SEER PEDIATRIC MONOGRAPH

Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995

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Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995

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FOREWORD

Cancer among children is a substantial public concern. Each year in the United States, approximately 12,400 children and adolescents younger than 20 years of age are diagnosed with cancer. Approximately 2,300 children and adolescents die of cancer each year, which makes cancer the most common cause of disease-related mortality for children 1-19 years of age. This monograph assembles under one cover the most detailed information available on the incidence of childhood cancer in the United States. These population-based data will be extremely important in furthering our understanding of the variations in childhood cancer by histologic type and primary site and the variations in incidence of these cancers over time. The monograph provides information about childhood cancer incidence and mortality rates that can enhance the level of public discourse, and it can be used in planning research that will help us to better understand these cancers and their causes.

Unlike adult cancers that are usually tabulated by primary site, the childhood cancers are more meaningfully grouped by histologic type and primary site based on the recently developed International Classification of Childhood Cancer (ICCC). The monograph details incidence for 1975-1995 and survival by ICCC group and by patient demographic characteristics. For each of the major ICCC groups, information on known risk factors is also presented.

The monograph emphasizes not only ICCC group but also age as important factors in childhood cancer incidence. The cancers discussed include those occurring in children younger than 15 years of age as well as those occurring in adolescents up to age 19 years. Some cancers such as neuroblastoma and hepatoblastoma have highest rates among infants and young children, while others such as Hodgkin's disease, germ cell tumors (e.g., testicular cancer) and bone cancers have higher rates among adolescents. It is important that different distributions of cancer types by age be considered when research programs are developed to improve outcomes for children and adolescents with cancer.

I would like to thank and congratulate the scientists at the National Cancer Institute (NCI) and at the various universities and institutions across the United States who collaborated to make this monograph possible including the Epidemiology and Cancer Control Strategy Group of the NCI-supported Children's Cancer Group, which provided the review of risk factors. I would also like to thank all of the individuals who make the SEER Program a reality: staff members of the SEER population-based registries, Information Management Services, Inc., and NCI. It is through their diligence that these data have been collected, analyzed, and interpreted. The monograph highlights the importance of the SEER Program as a national resource. I believe that this document will prove to be a seminal reference work on childhood cancer for scientists, policy makers and the public. All of us look forward to the extensive use of this information and the stimulation of scientific thought that it will engender and ultimately, the reduction of cancer incidence and mortality in children.

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Acknowledgments: Risk Factor Tables

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INTRODUCTION

Nearly 30 percent of the United States (US) population is younger than 20 years of age. Although cancer is rare among those younger than 20 years of age, it is estimated that approximately 12,400 children younger than 20 years of age were diagnosed with cancer in 1998 and 2,500 died of cancer in 1998 [1]. As a cause of death, cancer varies in its relative importance over the age range from newborn to age 19. Based on data for 1995, in infants younger than one year of age, there were fewer than one hundred cancer deaths (representing only 0.2% of infant deaths), making it a minor cause of death in comparison to other events during the perinatal period. For children between one and nineteen, cancer ranked fourth as a cause of death behind unintentional injuries (12,447), homicides (4,306), and suicides (2,227). The probability of developing cancer prior to age 20 varies slightly by sex. A newborn male has 0.32 percent probability of developing cancer by age 20, (i.e., a 1 in 300 chance). Similarly a newborn female has a 0.30 percent probability of developing cancer by age 20, (i.e., a 1 in 333 chance) [2].

Childhood cancer is not one disease entity, but rather is a spectrum of different malignancies. Childhood cancers vary by type of histology, site of disease origin, race, sex, and age. To explain some of these variations, this monograph presents detailed cancer incidence and survival data for 1975-95, based on nearly 30,000 newly diagnosed cancers arising in children during this 21-year interval in the United States (US). Cancer mortality data collected for the entire US are also shown for the same time period.

MATERIALS AND METHODS (for definitions and additional details, see the technical appendix at end of chapter):

Sources of data

The population-based data used in this monograph for incidence and survival are from the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute (NCI) [2]. Information from five states (Connecticut, Utah, New Mexico, Iowa, and Hawaii) and five metropolitan areas (Detroit, Michigan; Atlanta, Georgia; Seattle-Puget Sound, Washington; San Francisco-Oakland, California; and Los Angeles, California) comprising about 14% of the United States' population are used in this monograph. While Los Angeles did not officially become a SEER area until 1992, the long standing cancer registry in Los Angeles provided a special childhood data file for this study which included population-based cancer incidence data back to 1975. This monograph includes 29,659 cancers diagnosed between 1975 and 1995 in persons younger than 20 years of age who resided in the SEER areas listed above: 19,845 cases for those younger than 15 years of age and 9,814 cases for adolescents aged 15-19 years.

The mortality data are for the same time period but cover all cancer deaths among children in the total United States. Data based on underlying cause of death were provided by the National Center for Health Statistics (NCHS).

Table 1: Percent distribution of childhood cancers by ICCC category and age group, all races, both sexes, SEER, 1975-95

	Age					
	<5	5-9	10-14	15-19	<15	<20
All Sites - Number of cases	9,402	5,024	5,419	9,814	19,845	29,659
	%	%	%	%	%	%
All Sites	100.0	100.0	100.0	100.0	100.0	100.0
I(total) - Leukemia	36.1	33.4	21.8	12.4	31.5	25.2
Ia - Lymphoid Leukemia	29.2	27.2	14.7	6.5	24.7	18.7
Ia - excl. Acute Lymphoid	0.2	0.3	0.2	0.1	0.2	0.2
Acute Lymphoid	29.0	27.0	14.5	6.4	24.5	18.5
Ib - Acute Leukemia	4.6	4.1	5.4	4.1	4.7	4.5
Ib - excl. Acute Myeloid	1.9	0.9	1.6	0.9	1.5	1.3
Acute Myeloid	2.8	3.2	3.8	3.2	3.2	3.2
Ic - Chronic myeloid leukemia	0.6	0.7	0.9	1.2	0.7	0.9
Id - Other specified leukemias	0.2	0.2	0.1	0.1	0.2	0.2
Ie - Unspecified leukemias	1.4	1.2	0.8	0.5	1.2	1.0
II(total) - Lymphomas and reticuloendothelial neoplasms	3.9	12.9	20.6	25.1	10.7	15.5
IIa - Hodgkins' disease	0.4	4.5	11.4	17.7	4.4	8.8
IIb - Non-Hodgkins' Lymphoma	2.0	5.2	6.1	6.0	4.0	4.6
IIc - Burkitt's lymphoma	0.8	2.4	1.9	0.6	1.5	1.2
IId - Miscellaneous lymphoreticular neoplasms	0.4	0.2	0.3	0.2	0.3	0.3
IIe - Unspecified lymphomas	0.3	0.7	0.9	0.7	0.6	0.6
III(total) - CNS and miscellaneous intracranial and intraspinal neoplasms	16.6	27.7	19.6	9.5	20.2	16.7
IIIa - Ependymoma	2.6	1.3	1.1	0.5	1.9	1.4
IIIb - Astrocytoma	6.7	14.2	11.8	6.0	10.0	8.7
IIIc - Primitive neuroectodermal tumors	4.3	6.3	3.1	1.0	4.5	3.3
IIId - Other gliomas	2.2	5.0	2.9	1.5	3.1	2.6
IIIe - Miscellaneous intracranial and intraspinal neoplasms	0.2	0.3	0.3	0.3	0.3	0.3
IIIf - Unspecified intracranial and intraspinal neoplasms	0.5	0.6	0.4	0.2	0.5	0.4
IV(total) - Sympathetic nervous system	14.3	2.7	1.2	0.5	7.8	5.4
IVa - Neuroblastoma and ganglioneuroblastoma	14.0	2.6	0.8	0.3	7.5	5.1
IVb - Other sympathetic nervous system tumors	0.3	0.1	0.3	0.1	0.3	0.2
V(total) - Retinoblastoma	6.3	0.5	0.1	0.0	3.1	2.1
VI(total) - Renal tumours	9.7	5.4	1.1	0.6	6.3	4.4
VIa - Wilms' tumor, rhabdoid and clear cell sarcoma	9.7	5.2	0.7	0.2	6.1	4.2
VIb - Renal carcinoma	0.1	0.1	0.4	0.4	0.2	0.2
VIc - Unspecified malignant renal tumors	0.0	0.0	0.0	0.0	0.0	0.0

Table 1 (cont'd): Percent distribution of childhood cancers by ICCC category and age group, all races, both sexes, SEER, 1975-95

	Age					
	<5	5-9	10-14	15-19	<15	<20
All Sites - Number of cases	9,402	5,024	5,419	9,814	19,845	29,659
	%	%	%	%	%	%
VII(total) - Hepatic tumors	2.2	0.4	0.6	0.6	1.3	1.1
VIIa - Hepatoblastoma	2.1	0.2	0.1	0.0	1.0	0.7
VIIb - Hepatic carcinoma	0.1	0.3	0.5	0.5	0.3	0.3
VIIc - Unspecified malignant hepatic tumors	0.0	0.0	0.0	0.0	0.0	0.0
VIII(total) - Malignant bone tumors	0.6	4.6	11.3	7.7	4.5	5.6
VIIIa - Osteosarcoma	0.2	2.2	6.6	4.4	2.4	3.1
VIIIb - Chondrosarcoma	0.0	0.1	0.6	0.6	0.2	0.3
VIIIc - Ewing's sarcoma	0.3	2.1	3.7	2.3	1.7	1.9
VIIId - Other specified malignant bone tumors	0.1	0.1	0.3	0.3	0.2	0.2
VIIIe - Unspecified malignant bone tumors	0.0	0.1	0.1	0.1	0.1	0.1
IX(total) - Soft-tissue sarcomas	5.6	7.5	9.1	8.0	7.0	7.4
IXa - Rhabdomyosarcoma and embryonal sarcoma	3.4	4.2	2.8	1.9	3.4	2.9
IXb - Fibrosarcoma, neurofibrosarcoma and other fibromatous neoplasms	1.0	1.4	3.1	3.1	1.7	2.1
IXc - Kaposi's sarcoma	0.0	0.1	0.0	0.1	0.0	0.1
IXd - Other specifed soft-tissue sarcomas	0.7	1.2	2.2	2.1	1.3	1.5
IXe - Unspecifed soft-tissue sarcomas	0.4	0.7	1.0	0.9	0.6	0.7
X(total) - Germ-cell, trophoblastic and other gonadal tumors	3.3	2.0	5.3	13.9	3.5	7.0
Xa - Intracranial and intraspinal germ-cell tumors	0.2	0.8	1.3	0.9	0.7	0.7
Xb - Other and unspecified non-gonadal germ-cell tumors	1.7	0.1	0.5	1.4	1.0	1.1
Xc - Gonadal germ-cell tumors	1.4	1.1	3.0	9.4	1.7	4.2
Xd - Gonadal carcinomas	0.0	0.0	0.4	1.9	0.1	0.7
Xe - Other and unspecified malignant gonadal tumors	0.0	0.1	0.1	0.3	0.1	0.1
XI(total) - Carcinomas and other malignant epithelial neoplasms	0.9	2.5	8.9	20.9	3.5	9.2
XIa - Adrenocortical carcinoma	0.2	0.1	0.1	0.1	0.1	0.1
XIb - Thyroid carcinoma	0.1	1.0	3.5	7.4	1.2	3.3
XIc - Nasopharyngeal carcinoma	0.0	0.1	0.7	0.8	0.2	0.4
XId - Malignant melanoma	0.4	0.7	2.0	6.8	0.9	2.9
XIe - Skin carcinoma	0.0	0.0	0.1	0.1	0.0	0.0
XIf - Other and unspecified carcinomas	0.2	0.7	2.5	5.7	1.0	2.5
XII(total) - Other and unspecified malignant neoplasms	0.5	0.3	0.6	0.8	0.5	0.6
XIIa - Other specified malignant tumors	0.1	0.1	0.1	0.3	0.1	0.1
XIIb - Other unspecified malignant tumors	0.4	0.3	0.5	0.5	0.4	0.4

In order to calculate rates, population estimates were obtained from the Bureau of the Census. In 1990 there were 7,179,865 children residing in the SEER areas younger than 15 years of age and 9,436,324 younger than 20 years of age. In the 1990 census, there were about 72 million children younger than 20 years of age in the whole United States. Twenty-two percent of the US population is younger than 15 years of age and an additional 7% are 15-19 years of age. Annual population estimates include estimates by 5-year age groups (<5,5-9,10-14,15-19). Enumeration of the population at risk by single years of age was available only for the census years 1980 and 1990. The US Bureau of the Census provides intercensal population estimates by 5-year age groups, but not by single years of age. Therefore, the population estimates for 1980 were used in rate calculations for cases diagnosed from 1976-84 and the 1990 estimates were used for cases diagnosed from 1986-94. Whenever rates by single year of age are shown, the rates are centered around a decennial census year, namely, 1976-84 and 1986-94 or the two sets of years combined.

Calculation of rates (see technical appendix)

The incidence and mortality rates are the annual rates per million person years. For simplicity, these are labeled as rates per million. Rates representing more than 5-years of age are age-adjusted to the 1970 US standard million population. Survival rates are expressed as percents.

Classification of site and histologic type

The SEER program classifies all cases by cancer site and histologic type using the *International Classification of Diseases for Oncology, Second Edition* (ICD-O-2) [3]. In contrast to most cancer groupings, which are usually categorized by the site of the cancer, the pediatric classification is determined mostly by histologic type. The SEER data have been grouped according to the International Classification of Childhood Cancers (ICCC) specifications [4] with a couple of exceptions for brain cancer. Please refer to Table 1 for the distribution by ICCC groupings and age group.

Histologic confirmation

In the SEER program most of the pediatric cancers (95%) are histologically confirmed. This is important because most childhood cancer classifications are based on histologic types: leukemia, lymphoma, retinoblastoma, neuroblastoma, etc. The percentage of histologically confirmed cases, however, does vary by ICCC category ranging from a low of 90 percent for the central nervous system (CNS) (ICCC group III) to a high of 99 percent for leukemia (ICCC group I).

OVERVIEW OF CHILDHOOD CANCER PATTERNS

All sites combined

While grouping all cancer sites together may be helpful to understanding the overall cancer burden in young Americans, it masks the contributions of each primary site/histology. Therefore, most of the emphasis of this monograph is on individual primary site or histologic groupings; a separate chapter is shown for each of the ICCC groupings except group XII which has few cases.

Overall trends

While the incidence rates for some forms of childhood cancer have increased since the mid-1970s, death rates have declined dramatically for most childhood cancers and survival rates have improved markedly since the 1970's. Each year approximately 150 children out of every million children younger than 20 years of age will be diagnosed with cancer. The

overall cancer incidence rate increased from the mid-1970's, but rates in the past decade have been fairly stable (Figure 1). During the last time period, 1990-95, there is an indication of a leveling off or slight decline in the overall incidence rates for each of the 5-year age groups (data not shown). The overall childhood cancer mortality rates have consistently declined throughout the 1975-95 time period (Figure 1). Note that the data are plotted at the mid-year point throughout this monograph.

Sex

For all sites combined, cancer incidence was generally higher for males than females during the 21-year period (Figure 2). Yet again, an all-sites-combined-rate masks the sites/histologies for which there is a female predominance. For some sites/histologies, there are other factors such as age where there are differences by sex. For example, males have somewhat higher rates of Hodgkin's disease for children younger than 15 years of age, but females have higher rates for adolescents, 15-19 years of age.

Figure 1: Trends in age-adjusted* SEER incidence & U.S. mortality rates for all childhood cancers age<20, all races, both sexes, 1975-95

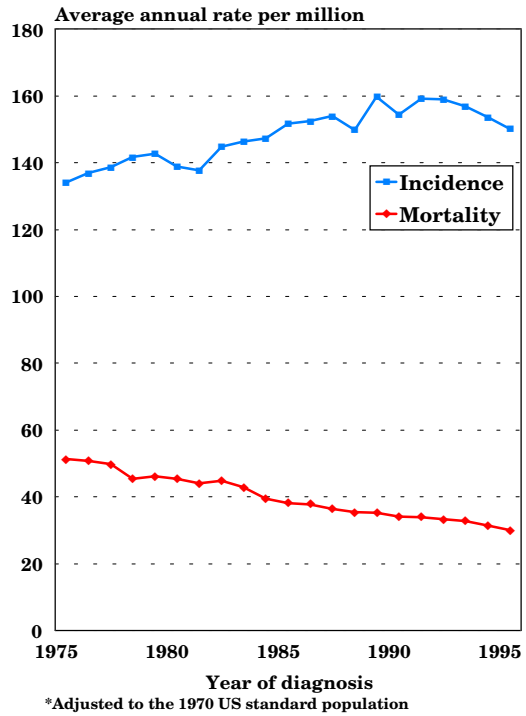
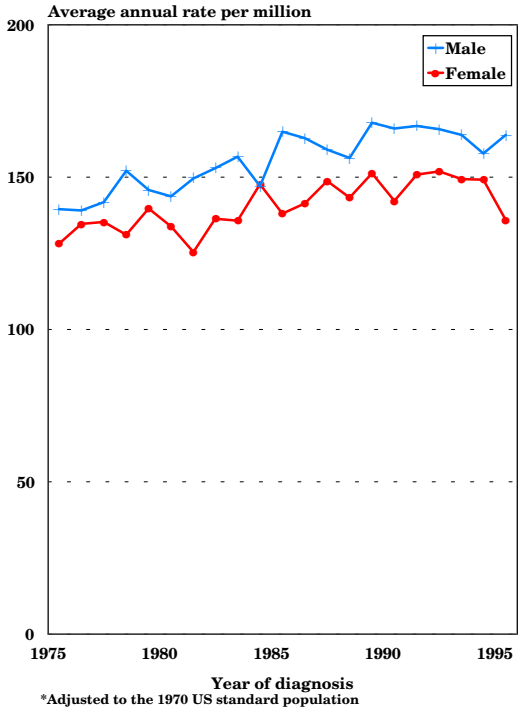


Figure 2: Trends in age-adjusted* incidence rates for all childhood cancers by sex, age <20 all races combined, SEER, 1975-95



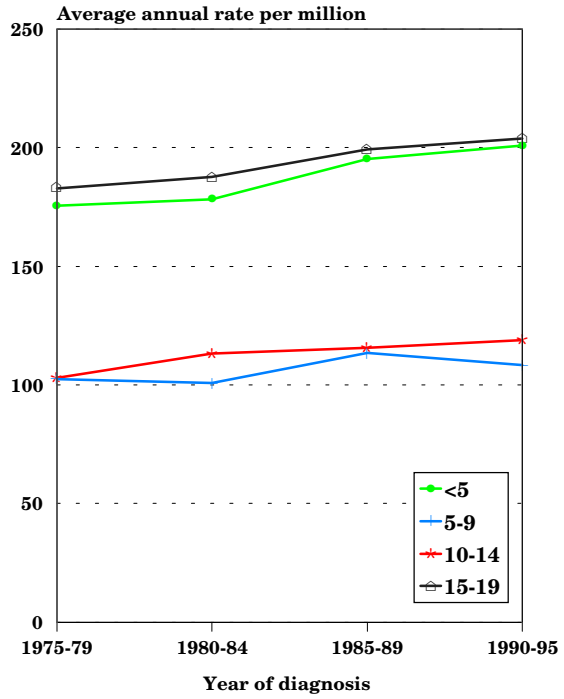
Age (5-year age groups)

The average age-specific incidence rates for each of the four calendar periods of observation show similar and much higher cancer rates for the youngest (younger than 5 years of age) and oldest (15-19 years of age) age groups than the two intermediary age groups (Figure 3). Even though those aged 15-19 years and those younger than 5 years of age have similar incidence rates, they have different mixtures of sites and histologies. The cancer incidence rates for 5 to 9 year olds are similar to those seen among 10-14 year olds.

Age and ICCC group

Fifty-seven percent of the cancers found among children younger than 20

Figure 3: Trends in age-specific incidence rates for all childhood cancers by age, all races both sexes, SEER, 1975-95



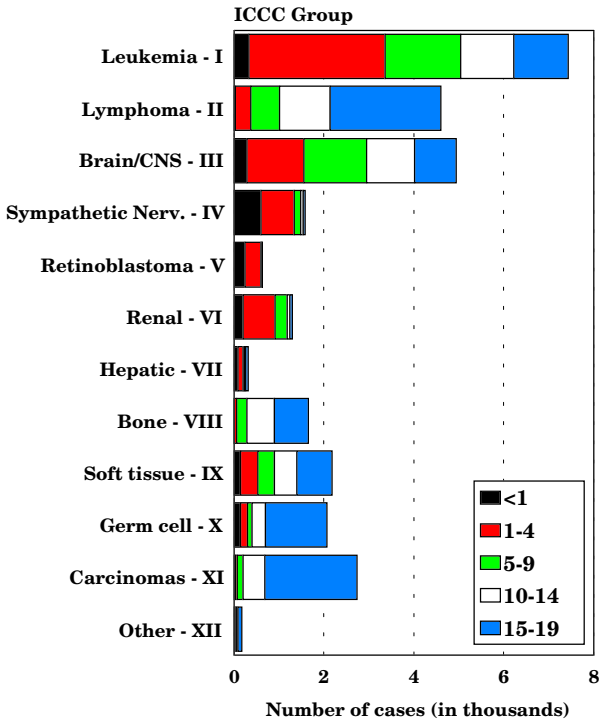
years of age were leukemia, malignant tumors of the central nervous system (CNS) or lymphoma. The relative percentage, however, varied by age group (Table 1). Leukemia was the most common diagnosis for those younger than 5, 5-9, and 10-14 years of age but the relative proportion of it decreased as age increased, from 36 percent for those younger than 5 years of age to only 12 percent for adolescents 15-19 years of age. For 15-19 year olds, lymphomas were the most common diagnosis, comprising one-fourth of the cases. The second most common type of cancer was malignant tumors of the central nervous system for younger than 5 and 5-9 years of age, and lymphoma for 10-14 and leukemia for 15-19 year olds (Table 1).

