancy and the largest rural trend.

Table 43.

Urban and rural time trends in the incidence of combined astrocytoma and glioma NOS, 1969-80
Iowa whites, ages 0-14
Rates per million per year
(Numbers of cases)

Urbanization	1969-71	1973-76	1977-80	Ratio 1977-80/1969-71
Method I				
Low*	15.1 (15)	9.9 (12)	22.3 (25)	1.5
Moderate	6.3 (4)	15.6 (12)	17.1 (12)	2.7
High	13.6 (10)	8.9 (8)	13.5 (11)	1.0
Method II				
Low**	13.2 (19)	11.9 (21)	19.8 (32)	1.5
High	11.5 (10)	10.5 (11)	16.7 (16)	1.5

*χ^2_{trend}=17.6, p=.18
**χ^2_{trend}=2.1, p=.15

Table 44.

Urban-rural time trends in the incidence of Combined astrocytoma and glioma NOS, 1969-80
Iowa whites, under age 10
Rates per million per year
(Numbers of cases)

Urbanization	1969-71	1973-76	1977-80	Ratio 1977-80/1969-71
Method I				
Low*	11.4 (7)	9.1 (7)	26.3 (19)	2.3
Moderate	7.3 (3)	10.0 (5)	15.4 (7)	2.1
High	12.5 (6)	6.9 (4)	15.1 (8)	1.2
Method II				
Low**	11.1 (10)	9.8 (11)	22.9 (24)	2.1
High	10.6 (6)	7.3 (5)	16.1 (10)	1.5

*χ^2_{trend}=4.8, p=.03
**χ^2_{trend}=4.7, p=.03

4. Astrocytoma, glioma NOS, and cancer NOS combined

As some cancers NOS might be astrocytomas, cancers NOS were included with astrocytomas and gliomas NOS. A further decrease in the rural trend with the addition of cancers NOS would provide more evidence that the shift of rural cancers NOS into more specific categories contributed to the astrocytoma increase. However, this worst case analysis would overestimate the effect of NOS groups on urban-rural differences, as probably not all gliomas NOS and cancers NOS were astrocytomas.

Including cancers NOS did decrease the rural trends slightly, but hardly affected urban-rural differences in rate increases (Tables 45 and 46). None of the trends were statistically significant. The rates for children under age ten in rural areas (Method I) increased the most and came closest to significance ($p=.06$).

Table 45.

Urban and rural time trends in the incidence of combined astrocytoma, glioma NOS, and cancer NOS, 1969-80
Iowa whites, ages 0-14
Rates per million per year
(Numbers of cases)

Urbanization	1969-71	1973-76	1977-80	Ratio 1977-80/1969-71
Method I				
Low*	17.1 (17)	11.5 (14)	22.3 (25)	1.3
Moderate	9.5 (6)	18.2 (14)	17.1 (12)	1.8
High	16.3 (12)	10.0 (9)	14.7 (12)	0.9
Method II				
Low	16.0 (23)	14.2 (25)	19.8 (32)	1.2
High	13.8 (12)	11.5 (12)	17.8 (17)	1.3

χ^2_{trend}=3.62, p=.06

Table 46.

Urban and rural time trends in the incidence of combined astrocytoma, glioma NOS, and cancer NOS, 1969-80
Iowa whites, under age 10
Rates per million per year
(Numbers of cases)

Urbanization	1969-71	1973-76	1977-80	Ratio 1977-80/1969-71
Method I				
Low	13.0 (8)	10.4 (8)	26.3 (19)	2.0
Moderate	12.2 (5)	12.0 (6)	15.4 (7)	1.3
High	16.7 (8)	6.9 (4)	17.0 (9)	1.0
Method II				
Low	14.4 (13)	11.6 (13)	22.9 (24)	1.6
High	14.1 (8)	7.3 (5)	17.7 (11)	1.3

5. All childhood brain cancer

If a real urban-rural difference in the rise of astrocytoma rates occurred without any differences in the trends of other cell types, the total childhood brain cancer rate would have increased more in rural than urban areas. The increases between 1969 and 1980 in all urbanization strata were small and not significant (Tables 47 and 48). Rural areas showed a greater increase than did urban areas by Method I, but not by Method II.

Table 47.

Urban and rural time trends in the incidence of childhood brain cancer, 1969-80
Iowa whites, ages 0-14
Rates per million per year
(Numbers of cases)

Urbanization	1969-71	1973-76	1977-80	Ratio 1977-80/1969-71
Method I				
Low	24.2 (24)	14.0 (17)	29.4 (33)	1.2
Moderate	23.6 (15)	22.1 (17)	24.3 (17)	1.0
High	23.0 (17)	16.8 (15)	23.4 (19)	1.0
Method II				
Low	24.9 (36)	17.0 (30)	27.1 (44)	1.1
High	23.0 (20)	18.1 (19)	26.2 (25)	1.1

Table 48.

Urban and rural time trends in the incidence of childhood brain cancer, 1969-80
Iowa whites, under age 10
Rates per million per year
(Numbers of cases)

Urbanization	1969-71	1973-76	1977-80	Ratio 1977-80/1969-71
Method I				
Low	22.7 (14)	14.3 (11)	34.6 (25)	1.5
Moderate	36.6 (15)	14.1 (7)	26.4 (12)	0.7
High	22.9 (11)	13.8 (8)	26.5 (14)	1.2
Method II				
Low	26.6 (24)	15.2 (17)	31.5 (33)	1.2
High	24.7 (14)	13.2 (9)	27.4 (17)	1.1

6. Summary

The increase in astrocytoma incidence occurred mostly in rural areas in which a four- to five-fold increase was observed. More specific diagnosis explained most of the rural increase, although a doubling of rate in rural areas in children under ten (Method I) remained. The analyses could not distinguish between a real increase and one due to improved ascertainment of cases. Other changes in diagnosis and chance remained possible explanations, as the total brain cancer rate did not show a convincing increase.

Time trends of astrocytoma rates by site

Previous sections showed increased rates of astrocytoma in Iowa, especially in the rural areas. This section investigates the time trends for astrocytomas by anatomic site. Cerebral astrocytomas are not as rapidly fatal without treatment as astrocytomas in other locations. Thus, an increased rate of only cerebral astrocytomas might suggest that the increasing astrocytoma rate resulted from improved ascertainment of slowly progressing tumors and not from a real change in incidence. Time trends were calculated first, for the state of Iowa and then, for areas in Iowa with low, moderate, and high degrees of urbanization. All rates presented in this section include both astrocytomas and gliomas NOS in order to adjust for diagnostic differences among time periods and areas with different degrees of urbanization.

In Iowa, the rates of cerebral and cerebellar astrocytomas and gliomas NOS increased by 90% and 125%, respectively. The upward trend was significant for the cerebellar tumors, but not for those tumors in the cerebrum. No trend in the incidence of brain stem tumors occurred. Table 49 shows the time trends for Iowa.

Table 49.

Time trends in the incidence of
combined astrocytoma and glioma NOS by site, 1969-80
Iowa whites, ages 0-14
Rates per million per year
(Numbers of cases)

Site	1969-71	1973-76	1977-80	Ratio 1977-80/1969-71
Cerebrum*	3.4 (8)	3.5 (10)	6.5 (17)	1.9
Cerebellum**	2.5 (6)	1.7 (5)	5.7 (15)	2.3
Brain stem	1.7 (4)	1.7 (5)	1.5 (4)	0.9

*$\chi^2_{trend}=2.69$, p=.10
**$\chi^2_{trend}=3.85$, p=.05

When degree of urbanization was considered, each time-site specific rate resulted from a small number of cases. Despite the small numbers, a few observations were made. The rate of cerebral astrocytoma increased in rural but not urban Iowa (Table 50). By both methods of defining urbanization, the rates in rural areas increased close to three-fold, a significant trend. A significant eight-fold increase occurred in children under age ten (Table 51).

The increase in the rate of cerebellar astrocytomas appeared greater in rural than urban areas by Method I, but Method II showed a smaller difference (Table 52). None of the trends was statistically significant. The trends in the rural areas came closest to significance with p-values of .09 and .08 for Method I and Method II, respectively. The number of cases was too small to investigate trends in children under age ten.

The number of brain stem tumors was small and no trends were observed (Table 53).

In summary, the rates of astrocytomas in the cerebellum and cerebrum increased in Iowa between 1969 and 1980, while that of brain stem astrocytomas hardly changed. The rate of cerebellar astrocytomas rose significantly for the state and rose more in the rural than the urban areas, although neither

urban nor rural trends were significant. The rate of cerebral astrocytomas also showed a greater increase in rural than urban areas. The increases were statistically significant in the rural areas, especially for children under age ten. For the state of Iowa, the rise in incidence rates of cerebral astrocytomas was of borderline significance.

Table 50.

Urban and rural time trends in the incidence of cerebral astrocytoma, 1969-80
Iowa whites, ages 0-14
Rates per million per year
(Numbers of cases)

Urbanization	1969-71	1973-76	1977-80	Ratio 1977-80/1969-71
Method I				
Low*	4.0 (4)	2.5 (3)	10.7 (12)	2.7
Moderate	0.0 (0)	6.5 (5)	2.9 (2)	-
High	5.4 (4)	2.2 (2)	3.7 (3)	0.7
Method II				
Low**	2.8 (4)	3.4 (6)	8.0 (13)	2.9
High	4.6 (4)	3.8 (4)	4.2 (4)	0.9

*χ^2_{trend}=4.2, p=.04
**χ^2_{trend}=4.3, p=.04

Table 51.

Urban and rural time trends in the incidence of cerebral astrocytoma, 1969-80
Iowa whites, under age 10
Rates per million per year
(Numbers of cases)

Urbanization	1969-71	1973-76	1977-80	Ratio 1977-80/1969-71
Method I				
Low*	1.6 (1)	2.6 (2)	12.5 (9)	7.8
Moderate	0.0 (0)	4.0 (2)	2.2 (1)	-
High	6.3 (3)	1.7 (1)	3.8 (2)	0.6
Method II				
Low**	1.1 (1)	2.7 (3)	9.5 (10)	8.6
High	5.3 (3)	2.9 (2)	3.2 (2)	0.6

*χ^2_{trend}=7.0, p=.008
**χ^2_{trend}=7.6, p=.006

Table 52.

Urban and rural time trends in the incidence of cerebellar astrocytoma, 1969-80
Iowa whites, ages 0-14
Rates per million per year
(Numbers of cases)

Urbanization	1969-71	1973-76	1977-80	Ratio 1977-80/1969-71
Method I				
Low	2.0 (2)	1.6 (2)	6.2 (7)	3.1
Moderate	1.6 (1)	2.6 (2)	5.7 (4)	3.6
High	4.1 (3)	1.1 (1)	4.9 (4)	1.2
Method II				
Low	2.1 (3)	1.7 (3)	5.6 (9)	2.7
High	3.4 (3)	1.9 (2)	6.3 (6)	1.9

Table 53.

Urban and rural time trends in the incidence of brain stem astrocytoma, 1969-80
Iowa whites, ages 0-14
Rates per million per year
(Numbers of cases)

Urbanization	1969-71	1973-76	1977-80	Ratio 1977-80/1969-71
Method I				
Low	3.0 (3)	2.5 (3)	0.9 (1)	0.3
Moderate	1.6 (1)	1.3 (1)	4.3 (3)	2.7
High	0.0 (0)	1.1 (1)	0.0 (0)	-
Method II				
Low	2.8 (4)	2.3 (4)	1.9 (3)	0.7
High	0.0 (0)	1.0 (1)	1.1(1)	-

Summary

Incidence rates generally changed little between 1969 and 1980 for the combined registries which reported data for all 11 years of the TNCS and SEER programs. The rate of astrocytoma, however, increased 33%. Iowa experienced a 1980 rate 70% greater than that in 1969, and accounted for most of the observed increase in the combined areas. The trend in Iowa occurred in males and females under age ten and was largely explained by declining rates of glioma NOS and cancer NOS. The rural areas experienced a larger increase in astrocytoma rates than did urban areas, especially for children under age ten. Combining astrocytomas, gliomas NOS, and cancers NOS eliminated most of the rural increase and the urban-rural discrepancy for children under age 15. A doubling of rate ($p=.06$) remained for rural children under age ten. Both cerebellar and cerebral tumors contributed to the greater rural than urban increase, although only the rural increase in the rate of cerebral tumors was significant.