Figure 4 shows the numbers of cases used in this study by ICCC group and age. Leukemia (group I) had the largest number of cases. Note that these numbers are over the period 1975 to 1995 for the SEER areas and do not represent the total number of childhood cancers in the US in one year. These numbers indicate the reliability in the incidence and survival rates, i.e. large numbers imply stable rates and small numbers imply unstable rates. Even though ICCC groups I-III have most of the cases, there are differences by age group: group I has more 1-4 year olds, group II has more 15-19 year olds and group III has nearly equal numbers for each age group. There are less than 1,000 cases each in groups V, VII and XII. Groups VIII-XI tend to have fewer children younger than 10 years of age compared to 10-19 years of age.

Incidence by ICCC group

Figure 5 shows the incidence rates per million children for each of the ICCC groups. The highest rates are for groups I (leukemia), II (lymphoma), and III (CNS).

Figure 4: Number of cases of all childhood cancers by ICCC and age group, all races both sexes, SEER, 1975-95

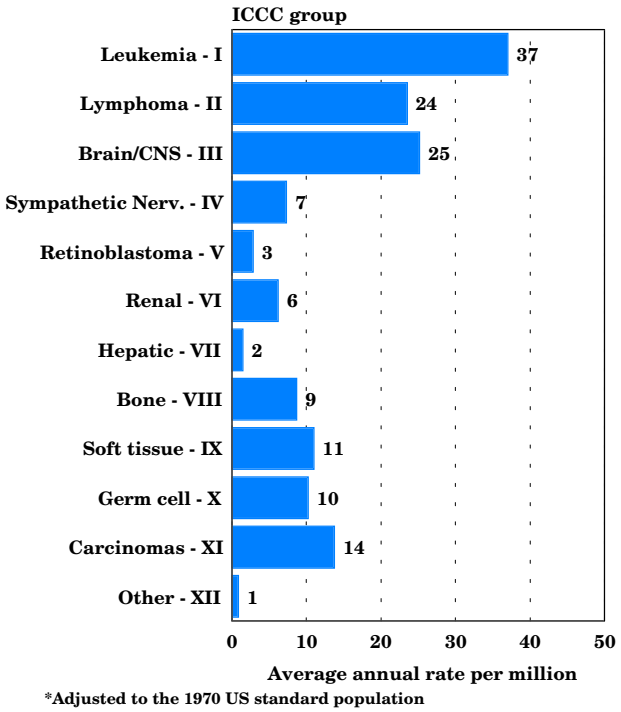


While the ICCC major groupings indicate which broad groups of sites/histologies are important, the sub-groups under each are necessary to really delineate which histologies are driving these rates. More detailed information on the ICCC groups and subgroups are contained in other chapters.

Race / ethnicity

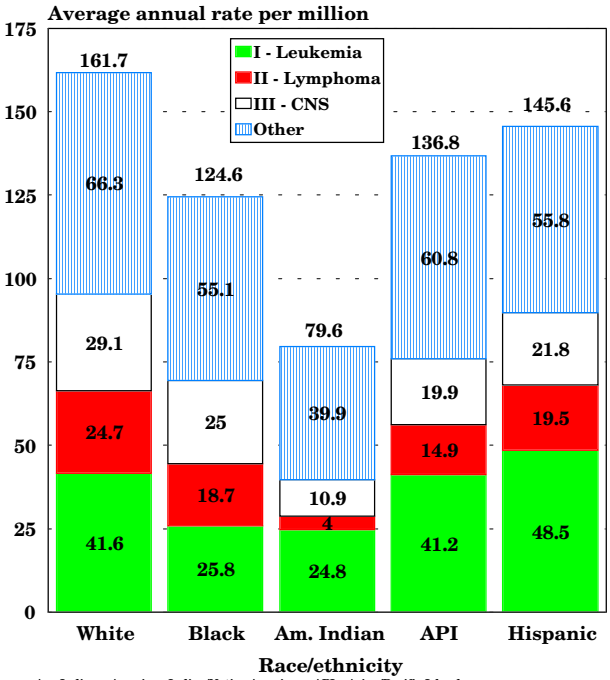
For many adult cancers, blacks have higher incidence rates than whites. For children, however, black children had lower incidence rates in 1990-95 than white children overall and for many of the specific sites (Figure 6). The time period, 1990-95, was used for racial/ethnic comparisons because it was the only time period except for the decennial census years (1980 and 1990) for which the Census Bureau provided population estimates for racial groups other than white and black. The largest racial difference was for leukemia (ICCC I) where the rate for whites (41.6 per million)

Figure 5: Age-adjusted* incidence rates for childhood cancer by ICCC group, age <20, all races both sexes, SEER, 1975-95



*Adjusted to the 1970 US standard population

Figure 6: Age-adjusted* incidence rates for childhood cancer by ICCC group and race/ethnicity age <20, both sexes, SEER, 1990-95



Am. Indian = American Indian/Native American; API = Asian/Pacific Islander
Hispanic = Hispanic of any race and overlaps other categories

*Adjusted to the 1970 US standard population

was much higher than that for blacks (25.8 per million). Cancer incidence rates for Hispanic children and Asian/Pacific Islander children were intermediate to those for whites and blacks. The rates for Asian/Pacific Islanders were similar to whites for leukemia but lower than whites for CNS and lymphomas. The incidence rates for American Indians were much lower than any other group.

Single year of age

For all sites combined, incidence varied by age with the highest rates in infants. The incidence rates declined as age increased until age 9 and then the incidence rates increased as age increased after age 9. The pattern, however, varied widely by ICCC group and single year of age. For example, high rates were seen among the very young for retinoblastoma (ICCC group V) and among adolescents for lymphoma

Age-specific incidence rates for childhood cancer by ICCC group, all races, both sexes, SEER 1986-94

Figure 7

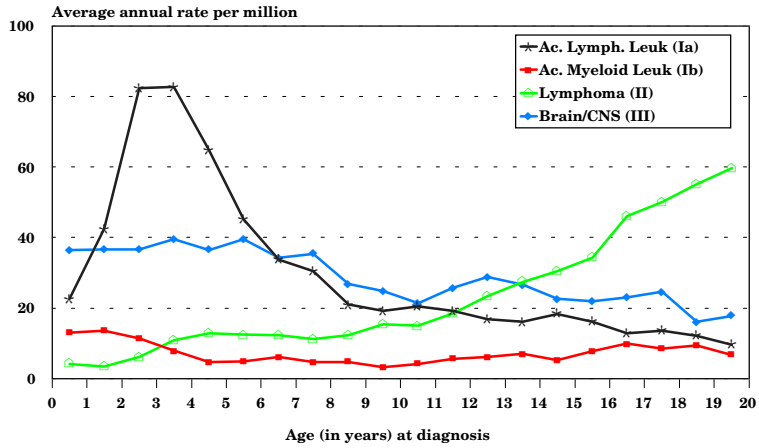


Figure 8

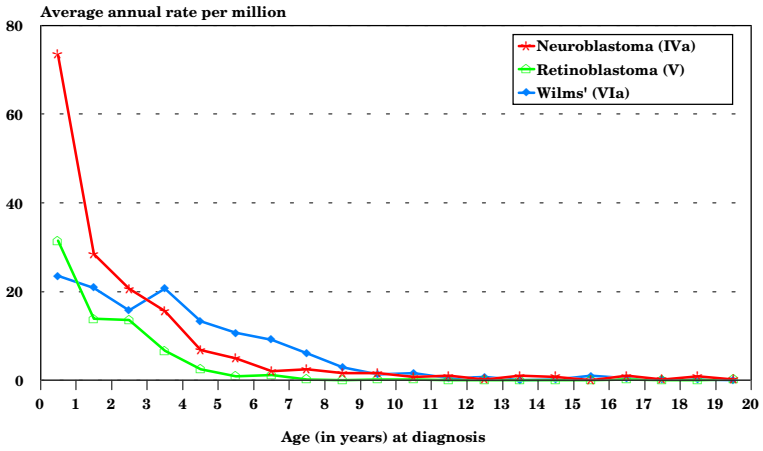
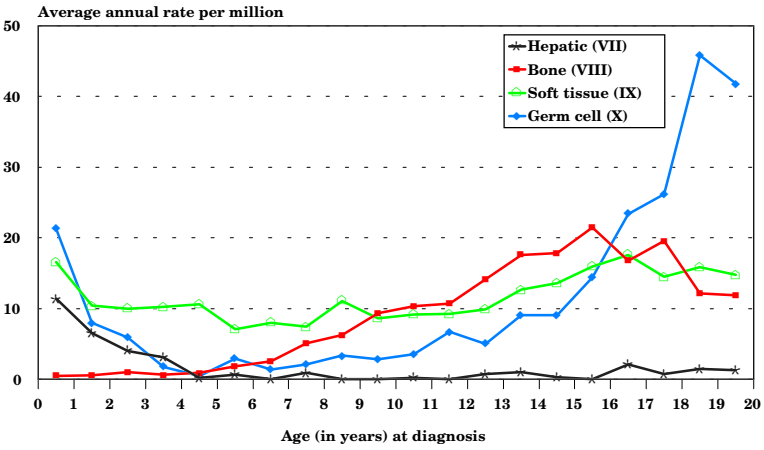


Figure 9



(ICCC group II) and germ cell (ICCC group X) for 1986-94 (Figures 7-9). Among those older than 9 years of age, there were very low incidence rates for neuroblastoma (ICCC group IVa), retinoblastoma (ICCC group V), Wilms' tumor (ICCC group VIa), and hepatic tumors (ICCC group VII).

SURVIVAL

The cancer survival rate for children has greatly improved over time. Even since the mid-1970s there have been large improvements in short term and long term survival (Figure 10). There were improvements in survival for many forms of childhood cancer (Figure 11). The principal reason for the gain for total childhood cancer is due to the improvement in the survival of leukemia, especially acute lymphocytic leukemia, which includes about a third of the pediatric cases. This is due primarily to improvements resulting from more efficacious chemotherapy agents.

Figure 10: Trends in relative survival rates for all childhood cancers, age <20, all races, both sexes SEER (9 areas), 1975-94

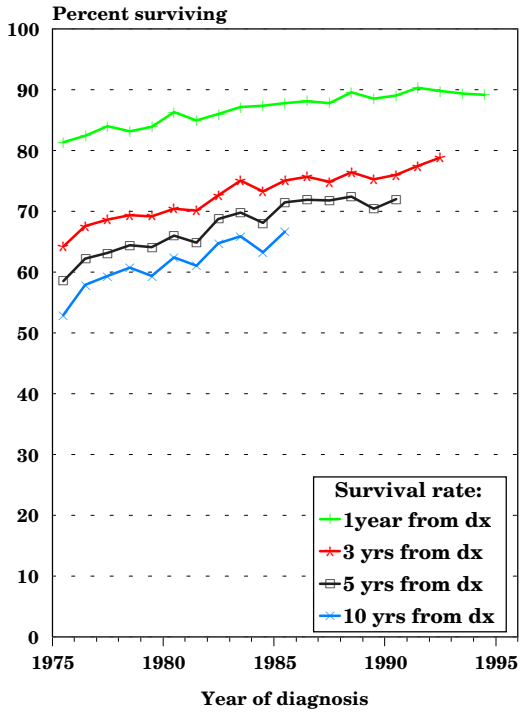
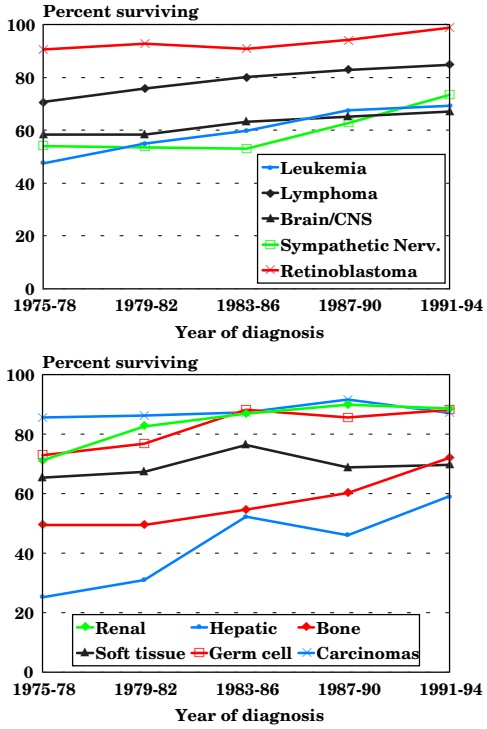


Figure 11: Trends in 5-year relative cancer survival rates by ICCC group, age <20 all races, both sexes, SEER (9 areas), 1975-94



RISK FACTORS

Throughout this monograph, there are discussions of potential causes and risk factors for individual childhood cancers. The discussion below provides background for considering the strength of the epidemiological evidence available for each risk factor. Since the evidence on risk factors varies, each risk factor table has the factors characterized by one of the following:

- Known risk factors: Most epidemiologists consider these characteristics or exposures to be 'causes' of the particular cancer. The scientific evidence meets all or most of the criteria described earlier. However, many individuals in the population may have the characteristic or

exposure and not develop cancer because there are other contributory factors.

- Suggestive but not conclusive evidence: The scientific evidence linking these characteristics or exposures to the particular cancer meets some but not all of the criteria described earlier.

- Conflicting evidence: Some studies show the putative risk factor to be associated with higher risk but others show no increased risk or lower risk.

- Limited evidence: Very few studies have investigated the putative risk factor. The existing studies may have investigated the exposure in a superficial manner or methodologic issues may make the results difficult to interpret.

Finding causes of any disease is usually a long, slow process. Epidemiologists find clues in one study that they follow-up in later studies. Only some of the clues are useful. Current studies are designed to help us learn whether or not previously identified clues are likely to lead us to the causes of a particular cancer. No one study is likely to prove that a particular exposure definitely causes a particular cancer. No single study nor even a large number of epidemiologic studies will enable a parent to know why his or her child developed cancer. However, each well designed and well executed study will bring us closer to understanding the causes of these cancers within populations of children.

Multifactorial etiology

We also do not expect that all children with a particular cancer developed it for the same reason. In other words, we do not think that one exposure, behavior or genetic trait explains all or even a majority of instances of a particular cancer. Rather, we expect that a number of exposures and characteristics of children each contribute to a proportion of instances of a particular cancer.

No one factor determines whether an individual will develop cancer, even if a specific exposure explains a high proportion of the occurrence of a specific cancer. Rather, it is the interaction of many factors that produces cancer. This concept is referred to as the multiple causation or multifactorial etiology. The factors involved may be genetic, constitutional or behavioral characteristics of the individual or factors external to the individual. Among the many types of factors that might play a role are genetic, immune, dietary, occupational, hormonal, viral, socioeconomic, lifestyle, and other characteristics of the individual and the biologic, social, or physical environment.

The concept of multiple causation has direct implications for the interpretation of research on the causes of cancer. Suppose that combinations of laboratory and epidemiologic studies have shown that exposure to chemical X causes leukemia. We know that other factors must play a role since not all children who were exposed to chemical X developed leukemia. Thus, there must be other factors that determine which of the children exposed to chemical X will develop leukemia.

Associations versus causes

Frequently, newspapers and television report that some chemical, dietary habit, or household product is purported to increase the risk of cancer. These news stories tell us about associations between an exposure and a cancer. In other words, more of the people who developed cancer than those without cancer had the exposure. However, an association between an exposure and

cancer does not necessarily mean that the exposure causes cancer.

As an example, suppose a case-control study (see Technical Appendix) finds that more of the mothers of children with acute lymphoblastic leukemia (ALL) than mothers of controls used medication Y during pregnancy. It is possible that medication Y causes ALL, but there are also other explanations. It may be that mothers of children with ALL were more accurate in their reporting of medication use than the control mothers. Since mothers are asked in these studies to recall their use of medication and other substances during a pregnancy 5 or 10 years in the past, it is certain that their reporting is not completely accurate. Mothers of children with cancer have probably thought about their exposures during the relevant pregnancies more intently than control mothers in their search for an explanation of their children's illness. Case mothers may remember short episodes of medication use whereas control mothers may have forgotten them. Differences in the level of recall between mothers of cases and mothers of controls may be real or may reflect less accurate recall of either group of mothers. This type of differential recall may lead to erroneous results for either group; such differential recall would lead to inaccurate or biased results, a problem designated as recall bias. A recall bias would lead to an association or disassociation between the medication and cancer which would not be causal but spurious or false. Another explanation of an association between the medication and cancer is that medication Y is used to treat a medical condition and that the condition rather than the medication confers the risk. Epidemiologists would say that the condition is a confounder of the observed association between the medication and cancer.

How do epidemiologists decide whether an association between an exposure and a disease is one of cause and effect? The methods and processes of epidemiology and their limitations make it nearly impossible for a single study to prove that an exposure causes a disease. There must be a number of studies that epidemiologists can evaluate using a set of criteria. The criteria are described briefly but the order in which they are described does not signify relative importance.

1. Other possible explanations of the observed association must be ruled out, such as the medical condition rather than the medication. In another example, if one investigates an association between eating hot dogs and developing a specific cancer, one must determine whether high dietary fat intake or infrequent fruit eating explains the association and rule out these factors before concluding hot dog consumption is related to risk.

2. Epidemiologists consider the strength of the association, that is, the relative risk (see Technical Appendix). An exposure associated with a ten-fold increase in risk is more likely to be a true cause than an exposure associated with a two-fold increase.

3. The consistency of an association is considered. An association observed in many different studies in different populations using different study methods is likely to be true.

4. The observation of a dose-response relationship between the exposure and the disease increases confidence that the exposure is really related to the disease. In a dose-response relationship, the risk of disease increases or decreases as the amount of the exposure increases or decreases. For example, the relationship between cigarette smoking

and lung cancer shows a dose-response in that heavy smokers have a higher risk than light smokers.

5. The association must be temporally correct meaning that we must be sure that the exposure actually preceded development of the disease. For example, a study might report that barbiturate use increased the risk of brain tumors. However, barbiturates are used to control seizures, which are often an early symptom of a brain tumor. Therefore, it may not be clear if barbiturate use actually preceded the development of the brain tumor or if barbiturates were used to treat an early symptom before the brain tumor was diagnosed.

6. A biologically plausible association is more likely to be true than one without other supporting evidence. For example, we have more confidence that chemical X causes brain tumors in humans if it is known to cause brain tumors in animals.

All or most of these six criteria must be met before an association between a disease and an exposure is considered a causal association.

Structure of monograph

This monograph consists of a chapter for each of the principal types of pediatric cancers as designated by the ICCC. The ICCC designated group is also used as the chapter number except for group XII which is less than 6% of the total and is not shown in a separate chapter. Each of these chapters discusses incidence, mortality, and survival rates of the patients, as well as trends in these measures by demographic characteristics. Risk factors are also described. The estimated number of cases in the US for 1998 is given in each chapter. These numbers are based on the American Cancer Society's overall cancer estimate of 12,400 [1] cases and on the SEER site distribution for 1990-95.

In addition, there are separate chapters on children younger than 1 year of age, adolescents, and incidence vs. mortality trends. The monograph is also available from the SEER home page under publications (http://www-seer.ims.nci.nih.gov). There is a technical appendix at the end of this chapter which defines terms used in the Introduction and in other chapters; it also provides more details on methods and data sources.

TECHNICAL APPENDIX

Age-adjusted rate: An age-adjusted rate is a weighted average of the age-specific cancer incidence (or mortality) rates, where the weights are the proportions of persons in the corresponding age groups of a standard population. The potential confounding effect of age is reduced when comparing age-adjusted rates computed using the same standard population. For this report, the 1970 United States standard million is used as the standard in computing all age-adjusted rates. Since rates of childhood cancer vary widely by 5-year age group, age-adjustment was used for any age group representing more than one 5-year grouping. Age-adjustment was performed by 5-year age group and weighted by the 1970 US standard million population.

Age-specific rates: Age-specific rates are usually presented as a rate per million. The numerator of the rate is the number of cancer cases found in a particular 5-year age group in a defined population divided by the number of individuals in the same 5-year age group in that population. In this publication, there are some rates by single year of age for time periods around the Census. Population estimates by single year of age, race, sex, and geographic region are not generally available for intercensal years. The rates by single year of age are plotted at half years. For example, the rate for children age 1 year is plotted at 1.5 years since they are an average 1 1/2 years of age.

Case-control study: A case-control study is an epidemiologic study in which a group of individuals with a disease, the cases, are compared to a group of individuals without the disease, the controls.

Exposures or characteristics that are more common in the cases than in the controls may be causes of the disease. Exposures or characteristics that are equally common in the cases and controls cannot be causes of the disease. Almost all studies of childhood cancer are case-control studies because this type of study is very useful in studying relatively uncommon diseases.

Cohort study: A cohort study is an epidemiologic study in which the incidence of disease is compared between a group of individuals with an exposure or characteristic and a group without that exposure or characteristic. For example, smokers and nonsmokers are followed and the incidence of heart disease is compared in the two groups. Or, the incidence of breast cancer is compared in women with and without a BRCA1 gene mutation. This type of study is rarely feasible in investigating the etiology of childhood cancer. Since childhood cancer is rare, especially if we consider that each cancer should be studied separately, huge numbers of children (a few hundred thousand) would have to be followed to determine which children developed cancer.

EAPC (Estimated Annual Percent Change): The Estimated Annual Percent Change (EAPC) was calculated by fitting a regression line to the natural logarithm of the rates (r) using calendar year as a regressor variable, i.e. $y = mx + b$ where $y = \text{Ln } r$ and x = calendar year. The EAPC = $100*(e^m - 1)$. Testing the hypothesis that the Annual Percent Change is equal to zero is equivalent to testing the hypothesis that the slope of the line in the above equation is equal to zero. The latter hypothesis is tested using the t distribution of m/SE_m with the number of degrees of freedom equal to the number of calendar years minus two. The standard error of m, i.e. SE_m, is obtained from the fit of the regression [5]. This calculation assumes that the rates increased/decreased at a constant rate over the entire calendar year interval. The validity of this assumption has not been assessed. In those few instances where at least one of the rates was equal to zero, the linear regression was not calculated. The differences between incidence and mortality trends for the time period 1975-79 versus those for the most recent five-year period are tested for statistical significance using a t statistic with six degrees of freedom defined as the difference in the regression coefficients divided by the standard error of the difference [5].