ECOLOGICAL ANALYSES

Urban-rural differences

Introduction

Reports on urban-rural differences in childhood brain cancer rates conflict. Since one study was of the entire U.S. (41) and the other was of Minnesota (59), regional variation in urban-rural differences might explain the discrepancies. The present study investigated urban-rural differences to provide an analysis based on recent incident cases and to look for regional variation.

Urban-rural differences in the rate of all childhood brain cancer and the major cell types were investigated for Iowa and for the three southwestern states combined (Utah, New Mexico, Colorado). When astrocytoma rates were studied, results for astrocytoma alone and for astrocytoma and glioma NOS combined are presented, the latter to adjust for possibly more accurate diagnosis in urban areas. A similar analysis of ependymoma rates was done for only Connecticut, which had a relatively large number of cases.

Other analyses attempted to describe more accurately urban-rural differences in astrocytoma rates. As time trends in urban and rural Iowa differed, an accurate comparison of urban-rural differences required examination of astrocytoma rates by time period. The remaining analyses investigated urban-rural differences in astrocytoma rates by location in the brain. As some evidence suggests that astrocytomas at different sites are separate disease entities, such analyses might uncover urban-rural differences not seen in the previous analyses.

Counties were divided by degree of urbanization in two ways. Method I used the census variable, proportion of population living in places with 2500 or more inhabitants. Method II used another census variable, proportion of

population living in cities of 50,000 or more. Both methods are explained in chapter 2.

Iowa

In Iowa, the low urbanization areas had similar rates of childhood brain cancer, higher rates of astrocytoma, and lower rates of medulloblastoma than highly urbanized areas (Table 54).

By both Method I and Method II, the low urbanization areas experienced slightly higher rates of astrocytoma and of glioma NOS. The difference was larger using Method I. The two-fold rural excess of glioma NOS implied that fewer gliomas were specifically diagnosed in the rural areas than in the urban areas. Thus, the combined astrocytoma-glioma NOS rate would provide a more accurate comparison than would the rate of astrocytoma alone. By Method I, the combined rate was 32% higher in the rural than in the urban counties; the intermediate counties experienced an intermediate rate. The trend, however, was not statistically significant ($\chi^2_{trend}=1.51$, p=.22). Method II reduced the urban-rural difference by half. The rates for the other category that could contain astrocytomas, cancer NOS, were small and similar in urban, intermediate, and rural counties.

By either method, urban areas experienced a medulloblastoma rate close to twice that of the rural areas. The urban-rural difference approached significance (Method II, Z=1.85, p=.06). The intermediate areas had an intermediate rate, but the trend was not significant ($\chi^2_{trend}=1.88$, p=.17). The glioma NOS group probably included a small number of medulloblastomas, but probably not enough to eliminate the urban excess.

Southwestern states

The urban-rural differences observed in three southwestern states were smaller than and sometimes opposite from those seen in Iowa and

dependent on the urban classification used (Table 55). The two methods gave conflicting results for astrocytoma and for astrocytoma-glioma NOS. Differences in medulloblastoma rates were opposite from those in Iowa. Southwestern urban counties experienced a lower medulloblastoma rate than rural counties.

Method I gave the larger difference of 50%, but it was not significant ($Z=.96$, $p=.34$).

Table 54.

Urban and rural incidence of childhood brain cancer
by histologic group
Iowa whites, ages 0-14
Rates per million per year
(Numbers of cases)

Method I.

Urbanization	Brain	Medullo-blastoma	Astro-cytoma	Glioma NOS	Com-bined*	Cancer NOS
Low	22.2 (74)	3.0 (10)	12.9 (43)	2.7 (9)	15.6 (52)	1.2 (4)
Moderate	23.3 (49)	4.8 (10)	9.0 (19)	4.3 (9)	13.3 (28)	1.9 (4)
High	20.9 (51)	5.3 (13)	10.6 (26)	1.2 (3)	11.8 (29)	1.6 (4)
Method II.						
Low	22.4 (108)	3.1 (15)	11.8 (57)	3.1 (15)	14.9 (72)	1.7 (8)
High	22.2 (64)	5.9 (17)	10.8 (31)	2.1 (6)	12.9 (37)	1.4 (4)

*Astrocytoma and glioma NOS

Table 55.

Urban and rural incidence of childhood brain cancer by histologic group
Colorado, New Mexico, and Utah
Whites, ages 0-14
Rates per million per year
(Numbers of cases)

Method I.

Urbanization	Brain	Medullo-blastoma	Astro-cytoma	Glioma NOS	Com-bined*	Cancer NOS
Low	22.4 (21)	7.5 (7)	8.5 (8)	2.1 (2)	10.6 (10)	1.1 (1)
Moderate	18.9 (25)	3.8 (5)	9.8 (13)	2.3 (3)	12.1 (16)	0.0 (0)
High	19.8 (96)	5.0 (24)	9.7 (47)	2.3 (11)	12.0 (58)	1.5 (7)
Method II.						
Low	21.4 (50)	5.6 (13)	10.7 (25)	1.7 (4)	12.4 (29)	0.9 (2)
High	20.0 (87)	4.8 (21)	9.7 (42)	2.5 (11)	12.2 (53)	1.4 (6)

*Astrocytoma and glioma NOS

Comparison of results in Iowa and the southwestern states

Iowa and the three southwestern states showed small and sometimes opposite urban-rural differences. The two methods of classifying counties according to urbanization gave similar results in Iowa, but sometimes opposite results in the southwestern states.

Rural astrocytoma and astrocytoma-glioma NOS rates slightly exceeded urban rates in Iowa. In the southwestern states, however, no consistent pattern emerged.

Iowa and the southwestern states exhibited opposite trends in medulloblastoma rates. In Iowa, urban areas experienced higher rates of medulloblastoma, but the rural areas had higher rates in the southwestern states.

Ependymoma

Urban-rural differences in ependymoma rates were studied in Connecticut, as no other state had enough cases to do so. The urban/rural classification used was similar to Method II in that it was based on the census variable, proportion of population living in urbanized areas of 50,000 or more inhabitants. However, the cutoff points were adjusted to fit the distribution of urbanization levels of the state's eight counties (see Methods).

The urban counties experienced a rate of ependymoma 2.4 times that of the rural counties; the moderately urbanized areas had an intermediate rate (Table 56). The rates in the low and moderate counties, however, were based on only two cases each, and the trend was not significant. Ependymomas that were diagnosed as gliomas NOS or cancers NOS could explain the difference only if nonspecific diagnoses occurred more frequently in rural areas. However, about the same proportion of cases in all areas were gliomas NOS--one of 14 in the rural areas, one of 13 in the intermediate areas, and 10 of 90 in the urban areas. Only one cancer NOS case occurred.

Table 56.

Urban and rural incidence of childhood ependymoma*
Connecticut whites, ages 0-14
Rates per million per year

Urbanization	Rate	No. cases
Low	1.8	2
Moderate	3.1	2
High	4.3	16

* $\chi^2_{trend}=1.49$, p=.22

Urban-rural differences adjusted for time period

As the rates of astrocytoma and of astrocytoma and glioma NOS combined rose and the magnitude of the increase differed between urban and rural areas, urban-rural differences were examined by time period (Tables 57 and 58). The rural rates of astrocytoma were lower than the urban rates in the first time period, but exceeded the urban rates in the last time period (Table 57). To adjust for the apparent shift of cases from the glioma NOS to the astrocytoma category in rural areas, urban-rural differences in the combined rate were studied. The rural combined rates generally exceeded those of urban areas in all three time periods. In only one comparison of 12 did urban rates exceed rural rates. The rural excess increased slightly with time (Table 58).

Table 57.

Time trends in rural-urban ratios of childhood astrocytoma incidence, 1969-80 Iowa whites

Age	1969-71	1973-76	1977-80
Under 15			
Method I	.83	1.1	1.6
Method II	.87	1.2	1.2
Under 10			
Method I	.47	.75	1.6
Method II	.63	.85	1.4

Table 58.

Time trends in rural-urban ratios of childhood astrocytoma and glioma NOS incidence, 1969-80 Iowa whites

Age	1969-71	1973-76	1977-80
Under 15			
Method I	1.1	1.1	1.7
Method II	1.1	1.1	1.2
Under 10			
Method I	0.9	1.3	1.7
Method II	1.0	1.3	1.4

Astrocytoma rates by site

Urban-rural analyses of astrocytoma incidence at different sites might have uncovered differences not seen previously. All rates in this section include both astrocytomas and gliomas NOS. The combined rate reduced possible bias and allowed analysis of brain stem astrocytomas, of which most were diagnosed as glioma NOS.

In Iowa, rural areas experienced higher rates of brain stem astrocytomas-gliomas NOS by both methods (Method I, $Z=1.7$, $p=.09$). Cerebellar rates differed little by urbanization. Cerebral rates showed a rural excess by

Method I, which almost disappeared using Method II. Table 59 shows these results. A difference in the proportion of these cases with brain NOS as the tumor site would confound these results; however, that proportion was 0.24, 0.21, and 0.28 for low, moderate, and high urbanization strata, respectively.

As in Iowa, the three southwestern states showed a higher rural rate of brain stem gliomas. However, the difference decreased greatly when the analysis was done by method II. Urban and rural rates of cerebral astrocytomas did not differ. The analyses of cerebellar astrocytomas-gliomas NOS showed higher urban rates in one analysis and similar urban and rural rates in the other. Table 60 shows these results for the southwestern states.

Table 59.

Urban and rural incidence of childhood astrocytomas and gliomas NOS by site Iowa whites, ages 0-14 Rates per million per year (Numbers of cases)

Urbanization	Cerebral	Cerebellar	Brain stem	All astrocytomas and gliomas NOS
Low	5.7 (19)	3.3 (11)	2.1 (7)	15.6 (52)
Moderate	3.3 (7)	3.3 (7)	2.4 (5)	13.3 (28)
High	3.7 (9)	3.3 (8)	0.4 (1)	11.8 (29)
Method II				
Low	4.8 (23)	3.1 (15)	2.3 (11)	14.9 (72)
High	4.2 (12)	3.8 (11)	0.7 (2)	12.9 (37)

Table 60.

Urban and rural incidence of childhood astrocytomas and gliomas NOS by site
Colorado, New Mexico, and Utah
Whites, ages 0-14
Rates per million per year
(Numbers of cases)

Urbanization	Cerebral	Cerebellar	Brain stem	All astrocytoma and glioma NOS
Low	4.3 (4)	0.0 (0)	4.3 (4)	10.6 (10)
Moderate	3.8 (5)	2.3 (3)	1.5 (2)	12.1 (16)
High	4.3 (21)	3.3 (16)	1.2 (6)	12.0 (58)
Method II				
Low	4.3 (10)	2.1 (5)	2.1 (5)	12.4 (29)
High	4.6 (20)	3.0 (13)	1.4 (6)	12.2 (53)

Urban-rural differences in astrocytoma rates by site and time period are shown in Tables 61 and 62. Too few brain stem tumors occurred to permit analysis. In the last time period, rural rates of cerebral astrocytoma exceeded urban rates. No consistent differences in cerebellar astrocytoma rates occurred.

Table 61.

Time trends in rural-urban ratios of cerebral astrocytoma and glioma NOS incidence, 1969-80
Iowa whites, ages 0-14

	1969-71	1973-76	1977-80
Method I	0.7	1.1	2.9
Method II	0.6	0.9	1.9

Table 62.

Time trends in rural-urban ratios of cerebellar astrocytoma and glioma NOS incidence, 1969-80 Iowa whites, ages 0-14

	1969-71	1973-76	1977-80
Method I	0.5	1.5	1.3
Method II	0.6	0.9	0.9

In summary, rural areas in Iowa and in the southwestern states experienced higher rates of brain stem astroctyomas-gliomas NOS than did urban areas. The difference in rates in Iowa was of borderline significance. No other differences occurred in both Iowa and the southwestern states. Differences that did occur were usually observed with only one of the two methods. When similar comparisons were made for rates in Iowa by time period, rates of cerebral and cerebellar astrocytomas-gliomas NOS in urban areas exceeded those in rural areas in 1969-71. In 1977-80, however, cerebral astrocytoma rates were greater in rural areas and cerebellar astrocytoma rates were about equal in urban and rural areas.

Summary

Urban-rural differences were generally small and not statistically significant. A few observations by cell type were of interest. Rural rates for brain stem gliomas exceeded urban rates in both Iowa and the three southwestern states. Iowa and the southwestern states showed conflicting urban-rural differences in medulloblastoma rates. The urban rate in Iowa was greater than the rural rate ($p=.06$). The rural areas of Iowa experienced a higher combined astrocytoma-glioma NOS rate than urban areas. The difference was not statistically significant, but it was consistent across time period and urban definition. Astrocytomas-gliomas NOS in the cerebrum and the brain stem contributed to the rural excess.

Population density

As described in Methods, counties with more than 70% of their populations living in cities of 50,000 or more in 1980 were divided into four strata of population density--fewer than 100, 100-350, 351-700, and more than 1500 persons per square kilometer. No counties had densities between 700 and 1500 persons per square kilometer. Incidence rates by cell type were calculated for each stratum.

Incidence of childhood brain cancer showed no trend with increasing population density, nor did any of the cell types, except astrocytoma (Table 63). Astrocytoma rates increased with population density; the stratum of highest density had a rate 24% higher than the stratum of lowest density. When astrocytoma and glioma NOS were combined, the trend remained. Neither trend, however, was significant.

Table 63.

Childhood brain cancer incidence by population density
in highly urbanized areas
Whites, ages 0-14
Rates per million per year
(Numbers of cases)

Persons/ square km	Astro-cytoma*	Medullo-blastoma	Glioma NOS	Combined**	All brain
<100	9.4 (23)	4.1 (10)	3.7 (9)	13.1(32)	20.9 (51)
100-350	9.8 (60)	7.0 (43)	3.1 (19)	12.9 (79)	23.5 (144)
351-700	10.4 (103)	7.0 (69)	3.5 (35)	13.9 (138)	24.6 (244)
>1500	11.7 (47)	3.5 (14)	3.7 (15)	15.4 (62)	21.6 (87)

* χ^2_{trend}=.96, p=.32

** χ^2_{trend}=.98, p=.32

GEOGRAPHIC ANALYSES

Geographic variation

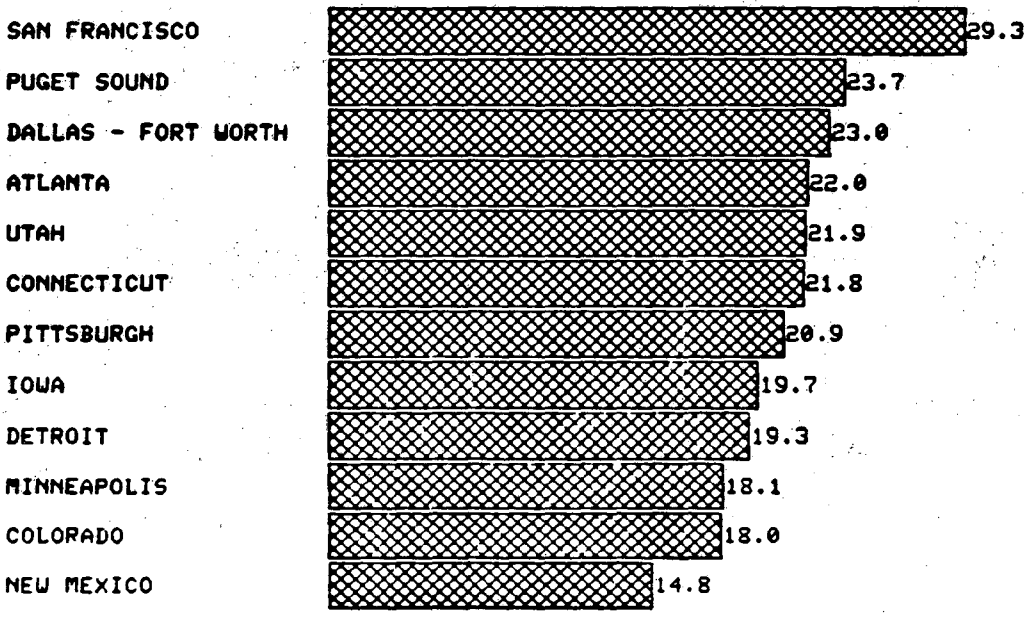
Environmental, genetic, or medical care factors affecting the incidence and diagnosis of childhood brain cancer would result in geographic variation of rates. Geographic variation in rates for whites across the 12 TNCS and SEER registries included in this study was investigated. The extent of the variation in incidence rates of all childhood brain cancers and of each major cell type was studied. To determine if the variation resulted from different degrees of urbanization among areas, incidence rates were calculated and geographic variation assessed for the urbanized parts of each area. Whether the extent of geographic variation changed over the 11-year period was also investigated.

Some of the figures in this section present age-adjusted rates, which hardly differed from the crude rates. All significance tests were done on crude rates.

The incidence of childhood brain cancer and of each major cell type showed geographic variation that at minimum approached significance. Childhood brain cancer rates varied about two-fold across areas; the variation was significant (Fig. 6). SFO had the highest rate. Astrocytoma, medulloblastoma, and glioma NOS rates showed substantial interarea variation with two to three-fold differences in rates (Fig. 7 and 8). These results were of borderline significance. The analysis of geographic variation of ependymoma rates included only the six most populous areas, so that the rates would be relatively stable. The variation in rates was almost four-fold and was significant (Fig. 9).

Figure 6.

Incidence of childhood brain cancer
in 12 TNCS and SEER registries
Whites, age 0-14
Rates per million per year

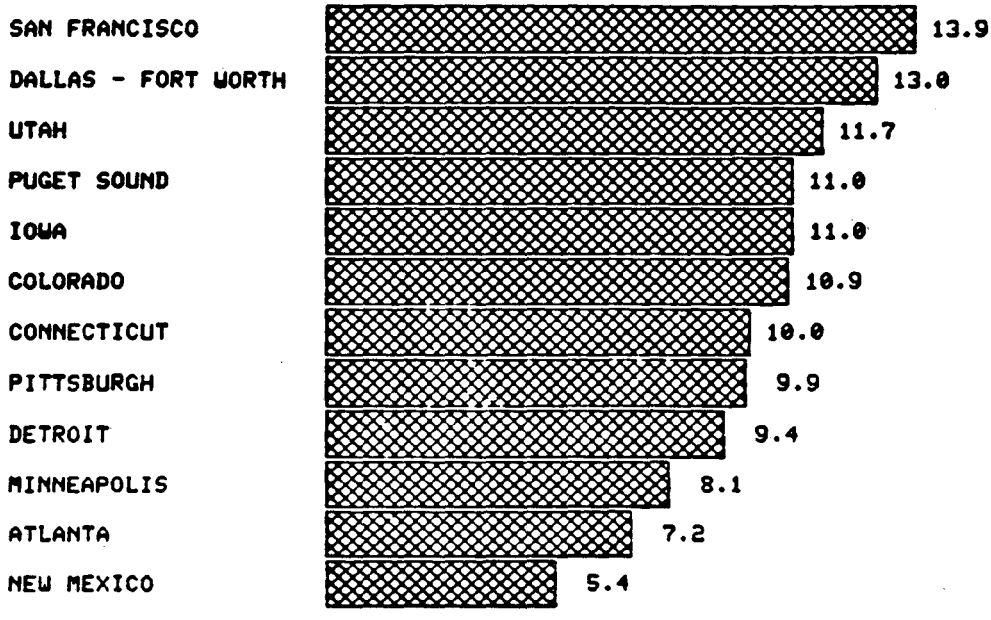


χ^2=24.3, df=11, p=.01

SFO contributed more than 50% of the χ^2 value.

Figure 7.

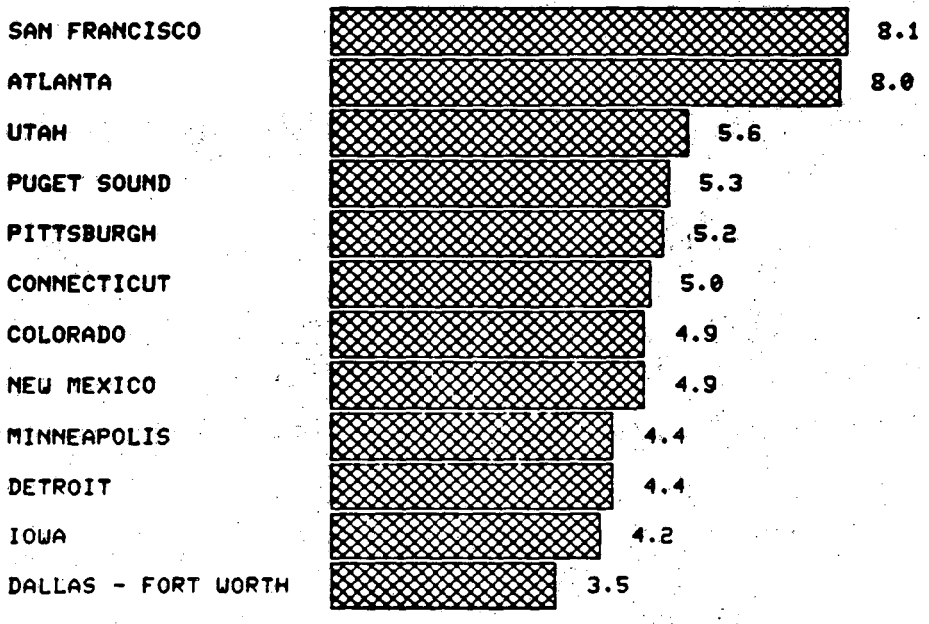
Incidence of childhood astrocytoma
in 12 TNCS and SEER registries
Whites, age 0-14
Rates per million per year



χ^2=17.6, df=11, p=.09

Figure 8.

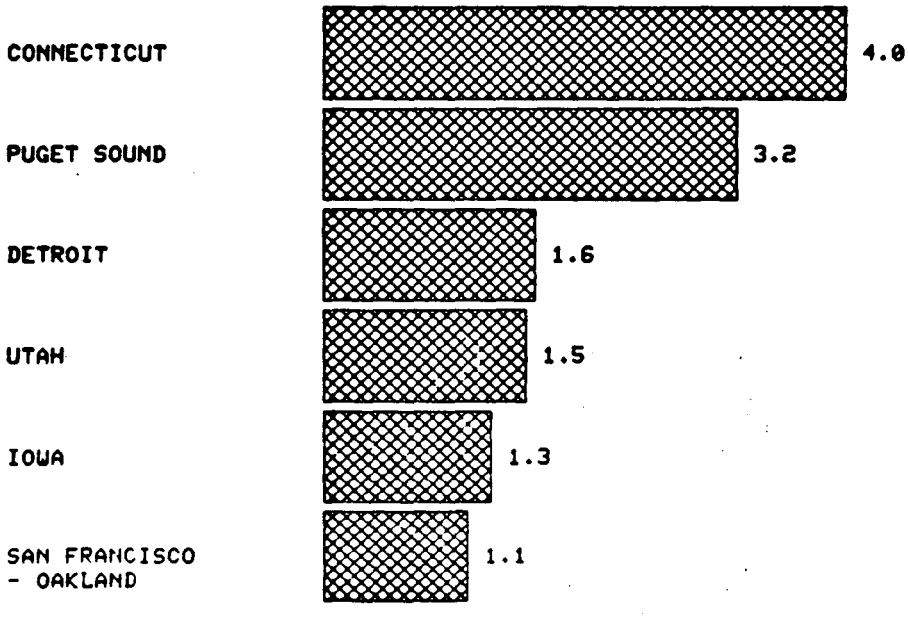
Incidence of childhood medulloblastoma
in 12 TNCS and SEER registries
Whites, age 0-14
Rates per million per year



χ^2=16.5, df=11, p=.12

Figure 9.