Follow-up: SEER areas attempt to follow-up all cases till death. Although the overall proportion of cancer patients of all ages who are lost to follow-up is only about 5%, for pediatric cases (age 0-19) it is much larger - about 14%. Since survival rates are relatively high, follow-up can be difficult, especially as the child gets older. When children leave their parents' home, they change addresses and, especially for females, they may change last names.

ICCC classification: At the time the World Health Organization's (WHO) International Agency for Research on Cancer (IARC) published their first monograph on Childhood Cancer [6] in 1988, Dr. R. Marsden published an annex giving a classification scheme for childhood cancer that consisted of 12 groups based chiefly on histologic type. The classification by Marsden has been modified and is now called the International Classification of Childhood Cancers [4].

Incidence rate: The cancer incidence rate is the number of new cancers of a specific site/type occurring in a specified population during a year, expressed as the number of cancers per one million people. It should be noted that the numerator of the rate can include multiple primary cancers occurring in one individual. This rate can be computed for each type of cancer as well as for all cancers combined. Except for five-year age-specific rates, all incidence rates are age-adjusted to the 1970 US standard million population. Rates are for invasive cancer only, unless otherwise specified.

Mortality data: The mortality data are from public use files provided by the National Center for Health Statistics (NCHS) and cover all deaths in the United States. All mortality rates were based on the underlying cause of death. The rates presented for 1975-1978 were coded to the *International Classification of Diseases* - 8th revision and for 1979 to 1995 to the ICD 9th revision [7]. Unfortunately mortality of all specific groups of the ICCC pediatric classification are not available from US mortality files due to the fact that the codes used for coding death certificates do not include such morphologic types as neuroblastomas and retinoblastomas. Certain groups can be identified as specific entities on death certificates: Leukemias, Lymphomas, Bones, Brain and other CNS tumors, and Hodgkin's and Non-Hodgkin's lymphoma. However, such types of cancer as Retinoblastomas, Germ cell tumors, Wilms' tumor, and certain carcinomas can not be identified on death certificates. Even though neuroblastomas are not coded separately, they were coded to different groups in the ICD-8 and ICD-9. For these analyses to make the data comparable over time, deaths coded to sympathetic nervous system in the 8th revision were combined with adrenal in the 9th revision.

Mortality rate: The cancer mortality rate is the number of deaths with cancer given as the underlying cause of death occurring in a specified population during a year, expressed as the number of deaths due to cancer per one million people. This rate can be computed for each type of cancer as well

as for all cancers combined. Except for age-specific rates, all mortality rates are age-adjusted to the 1970 US standard million population.

Population data: Population estimates are obtained each year from the US Bureau of the Census at the county level by five-year age group (0-4, 5-9,..., 85 and over), sex, and race (including white and black). SEER areas make county estimates for each state available on the SEER areas Home Page (http://www-seer.ims.nci.nih.gov) for race (whites, blacks, non-white), 5-year age group, sex, and year of diagnosis (each year 1973 to 1995). Additional estimates can be obtained from the US Census Bureau Home Page.

US Bureau of the Census (BOC) population estimates for Hawaii were altered according to independent estimates developed from sample survey data collected by the Health Surveillance Program (HSP) of the Hawaii Department of Health. For Hawaii, the all races and black populations are the same as those sent by the BOC. Proportions of the population by different racial groups from the HSP were used to generate estimates for whites, etc. Since the HSP survey was for all of Hawaii and not by county, population estimates were not broken down by county. The white population estimates for Hawaii provided by the BOC are generally larger than those generated by the HSP. Since whites in Hawaii account for less than two percent of the total white population represented by the SEER reporting areas, white incidence rates for the entire SEER Program are not noticeably affected. Procedures for calculating rates by race for Hawaii are currently under review.

Primary site/histology coding: Originally data for site and histologic type were coded by the *International Classification of Diseases for Oncology* (ICD-O) [8], but in 1990, ICD-O was revised and republished as the *International Classification of Diseases for Oncology,* 2nd Edition (ICD-O-2) [7]. SEER areas began using ICD-O-2 for cases diagnosed in 1992 and machine converted all previous data to ICD-O-2. Most data for Non-Hodgkin's Lymphoma (NHL) can be classified by the Working Formulation (WF) based on a conversion from ICD-O-2.

Relative risk: Whether or not an exposure increases the risk of cancer and how much it does is expressed in a measure called relative risk. The relative risk is the risk of disease in those with the exposure divided by the risk of disease in those without the exposure.

- Relative risk less than 1.0 - the exposure appears to lower the risk of the disease. For example, a relative risk of 0.75 for taking vitamin X supplements indicates that those who took vitamin X had a risk that was 75% of that for individuals who did not take vitamin X. Or, taking vitamin X lowered one's risk by 25%.

- Relative risk of 1.0 - the exposure does not affect the risk of the disease; the risk is the same in those with the exposure as in those without the exposure.

- Relative risk greater than 1.0 - the exposure appears to increase the risk of the disease. For example, a relative risk of 3 for taking medication Y indicates that those taking the medication had a risk that was three times that of those not taking the medication.

Relative survival rate: The relative survival rate is calculated using a procedure described by Ederer, Axtell, and Cutler [9] whereby the observed survival rate is adjusted for expected mortality. The relative survival rate represents the likelihood that a patient will not die from causes associated specifically with their cancer at some specified time after diagnosis. It is always larger than the observed survival rate for the same group of patients.

Risk factor: A risk factor is a characteristic or exposure that increases the risk of disease. A risk factor might be exposure to high levels of radon, having a diet low in vitamin A, having a family history of colon cancer, or having a high cholesterol level.

SEER Program: This program started in 1973, as an outgrowth of the NCI's Third National Cancer Survey. NCI contracts out with various medically oriented non-profit organizations, local city or state Health Departments or Universities for collection of these data. Contracts for collecting this data are with the entire states of Connecticut, Iowa, New Mexico, Utah, and Hawaii and with the metropolitan areas of Los Angeles, California; Detroit, Michigan; San Francisco-Oakland and San Jose-Monterey, California; Seattle-Puget Sound, Washington; and Atlanta, Georgia. These organizations collect data on all cancers except basal and squamous cell skin cancers. Although data are collected on all people having cancer, the material for this study used children from birth through age 19 years. Only residents of the areas designated above are included so that the base populations can be properly determined.

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HIGHLIGHTS

Incidence

- For the years from 1990-95, the leukemias represented 31% of all cancer cases occurring among children younger than 15 years of age and 25% of cancer cases occurring among those younger than 20 years of age. In the US there are approximately 3,250 children diagnosed each year with leukemia and 2,400 with acute lymphoblastic leukemia (ALL).
- The relative contribution of leukemia to the total childhood cancer burden varies markedly with age, being 17% in the first year of life, increasing to 46% for 2 and 3 year olds, and then decreasing to only 9% for 19 year olds (Figure I.1).
- The two major types of leukemia were ALL comprising nearly three-fourths and acute non-lymphocytic comprising 19%.
- There was a sharp peak in ALL incidence among 2-3 year olds (> 80 per million) which decreases to a rate of 20 per million for 8-10 year olds. The incidence of ALL among 2-3 year olds is approximately 4-fold greater than that for infants and is nearly 10-fold greater than that for 19 year olds (Figure I.2a).
- Leukemia rates are substantially higher for white children than for black children, with rates of 45.6 versus 27.8 per million for the period from 1986-95 for children 0-14 years old (Table I.4). This difference between white and black children is most apparent when examining rates of leukemia by single year of age (Figure I.3), with a nearly 3-fold higher incidence at 2-3 years of age for white children compared to black children.
- The incidence of leukemia among children younger than 15 years of age has shown a moderate increase in the past 20 years (Figure I.4) with the trend primarily reflecting an increase in ALL incidence during this period. The rates of leukemias other than ALL did not appear to increase from 1977 to 1995 (Figure I.5)

Survival

- Survival for children with ALL has markedly improved since the early 1970s, and overall survival for all children with ALL is now approximately 80% (Figure I.8). A number of improvements in treatment during this period have undoubtedly contributed to the improved survival.
- Survival for children with ALL is very dependent upon age at diagnosis, with the most favorable outcome observed for children older than 1 year of age and younger than 10 years of age.

Risk factors

- With the exception of prenatal exposure to x-rays and specific genetic syndromes, little is known about the causes of childhood ALL (Table I.5).
- Different risk factors are emerging for childhood AML that distinguish the disease from ALL, and this may provide avenues for future epidemiological studies (Table I.6).

INTRODUCTION

The leukemias of childhood are cancers of the hematopoietic system, involving in most cases, malignant transformation of lymphoid progenitor cells [1] and less commonly transformation of myeloid progenitor cells [2]. The leukemias account for the largest number of cases of childhood cancer and are the primary cause of cancer related mortality of children in the United States. Approximately 3,250 children and adolescents younger than 20 years of age are diagnosed with leukemia each year in the US, of which 2,400 are acute lymphoblastic leukemia. For the years from 1986-94, the leukemias represented 32% of all cancer cases occurring among children younger than 15 years of age and 26% of cancer cases occurring among those younger than 20 years of age. However, the relative contribution of leukemia to the total childhood cancer burden varied markedly with age, being 17% in the first year of life, increasing to 46% for 2 and 3 year olds, and then decreasing to only 9% for 19 year olds. To further illustrate the contribution Figure I.1 gives the incidence rates for both leukemia and total cancer (the sum of leukemia and non-leukemia) by single year of age.[1]

This chapter focuses on the following topics related to the incidence of leukemia among children in the United States: (1) the relative frequencies of the leukemia subtypes that occur among children; (2) variation in the incidence of the specific types of leukemia by age; (3) differences in incidence between males and females; (4) differences in incidence between white and black children; and (5) variation in leukemia incidence over time. In terms of survival for children with leukemia, the chapter focuses on three primary topics: (1) comparison of survival rates for children with ALL and AML; (2) the impact of age at diagnosis on survival; and (3) the remark-

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

Figure I.1: Total childhood cancer age-specific incidence rates by leukemia versus non-leukemia, all races, both sexes, SEER, 1986-94

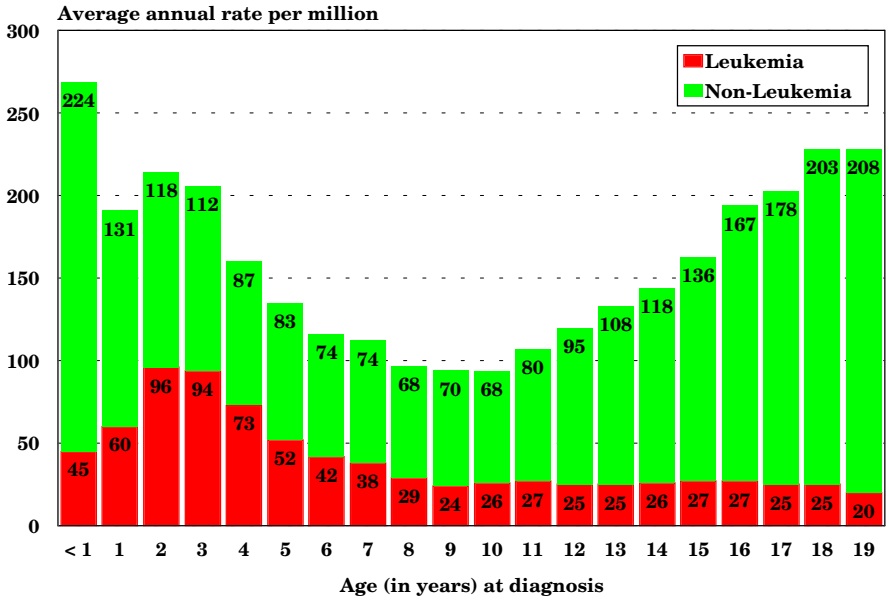


Table I.1: Percent distribution within ICCC subcategories for leukemia and age-adjusted* incidence rates for specific ICD-O codes, age <20, all races, both sexes, SEER, 1975-95

Diagnostic Group	Specific Diagnosis:	Rate per million	% of Cases
Ia: Lymphoid leukemia		29.2	100.0%
	9820: Lymphoid leukemia, NOS		0.2%
	9821: Acute lymphoblastic		99.2%
	9822: Subacute lymphoid		0.0%
	9823: Chronic lymphocytic		0.1%
	9824: Aleukemic lymphoid		0.2%
	9825: Prolymphocytic leukemia		0.1%
	9826: Burkitt's cell leukemia		0.5%
	9827: Adult T-cell		0.0%
	9850: Lymphosarcoma cell		0.0%
Ib: Acute non-lymphocytic		7.6	100.0%
	9840: Erythroleukemia		0.4%
	9841: Acute erythremia		0.2%
	9861: Acute myeloid leukemia		68.7%
	9864: Aleukemic myeloid		0.0%
	9866: Acute promyelocytic		7.1%
	9867: Acute myelomonocytic		9.3%
	9891: Acute monocytic leukemia		9.1%
	9894: Aleukemic monocytic		0.0%
	9910: Acute megakaryoblastic		5.1%
Ic: Chronic myeloid leukemia		1.3	100.0%
	9863: Chronic myeloid leukemia		98.6%
	9868: Chronic myelomonocytic		1.4%
Id: Other specified leukemias		0.2	100.0%
	9830: Plasma cell leukemia		0.0%
	9842: Chronic erythremia		0.0%
	9860: Myeloid leukemia, NOS		33.3%
	9862: Subacute myeloid		0.0%
	9870: Basophilic leukemia		0.0%
	9880: Eosinophilic leukemia		0.0%
	9890: Monocytic leukemia, NOS		8.3%
	9892: Subacute monocytic		0.0%
	9893: Chronic monocytic		0.0%
	9900: Mast cell leukemia		0.0%
	9930: Myeloid sarcoma		58.3%
	9931: Acute panmyelosis		0.0%
	9932: Acute myelofibrosis		0.0%
	9940: Hairy cell leukemia		0.0%
	9941: Leukemia		0.0%
Ie: Unspecified leukemias		1.2	100.0%
	9800: Leukemia, NOS		20.5%
	9801: Acute leukemia, NOS		79.5%
	9802: Subacute leukemia, NOS		0.0%
	9803: Chronic leukemia, NOS		0.0%
	9804: Aleukemia leukemia, NOS		0.0%

*Adjusted to the 1970 US standard population

able improvements in survival rates for children with ALL during the past 20 years.

Classification system

Before discussing topics related to childhood leukemia incidence and outcome, it is necessary to describe the specific diagnoses that are included among the Diagnostic Groups for leukemia of the International Classification of Childhood Cancer (ICCC). Table I.1 illustrates that acute lymphoblastic leukemia (ALL) accounted for approximately 99% of cases among the lymphoid leukemia (Ia) diagnostic group, so that this ICCC diagnostic group is essentially synonymous with ALL. The "acute non-lymphocytic leukemia" diagnostic category Ib is henceforth referred to as the acute myeloid leukemia (AML) category since this is the preferred terminology [3], and it encompasses the various subtypes of AML that occur in children. The other three ICCC diagnostic categories combined accounted for only 6-7% of total leukemia cases in children. The chronic myeloid leukemias diagnostic group (Ic) included approximately 3% of leukemia cases occurring in the younger than 20 years of age group during the period from 1990-95, while the "other specified leukemia" diagnostic group (Id) included fewer than 1% of the leukemia cases. Approximately 3% of leukemia cases were included in the unspecified leukemia category (Ie) for the period from 1990-95.

INCIDENCE

Age-specific incidence

Table I.2 shows the incidence and relative proportion of specific diagnostic categories by 5-year age groups. For the younger than 15 years of age, ALL represented 78% of leukemia cases, while the AML subgroup (Ib) represented 16% of cases. The relative frequency of AML increased in the second decade of life as that of ALL decreased. While AML represented only 13-14% of leukemia cases in the first 10 years of life, it accounted for 36% of leukemia cases among 15-19 year olds. The incidence and relative contribution of the chronic myeloid leukemias also increased with age, representing about 9% of cases among 15-19 year olds.

As is apparent from Table I.2, the incidence of leukemia among children varied considerably with age. Figure I.2a illustrates that this variation was the result of a sharp peak in ALL incidence among 2-3 year old children (incidence over 80 per million), which returned to a rate of 20 per million for 8-10 year old children. The incidence of ALL among 2-3 year old

Table I.2: Age-adjusted incidence rates per million for specific leukemia by age groups all races, both sexes, SEER, 1990-95

Age (in years) at diagnosis	<5	5-9	10-14	15-19	<15*
Total leukemia	72.4 (100%)	38.0 (100%)	25.9 (100%)	26.0 (100%)	43.8 (100%)
ALL	58.1 (80%)	30.6 (81%)	17.4 (67%)	13.0 (50%)	34.0 (78%)
AML (Ib)	10.3 (14%)	5.0 (13%)	6.2 (24%)	9.3 (36%)	7.0 (16%)
CML (Ic)	1.1 (2%)	0.7 (2%)	1.1 (4%)	2.2 (9%)	1.0 (2%)
Other specified leukemias (Id)	0.3 (-)	0.3 (1%)	0.1 (-)	0.1 (-)	0.2 (1%)
Unspecified leukemias (Ie)	2.2 (3%)	1.0 (3%)	0.6 (2%)	1.1 (4%)	1.2 (3%)

* Rates are adjusted to the 1970 US standard population. Numbers in parentheses represent the percentage of the total cases for the specific age group.

children was approximately 4-fold greater than that for infants and was nearly 10-fold greater than that for 19 year olds. The distinctive shape of the age-incidence curve for ALL can be well-described by a mathematical model which assumes that childhood ALL results from two events required for full malignant transformation with the first of these events occurring *in utero* [4]. Experimental confirmation has been obtained for the initiation of childhood ALL *in utero* [5,6].

The incidence of AML in children also varied with age (Figure I.2b), but with a different pattern than that for ALL. AML rates were highest in the first 2 years of life, but subsequently decreased with a nadir at approximately 9 years of age, followed by slowly increasing rates during the adolescent years. The incidence of leukemia cases in the "chronic myeloid leukemia" category (Ic) likewise showed substantial variation with age. As shown in Figure I.2c, there was a peak in inci-

Figure I.2a: ALL (Ia): 1986-94, and AML (Ib): 1976-84 and 1986-94 age-specific incidence rates, all races both sexes, SEER

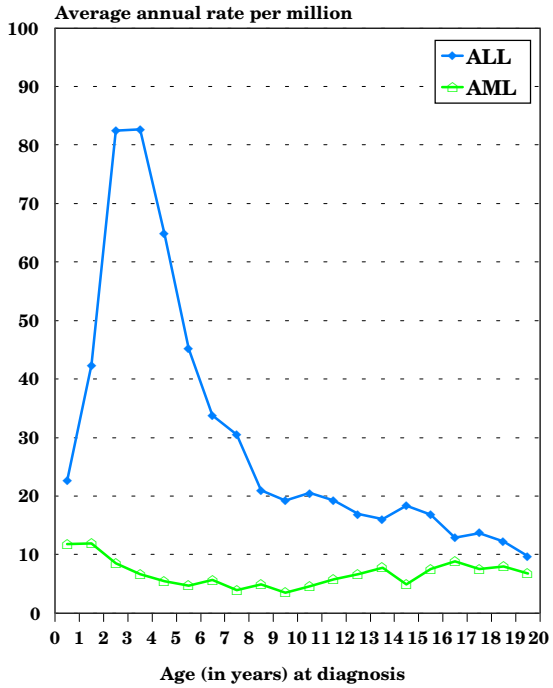
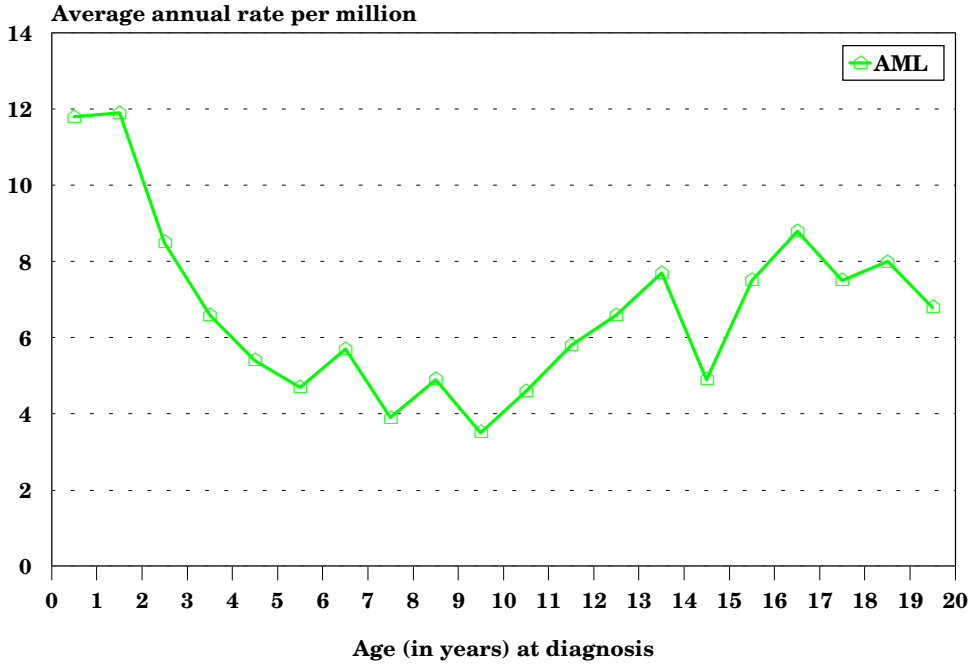
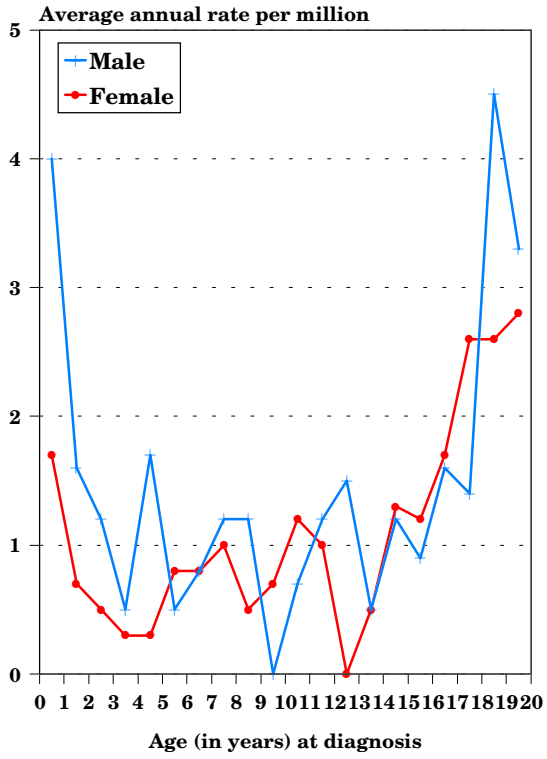


Figure I.2b: AML (Ib) age-specific incidence rates, all races both sexes, SEER, 1976-84 and 1986-94 combined



dence for males in the first year of life, with subsequent lower rates for both males and females until the late teen years. The increase in CML incidence in the later teen years appeared to represent the early portion of the increasing incidence curve for adult-type CML [7]. On the other hand, the cases coded as "chronic myeloid leukemia" in the first few years of life almost certainly reflect cases of juvenile myelomonocytic leukemia (previously termed juvenile chronic myeloid leukemia), a diagnosis associated primarily with young males [8,9].