Incidence of childhood ependymoma
in 12 TNCS and SEER registries
Whites, age 0-14
Rates per million per year



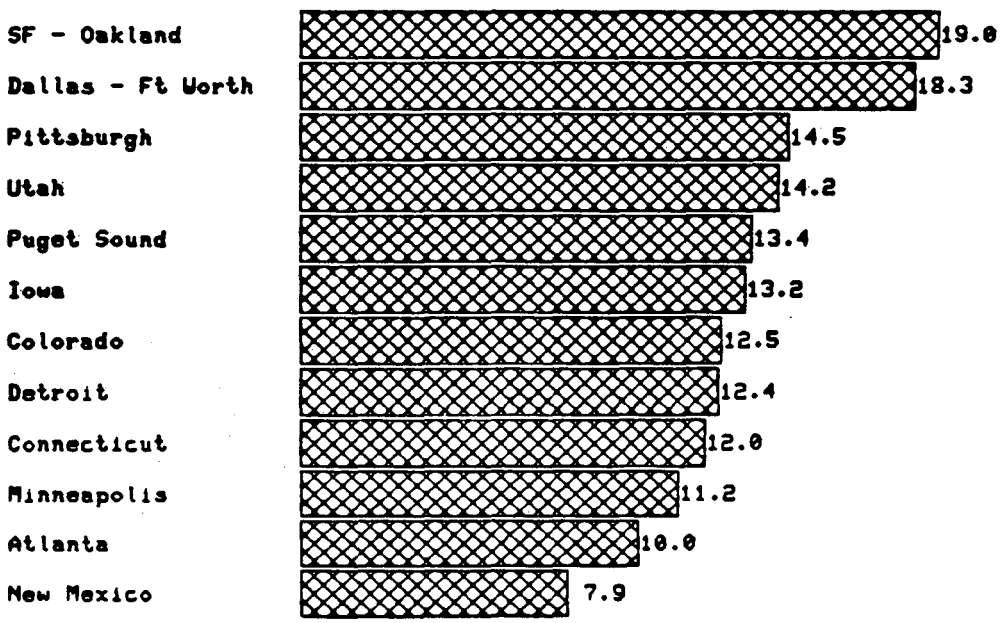
χ^2=15.22, df=5, p=.01

Geographic variation in the proportion of cases diagnosed as gliomas NOS could explain at least part of the observed variation of the specific cell types. In other words, rates might appear to vary if areas with apparently low rates had a large proportion of cases in the glioma NOS group and areas with high rates had low proportions. To assess whether this were so, the analyses were repeated after distribution of the glioma NOS cases into the specific glioma categories, according to the site and type distribution for each geographic area. These analyses assumed that at each site within the brain, the gliomas NOS were distributed among the specific glioma types identically to the cases with detailed diagnoses.

After this distribution of glioma NOS cases, the geographic variation of astrocytomas reached statistical significance. Pittsburgh moved from having the eighth highest rate to having the third highest rate; the ranking of the other areas remained virtually unchanged as did the ratio of the highest to lowest rates. As this redistribution of glioma NOS cases reclassified 77% of them as astrocytomas, the changes in the numbers of medulloblastomas and ependymomas were small and consequently, had little effect on the extent of variation, the rank of geographic areas, or on the value of the χ^2 statistic. Combining the astrocytoma and glioma NOS cases into one category gave the registries virtually the same rank and the variation virtually the same significance as proportionally distributing the glioma NOS cases (Fig. 9). Table 64 summarizes the analyses of geographic variation of childhood brain cancer rates by cell type.

Figure 10.

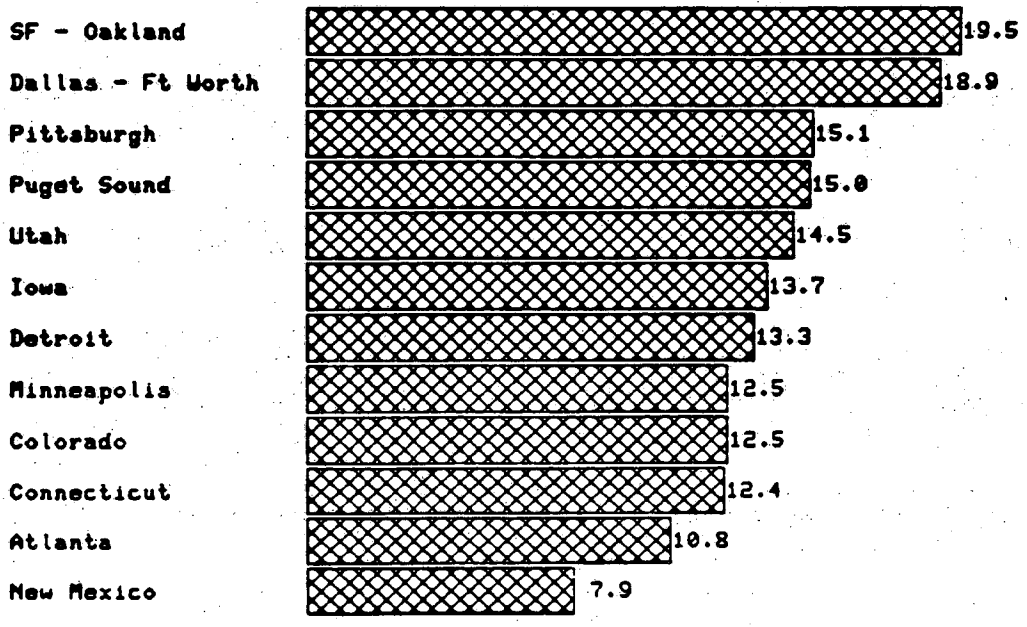
Incidence of childhood astrocytoma and glioma NOS
with glioma NOS cases proportionally distributed
In 12 TNCS and SEER registries
Whites, age 0-14
Rates per million per year



χ^2=25.0, df=11, p=.009

Figure 11.

Incidence of childhood astrocytoma and glioma NOS combined
in 12 TNCS and SEER registries
Whites, age 0-14
Rates per million per year



χ^2=24.1, df=11, p=.01

Table 64.

Geographic variation of

childhood brain cancer incidence

12 TNCS and SEER registries

Whites, ages 0-14

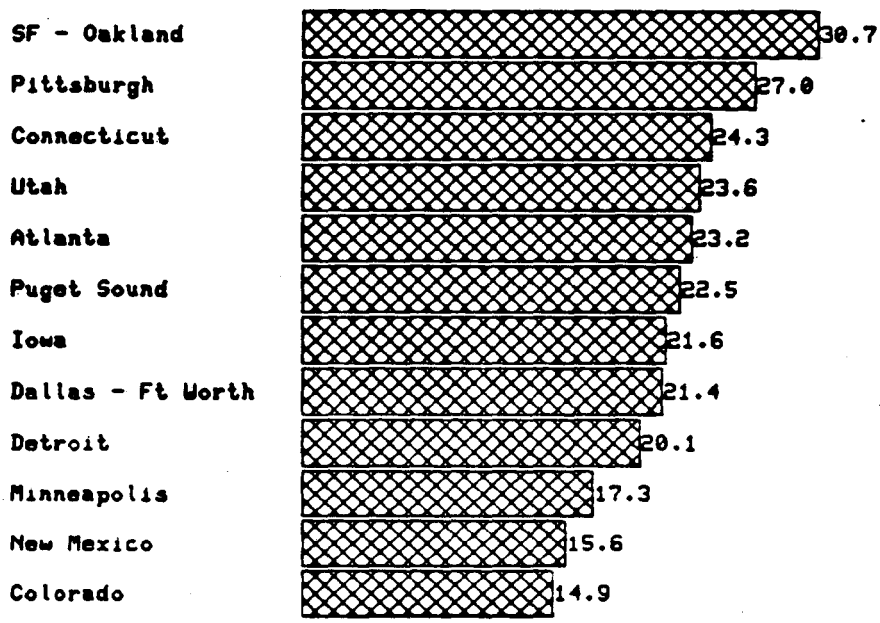
Type	Lowest Rate	Highest Rate	High/Low Ratio	p-value	# cases
All	N.Mexico	SFO	1.8	.01	1049
Astrocytoma	N.Mexico	SFO	2.7	.09	482
plus glioma NOS*	N.Mexico	SFO	2.4	.009	618
plus glioma NOS	N.Mexico	SFO	2.5	.01	649
Glioma NOS	Colorado	DFW	3.7	.08	165
Medulloblastoma	DFW	SFO	2.3	.12	243
Ependymoma	SFO	Conn	3.7	.002	67

*glioma NOS cases distributed according to site-type distribution

The fact that some registries were urban metropolitan areas while others included urban and rural areas might explain the geographic variation observed. In order to study more comparable areas, geographic variation was investigated including only highly urbanized counties (counties having at least 70% of their population living in urbanized areas of 50,000 or more inhabitants). The ratios of the highest to the lowest rates, the p-values of the χ^2 test and the rank of the geographic areas did not differ substantially from those calculated using the entire registry areas (Table 65, Fig. 12-14). Table 66 gives the total area rates and urbanized area rates for the six registries with substantial rural populations.

Figure 12.

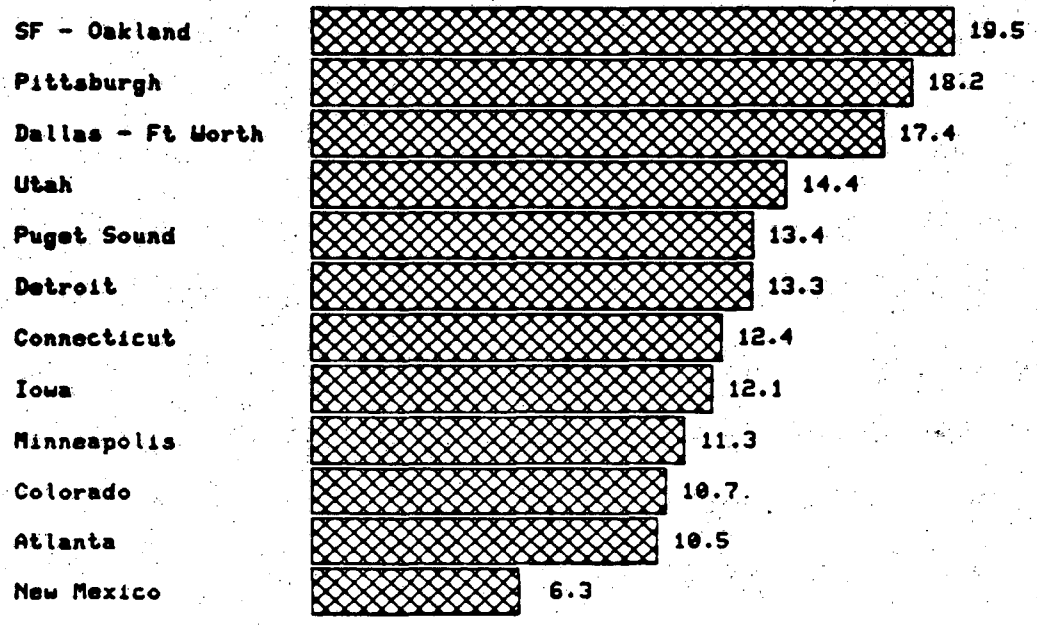
Incidence of childhood brain cancer
in the urbanized parts of 12 TNCS and SEER registries
Whites, age 0-14
Rates per million per year



χ^2=26.6, df=11, p=.005

Figure 13.

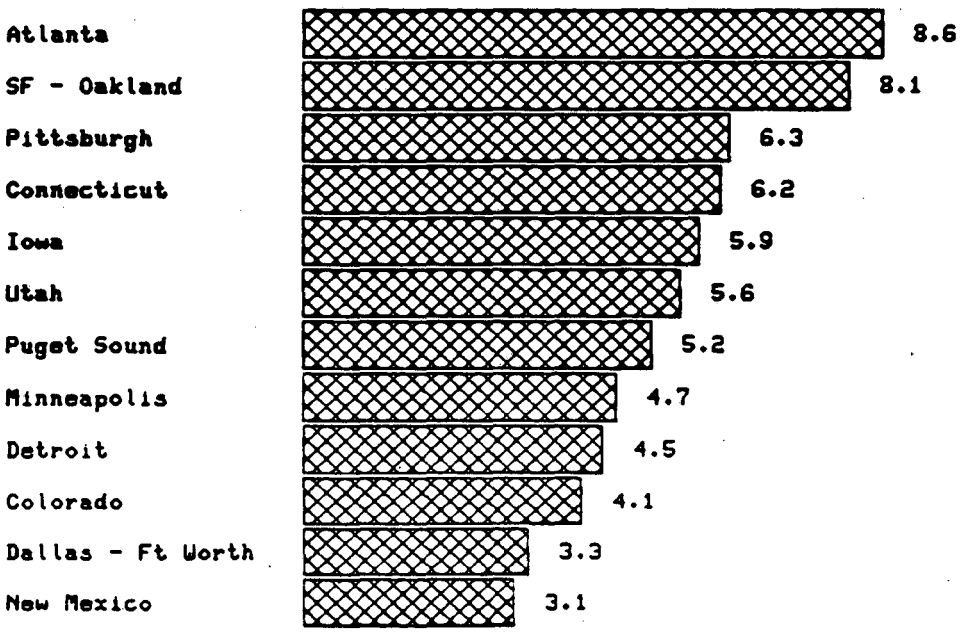
Incidence of childhood astrocytoma-glioma NOS
in the urbanized parts of 12 TNCS and SEER registries
Whites, age 0-14
Rates per million per year



χ^2=22.9, df=11, p=.02

Figure 14.

Incidence of childhood medulloblastoma
in the urbanized parts of 12 TNCS and SEER registries
Whites, age 0-14
Rates per million per year



χ^2=15.0, df=11, p=.18

Table 65.

Geographic variation of childhood brain cancer incidence
Urbanized parts of 12 TNCS and SEER areas
Whites, ages 0-14

Type	Lowest Rate	Highest Rate	High/Low Ratio	p-value	# cases
All	Colorado	SFO	2.1	.005	793
Astrocytoma	N.Mexico	SFO	3.0	.20	357
plus glioma NOS	N.Mexico	SFO	3.1	.02	488
Medulloblastoma	N.Mexico	Atlanta	2.8	.18	199

Table 66.

Comparison of incidence in entire registries and urbanized portions
Selected cell types
Whites, ages 0-14

	Astrocytoma and glioma NOS		Medulloblastoma	
	Entire area	Urbanized parts	Entire area	Urbanized parts
Puget Sound	15.0	13.4	5.3	5.2
Utah	14.5	14.4	5.6	5.6
Iowa	13.7	12.1	4.2	5.9
Colorado	12.5	10.7	4.9	4.1
Connecticut	12.4	12.4	5.0	6.2
New Mexico	7.9	6.3	4.9	3.1

To assess whether the extent of geographic variation changed with time, childhood brain cancer rates in three time periods were studied. The last two periods included the same geographic areas, the SEER registries, while the first period included the TNCS areas. The greatest geographic variation occurred in the middle time period, 1973-76 (Table 67); the variation was more than two-fold and was significant. The other two time periods showed nonsignificant variation despite similar numbers of cases as in the middle years.

Table 67.

Geographic variation of childhood brain cancer incidence
Three time periods, 1969-80
Whites, ages 0-14

Years	Lowest Rate	Highest Rate	High/Low Ratio	p-value	No. cases
1969-71	Colorado	SFO	1.7	.09	336
1973-76	Atlanta	SFO	2.3	.03	333
1977-80	N Mexico	SFO	1.8	.43	384

In conclusion, childhood brain cancer rates varied about two-fold across the 12 geographic areas. Rates of ependymoma and astrocytoma (after redistribution of the gliomas NOS) showed significant geographic variation. Medulloblastoma rates showed a degree of geographic variation similar to that of astrocytoma rates, but the variation was not statistically significant. The extent of variation by cell type changed little when only the urbanized parts of each registry were included. The geographic variation of all childhood brain cancer reached significance in only the middle time period, 1973-76; there was no indication that the extent of variation was either increasing or decreasing.

Correlation with physician concentration

Kurtzke observed that age-adjusted brain cancer mortality rates correlated with the concentration of physicians in the U.S. He attributed the geographic variation in mortality to variation in the use of medical services (57). To consider the same issue in the SEER and TNCS areas, Spearman's correlation coefficients for the incidence rates of brain cancer with the number of physicians per 100,000 persons were calculated (Table 68). The covariation of childhood brain cancer incidence with physician concentration was almost significant. (Fig. 15 shows the scattergram.) If the covariation were due to better diagnosis in areas with more physicians, then the covariation should have decreased with time and been smaller in the most recent time period. On the other hand, the rates for the most recent time period would be less stable. The rates for the most recent period, 1977-80, did not correlate with physician concentration. As a comparison, coefficients were calculated for adult brain cancer rates. Adult brain cancer rates covaried with physician concentration to a significant extent for the entire period, 1969-80, and for the most recent period, 1977-80.

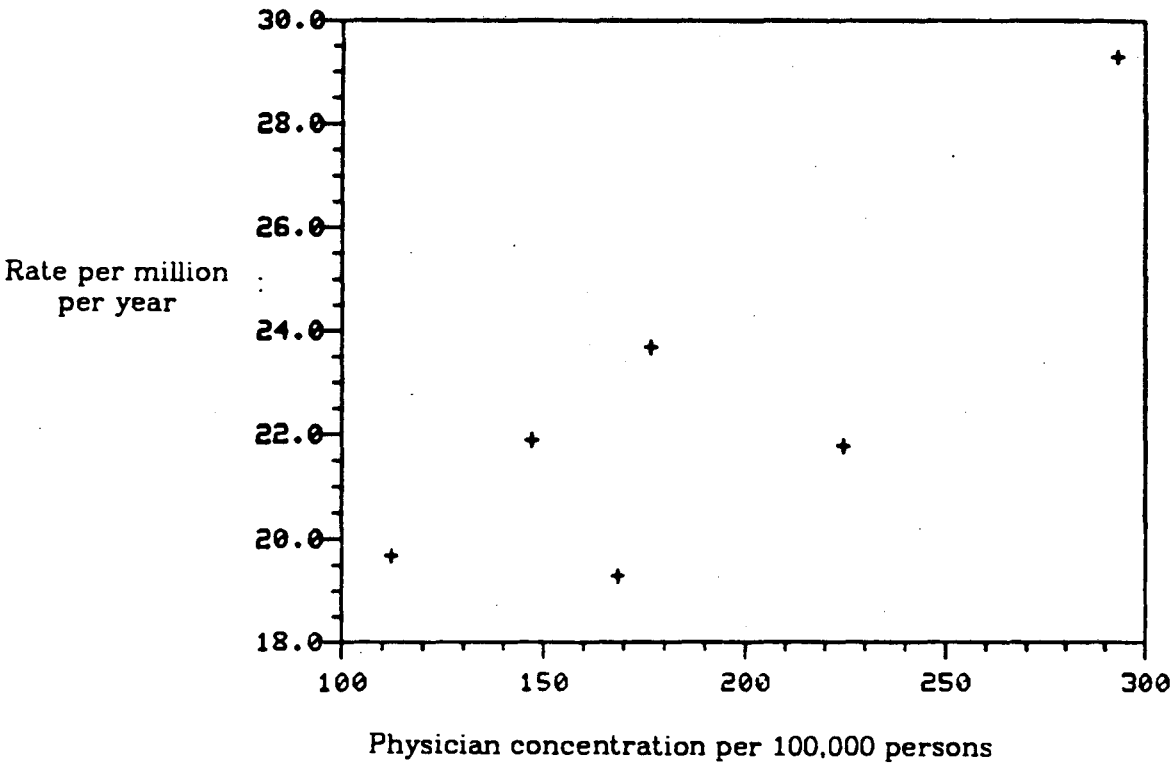
Table 68.

Correlation of
physician concentration and brain cancer incidence
Spearman's rank correlation coefficients

Age group	Years	R	p (one-sided)
Children	1969-80	0.60	.10
Children	1977-80	0.12	.39
Adults	1969-80	0.53	.04
Adults	1977-80	0.76	.01

Figure 15.

Physician concentration and
childhood brain cancer incidence
Six SEER registries, 1969-80
Whites, age 0-14



Covariation of histologic types

If two cell types had similar etiologies, we would expect their incidence rates to covary geographically. Covariation can be studied by correlation coefficients. In this study, rates by cell type in the areas with smaller populations were unstable, but excluding these areas resulted in too few points with which to calculate meaningful correlation coefficients. However, if the incidences covaried, cases of the two types would be distributed similarly among the 12 geographic areas. The geographic distributions of the major cell types, astrocytoma, medulloblastoma, and ependymoma were compared. A χ^2 test demonstrated that the geographic distribution of astrocytomas and medulloblastomas did not differ significantly (χ^2=12.9, df=11, p=.30). Excluding areas with small numbers of cases would increase the likelihood of seeing a significant difference, if one existed. Inclusion of only the six most populous areas did not change the result, nor did combining astrocytomas and gliomas NOS.

In contrast, comparisons of ependymomas with either astrocytomas or medulloblastomas showed that this rare cell type had a distinct geographic distribution (χ^2=17.9, df=5, p=.003 for astrocytomas and χ^2=16.0, df=5, p=.007 for medulloblastomas). These analyses used the six areas with large populations and relatively stable ependymoma rates. The results changed little when astrocytomas and gliomas NOS were considered together. Connecticut with 20 cases of ependymoma contributed a major proportion of the χ^2 values. Table 69 shows the distribution of the three major cell types in the six largest areas for whites, 1973-80.

Table 69.

Distribution of major cell types by geographic area
Six TNCS and SEER registries
Whites, ages 0-14
1973-80

Registry	Astrocytoma		Medulloblastoma		Ependymoma		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
SF - Oakland	53	59	33	37	4	4	90	100
Connecticut	50	53	25	26	20	21	95	100
Iowa	65	69	22	23	7	7	94	100
Detroit	58	60	28	29	10	10	96	100
Utah	38	62	18	30	5	8	61	100
Puget Sound	42	57	20	27	12	16	74	100
Total	306	60	146	29	58	11	510	100

In summary, the astrocytoma rate appeared to covary with the medulloblastoma rate. More accurately, there was no evidence that astrocytoma and medulloblastoma rates did not covary geographically. Ependymomas, however, did differ in geographic distribution from astrocytomas and medulloblastomas; most of the difference resulted from the high rate of ependymoma in Connecticut.

COMPARISONS WITH SELECTED CANCERS

Correlation with adult brain cancer rates

In order to investigate the possibility of similar causes of childhood and adult brain cancers, Spearman's rank correlation coefficients between brain cancer rates of children and age-adjusted rates of adults were calculated for whites. The same analysis was done for the most recent time period, in which underascertainment, if it existed in the earlier years, should have been low. Adult and childhood brain cancer rates showed evidence of covariation in the entire period 1969-80 but not in the most recent time period. The combined astrocytoma-glioma NOS rates gave weaker evidence of correlation.

For these analyses, adults were defined as age 25 and older. Total brain cancer and astrocytoma rates were studied, since no other cell types occurred frequently enough to permit analysis. Analyses using rates for all 12 geographic areas would result in more reliable correlation coefficients, i.e., based on the maximum number of points. However, the smaller areas had fewer cases and less stable rates and would dilute any correlation that existed. The results for total brain cancer rates are presented including all areas and including only the six largest areas. For astrocytoma, only the results based on six areas are presented. The maximum number of areas for analyses of 1977-80 rates is eight. The correlation coefficients are shown in Table 69.

The incidence of childhood and adult brain cancer covaried geographically. The correlation was of borderline significance with all 12 areas and significant with six areas. Fig. 16 shows the scattergram of childhood and adult brain cancer rates for the six areas.

More pertinent to the question of similar etiology are the correlation coefficients by cell type. Only astrocytoma occurred frequently enough in both children and adults to permit calculation of correlation coefficients. The

analyses were done for the combined astrocytoma-glioma NOS group to avoid bias, as a smaller proportion of adults than children had histologically confirmed astrocytoma diagnoses. The correlation for childhood and adult astrocytoma-glioma NOS was of borderline significance for the six largest areas. Fig. 17 shows the scattergram for the combined astrocytoma and glioma NOS rate.

If the covariation was due to more complete ascertainment in areas with greater access to specialized medical care, the correlation in the most recent time period should have been smaller or nonexistent. The rates in the shorter time period would also have been less stable, making it less likely to observe a correlation did exist. In the most recent time period, the correlation coefficient for childhood and adult brain cancer was small and not significant. Fig. 18 shows the scattergram for the six largest areas. Including all eight or the largest six areas reporting data in 1977-80, the correlation coefficients for childhood and adult astrocytoma-glioma NOS rates were not significant.

Table 70 summarizes the results presented in this section.

Table 70.

Correlation of childhood and adult brain cancer incidence
Spearman's rank correlation coefficients

Adult and childhood brain cancer rates	R	p (one-sided)
1969-80, 12 areas	0.41	.095
1969-80, 6 areas	0.89	.009
1977-80, 8 areas	0.24	.29
1977-80, 6 areas	-0.14	.39
Adult and childhood astrocytoma-glioma NOS rates		
1969-80, 12 areas	-0.11	.37
1969-80, 6 areas	0.60	.10
1977-80, 8 areas	0.33	.21
1977-80, 6 areas	-0.53	.14

Figure 16.