Figure I.2c: Chronic myeloid leukemia age-specific incidence rates, all races, both sexes SEER, 1976-84 and 1986-94 combined



Sex-specific incidence

Table I.3 illustrates the incidence of the various leukemia types separately for males and females for the years 1990-95. The incidence of ALL among children younger than 15 years of age was consistently higher among males (approximately 20%) relative to females. For the 15-19 year olds, however, the male preponderance was greater, with males having a 2-fold higher ALL incidence than females. The incidence of AML was similar for males and females for all age groups. For the CML category, there was a 4-fold higher rate for males than females for the younger than 5-year age group, a difference that was not present for older age groups. As noted above, these cases likely represent juvenile myelomonocytic leukemia, which has a known male predominance [9].

Table I.3: Male to female ratios of age-adjusted leukemia incidence rates per million by type and age group, all races, SEER, 1990-95

	<5 Yrs Rate M/F Ratio	5-9 Yrs Rate M/F Ratio	10-14 Yrs Rate M/F Ratio	15-19 Yrs Rate M/F Ratio	<15 Yrs Rate* M/F Ratio	<20 Yrs Rate* M/F Ratio
Total leukemia	M = 78.5 F = 65.9 M/F = 1.2	M = 40.3 F = 35.7 M/F = 1.1	M = 28.4 F = 23.1 M/F = 1.2	M = 28.4 F = 23.4 M/F = 1.2	M = 47.4 F = 40.1 M/F = 1.2	M = 42.7 F = 36.0 M/F = 1.2
ALL	M = 63.7 F = 52.3 M/F = 1.2	M = 32.2 F = 29.0 M/F = 1.1	M = 18.8 F = 16.0 M/F = 1.2	M = 17.2 F = 8.6 M/F = 2.0	M = 36.7 F = 31.2 M/F = 1.2	M = 31.9 F = 25.6 M/F = 1.2
AML (Ib)	M = 10.0 F = 10.6 M/F = 0.9	M = 5.8 F = 4.3 M/F = 1.3	M = 6.7 F = 5.7 M/F = 1.2	M = 8.3 F = 10.4 M/F = 0.8	M = 7.4 F = 6.7 M/F = 1.1	M = 7.6 F = 7.6 M/F = 1.0
Chronic myeloid leukemia (Ic)	M = 1.7 F = 0.4 M/F = 4.3	M = 0.4 F = 1.0 M/F = 0.4	M = 1.4 F = 0.9 M/F = 1.6	M = 1.6 F = 2.9 M/F = 0.6	M = 1.1 F = 0.8 M/F = 1.4	M = 1.3 F = 1.3 M/F = 1.0

*Adjusted to the 1970 US standard population

Table I.4: White to black ratios of age-adjusted leukemia incidence rates per million by type and age group, both sexes, SEER, 1986-95

	<5 Yrs Rate* W/B Ratio	5-9 Yrs Rate W/B Ratio	10-14 Yrs Rate W/B Ratio	15-19 Yrs Rate W/B Ratio	<15 Yrs Rate* W/B Ratio	<20 Yrs Rate* W/B Ratio
Total Leukemia	W = 77.2 B = 38.4 W/B = 2.0	W = 37.5 B = 28.6 W/B = 1.3	W = 27.4 B = 18.4 W/B = 1.5	W = 26.5 B = 15.2 W/B = 1.7	W = 45.6 B = 27.8 W/B = 1.6	W = 40.9 B = 24.7 W/B = 1.7
ALL	W = 63.2 B = 26.9 W/B = 2.4	W = 31.8 B = 1.8 W/B = 1.8	W = 19.8 B = 11.6 W/B = 1.7	W = 14.3 B = 6.4 W/B = 2.2	W = 36.8 B = 18.3 W/B = 2.0	W = 31.2 B = 15.4 W/B = 2.0
AML (Ib)	W = 10 B = 7.7 W/B = 1.3	W = 3.8 B = 6.1 W/B = 0.6	W = 5.3 B = 5.1 W/B = 1.0	W = 8.3 B = 7.1 W/B = 1.2	W = 6.2 B = 6.2 W/B = 1.0	W = 6.7 B = 6.4 W/B = 1.1

*Adjusted to the 1970 U.S. standard population

Black-white differences in incidence

Leukemia rates were substantially higher for white children younger than 15 years of age compared to black children, with rates of 45.6 versus 27.8 per million for the period from 1986-95 (Table I.4). This difference between white children and black children was most apparent when examining rates of leukemia by single year of age (Figure I.3), with a nearly 3-fold higher incidence at 2-3 years of age for white children compared to black children.

The difference in leukemia incidence was primarily the result of lower ALL rates among black children (Table I.4), with ALL incidence for white children younger than 5 years of age being more than twice that for black children (63.2 versus 26.9 per million). A lower ALL incidence for black children was observed for each 5-year age group up to 20 years of age. The incidence of AML, unlike that for ALL, was similar for white and black children for all age groups (Table I.4).

Figure I.3: Leukemia age-specific incidence rates for white (1986-94) and black (1976-84 and 1986-94) children, SEER

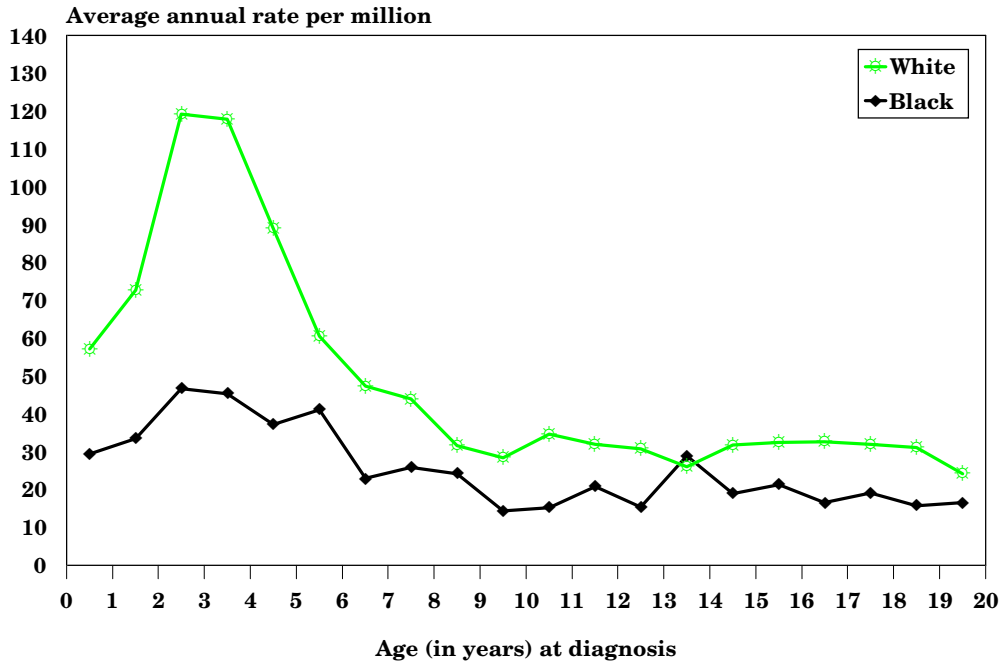
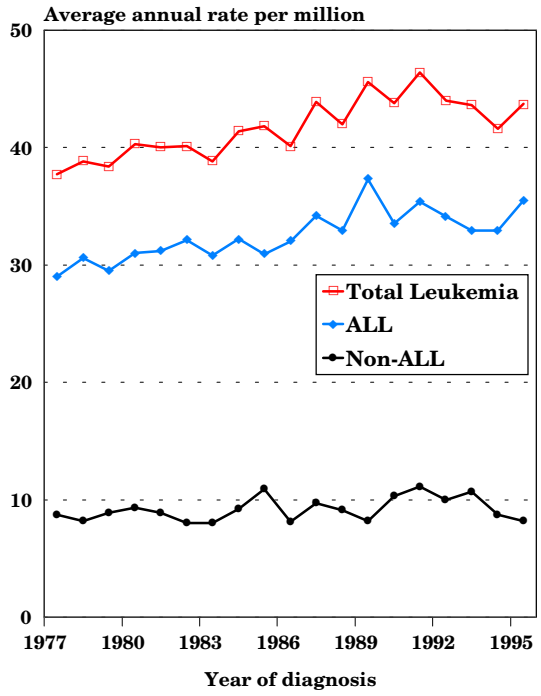


Figure I.4a: Trends in leukemia and ALL age-adjusted* incidence rates, age <15 all races, both sexes, SEER, 1977-95



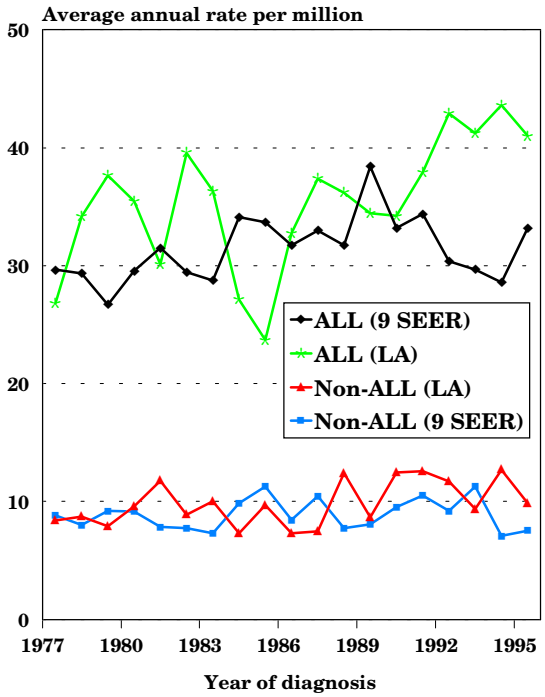
*Adjusted to the 1970 US standard population

TRENDS

The incidence of leukemia among children younger than 15 years of age increased in the past 20 years, as shown in Figure I.4a. The estimated annual percentage change (EAPC) for total leukemia for the period from 1977 to 1995 was 0.9% per year, with the trend primarily reflecting an increase in ALL incidence during this period (EAPC for ALL, 0.9%). The rates of leukemias, other than ALL, did not increase significantly from 1977 to 1995 (Figure I.5), although the small number of cases diagnosed each year for the less common leukemia types results in considerable scatter in year to year rates, which makes interpretations of trends difficult. The higher rate of nonspecific classification of leukemia cases (ICCC Category Ie) in the years prior to 1977 (greater than 5 per million in 1973 and 1974, but 1-2 per million after 1977), is the reason for restricting examinations of trends over time for specific leukemia diagnoses to the period from 1977 to 1995 [10].

While a model based on a constantly increasing rate can be applied to the ALL and the leukemia incidence data to estimate an EAPC, visual inspection of the incidence of ALL and total leukemia from 1977 to 1995 suggests that reality is more complicated (Figure I.4a). For example, ALL incidence for the 9 SEER areas and the Los Angeles area combined peaked in 1989, and rates have been 5-10% below this peak value in subsequent years. The situation is further complicated by different time trend patterns for ALL for the 9 SEER areas compared with the Los Angeles area. For the 9 SEER areas, ALL incidence has been more or less stable since 1984. On the other hand, ALL incidence for the Los Angeles area showed more variability, being higher in the late 1970s and early

Figure I.4b: Trends in ALL and non-ALL age-adjusted* incidence rates, age <15 all races, both sexes, SEER, 1977-95

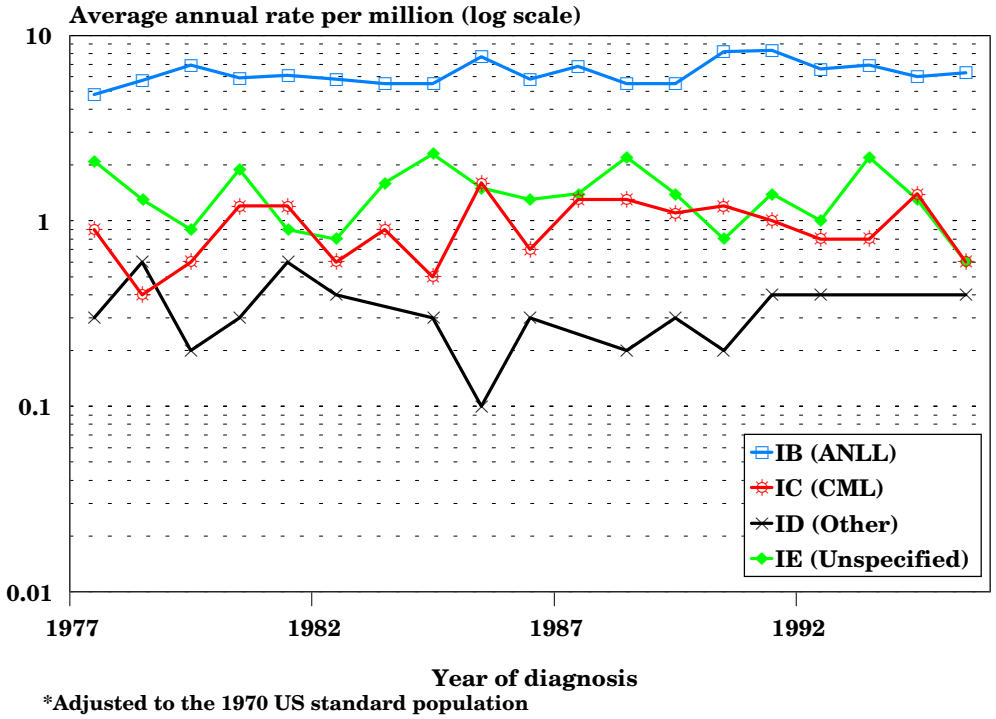


*Adjusted to the 1970 US standard population

1980s, then decreasing to a nadir in 1984-85, and subsequently increasing to rates higher than those for the 9 SEER areas (Figure I.4b). For 1990 to 1995, ALL rates can be calculated for Hispanic and non-Hispanic children. For non-Hispanic children, the ALL rates were similar between Los Angeles (LA) and the 9 SEER areas. However, the ALL rates for Hispanic children were higher than those for non-Hispanic children. Since over one-half of the children younger than 15 residing in Los Angeles were Hispanic, a much higher proportion than for the 9 SEER areas, the overall higher ALL rates in Los Angeles can be explained by the higher proportion of Hispanic children living in LA. In addition, between 1990 and 1995, there were increases in the population of Hispanic children under 15 and decreases in the population of non-Hispanic children under 15 in LA. This change in population characteristics would tend to produce increased rates of ALL due to the higher rates of ALL among Hispanic children. Therefore, the higher ALL rates in LA can be explained by the higher proportion of Hispanic children in LA, and the increase in ALL rates for LA can be at least partially explained by increases in the percentage of Hispanic children in LA. Ongoing monitoring of childhood leukemia trends, as well as epidemiologic and basic laboratory studies, are needed to develop a better understanding of the pathogenesis of childhood leukemia and an enhanced ability to explain changes in leukemia incidence over time.

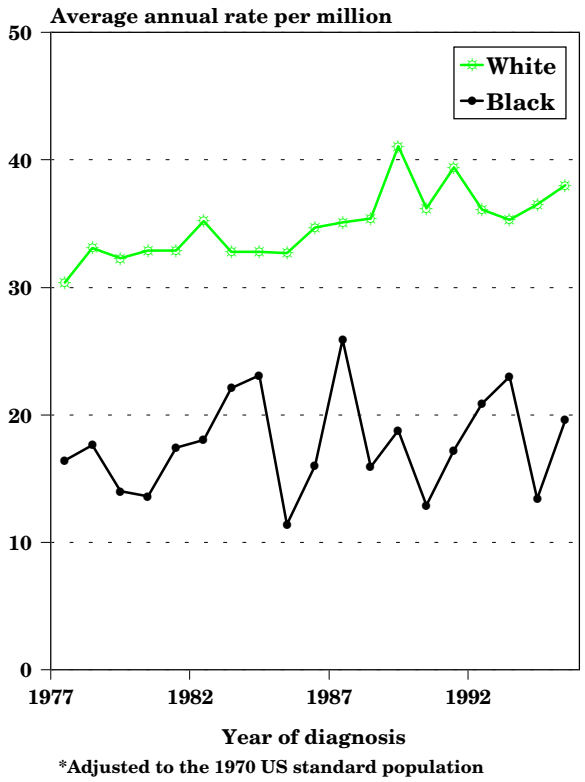
Figure I.6 illustrates the incidence of ALL for white and black children for the period from 1977 to 1995. While the incidence of ALL for white children increased at an overall rate of approximately 1% per year since 1977, there was no apparent increase in ALL rates for black children during this same period.

Figure I.5: Trends in non-ALL leukemia age-adjusted* incidence rates age <15, all races, both sexes, SEER, 1977-95



*Adjusted to the 1970 US standard population

Figure I.6: Trends in ALL age-adjusted* incidencerates by race, age <15 both sexes, SEER, 1977-95



*Adjusted to the 1970 US standard population

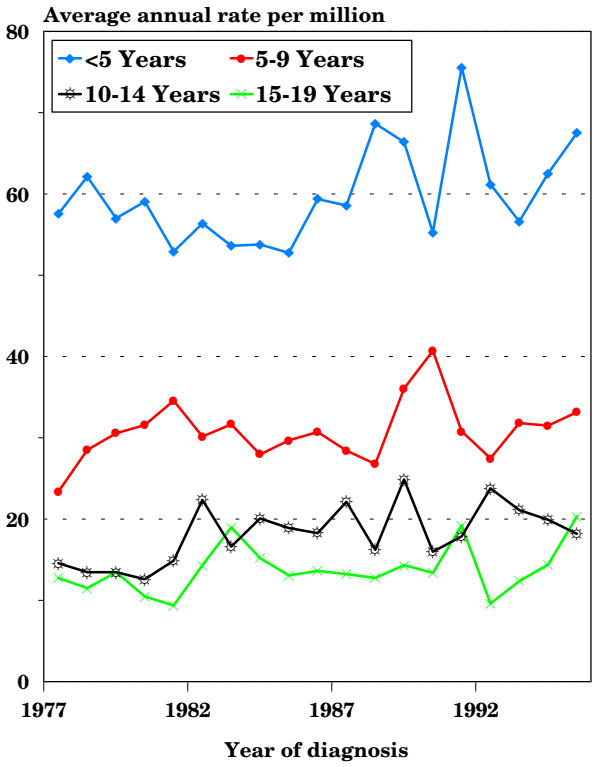
Figure I.7 illustrates the variation in ALL incidence for white children for specific 5-year age groups. Incidence rates for white children 0-4, 5-9, 10-14, and 15-19 years of age demonstrated modest increases when the entire time period was considered. Because the incidence of ALL was greater for those younger than 5 years of age than for the older age groups, the increasing rates for those younger than 5 years of age accounted for the largest proportion of the overall increase in ALL rates for white children.

SURVIVAL

Survival for children with ALL markedly improved from 1975-84 to 1985-94, with 5-year survival rates for children younger than 20 years of age increasing from 61% to 77% (Figure I.8). A number of improvements in treatment during this period have undoubtedly contributed to the improved survival rate, including: a) identification of increasingly effective methods of central nervous system prophylaxis [1]; b) identification of the contribution of treatment intensification to improved outcome for selected groups of patients [27-29]. Examples of effective methods of treatment intensification include use of post-induction consolidation with high-dose methotrexate [28, 29] and use of post-remission re-induction/re-consolidation regimens ("delayed intensification") [27].

Survival for children with ALL is very dependent upon age at diagnosis. For the years 1985-94, 5-year survival rates were highest for the 1-4 year age group and the 5-9 year age group (85% and 80%, respectively) (Figure I.8). Infants had the poorest outcome (37% 5-year survival rate), fol-

Figure I.7: Trends in ALL age-specific incidence rates by year of diagnosis, white children both sexes, SEER, 1977-95

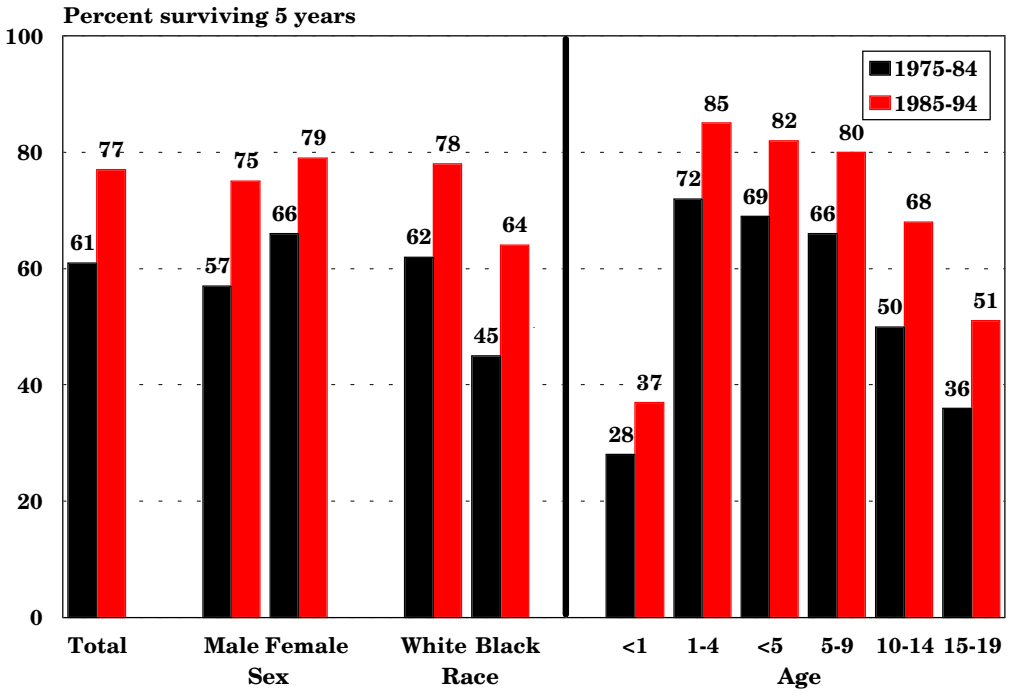


lowed by the 15-19 year age group (51% 5-year survival rate). The favorable prognosis of 1-9 year old children is likely related to the relatively high proportion of cases in this age range with favorable biological subtypes (e.g., cases with hyperdiploid DNA content or with the TEL-AML1 gene rearrangement) [30-32]. The poor prognosis for infants with ALL reflects the high frequency of cases with rearrangements of the MLL gene on chromosome band 11q23 [33,34]. The less favorable outcome for adolescents and young adults is likely due in part to the increased relative frequency of higher risk ALL subtypes (e.g., Philadelphia chromosome positive ALL and T-cell ALL).

For the younger than 20 year old population, 5-year survival rates were slightly higher for females than for males (79% versus 75%) (Figure I.8). Five-year survival rates for black children younger than 20 years of age with ALL were lower than for white children (64% versus 78%). While the poorer outcome for black children with ALL could represent differences between black and white children in the pharmacokinetics or pharmacodynamics of the drugs used for ALL treatment or differences in access to health care, the relative paucity among black children of the most curable ALL subtypes that occur at higher incidence among white children younger than 10 years of age may also contribute to the poorer outcome observed for black children.

Survival for children with AML was substantially lower than that for children with ALL (Figure I.9). While outcome for children with AML improved significantly from 1975-84 to 1985-94, 5-year survival rates were only 41% for the period 1985-94 for the younger than 20 year old age group. In contrast to ALL, older children and adolescents with AML had outcome that was similar to that observed for the

Figure I.8: ALL 5-year relative survival rates by sex, race, age and time period, SEER (9 areas), 1975-84 and 1985-94



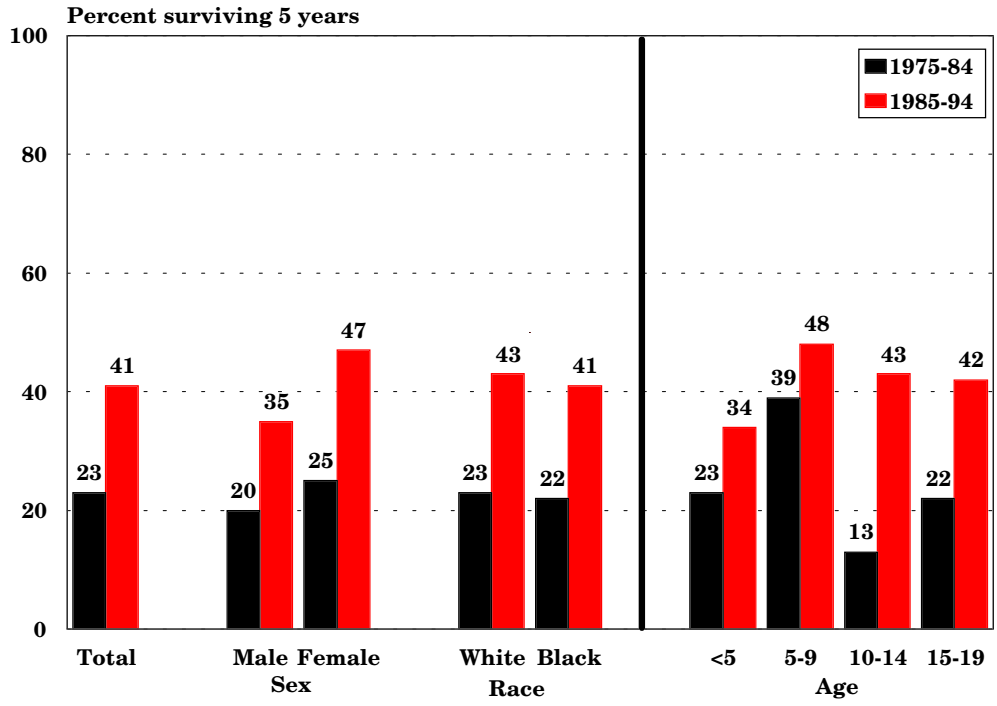
younger than 5-year age group, with the younger than 5-year age group having somewhat lower outcome than for the older age groups. As was the case for ALL, outcome for females with AML was somewhat better than outcome for males. In contrast to the poorer outcome for black children with ALL, for AML outcome was similar for white and for black children younger than 20 years of age.

RISK FACTORS

Tables I.5 and I.6 summarize current knowledge of the causes of childhood ALL and AML. With the exception of prenatal exposure to x-rays and specific genetic syndromes, little is known about the causes of and risk factors for childhood ALL [13]. It is important to note that ALL is a heterogeneous grouping of biological subtypes of leukemia, and smaller studies of the past may have lacked sufficient statistical power to examine potential risk factors. Thus, one emerging theme concerning the etiology of childhood ALL is the need to separately study different biological groups of ALL. For example, the cases of ALL that arise in infants and that have rearrangements of the MLL gene on chromosome 11 appear to have different epidemiological associations than cases that arise in young children that typically have B-precursor ALL immunophenotype and hyperdiploid DNA content [14-16]. Recognition of the need to study these different ALL subtypes independently has been one impetus for larger studies of the etiology of ALL. In these larger studies some intriguing associations have emerged that can be followed up further in more focused investigations. For example, high birth weight and maternal history of fetal loss have been associated primarily with ALL occurring in children younger than 2 years of age [17-19].

From a global perspective, childhood ALL appears to be much more common in

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



countries of the developed world than in those of the developing world, a difference that has been attributed to different patterns of exposure of children in these populations to infectious agents [20,21]. A delayed pattern of infections, as found in countries such as the United States, is hypothesized to somehow cause (or allow) ALL to occasionally develop, possibly through alterations in immune function. However, in the absence of an understanding of specific infectious agents or specific immune perturbations associated with the pathogenesis of ALL, it is not possible to apply these theories to explain the trends in incidence for childhood ALL observed in the United States since the 1970s.

Table I.5: Current knowledge on causes of acute lymphoblastic leukemia (ALL)

Exposure or Characteristic	Comments	References
Known risk factors		
Sex	Overall, there is about a 30% higher incidence in males compared to females.	16,22,36
Age	There is a peak in the incidence between the ages of about 2 and 5.	16,22,36
Race	There is an approximate 2-fold higher risk in white children compared to black children.	16,22,36
Higher socioeconomic status	Increased risk has been fairly consistently associated with the most common ALL (diagnosed at ages 2 - 5 years). It is unknown what aspect of higher SES is relevant but higher age of exposure to infectious agents has been hypothesized.	16,22,36,37
Ionizing radiation (in utero)	In past studies, there was a consistent, increased risk (about 1.5 fold) of leukemia associated with prenatal diagnostic x-ray exposure. However, this is unlikely to be an important risk factor for childhood leukemia today due to fewer x-rays, increased shielding, and lower radiation levels.	16,22,36,38,39
Ionizing radiation postnatal (therapeutic)	Therapeutic radiation for such conditions as tinea capitis and thymus enlargement has been associated with an increased risk.	16,22,36,40
Down syndrome, neurofibromatosis, Shwachman syndrome, Bloom syndrome, ataxia telangiectasia, Langerhans cell histiocytosis, and Klinefelter syndrome	Increased occurrence is associated with these genetic conditions and is particularly apparent in children with Down syndrome for whom there is a reported 20-fold increased risk of leukemia.	16,22,26,36
Factors for which evidence is suggestive but not conclusive		
High birth weight (> 4000 grams)	Several studies have reported an elevated risk (approximately 2-fold) in larger babies, particularly for children diagnosed younger than two years of age.	16,22,36,41
Maternal history of fetal loss prior to the birth of the index child	Approximately 2-5 fold increased risk of leukemia has been noted in a few studies; particularly in children diagnosed younger than two years of age.	16,18,22,36,42
Maternal age > 35 at pregnancy	A slight increased risk has been somewhat inconsistently associated with older maternal age.	16,22,36
First born or only child	Slight increased risk reported but birth order may be surrogate marker for exposure to infectious agent.	16,22,36

Table I.5 (cont'd): Current knowledge on causes of acute lymphoblastic leukemia (ALL)

Factors for which evidence is inconsistent or limited		
Smoking prior to and during pregnancy	Some studies have reported an increased risk associated with maternal smoking during pregnancy but others have not. A few recent studies have suggested a modest increased risk (about 1.5 fold) associated with paternal smoking prior to pregnancy.	16,22,36,43-48
Parental occupations and occupational exposures	Isolated reports associated with parental exposure to motor vehicle exhaust, hydrocarbons, and paints. This is the subject of several current epidemiologic studies.	16,22,36
Postnatal infections	Evidence is very inconsistent.	16,22
Diet	A few reports have suggested that meat consumption (particularly, cured meats) is associated with an increased risk. Maternal diet and childhood leukemia has not been explored in any detail and further study is warranted.	49,50
Electromagnetic fields	A few studies have reported a slight increased risk for children living near high voltage power lines; others have reported no association. A recent large study of U.S. children with ALL found little or no association between risk of ALL and electromagnetic field exposure. Other large epidemiologic studies evaluating this exposure are ongoing.	16,22,51-54
Vitamin K prophylaxis in newborns	Although an increased risk of ALL was first reported in the early 1990's, several large studies since then have found no association.	16,22,55-60
Maternal alcohol consumption during pregnancy	Unlikely to be an important risk factor for ALL (but see AML).	16,22
Postnatal use of chloramphenicol	One study reported quite substantial increased risks (approximately 10-fold) with postnatal use of this broad-spectrum antibiotic.	61
Factors unrelated to risk		
Ultrasound		16,22

*Note that the majority of these risk factors have been reviewed recently in references 16,22,36; only selected references are presented for additional reading.

Different risk factors are emerging for childhood AML that distinguish the disease from ALL, and this may provide avenues for future epidemiological studies. For example, exposure to specific chemotherapy agents has been associated with an increased risk of childhood AML, in contrast to the rarity of treatment-related ALL [22-24]. With this information, it may be possible to design epidemiological studies to examine exposures to environmental agents that have a biologic nature that is similar to these chemotherapy agents [14]. Further, associations with factors such as benzene and pesticides that have emerged in a few studies suggest that childhood AML may share risk factors with adult AML, and this is being investigated in several large epidemiological studies [25]. Finally, as for ALL, the associations of AML with genetic syndromes are compelling, as illustrated by the magnitude of risk of AML in Down syndrome [26].

SUMMARY

ALL is by far the most common type of leukemia occurring in children and shows a distinctive age-distribution pattern, with a marked incidence peak at 2-3 years of age.

Table I.6: Current knowledge on causes of acute myeloid leukemia (AML)

Exposure or Characteristic	Comments	References
Known risk factors		
Race	The highest incidence rates are reported in the Hispanic children.	16,22,36
Chemotherapeutic agents	Increased risk is associated with prior exposure to alkylating agents or epipodophyllotoxins.	16,22,36,62,63
Ionizing radiation (*in utero*)	In past studies, there was a consistent, increased risk (about 1.5 fold) of leukemia associated with prenatal diagnostic x-ray exposure. However, this is unlikely to be an important risk factor for childhood leukemia today due to fewer x-rays, increased shielding, and lower radiation levels.	16,22,36
Down syndrome, neurofibromatosis, Shwachman syndrome, Bloom syndrome, familial monosomy 7, Kostmann granulocytopenia, Fanconi anemia	Increased occurrence associated with these genetic conditions, particularly with Down syndrome. One report suggests as high as a 500-fold increased risk of a specific type of AML in Down syndrome.	16,22,26,36
Factors for which evidence is suggestive but not conclusive		
Maternal alcohol consumption during pregnancy	Three studies have reported an increased risk (approximately 1.5-2 fold) in mothers who drank alcoholic beverages during pregnancy. These associations have been particularly apparent in children diagnosed younger than three years of age.	16,22,36,64
Parental and child exposure to pesticides	Increased risk has been noted in a few studies and in adult AML data; subject of several current investigations.	16,22,25,36,45
Parental exposure to benzene	Exposure has been associated with an increased risk in several studies; again follows adult AML data; also subject of several current investigations.	16,22,36,45
Factors for which evidence is inconsistent or limited		
Maternal use of recreational drugs during pregnancy	One report suggested that maternal marijuana use during pregnancy was associated with increased risk.	65
Radon	A few correlational studies have suggested an increased risk of childhood and adult AML in areas with high radon concentrations; this is a subject of several current epidemiologic studies of AML.	16,22,36
Postnatal use of chloramphenicol	As in ALL, one study found quite substantial increased risks of AML (approximately 10-fold) with postnatal use of this broad-spectrum antibiotic.	61

*Note that the majority of these risk factors have been reviewed recently in references [16,22,36]; only elected references are presented for additional reading.

The peak at 2-3 years of age is much less apparent for black children than for white children, with this difference accounting for the substantially lower incidence of ALL observed for black children. By contrast with ALL, the age-distribution pattern for AML shows highest rates in the first two years of life, with decreasing incidence until 10 years of age followed by increasing rates thereafter. Again in contrast to ALL, the incidence of AML in black children and white children is similar.

The improvement in survival for children with ALL over the past 35 years is one of the great success stories of clinical oncology. Survival rates for childhood ALL were below 5% in the early 1960s, but are now approaching 80% [35]. Outcome for children with AML has also improved, but 5-year survival rates have increased to only the 40% range. Black children with ALL have poorer outcome than do white children, but for AML there is similar outcome for black children and white children. Since the peak in ALL incidence at 2-3 years of age is much lower for black children than for white children and since these ALL cases in young children are known to have the most favorable prognosis, the poorer outcome for black children may reflect in part a different distribution of biological subtypes of ALL in black children compared to white children.

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HIGHLIGHTS

Incidence

- Approximately 15% of childhood malignancies were lymphomas making them the third most frequent type of cancer in children following leukemia and malignant brain tumors. The percentage of childhood cancer that were lymphoma varied by age from only 3% for children younger than 5 years of age to 24% for 15-19 year olds (Figure II.1).
- The two predominant types of lymphomas were Hodgkin's disease and the non-Hodgkin's lymphomas (NHL). For younger children NHL was more frequent than Hodgkin's disease, while the reverse was true for adolescents (Figure II.3).
- In the US, approximately 1,700 children and adolescents younger than 20 years of age are diagnosed with lymphomas each year of which approximately 850-900 are cases of Hodgkin's disease and 750-800 are cases of NHL.
- The most common subtypes of Hodgkin's disease were nodular sclerosis (70% of cases); mixed cellularity (16% of cases); lymphocytic predominance (7% of cases); cases not otherwise specified (NOS) (6% of cases); and lymphocytic depletion subtype (<2% of cases) among children younger than 20 years of age. The relative frequencies of the mixed cellularity and nodular sclerosis subtypes were age and sex dependent (Figure II.2 and Table II.2).
- The incidence of Hodgkin's disease for children and adolescents younger than 20 years of age decreased slightly between 1975 and 1995, from 14.5 per million (1975-79) to 12.1 per million (1990-95) (Table II.3).
- The non-Hodgkin's lymphomas of children are a heterogeneous group of tumors, with Burkitt's and Burkitt-like tumors predominating among 5-14 year olds, and with diffuse large cell lymphomas being the most common subtype among 15-19 year olds (Figure II.9).
- The incidence of NHL varied much less by age than Hodgkin's disease (Figure II.3). NHL incidence increased up until age 4 years where it reached a plateau of approximately 10 per million (Figure II.4), which was maintained until the second decade of life when rates increased again.
- The incidence of NHL was higher in males than females (Figure II.10) and higher among whites than blacks (Figure II.12).
- The incidence of NHL among children younger than 15 years of age was fairly constant over the past 21 years, while there appeared to have been a slight increase in incidence for the 15-19 year old population (Table II.3 and Figure II.13).

Survival

- The 5-year survival rate was 91% for Hodgkin's disease (Figure II.8) for children and adolescents younger than 20 years of age, compared to 72% for NHL (Figure II.14).
- The 5-year survival rate for those younger than 20 years of age with NHL increased from 56% in 1975-84 to 72% in 1985-94 (Figure II.14).

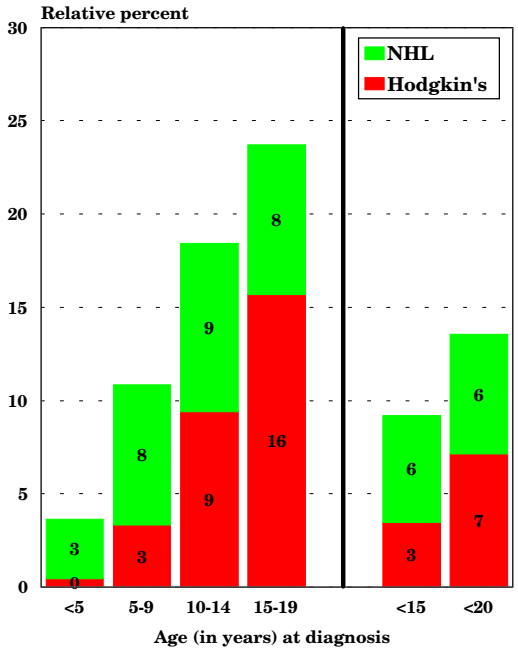
Risk factors

- For Hodgkin's disease arising in young adults, genetic susceptibility may be a factor for some cases, based on the greatly increased risk for Hodgkin's disease in young adult monozygotic twins of patients with Hodgkin's disease compared to the risk of dizygotic twins of patients with Hodgkin's disease (Table II.4).
- Congenital immunodeficiency syndromes and acquired immunodeficiency syndrome (AIDS) are associated with an increased risk of NHL (Table II.6).

INTRODUCTION

The lymphomas, combining Hodgkin's disease and the non-Hodgkin's lymphomas (NHL), are the third most frequent type of cancer in children following leukemia and malignant brain tumors. NHL and Hodgkin's disease are both malignancies of lymphoid cells, and each includes distinctive biological subtypes. In the US, approximately 1,700 children and adolescents younger than 20 years of age are diagnosed with lymphomas each year, of which 850-900 are Hodgkin's disease and 750-800 are non-Hodgkin's lymphoma. The lymphomas account for 10% of malignancies among children younger than 15 years of age and 15% of malignancies among those younger than 20 years of age. Figure II.1 illustrates that the contribution of Hodgkin's disease and the non-Hodgkin's lymphomas to the overall childhood cancer burden is markedly age dependent, increasing from only 3% of cancers among children younger than 5 years of age to 24% of cancers arising among those 15-19 years of age.

Figure II.1: Hodgkin's disease and NHL as a percent of total childhood cancer, by age, all races, both sexes SEER, 1990-95



MATERIAL AND METHODS

The International Classification for Childhood Cancers (ICCC) Group II of Lymphomas and Reticuloendothelial Neoplasms is divided into 5 subgroups [1]:

a. Hodgkin's disease;
b. Non-Hodgkin's lymphoma;
c. Burkitt's lymphoma;
d. Miscellaneous lymphoreticular neoplasms; and
e. Unspecified lymphomas.

Table II.1: Number of cases of lymphoma by type and sex, age <20, all races, SEER, 1975-95

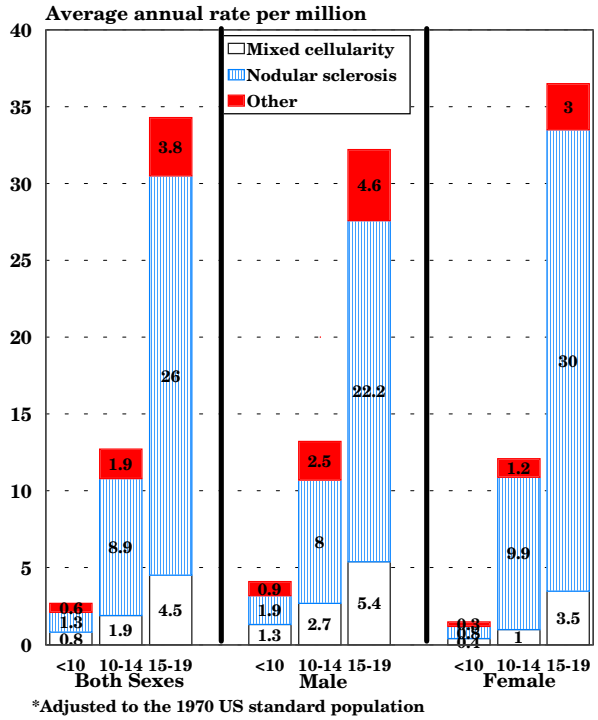
	Total	Males (%)	Females (%)
Total	4595	2734 (59%)	1861 (41%)
Hodgkin's (IIa)	2613	1353 (52%)	1260 (48%)
NHL (IIb,c,e)	1903	1334 (70%)	569 (30%)
Miscellaneous (IId)	79	47 (59%)	32 (41%)

Since only 3% of the registered childhood lymphomas and reticuloendothelial neoplasms in the Surveillance, Epidemiology and End Results (SEER) program for the period 1975-95 were not histologically confirmed, all cases were included in the analyses. Table II.1 shows the frequency distribution of these cases by sex among children younger than 20 years of age diagnosed with lymphoma. For the purposes of this chapter, Hodgkin's disease (defined by subgroup IIa) and NHL (defined by subgroups IIb, IIc, and IIe) are considered separately because of their distinctive nature. The miscellaneous lymphoreticular neoplasms (IId) are excluded from further analysis as there were few cases (only 79 cases) in this subgroup from 1975-95.