Childhood and adult brain cancer incidence
Six SEER registries, 1969-80
Whites

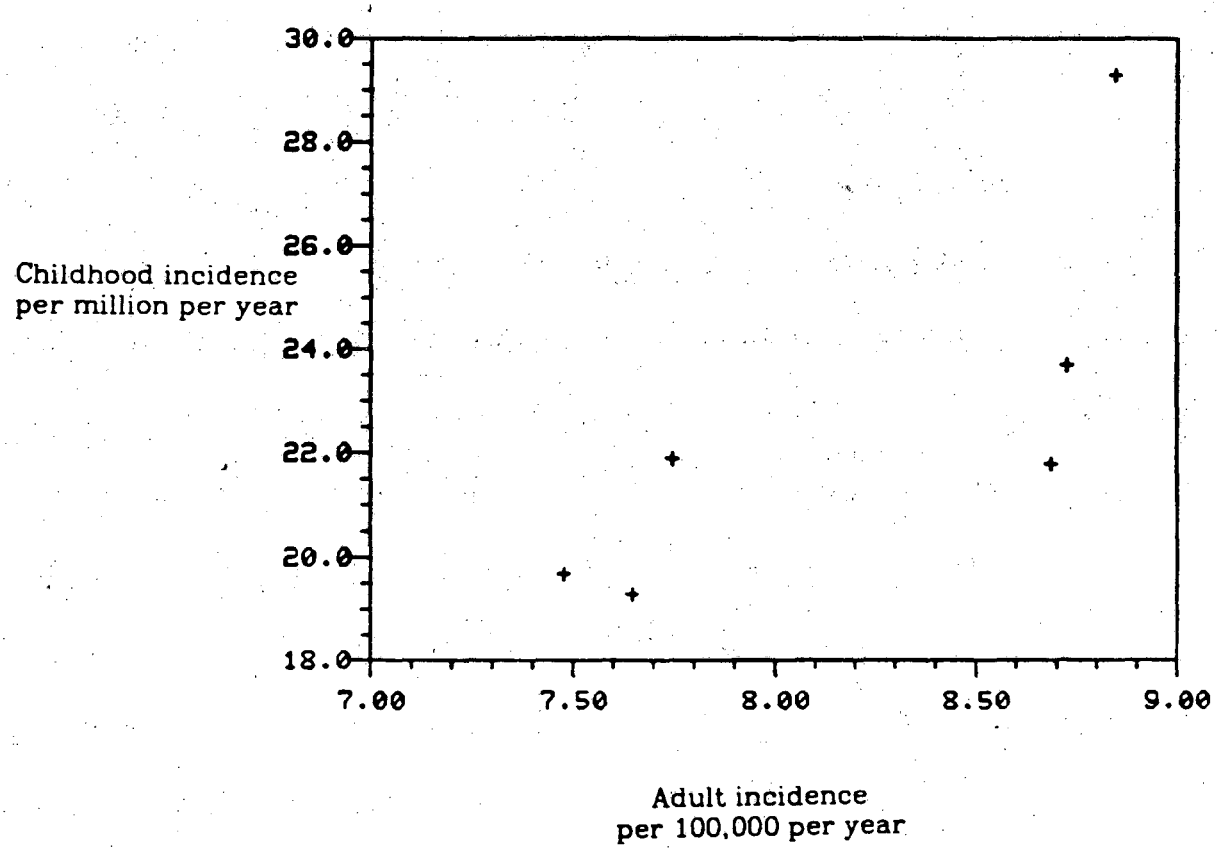


Figure 17.

Childhood and adult astrocytoma-glioma NOS incidence
Six SEER registries, 1969-80
Whites

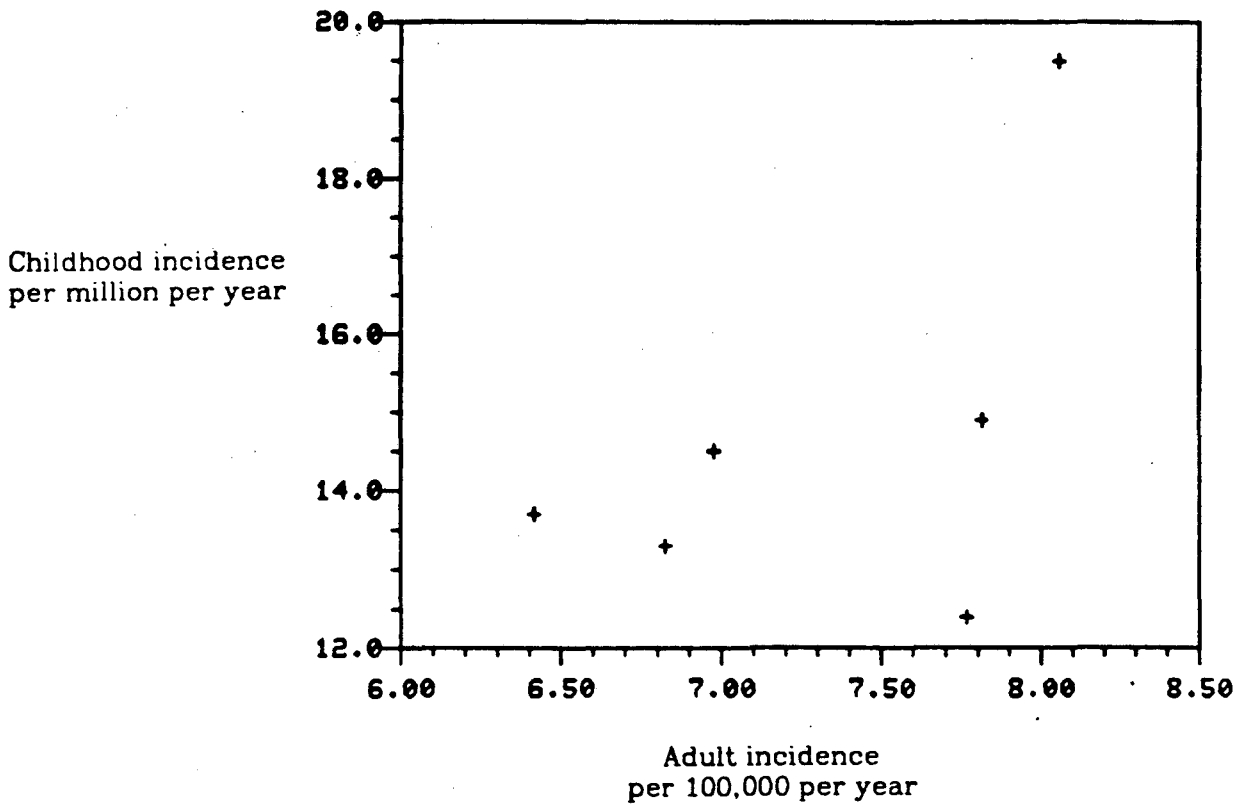
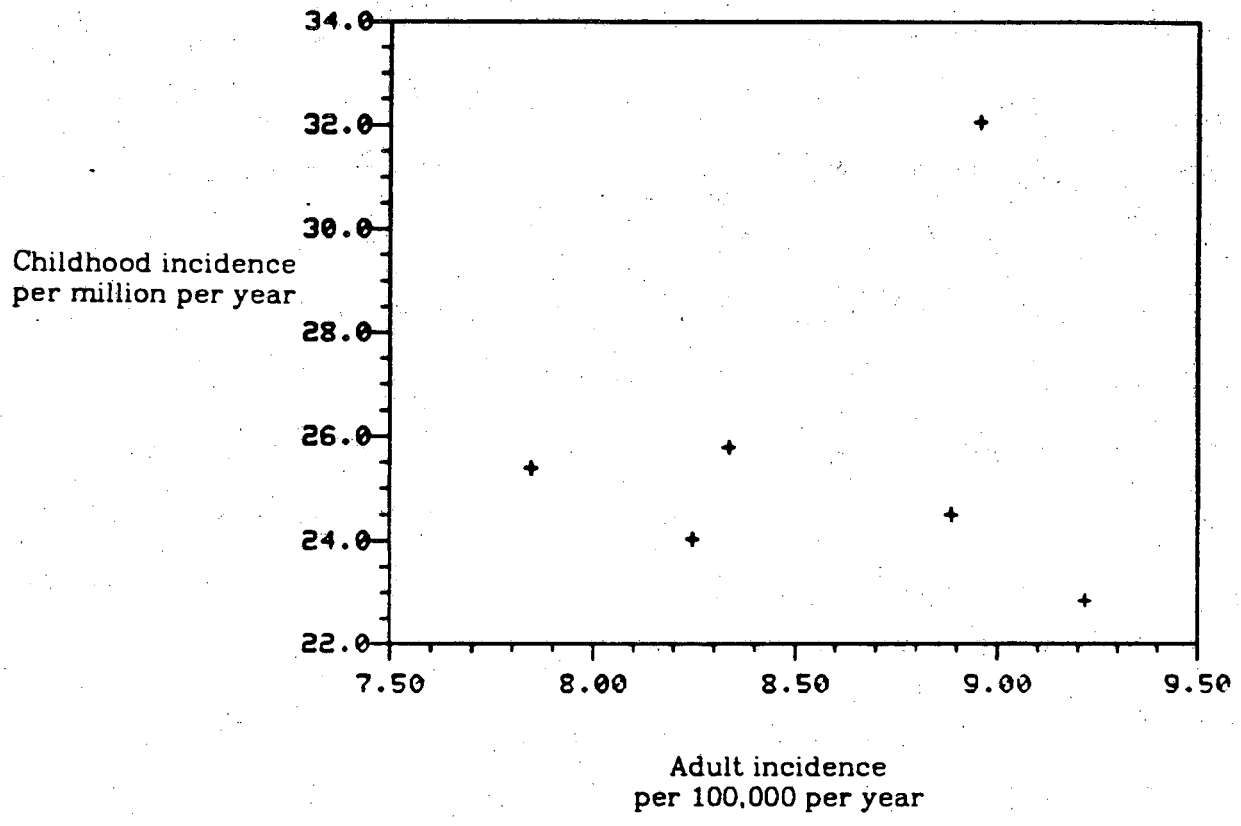


Figure 18.

Childhood and adult brain cancer incidence
Six SEER registries, 1977-80
Whites



Comparison with Childhood Leukemias

Diseases with similar descriptive epidemiologies and geographic occurrences are likely to have common etiologies. Childhood brain cancers and childhood leukemias were compared in order to assess the likelihood of similar causes. ALL and AGL, the major types of childhood leukemia, were each compared to astrocytoma, medulloblastoma, and ependymoma on race, sex, age, and geographic distribution. The inclusion of ALNOS cases (most of which were probably ALL cases (see Methods)) with ALL cases did not change any of the results reported in this section.

There was no brain cancer-leukemia pair that had similar age, sex, race, and geographic distributions. The table below summarizes the analyses described in detail in this section.

Table 71.

Comparison of brain cancers and leukemias
Demographic variables
Whites, age 0-14
12 TNCS and SEER registries

	Acute Lymphocytic Leukemia				Acute Granulocytic Leukemia			
Type	Age	Sex	Race	Geography	Age	Sex	Race	Geography
Astrocytoma	-	-	-	+	-	+	+	+
Medulloblastoma	-	+	-	+	-	-	+	+
Ependymoma	+	+	+	-	-	+	+	-

+ Similar distributions - Significantly different distributions

The age, sex, and race distributions of ALL differed significantly from those of astrocytoma. ALL cases were younger (χ^2=129.4, df=2, p<.001), more likely to be male (χ^2=5.7, df=1, p=.02), and more likely to be white (χ^2=15.1, df=1, p<.001) than astrocytoma cases. A χ^2 test showed no variation in the proportion of ALL and astrocytoma cases by geographic area (χ^2=13.5, df=11,

p=.26). Including all 12 areas and/or all the acute leukemia NOS cases did not change this observation.

Astrocytoma and AGL differed in age distribution, but had similar sex (χ^2=.02, df=1, p=.88) and race (χ^2=.21, df=1, p=.65) distributions. Astrocytoma cases were significantly older than AGL cases. The mean ages were 7.8 years for astrocytomas and 7.1 for AGL (F=4.5, p=.03). A χ^2 test did not give evidence for different geographic distributions for the two cancers (χ^2=13.7, df=11, p=.25).