HODGKIN'S DISEASE

Hodgkin's disease is an unusual malignancy of lymphoid cells whose distinctive hallmark is the Reed-Sternberg cell. In most cases Reed-Sternberg cells appear to be clonal in nature and from the B lymphocyte lineage, as evidenced by immunoglobulin gene rearrangements in these cells [2-5]. Reed-Sternberg cells account for only a small percentage of the tumor mass [6], with most of the tumor composed of a reactive infiltrate of lymphocytes, plasma cells, and eosinophils. The Reed-Sternberg cells of some patients with Hodgkin's disease contain copies of the Epstein-Barr virus (EBV) genome [7,8]. Detection of EBV in Reed-Sternberg cells is more common among cases diagnosed in young children and for cases of the mixed cellularity subtype [7,8] (see Histologic subtype and Risk Factors sections below).

Figure II.2: Hodgkin's disease age-adjusted* incidence rates by Rye classification, sex and age all races, SEER (10 areas), 1977-95



*Adjusted to the 1970 US standard population

Table II.2: Percent distribution of Hodgkin's by subtype, age and sex all races, SEER, 1975-95

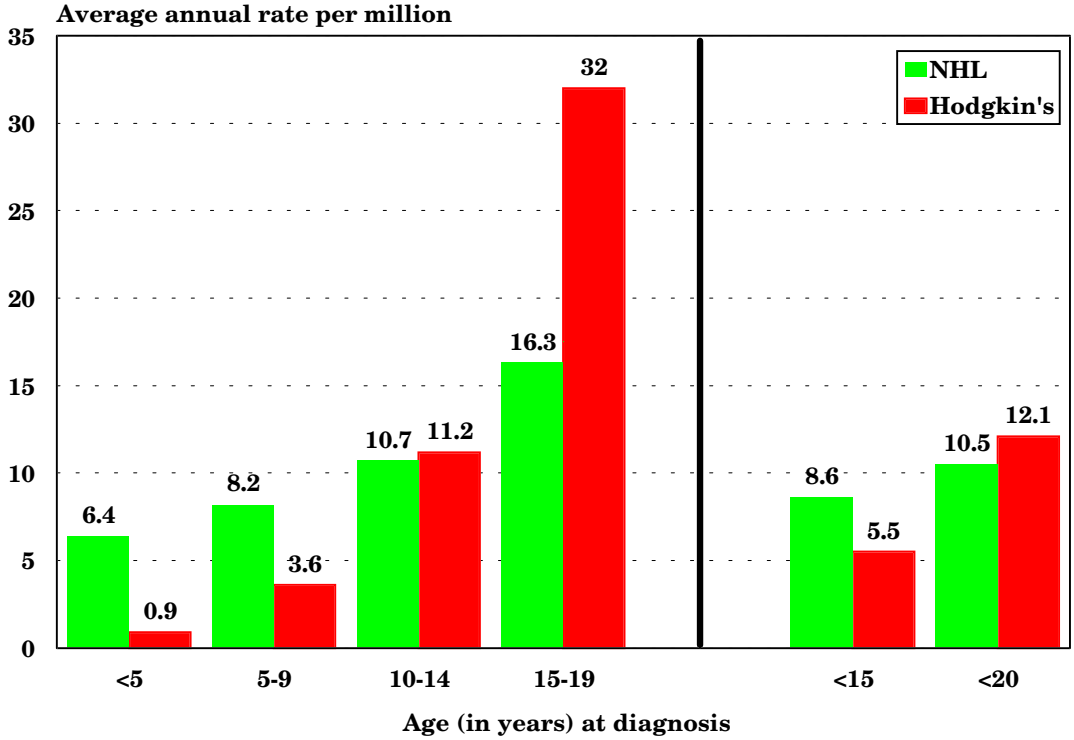
Age (in years) at diagnosis	<10			10-14			15-19		
	Both	M	F	Both	M	F	Both	M	F
Mixed Cellularity	32%	34%	25%	15%	21%	9%	13%	17%	10%
Nodular Sclerosis	46%	44%	51%	69%	59%	79%	74%	67%	81%
Lymphocytic Predominance	14%	15%	12%	7%	10%	3%	5%	7%	2%

Histologic subtype

Childhood Hodgkin's disease, similar to that arising in adults, is usually classified according to the Rye classification scheme, which includes four histologic subtypes: lymphocytic predominance, mixed cellularity, lymphocytic depletion, and nodular sclerosis [9]. The lymphocytic predominance subtype is now recognized as having a distinctive biological and clinical behavior from the other subtypes of Hodgkin's disease and is relatively uncommon among children [10,11]. Among children younger than 20 years of age diagnosed with Hodgkin's disease during 1975-95, the nodular sclerosis subtype was by far the most common and accounted for 70% of all cases. Mixed cellularity was the second most common subtype (16% of cases), followed by lymphocytic predominance (7% of cases), and cases not otherwise specified (NOS), (6% of cases). The lymphocytic depletion subtype was distinctly uncommon (<2% of cases) among Hodgkin's disease cases diagnosed in those younger than 20 years of age.

The relative frequencies of the mixed cellularity and nodular sclerosis subtypes were age and sex dependent. Mixed cellularity subtype was more common among children younger than 10 years of age (32% of all Hodgkin's cases) than among those diagnosed at 10-14 or 15-19 years of age (15% and 13% of Hodgkin's cases, respectively) (Table II.2 and Figure II.2). Mixed cellularity was also more common among males than females in each age group.

Figure II.3: Hodgkin's disease and NHL age-specific and age-adjusted* incidence rates by age, all races, both sexes SEER, 1990-95



*Adjusted to the 1970 US standard population

Nodular sclerosis subtype accounted for the vast majority (81%) of Hodgkin's disease among 15-19 year old females, and a somewhat lower percentage (approximately 67%) of Hodgkin's disease among 15-19 year old males (Table II.2).

Age-specific incidence

The overall annual incidence rate for Hodgkin's disease among children younger than 20 years of age was 12.1 per million for the years 1990-95. For Hodgkin's disease, the contribution to overall childhood cancer incidence was less than 1% among children younger than 5 years of age, but increased to 16% for 15-19 year olds (Figure II.1). The incidence of Hodgkin's disease was markedly age dependent (Figures II.3 and II.4), with incidence increasing from less than one per million for children in the first 3 years of life, to

Figure II.4: Hodgkin's disease and NHL age-specific incidence rates, all races, both sexes SEER, 1976-84 and 1986-94

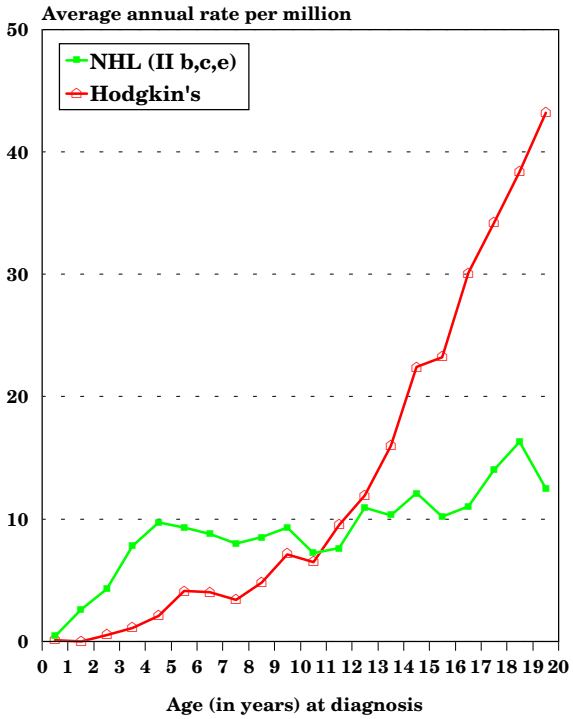
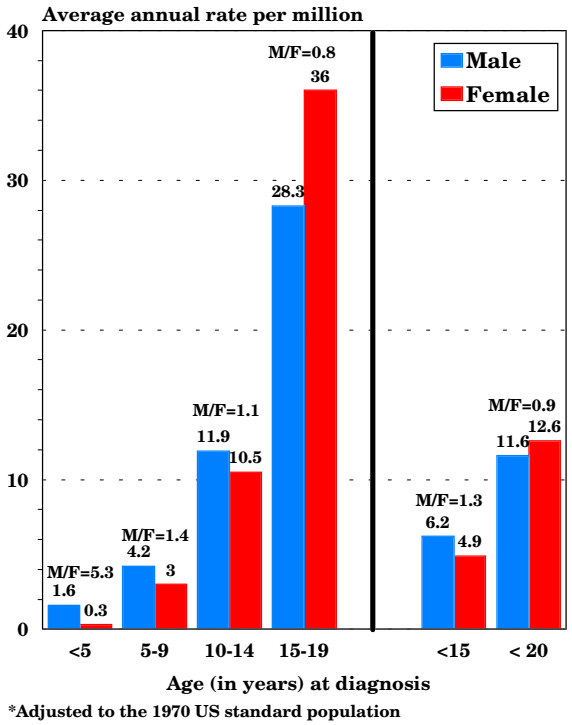


Figure II.5: Hodgkin's disease age-specific and age-adjusted* incidence rates by age and sex with male to female ratios (M/F) all races, SEER, 1990-95



*Adjusted to the 1970 US standard population

43.2 per million for 19 year olds (Figure II.4).[1] While the overall incidence of Hodgkin's disease for children younger than 20 years of age was similar to that for NHL (12.1 versus 10.5 per million, respectively) (Figure II.3), the incidence of Hodgkin's disease was 2-3 fold higher than NHL among 15-19 year olds, while the incidence of NHL was higher among those younger than 10 years of age (Figure II.4).

Sex-specific incidence

The incidence of Hodgkin's disease was slightly higher among females than males for children younger than 20 years of age during 1990-95 (M/F = 0.9) (Figure II.5).

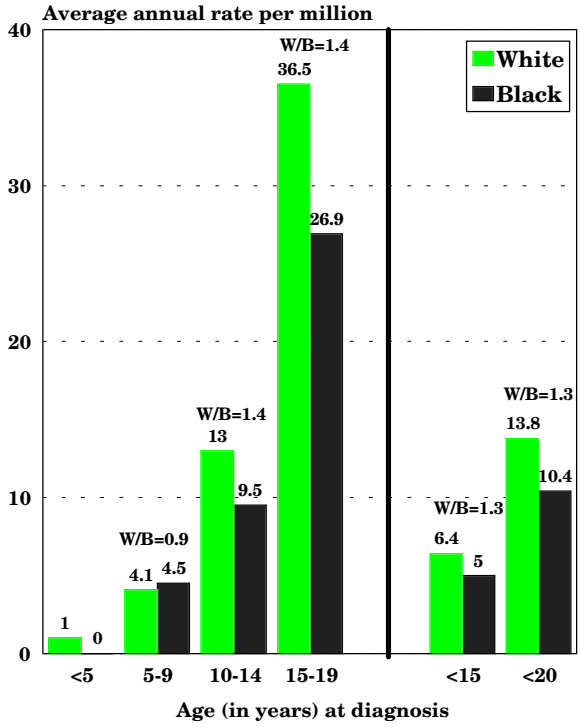
[1] Enumeration of the population at risk by single years of age was available only for the census years 1980 and 1990. The US Bureau of the Census provides intercensal population estimates by 5-year age groups, but not by single years of age. Therefore, the population estimates for 1980 were used in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

However, the differential by sex was age dependent. Among children younger than 15 years of age, Hodgkin's disease was more common among males (M/F = 1.3), with the differential greatest for children younger than 5 years of age (M/F = 5.3). However, for children diagnosed with Hodgkin's disease at ages 15-19 years, Hodgkin's disease incidence was higher among females (M/F = 0.8).

Black-white differences in incidence

When considering children younger than 20 years of age, black children had a lower incidence of Hodgkin's disease than white children (Figure II.6). However, the incidence was very similar for black and white children younger than 10 years of age. For those over 10 years of age, the ratio of white to black incidence was approximately 1.4:1.

Figure II.6: Hodgkin's disease age-specific and age-adjusted* incidence rates by age with white to black ratios (W/B) both sexes, SEER, 1990-95



*Adjusted to the 1970 US standard population

TRENDS

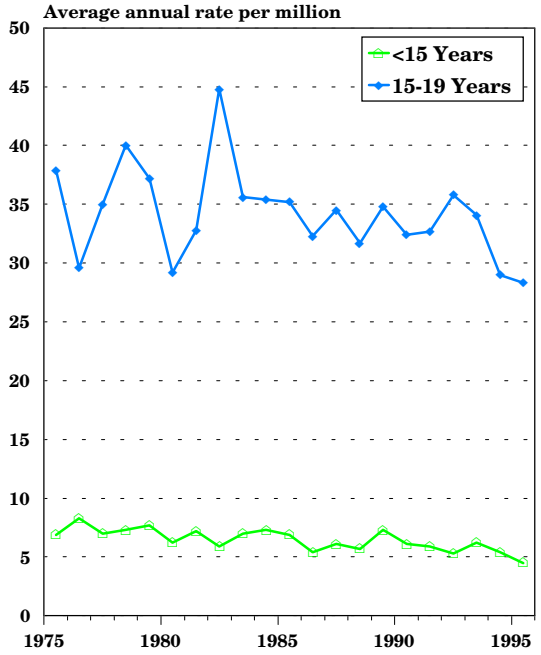
The age-adjusted incidence rate for Hodgkin's disease for children younger than 20 years of age decreased from 14.5 per million in 1975-79 to 12.1 per million in 1990-95 (Table II.3). The incidence for children younger than 15 years of age declined during this period from approximately 7.4 per million to 5.5 per million. The incidence for 15-19 year olds declined from 35.9 per million (1975-79) to 32.0 per million (1990-95) (Figure II.7). The decline in Hodgkin's incidence rates for the younger than 15 year age group occurred for both males and females [estimated annual percentage change (EAPC) of -2.0% and -1.4%, respectively]. The decline in incidence for 15-19 year olds appeared to be greater for males (EAPC = -1.4%) than for females (EAPC = -0.1%). A similar pattern of declining rates for males and stable rates for females was observed in regions of the United Kingdom for the years 1984-93 [12]. Another report described little change or slight decline in the occurrence of Hodgkin's disease among 20 populations from around the world for the period from the early 1970s to the 1980s [13]. In contrast to these reports, increasing incidence rates for the 15-24 year olds were reported for males and females in four geographical areas of the US for the period from 1947-50 to 1984-88 [13].

Table II.3: Hodgkin's and NHL age-adjusted* incidence rates all races, both sexes, SEER, 1975-79 through 1990-95

	1975-79	1980-84	1985-89	1990-95
Hodgkin's <15 years	7.4	6.7	6.3	5.5
Males	8.4	8.0	7.5	6.2
Females	6.4	5.3	5.1	4.9
Hodgkin's <20 years	14.5	13.8	13.1	12.1
Males	14.8	14.8	13.4	11.6
Females	14.2	12.8	12.8	12.6
NHL <15 years	8.5	8.1	8.6	8.5
Males	11.7	12.6	11.7	12.7
Females	5.2	3.4	5.3	4.2
NHL <20 years	9.1	9.7	10.0	10.5
Males	12.1	14.0	13.4	14.6
Females	5.9	5.2	6.5	6.1

*Adjusted to the 1970 US standard population

Figure II.7: Trends in Hodgkin's disease age-adjusted* incidence rates by age, all races, both sexes, SEER, 1975-95



*Adjusted to the 1970 US standard population

SURVIVAL

For cases diagnosed from 1985-94, the 5-year survival rate for Hodgkin's disease was 91% for children younger than 20 years of age (Figure II.8). White children had a slight survival advantage over black children (92% versus 84% 5-year survival), and males and females had similar outcome (90% versus 92% 5-year survival). Outcomes were also similar for children diagnosed younger than 15 years of age compared to 15-19 year olds (92% versus 90% 5-year survival).

RISK FACTORS (TABLE II.4)

Available epidemiological and molecular biological data suggest that Hodgkin's disease among children and adolescents represents at least two distinctive conditions [14-16]. In one condition, EBV genomic sequences are typically present in the Reed-Sternberg cells. This form of Hodgkin's disease is more common for

Figure II.8: Hodgkin's disease 5 year-relative survival rates by sex, race, age and time period SEER (9 areas), 1975-84 and 1985-94

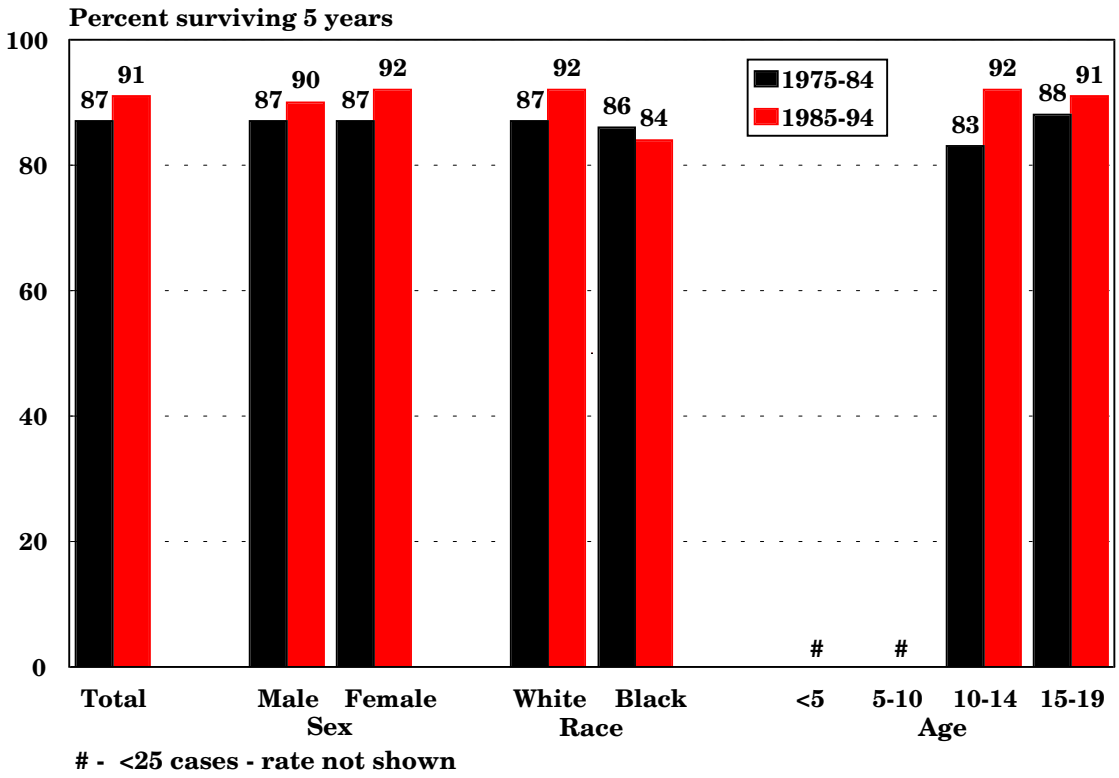


Table II.4: Current knowledge on causes of Hodgkin's disease in children

Exposure or Characteristic	Comments	References
Known to increase risk		
Family history of Hodgkin's disease	Monozygotic twins of young adult patients have a 99-fold increased risk. Other siblings have a 7-fold increased risk.	22,33,34
Epstein-Barr virus infection	EBV-associated HD is associated with mixed cellularity vs. nodular sclerosis histologic subtypes, children from economically less-developed vs. more-developed regions and young adult males vs. females. Additionally, history of infectious mononucleosis and high titer antibodies to EBV are associated with HD among young adults, although paradoxically HD cases among the young adult population typically do not have detectable EBV genomic sequences in tumor tissue.	7,8,16-18,20,21,35-37
Socioeconomic status	For young adult disease (ages 16-44), risk increases with socioeconomic status and with related characteristics such as small family size and single family housing. In children younger than 10 years of age, risk appears higher for lower socioeconomic status.	15,38-40
Social contacts	For young adult disease, having fewer siblings and childhood playmates is associated with higher risk. These findings suggest that infections in early childhood may reduce risk of young adult disease.	19,33
Factors for which evidence is inconsistent or limited		
Clustering	Young adult cases (age 16-45 years) tend to cluster more than older cases (age 46-70).	41

childhood cases occurring in developing countries compared to cases occurring in countries with higher socioeconomic status [7,8]. EBV involvement is also associated with male sex, mixed cellularity subtype, and young age at diagnosis [7,8,16-18]. However, the associated environmental and/or genetic factors that cause EBV infection, which is common among young children (particularly in developing countries), to result in Hodgkin's disease in a very small percentage of children are not understood. A second form of Hodgkin's disease is primarily of the nodular sclerosis subtype, arising in older adolescents and young adults living in more affluent societies [15,16]. In spite of observations suggesting a relationship between Hodgkin's disease among older adolescents/young adults and infectious mononucleosis and high titers of antibodies against EBV [19-21], cases of Hodgkin's disease in this population typically do not have EBV genomic sequences detectable in tumor tissue [7,8].

For Hodgkin's disease arising in young adults, genetic susceptibility may be a factor for some cases, based on the greatly increased relative risk for Hodgkin's disease occurring in both members of monozygotic twin pairs compared to the risk of occurrence in dizygotic twin pairs [22]. Further support for genetic predisposition to Hodgkin's disease is the consistently low incidence of Hodgkin's disease (especially of the nodular sclerosis subtype) among populations of East Asian ethnic origin and the high incidence (especially of mixed cellularity subtype) among some populations of South Asian origin, with these differences appearing to be independent of socioeconomic status [15].

NON-HODGKIN'S LYMPHOMA

The non-Hodgkin's lymphomas that develop in children are distinct from the more common forms of lymphomas in adults. While the lymphomas in adults are more commonly of low or intermediate grade, almost all of those that occur in children can be classified into one of four high-grade categories: 1) the Burkitt's and Burkitt-like lymphomas (small noncleaved cell lymphomas); 2) lymphoblastic lymphomas; 3) diffuse large B-cell lymphomas; and 4) anaplastic large cell lymphomas. Each of these types of childhood NHL is associated with distinctive molecular biological characteristics, with translocations resulting in activation of the C-MYC gene occurring in the Burkitt's and Burkitt-like lymphomas, translocations involving the TAL1 gene and the T-cell receptor genes typifying the lymphoblastic lymphomas, and translocations involving the NPM gene at chromosome band 5q35 in the anaplastic large cell lymphomas. These NHL categories are also associated with characteristic clinical presentations, with the Burkitt's and Burkitt-like lymphomas commonly present in the abdomen among US children (but in the jaws of young children in Africa), and with lymphoblastic lymphomas commonly present as large mediastinal masses. The lymphoblastic lymphomas of children are indistinguishable histologically from T-cell acute lymphoblastic leukemia (ALL). The clinical and biological characteristics of each of these categories of childhood NHL are summarized in Table II.5.

Histologic subtype

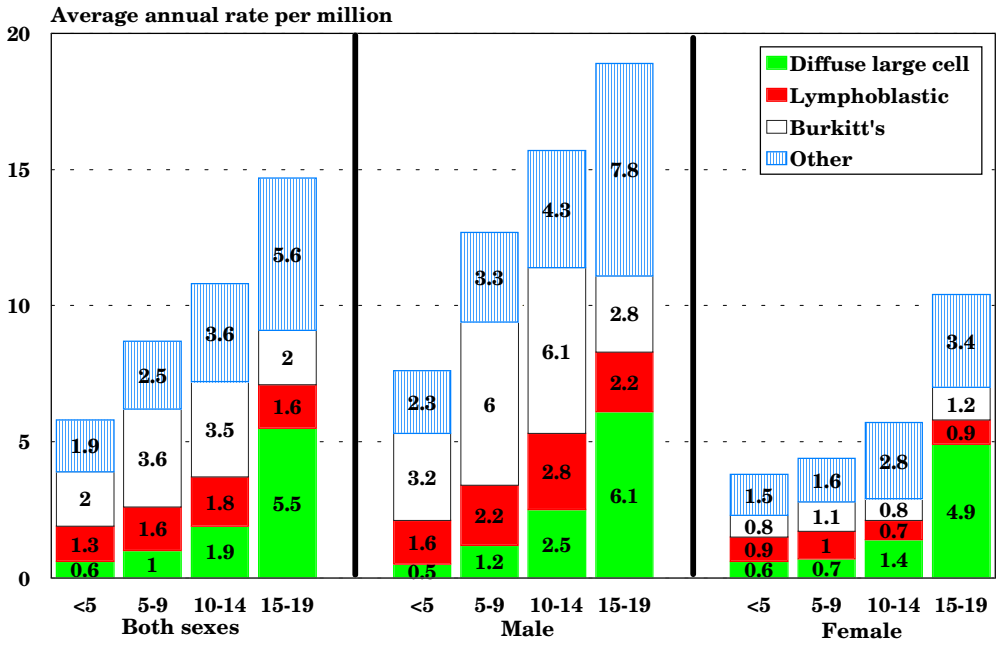
Figure II.9 illustrates the distinctive distributions by age and by sex of the NHL subtypes that predominate in US children in the geographic areas covered by the SEER Program. For Burkitt's and Burkitt's-like lymphoma, the incidence was much higher for males than for females. Five to fourteen year olds had higher rates than children younger than 5 years of age and adolescents 15-19 years of age. For children younger than 20 years of age, the incidence for the Burkitt's lymphomas was nearly 5.0-fold higher for males (3.2 per million) than for females (0.7 per million).

Table II.5: Major histopathological categories of non-Hodgkin's lymphoma in children*

Category (REAL)	Category (Working Formulation)	Clinical Presentation	Chromosomal Translocation	Genes Affected
Burkitt's and Burkitt-like lymphomas	ML small noncleaved cell	Intraabdominal (sporadic), jaw (endemic)	t(8;14)(q24;q32) t(2;8)(p11;q24) t(8;22)(q24;q11)	C-MYC, IgH IgK,Igλ
Lymphoblastic lymphoma, precursor T	Lymphoblastic convoluted and nonconvoluted	Mediastinal	MTS1/p16ink4a Deletion TAL1 t(1;14)(p34;q11) t(11;14)(p13;q11)	TAL1, TCRαδ, RHOMB1, HOX11
Anaplastic large cell lymphoma	ML immunoblastic or ML large cell	Variable	t(2;5)(p23;q35)	ALK, NMP
Diffuse large cell lymphoma	ML large cell	Variable	t(8;14)(q24;q32) in adults, but not well characterized in children	BCL2, IgH (in adults)

* Adapted from Shad and Magrath [31], and from Goldsby and Carroll [6].

Figure II.9: NHL age-specific incidence rates by histologic group sex, and age, all races, SEER (9 areas), 1977-95



In contrast to the Burkitt's lymphomas, the incidence of diffuse large cell lymphoma rose steadily with increasing age, with males showing somewhat higher incidence than females for the population younger than 20 year age group (M/F = 1.4). Lymphoblastic lymphoma occurred at similar frequency across all 5-year age groups, and like the other lymphoma subtypes for children younger than 20 years of age was more common in males than females (M/F = 2.5).

Age-specific incidence

The contribution of the non-Hodgkin's lymphomas to the overall cancer incidence increased from 3% for children younger than 5 years of age to 8-9% for 10-14 and 15-19 year olds (Figure II.1). Figure II.3 illustrates that the incidence of NHL varied much less by age than did Hodgkin's disease. The incidence of NHL rapidly increased in the first three years of life, before reaching a plateau rate of approximately 10 per million at around 4 years of age (Figure II.4). A similar age-incidence

Figure II.10: NHL age-specific incidence rates by sex, all races, SEER 1976-84 and 1986-94 combined

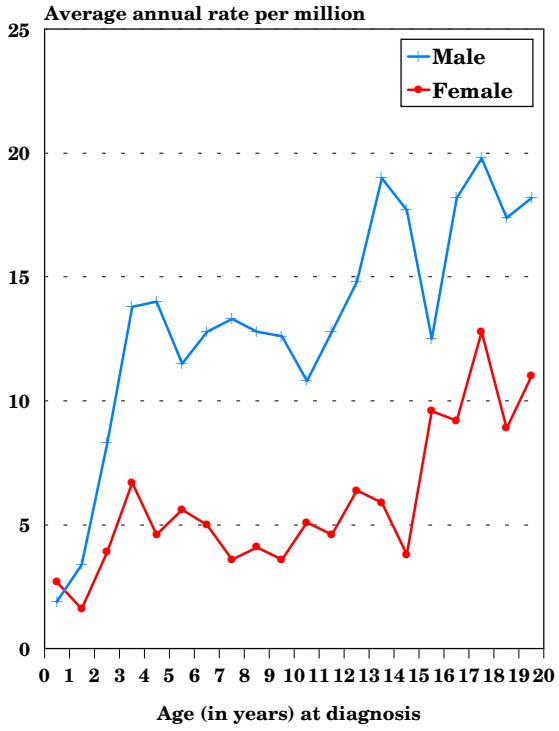
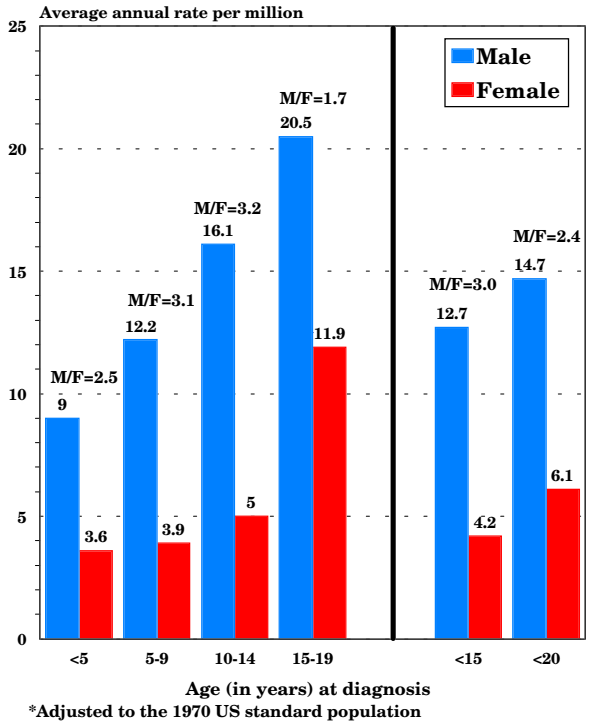


Figure II.11: NHL age-specific and age-adjusted* incidence rates by age and sex with male to female ratios (M/F), all races, SEER, 1990-95

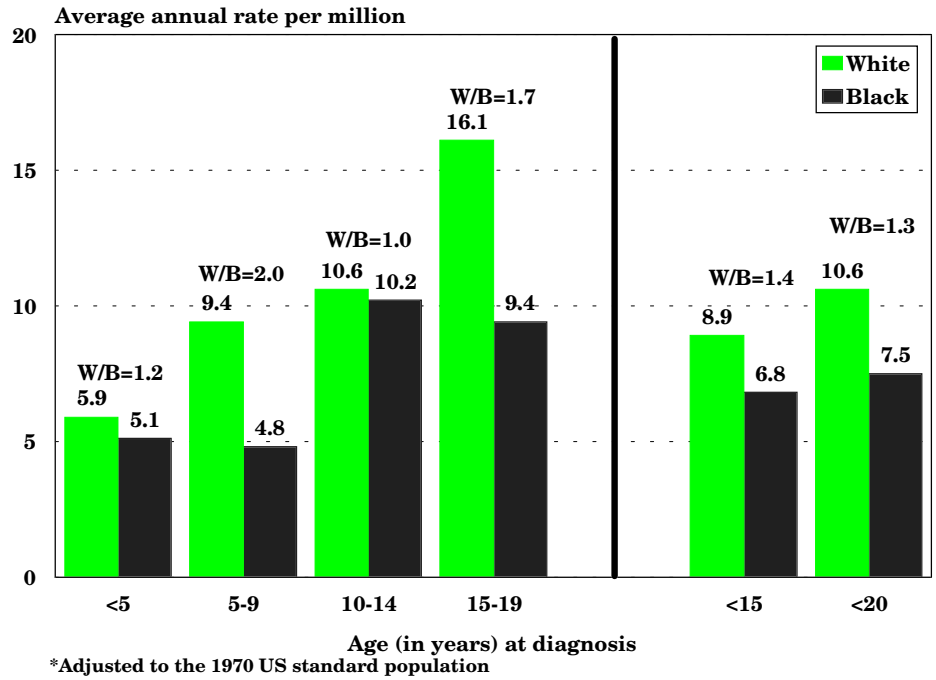


pattern was observed for males and females (Figure II.10), but the incidence rate among children older than 4 years of age was much higher for males than for females. While incidence rates for NHL remained fairly stable through the remainder of the first decade, the incidence began increasing after age 10 (Figures II.4 and II.10). Part of this increase in incidence among adolescents was due to higher rates for diffuse large cell lymphomas compared to rates for this subtype in younger children (Figure II.9).

Sex-specific incidence

There was a notable male predominance for NHL in children, with 70% of the cases occurring in males (Table II.1). The male predominance was seen for all age groups (Figures II.10 and II.11), although it was more pronounced for children younger than 15 years of age (M/F = 3.0)

Figure II.12: NHL age-specific and age-adjusted* incidence rates by age and race with white to black ratios (W/B) both sexes, SEER, 1990-95



compared to 15-19 year olds (M/F = 1.7). As noted in the preceding paragraph, the age-incidence pattern is similar for males and females, although incidence is higher at all age groups for males than females (Figure II.10).

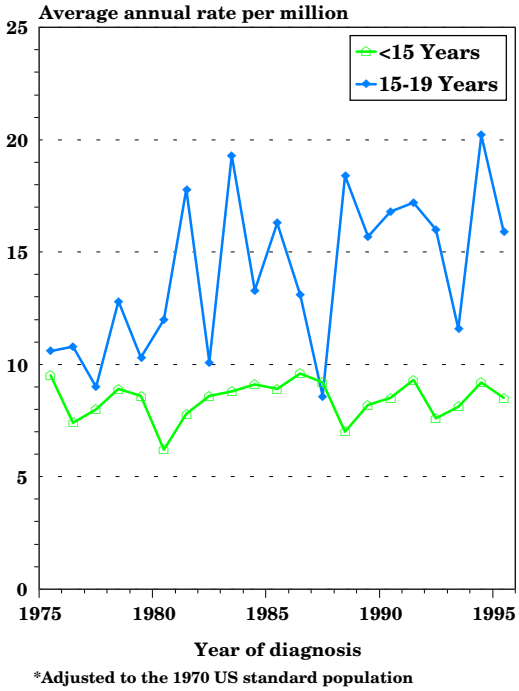
Black-white difference in incidence

The incidence of NHL among white children was 1.4-fold and 1.3-fold higher than that for black children for the younger than 15 years of age group and younger than 20 years of age group, respectively (Figure II.12). The difference in incidence between white and black children appeared greatest for children 5-9 years of age and 15-19 years of age (Figure II.12).

Trends in incidence rates

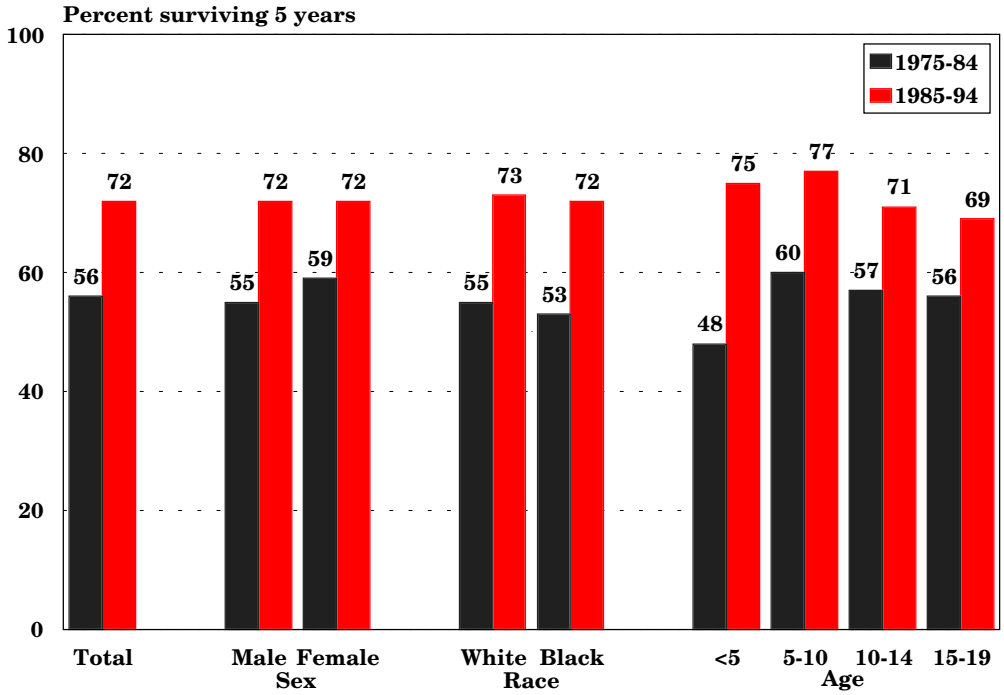
The incidence of NHL remained stable for children younger than 15 years of age from 1975 through 1995 (Table II.3). How-

Figure II.13: Trends in NHL age-adjusted* incidence rates, all races both sexes, SEER, 1975-95



*Adjusted to the 1970 US standard population

Figure II.14: NHL 5-year relative survival rates by sex, race, age and time period, SEER (9 areas), 1975-84 and 1985-94



ever, the incidence among 15-19 year olds increased from 10.7 per million (1975-79) to 16.3 per million (1990-95) (Figure II.13). This increase among the older adolescents/ young adults is similar to that reported for young adults older than 20 years of age [13,23].

SURVIVAL

The 5-year survival rate for children younger than 20 years of age with NHL was 72% for the years 1985-94, a substantial improvement from the 56% survival rate for the years 1975-84 (Figure II.14). For the most recent 10-year period, survival was similar for white and black children and was similar for males and females. During this 10-year period, children younger than 10 years of age had slightly better 5-year survival rates than did those 10-19 years of age (approximately 76% versus 70%).

RISK FACTORS (TABLE II.6)

The etiology of most cases of childhood NHL is unknown. In a small proportion of cases, childhood NHL is linked with various disorders of immune dysfunction. Congenital immunodeficiency syndromes (e.g., Wiskott-Aldrich, ataxia-telangiectasia, X-linked lymphoproliferative syndrome, and severe combined immunodeficiency) and acquired immunodeficiency syndrome (AIDS) from human immunodeficiency virus (HIV) infection are associated with an increased risk of NHL [24-26]. Persons who are immuno-compromised as a result of organ and bone marrow transplantation are also at increased risk of NHL [24,27,28]. EBV is associated with the endemic or 'African-type' Burkitt's lymphomas, but much less commonly with the sporadic Burkitt's lymphomas in the US [29-31]. Few epidemiologic studies of childhood cancer have focused exclusively on NHL, and most prenatal and perinatal exposures evaluated to date were not associated with increased or decreased risk [32].

SUMMARY

Overall, age-adjusted incidence rates for Hodgkin's disease and NHL were similar for children and adolescents younger than 20 years of age, although the age-specific incidence patterns are markedly different. Among young children, Hodgkin's disease is more common among males than females, whereas for older adolescents Hodgkin's disease is more common among females. Hodgkin's disease has a high 5-year relative survival rate, currently greater than 90%. For unknown reasons,

Table II.6: Current knowledge on causes of non-Hodgkin's lymphoma (NHL) in children

Exposure or Characteristic	Comments	References
Known risk factors		
Immunodeficiency	Immunosuppressive therapy, congenital immunodeficiency syndromes (e.g., ataxia telangiectasia), acquired immunodeficiency syndrome (AIDS) all predispose to NHL.	24-27,42,43
Substantial evidence implicating factor		
Epstein-Barr virus	EBV is associated with 'African-type' Burkitt's lymphoma, and chronic immune suppression due to malaria may be a co-factor in this situation. EBV is also associated with NHL in patients with immunodeficiency.	27,29-31,44,45
Factors for which evidence is inconsistent or limited		
Radiation	While a few studies report increased NHL risk in adults or children with ionizing or electromagnetic field (EMF) radiation, others report no association.	46-50

the incidence of Hodgkin's disease appears to be slowly decreasing for both younger children and for older adolescents. Substantial evidence implicates EBV in the etiology of a subset of Hodgkin's disease (primarily mixed cellularity subtype), but the mechanism by which EBV results in development of Hodgkin's disease and the potential role of co-factors are not understood.

The non-Hodgkin's lymphomas of children are a heterogeneous group of tumors, with Burkitt's and Burkitt-like tumors predominating among 5-14 year olds, and with diffuse large cell lymphomas being the most common subtype among 15-19 year olds. Particularly for the Burkitt's lymphomas, there is a marked sex differential, with males having a much higher incidence than females. Survival rates have improved substantially for NHL between the late 1970s and the late 1980s are now over 70%, with similar rates for both sexes and for whites and blacks. The incidence of NHL among children younger than 15 years of age appears fairly constant over the past 21 years, while there appears to have been a slight increase in incidence for the 15-19 year old age group. The etiology of childhood NHL is poorly understood, although a small proportion of cases arise in children with congenital or acquired severe immune dysfunction.

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HIGHLIGHTS

Incidence

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

Survival

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

Risk factors

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

INTRODUCTION

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

brain. This report only includes malignant CNS tumors.