Medulloblastoma and ALL had different age (χ^2=30.0, df=2, p<.001) and race (χ^2=10.9, df=1, p=.001) distributions, but similar sex (χ^2=2.2, df=1, p=.14) and geographic (χ^2=11.8, df=11, p=.38) distributions. The medulloblastoma cases were younger and more likely to be black. The mean age of medulloblastoma cases was 6.6 years compared to 5.4 years for ALL cases (F=19.3, p<.001).

Medulloblastoma and AGL cases had different age (χ^2=14.0, df=2, p<.001) and sex (χ^2=7.6, df=1, p=.006) distributions, but similar race (χ^2=.37, df=1, p=.54) and geographic (χ^2=14.8, df=11, p=.19) distributions. Medulloblastoma cases were younger and more likely to be male. The mean ages at diagnosis did not differ significantly (F=1.5, p=.22). AGL cases were 7.1 years old at diagnosis compared to 6.6 years for medulloblastoma cases.

Ependymoma resembled ALL in age (χ^2=3.3, df=2, p=.19), sex (χ^2=.38, df=1, p=.54) and race (χ^2=.0004, df=1, p=.98), but differed significantly in geographic distribution (χ^2=16.4, df=5, p=.006). Ependymoma cases were less likely to occur in SFO and more likely to occur in Connecticut and Puget Sound than ALL cases. The mean ages at diagnosis, 4.6 for ependymoma and 5.4 for ALL cases, did not differ significantly (F=2.4, p=.12).

Ependymoma and AGL cases differed in age (χ^2=13.8, df=2, p=.001) and geographic (χ^2=17.1, df=5, p=.004) distributions, but were similar in sex (χ^2=.015, df=1, p=.90) and race (χ^2=1.6, df=1, p=.21). The mean ages were 4.6

for ependymoma and 7.0 for AGL, a significant difference ($F=13.9$, $p<.001$). Ependymoma cases were younger, less likely to occur in SFO and Detroit, and more likely to occur in Connecticut and Puget Sound than AGL cases.

CHAPTER 5

Discussion

Time trends in histologic diagnoses

The rapid rise in astrocytoma rates concomitant with plummeting glioblastoma and astroblastoma rates must have reflected one or both of two possible trends. Either pathologists changed their diagnostic criteria so that more recent brain tumors were diagnosed by their derivative cell type rather than their clinical behavior, and/or physicians diagnosed more recent brain tumors earlier in their clinical course presumably because of changes in diagnostic procedures. The computed tomographic (CT) scan came into widespread use in the mid 1970s and has led to earlier diagnosis of brain tumors (Bruce Berg, Department of Neurology, UCSF, personal communication). Real changes in the incidences of these cancers seem unlikely because of the dramatic changes over the short time periods. The astrocytoma-glioblastoma shift should be taken into account, especially in analyses of time trends and comparisons of cell type distributions with earlier reports.

Distribution of cell types

The distribution of cell types observed here closely resembled that of earlier studies when similar histologic groupings were used. Data from this study and from two studies in the northeastern U.S. (6, 32) showed that about 50% of all gliomas were of astrocytic origin. Of the gliomas in this study, 8% were ependymomas compared to about 12% in the two earlier studies. In this study and a study by Kramer et al. (32), gliomas NOS accounted for 17% and 16% of the cases, respectively. Farwell et al. reviewed the slides of Connecticut Tumor Registry cases and reclassified some tumors, including, apparently, all gliomas

NOS, as they reported no such cases (6). The Connecticut study reported that 33% of the gliomas were medulloblastomas compared to 22% and 25% for the other two studies. Perhaps most of the unspecified gliomas were, in fact, medulloblastomas. However, in the present study, most gliomas NOS occurred in the brain stem, and most brain stem tumors were astrocytomas, implying that most gliomas NOS were astrocytomas. Medulloblastomas, on the other hand, occur almost exclusively in the cerebellum. Variation in diagnostic criteria by time and place may explain the discrepancy, especially since only 21% of the Connecticut cases in this study were medulloblastomas.

Race

Rates in whites slightly exceeded rates in blacks for all brain cancers combined and for all cell types except glioma NOS. The slight white excess corroborates earlier reports (32, 36). A recent report with relatively large numbers (94 nonwhite cases) observed nonwhite rates and white-nonwhite ratios similar to those found here, when this study's histologic groupings were applied (32). The undercount of blacks in the 1970 and 1980 censuses means that calculated rates for blacks overestimate the actual rates and the calculated racial differences in rates underestimate the true differences.

This study observed a racial difference in the age distribution of astrocytoma cases that has not been previously reported. The difference in age distribution might have reflected a real difference in age-incidence curves or a delay in diagnosis among blacks. Diagnostic delay, if present, should affect cerebral astrocytomas most and brain stem astrocytomas least, since the latter are rapidly fatal while the former can be compatible with survival for several years. In this study, the white-black difference in age distribution occurred for both cerebral and brain stem astrocytomas. The consistency of the racial difference regardless of tumor site suggests a real difference in age-incidence

curves.

The white-black difference in age distribution implies either genetic or environmental factors. An environmental factor could explain the observation if the effect of the exposure dffered with age and the age of exposure differed between whites and blacks.

Sex

White males and females experienced similar rates of all major cell types except medulloblastoma. Male medulloblastoma rates exceeded those of females by 66%; the difference in rates was statistically significant. The male-female rate ratio of 1.6 for medulloblastoma and about 1.0 for astrocytoma, glioma NOS, and combined astrocytoma and glioma NOS agree well with earlier studies, especially the largest (9). However, the present study observed a sex ratio of 1.1 for ependymoma which conflicts with the results of the largest study (9). That study included spinal cord tumors and reported a sex ratio of 1.5 with 195 ependymoma cases. An extreme male predominance for spinal cord ependymomas would explain the discrepancy in results. However, the data are sparse and conflicting; sex ratios of 5.0 and 0.7 have been reported for spinal ependymomas (6, 33).

Sex ratio

Investigators have observed that the sex ratio for childhood brain cancer changes around puberty and have speculated on hormonal factors (30). However, the differences in age-incidence curves and sex ratios of the two major cell types, astrocytoma and medulloblastoma, predict such a change in the sex ratio without invoking pubertal events. The sex ratios of these two cell types could be changing with age as well. In this study, the decline in the sex ratio with age resulted partly from the decreased proportion of medulloblastoma cases at older ages, but mostly from the decline in the sex ratio of astrocytoma.

The latter trend approached significance for astrocytomas alone and for astrocytomas and gliomas NOS combined. However, the trends differed. For astrocytoma alone, the increase in the proportion of females among the cases appeared to end by age 11 and certainly began in the very young age groups. For astrocytomas-gliomas NOS, the sex ratio was fairly constant and greater than one before age nine and after that, less than one.

The trend for astrocytoma alone may be more accurate than that for astrocytomas-gliomas NOS, as the latter group contains a small proportion of nonastrocytic gliomas. It seems unlikely that males and females had different probabilities of being diagnosed at a detailed level. In addition, the sex distribution of astrocytomas at the three main sites did not differ significantly. Thus, sex differences in the proportion of tumors in locations inaccessible to biopsy and, therefore, likely to be reported as glioma NOS rather than astrocytoma probably did not affect the sex ratio trend with age. The astrocytoma trend suggests that the change in sex ratio occurred by age 11, and thus, speculation on pubertal effects on the sex ratio may be unwarranted.

In contrast to the decline in the sex ratio for astrocytoma observed in this study, Spier observed that the sex ratio for mortality from CNS neoplasms (ICD 193) increased between ages 0 and 9 (35). A longer survival for females, as has been reported for medulloblastoma by Bloom et al. (21), or an increase with age in the sex ratio of medulloblastoma or the rarer cell types may explain the conflicting results.

In contrast to the findings of Gold and Gordis in Baltimore (30), no convincing changes occurred in the sex ratio of any cell type over the 11-year time period. The numbers in this study exceeded those in the study of Gold and Gordis which, in addition, included pituitary tumors among the intracranial tumors.

Site

Analyses of astrocytomas by site were done to determine whether in different locations, these tumors represent epidemiologically distinct diseases. Cerebral astrocytomas differed from cerebellar and brain stem astrocytomas in age distribution. A different age distribution could indicate more than one disease, or one disease in which the susceptibilities of sites vary with age or in which the time between occurrence of tumor and symptom production leading to diagnosis varies by site. A single disease hypothesis predicts similar epidemiological profiles of astrocytomas at each site. The data provide equivocal evidence. The three sites did not differ in sex distribution. The distribution by site differed nonsignificantly between whites and blacks ($p=.14$). Comparisons of geographic distribution between cerebral and cerebellar astrocytomas and between cerebral and brain stem astrocytomas generally showed differences approaching statistical significance. Cerebellar astrocytoma rates showed significant geographic variation ($p=.05$), but cerebral astrocytomas with the same number of cases did not. On the other hand, the three sites showed similar white-black differences in age distribution to those observed for all astrocytomas. In all these analyses, small numbers were a problem.

There is little information on the issue of astrocytomas at different sites. Some data on race ratios by site can be gleaned from the literature, since most gliomas NOS are probably brain stem astrocytomas, and most tumors reported as astrocytomas are not located in the brain stem. Clearly, inferences from these data are only tentative. An estimate of white-black rate ratios derived from published data showed a higher rate among blacks of glioma (other and unspecified), most of which were brain stem gliomas, according to the authors (30). The white-black ratio was 0.8 for glioma (based on 9 black and 18 white cases) compared to 1.4 for astrocytoma (15 black and 52 white cases).

This lends more credence to this study's observation of a higher black than white rate of brain stem astrocytoma. Kramer et al. also found a white-nonwhite ratio of under one (0.95) for glioma NOS (14 non-white and 57 white cases) and a ratio greater than one (1.4) for astrocytoma (32).

In conclusion, this study did not find strong evidence that astrocytomas at different sites are epidemiologically distinct, although geographic and racial distributions differed nonsignificantly. If astrocytomas represent only one disease entity, then changing susceptibility of sites with age and/or variation by site of the time between tumor occurrence and its diagnosis must explain the observed variation in age distributions.

Time trends

The incidence rate of astrocytoma increased significantly in Iowa between 1969 and 1980 in children under age ten. The increase could be real or a result of changes in histologic diagnosis. A trend toward more specific diagnosis seemed to explain much of the increase. Astrocytomas which were not biopsied would probably have been classified as glioma NOS or cancer NOS. If all gliomas NOS and cancers NOS were actually astrocytomas, the increase would have been only about one-third of the original 72%. For children under age ten, the increase would have been 50% compared to the original 250%. More accurate diagnosis, then, could explain part of the observed increase, although the assumption that all NOS cases were astrocytomas probably overestimated the effect. (Realistically, one would expect about 75% of gliomas NOS and 65% of cancers NOS to be astrocytomas.) The worst case analysis reduced the increase to a level which random variation could explain.

Two facts support the hypothesis that the remaining increase was a chance occurrence. First, the lack of convincing increase in the rate of all childhood brain cancers in Iowa suggests that the increase resulted from

changes in histologic diagnosis. Second, the higher rates in the most recent period were offset by rates in the middle period which were lower than in the first period. As the rates were not rising consistently, the highest rate in the most recent period may be a chance occurrence. More recent data do not support an increasing incidence. There were fewer average annual cases of childhood brain cancer and of astrocytomas in 1981, 1982, and 1983 than between 1977 and 1980, when the high rate occurred. There were between seven and eight astrocytomas per year in 1981-83 (Elaine Smith, Iowa Tumor Registry, personal communication), compared to nine to 15 in 1977-80. Since the population under age 15 was declining, conclusions based on numbers rather than rates must remain tentative.

The increase, however, might still have been real but not statistically significant due to the small number of cases. A true 25% or 50% increase in 11 years would be a serious concern and the possibility is worth exploring further. An artefact, such as diagnostic delay or diagnosis of malignant tumors as benign or unspecified, would result in an apparently increasing rate in rural Iowa as the diagnosis changed and became like that in the urban areas. The greater increase in rural than urban areas and the increase in cerebral astrocytomas and gliomas NOS suggest improved ascertainment as a possible cause. On the other hand, the increase in the incidence of cerebellar astrocytoma (more rapidly fatal than cerebral tumors) makes the possibility of improved ascertainment less likely. In addition, one would have to explain the lack of improved ascertainment in 10-14 year olds. If ascertainment and diagnosis were improving in rural areas, the rate would first increase and then decline and become level if the underlying rate did not change. More recent data from the Iowa SEER registry would indicate if the astrocytoma rate were continuing to increase or had levelled off.

Urban-rural differences in Iowa

The comparison of urban and rural rates of childhood brain cancer suggested that such differences may vary between regions of the country. In this study, the southwestern states showed differences in the opposite direction from those in Iowa, but were based on small numbers.

Urban-rural differences in Iowa were generally small. However, the urban rate of medulloblastoma was almost twice that of rural areas with the difference of borderline significance. The Norwegian data, referred to by Choi et al., showed the opposite--higher childhood medulloblastoma rates in rural areas. As the statistical significance in the present study is marginal and that in the Norwegian data not given, the real urban-rural difference in rates remains unknown.

The combined astrocytoma-glioma NOS rate for rural areas was higher than the urban rate in all time periods for children under age 15, and in the two most recent time periods for children under age 10. When all cancers NOS were included, the rural excess remained. Method I, with a higher concentration of farm residents in the rural category than Method II, showed the larger rural excess, consistent with farm residence and not small town residence as a risk factor. Previous studies provide evidence supporting this possible association with farm residence. Farm residents were overrepresented among brain cancer deaths in Minnesota compared to the state's population (59). In addition, two studies observed excess risk of cancer in children whose fathers were farmers (48, 93). Veterinarians (111), children exposed to farm animals or sick pets (49), and individuals with toxoplasma antibodies (88) also have been reported to be at increased risk of brain cancer.

The observed rural excess conflicted with other evidence. Urban areas experienced higher age-adjusted incidence rates of primary brain tumors in

Iowa in 1950 (60). Childhood and adult brain cancer, however, might exhibit different urban-rural patterns. Greenberg observed higher mortality rates from childhood nervous system cancer in urban areas (41). Patterns that vary by geographic region or between brain cancer and neuroblastoma might explain the discrepancy.

Population density

Astrocytoma rates increased with population density in urban areas, but the observation did not reach statistical significance. An association with population density would be consistent with an infectious etiology. However, the lack of significance and the lack of trend for all childhood brain cancers combined suggests the occurrence of the trend by chance.

Socioeconomic status

Urban astrocytoma cases were of slightly higher SES (as judged by the median census tract income) and medulloblastoma cases of slightly lower SES than the general urban population. Previous data on SES conflict. Researchers in Finland and Denmark found no social class difference between children with brain cancer and the general population (29, 45). If astrocytoma and medulloblastoma had different etiologies with opposing roles of SES, then for all brain cancers combined, there would be no apparent effect of SES. An excess risk of brain cancer was observed for a higher SES group in the U.S. in the 1950s (47). A higher risk of astrocytoma in high SES groups seems to conflict with the association noted above with higher population density, usually correlated with lower SES.

Geographic variation

This study provided evidence of geographic variation in childhood cancer rates. Differences in completeness of reporting among registries did not appear large enough to account for the observed variation, although differences

in procedures cannot be ruled out. The observed pattern generally resembled earlier reports that CNS tumor rates for all ages (57) and for children (36) were higher in the Pacific States (California, Oregon, Washington) and lower in the Mountain and Southern States than in the rest of the country. In the TNCS and SEER data, high rates occurred in San Francisco - Oakland and Seattle and low rates in New Mexico and Colorado.

Geographic variation in the accuracy of population estimates might explain the variation in rates. Dramatic changes in the reporting of race by Hispanics affected population estimates of whites between 1970 and 1980. In the 1970 census, 1% of Hispanics reported their race as "other" compared to 40% in 1980 (112). This study included Hispanic SEER cases with whites; the TNCS data did not have a Hispanic category. Thus, the appropriate population estimates would also combine Hispanics and other whites. In areas with sizeable Hispanic populations, estimates from interpolation between the 1970 and 1980 censuses would underestimate the "white" (including Hispanics) population. An accurate count of cases and an underestimated population figure would result in an overestimated rate. The rates most likely to be affected are those of SFO and New Mexico, which have large Hispanic populations. SFO and New Mexico also had the highest and lowest rates, respectively.

It seems unlikely that errors in the population estimates explain all of the geographic variation. For example, even if the SFO white population were underestimated by 20%, the childhood brain cancer rate would still be higher than the next highest rate. Correcting the New Mexico white population estimate would further lower the rates for that state. If the New Mexico and SFO population estimates were underestimated by the same amount, the ratio of the actual rates would be the same as that using the overestimated rates. The extent of actual geographic variation would be smaller than that reported here

only if the SFO estimate were more affected than that of New Mexico. That seems unlikely as a larger proportion of the New Mexico population than of the SFO population is Hispanic, and similar proportions of Hispanics in both places identified themselves as nonwhite in the 1980 census (113).

Kurtzke noted that CNS cancer age-adjusted mortality rates correlated with the concentration of physicians and attributed the observed variation to more complete ascertainment in areas with highly accessible medical care (57). In the present study, childhood brain cancer rates and physician concentration showed a correlation of 0.60. Because ascertainment of brain cancers probably rose in the 5 to 20 years since earlier studies, we would expect variation due to ascertainment be lower in this study. However, the extent of variation observed here (1.8-fold) was greater than the report on childhood rates in 1950-59 (1.3) (36) and about the same as that on adult rates in 1951-53 and 1961-63 (1.6,1.7) (57).

Most of the cell types individually showed geographic variation that at minimum approached significance. Astrocytoma rates varied slightly more than medulloblastoma rates, though the significance of the variation was similar for both. The variation of astrocytoma rates became significant when all or a proportion of gliomas NOS were included. The number of medulloblastoma cases, however, was less than half that of the combined astrocytomas and gliomas NOS. Thus, astrocytoma and medulloblastoma rates probably varied to a similar extent, despite the lack of statistical significance of the latter.

Surprisingly, ependymoma rates, based on only 58 cases, varied significantly across the six most populous areas. Connecticut with a rate 3.6 times that of SFO, contributed the major proportion of the significant χ^2_{trend} value. Diagnostic differences may explain the variation, as anaplastic astrocytomas, for example, can be mistaken for ependymomas.

The interpretation of the lack of significant geographic variation in the most recent time period is difficult. A decrease in the variation or the relatively small number of cases could explain the result. The former explanation is consistent with suggestions that quality of and access to medical care affect brain cancer rates; as tertiary medical care becomes more uniformly distributed across the country, variation in rates should decline. On the other hand, the rate in SFO was high in all three time periods and the difference between it and the next highest rate did not change with time. In addition, New Mexico experienced a low and constant rate for the two time periods in which data were collected there. The constant rate patterns in SFO and New Mexico suggest that these two areas have rates different from each other and probably from other areas. Small numbers might explain the lack of statistical significance of the geographic variation. For astrocytoma, over 600 cases were required for significance of a moderate degree of geographic variation. Less than 400 cases of brain cancer occurred between 1977 and 1980.

In summary, there was geographic variation in the incidence of most cell types not likely to be explained by variation in completeness of reporting or by underestimates of populations with high proportions of Hispanics. Although incidence was correlated with physician concentration, variation in ascertainment probably did not explain all of the geographic variation. There was no strong evidence that the extent of variation had changed over the 11-year period, but small numbers were a problem. The geographic variation itself could reflect environmental, genetic and/or medical care factors. Genetic factors associated with major white ethnic groups, such as Hispanics, are unlikely to be important risk factors as there was no association of incidence with location of such groups. Environmental risk factors are likely to exist. For example, the correlation with physician concentration might indicate prenatal or postnatal

medical factors, such as exposure to x-rays or drugs. On the other hand, the correlation might indicate risk factors associated with the urban and suburban areas in which doctors tend to live. Medical care factors are discussed below.

Comparison with childhood leukemias

The analyses comparing childhood leukemias and brain cancers gave little or no evidence for similar etiologies. No pair of AGL or ALL and a cell type of brain cancer had the same epidemiological profile with regard to sex,age, race, and geography. Ependymoma and ALL differed only in geographic distribution, and AGL and astrocytoma differed only in age distribution. Although ALL and astrocytoma cases differed in age, sex, and race, they did not differ in geographic distribution.

Covariation with adult rates

Childhood and adult rates covaried for total brain cancer but not for astrocytoma. Similar causes with different age-specific susceptibilities to cell types could explain the results.

Influence of medical care on rates of brain cancer

Investigators have invoked differences in ascertainment of brain tumors to explain variation in brain cancer rates among time periods, regions, nations, and races. Few data, however, support or quantify the effect of underascertainment. A recent study observed that Eastman Kodak Co. employees with brain cancer received pathological confirmation and sophisticated diagnostic procedures more frequently than other brain tumor patients living in the same area of New York or scattered throughout upstate New York (114); 80% of the brain tumors in Kodak employees were histologically confirmed compared to 60-62% in the other groups. The authors attributed the difference to the Kodak employees' access to high quality medical care through health insurance and employee medical services.

Similar effects were seen in this study. For example, no histologic confirmation was reported for 11% of white and 16% of black brain tumors, a significant difference. The difference in rate of confirmation did not result from the black excess of brain stem gliomas. Like black cases, cases in rural areas of Iowa diagnosed between 1969 and 1971 were less likely to be histologically confirmed than cases in urban areas (14% versus 0%; χ^2_{trend}=3.5, p=.06). Without brain stem tumors, the rates were 7% for rural areas and 0% for urban areas.

Not surprisingly, the lower rates of confirmation were accompanied by higher incidence rates in NOS categories. Thus, blacks had higher glioma NOS rates than whites, and rural Iowa higher rates than urban areas in 1969-71. Excluding brain stem tumors, the patterns were the same although the numbers were very small.

Clearly, cases occurring in two groups expected to have had less access to high quality medical care were less likely to be histologically confirmed and more likely to be classified as glioma NOS. Thus, access to medical care seems to affect brain cancer rates by cell type.

The more important question, however, is whether some cases of childhood brain cancer are never diagnosed. If so, is the proportion not diagnosed higher among blacks, other low SES groups, and rural residents? Little evidence exists to answer this question. Greenwald et al. in their study of Kodak employees suggested that brain tumors are underdiagnosed in the general population. They attributed observed associations of employment at Kodak and death from a brain tumor (ORs from two studies of 4.0 and 1.6) to underdiagnosis as their case-control study showed no exposure differences between Kodak employees with and without brain tumors. In addition, the incidence curve of brain cancer in Rochester, Minnesota increases progressively with age (42, 115), while in other studies rates peak between ages 60 and 70 and then decline. Researchers

attribute the difference to the high autopsy rate (i.e., more complete ascertainment) in Rochester (42, 115).

The only data on children come from a study of 12 intracranial neoplasms in Rochester (10). The incidence rate was about twice that of children in Connecticut. The authors attributed at least part of the difference to better ascertainment in Rochester, with its ready access to specialized medical care. Since brain cancer is fatal, if untreated, undiagnosed brain cancers should appear as deaths. They might appear as deaths without specified causes. Or, perhaps, the deaths appear as brain neoplasms of benign or unspecified nature. A cursory look at 1970 mortality data for ages 5-9 did not show a black excess of brain neoplasms of a benign or unspecified nature, or of nervous system neoplasms with an unspecified site. However, relatively more black than white children died of "other unknown and unspecified causes." These observations were based on small numbers of blacks. More research is needed on this issue in order to interpret geographic variation, increased incidence in rural Iowa, and lower black than white rates.

Conclusions

The descriptive and ecological analyses reported suggest areas of further research. Most important, perhaps, is the need to determine the effect of medical care on childhood brain cancer rates. For example, we need to know what proportion of childhood brain cancers are never diagnosed as such and whether excluding benign brain tumors and those of unspecified nature introduces bias in geographic and racial comparisons. Exposure to zoonotic microorganisms and pesticides warrants investigation because of the rural excess of astrocytoma. The age distribution of astrocytoma cases in developing countries should be investigated to distinguish between a genetic and environmental explanation of the white-black difference. If the age distribution of cases in a

nonblack developing country resembled that of whites, a genetic basis of the racial difference noted here would be suggested. On the other hand, incidence similarities between U.S. blacks and persons in developing countries would be reminiscent of Hodgkin's disease, in which the role of environmental factors, especially infectious agents, has been inferred partly from different age distributions in developed and developing countries (116).

Finally, this study helps illustrate the strengths and weaknesses of descriptive and ecological analyses of a relatively large population-based series of cases of a very rare disease. The comparisons of groups of cases between races or sexes, for example, were often informative. Analyses of ecological variables, such as population density and urban-rural residence, were difficult to interpret since the restriction to subpopulations appropriate for analysis led to small numbers.

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