Classification system

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

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

INCIDENCE

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

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

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

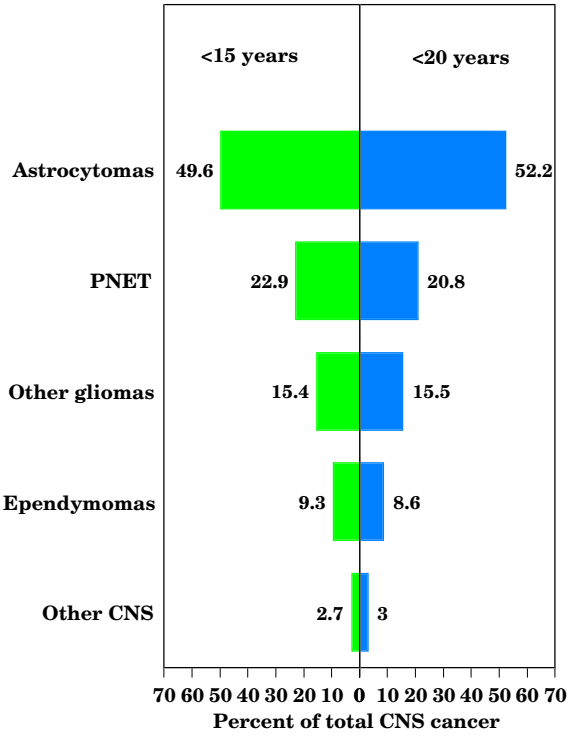


Figure III.2: Malignant CNS tumor age-specific incidence rates by anatomic site and age all races, both sexes, SEER, 1975-95

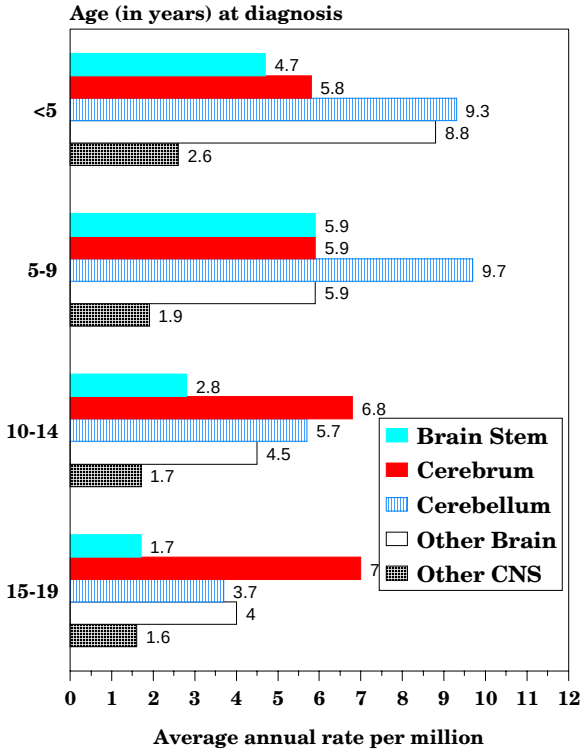
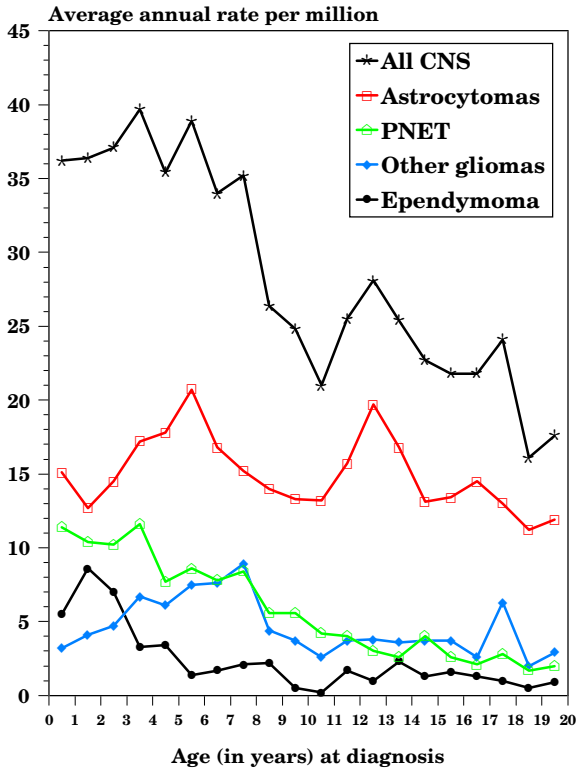


Figure III.3: Malignant CNS tumor age-specific incidence rates, all races, both sexes SEER, 1986-94



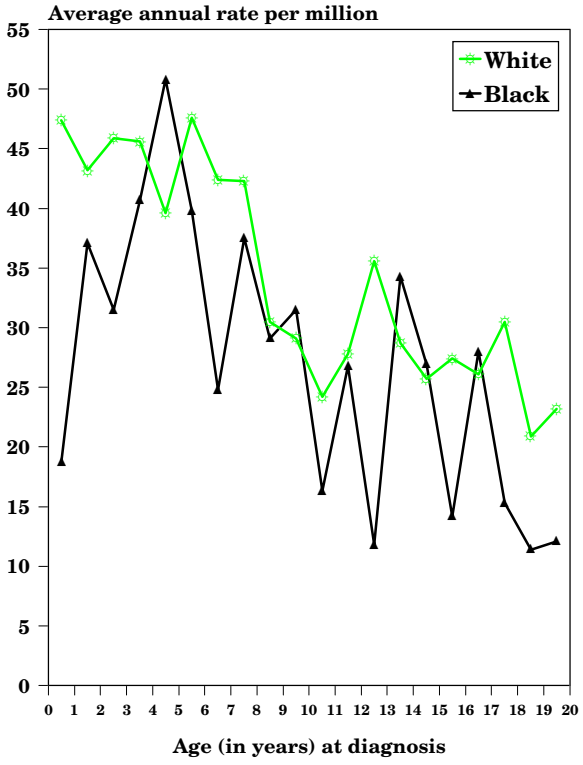
Age-specific incidence

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

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

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

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



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

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

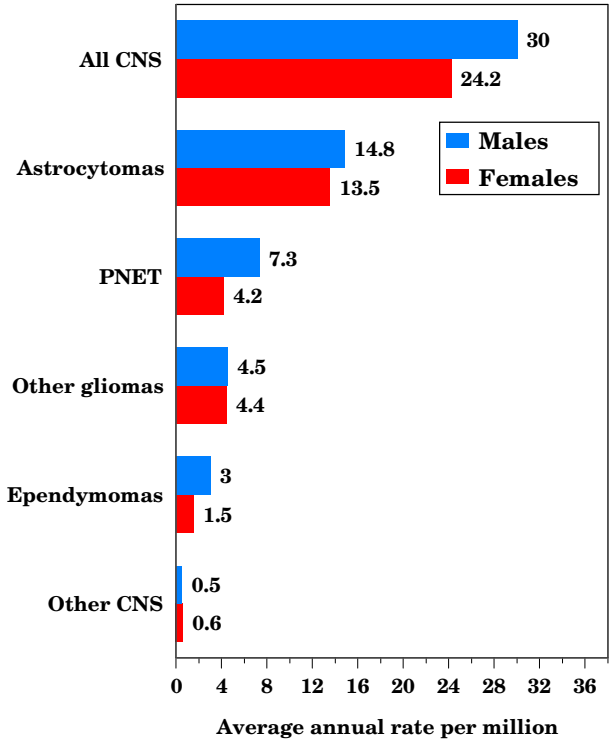
Sex-specific incidence

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

Black-white differences in incidence

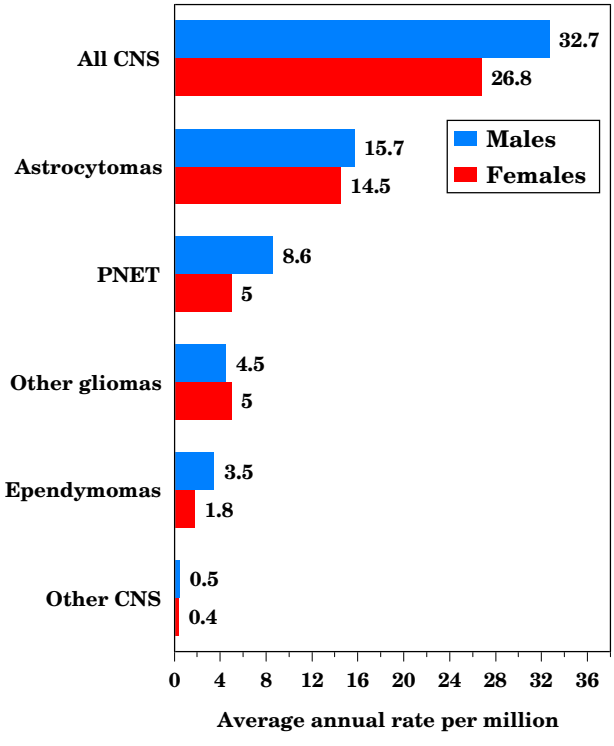
White children (28.5 per million) had an 18% higher average CNS incidence rate compared with black children (24.2 per million). Figure III.7 depicts overall inci-

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



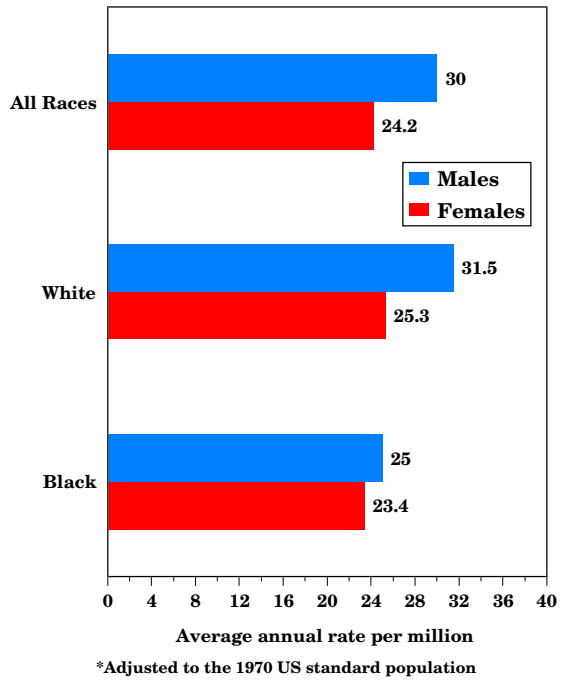
*Adjusted to the 1970 US standard population

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



*Adjusted to the 1970 US standard population

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



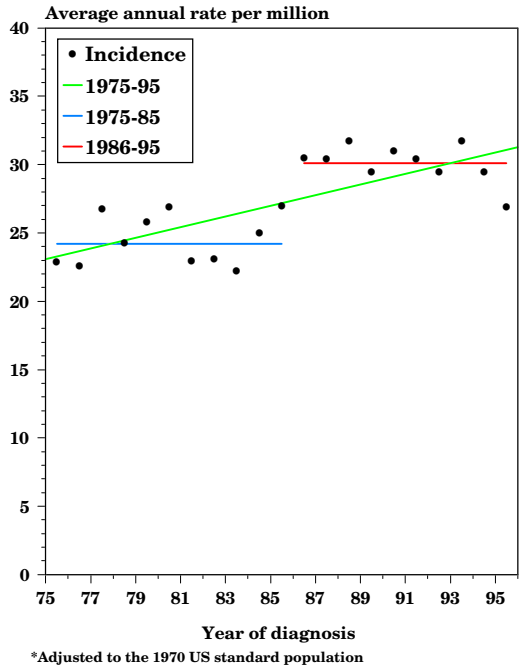
dence rates by sex for white children, black children, and all children combined. It is evident that the racial difference in CNS rates was primarily concentrated among males. There was only a slightly higher CNS cancer incidence rate among white compared with black females (8%), while the racial difference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

TRENDS

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

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

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



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

SURVIVAL

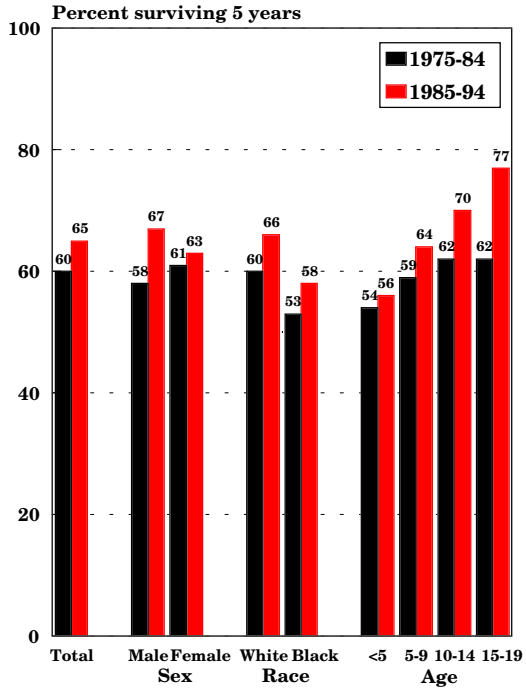
Although survival differs by histology, behavior, size and location of the malignancy, in general children with CNS cancer do not share the favorable prognosis of those with many other common pediatric neoplasms, such as acute lymphoblastic leukemia. Additionally, for children who do survive CNS cancer,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

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

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

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

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



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

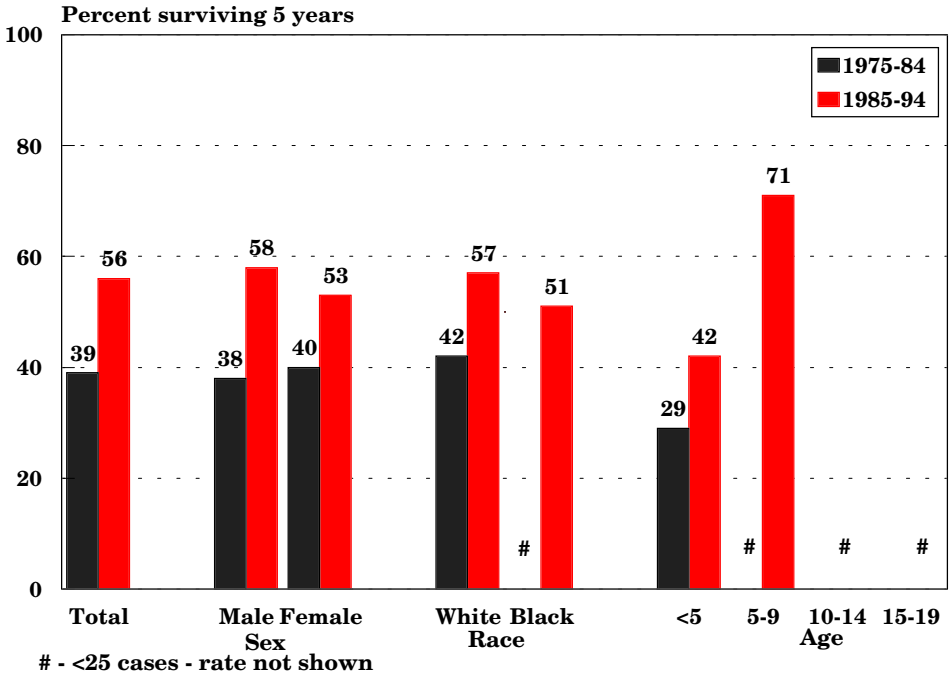
For all CNS cancer combined, survival probability increased with increasing age. Very young children with CNS cancer, especially infants with ependymoma or PNET, were at particularly high risk of

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

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

* less than 20 cases.

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



- <25 cases - rate not shown

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

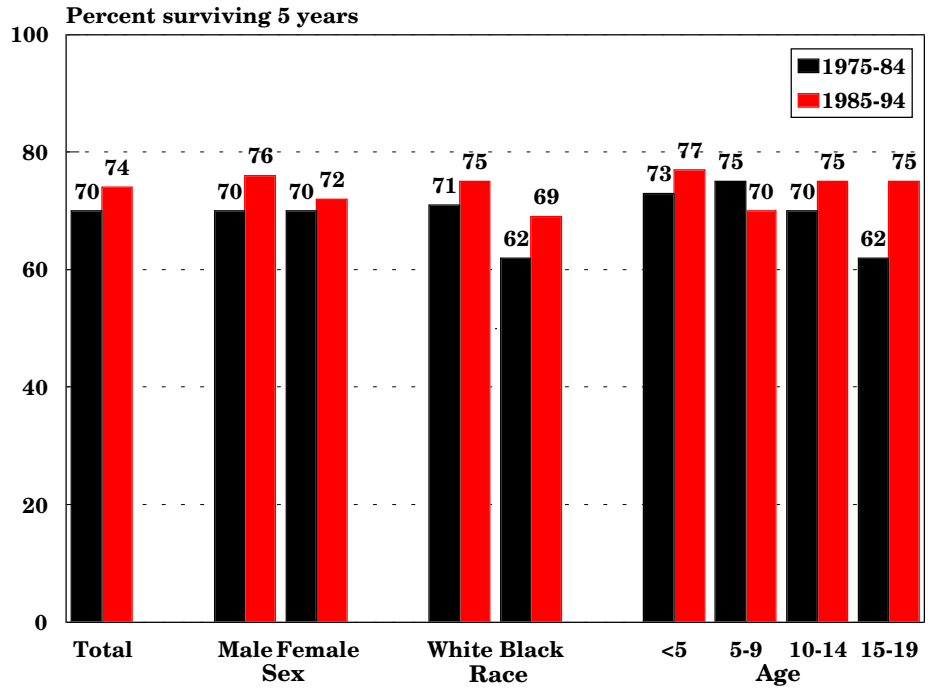


Figure III.12: PNET 5-year relative survival rates by sex, race, age and time period, SEER (9 areas), 1975-84 and 1985-94

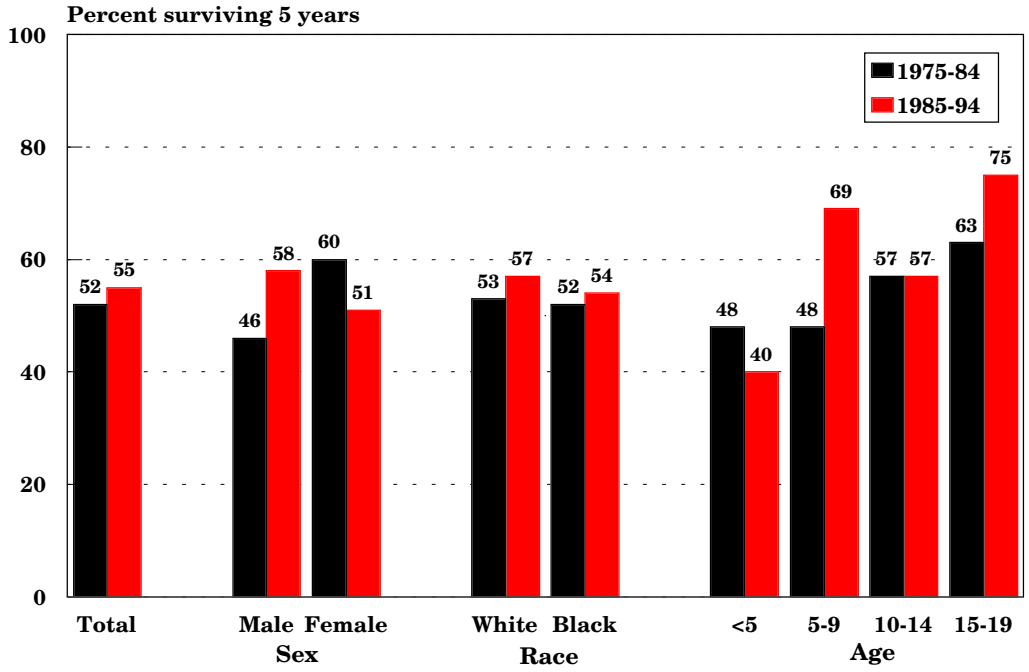


Figure III.13: Other gliomas 5-year relative survival rates by sex, race, age and time period, SEER (9 areas), 1975-84 and 1985-94

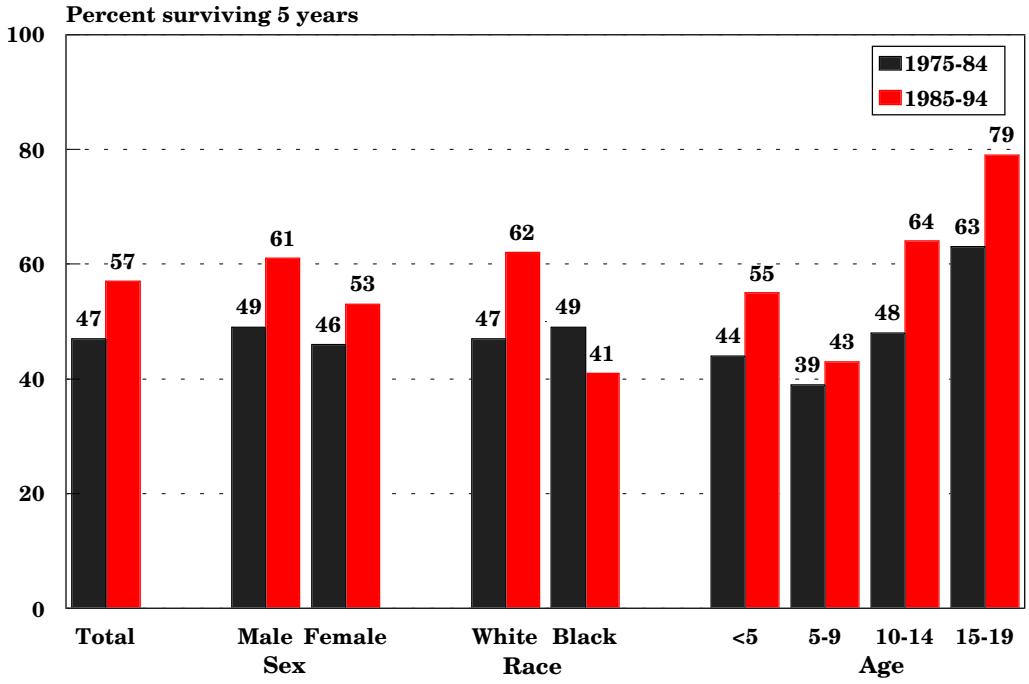


Table III.3: Current knowledge on causes of childhood brain tumors

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

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

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

RISK FACTORS

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

SUMMARY

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

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HIGHLIGHTS

Incidence

- In the US, approximately 700 children and adolescents younger than 20 years of age are diagnosed with tumors of the sympathetic nervous system each year, of which approximately 650 are neuroblastomas.
- Sympathetic nervous system tumors accounted for 7.8% of all cancers among children younger than 15 years of age.
- Over 97% of sympathetic nervous system tumors are neuroblastomas, embryonal malignancies of the sympathetic nervous system that occur almost exclusively in infants and very young children.
- Regardless of age, neuroblastomas most commonly occurred in the adrenal gland. Mediastinal tumors were more frequent in infants than in older children, while the opposite age pattern was observed for CNS tumors (Figure IV.1).
- The average age-adjusted annual incidence rate for all sympathetic nervous system cancers was 9.5 per million children.
- The occurrence of sympathetic nervous system malignancies was strongly age-dependent (Figure IV.2). For neuroblastomas alone, the incidence rate for both sexes combined during the second year of life (29 per million) was less than half that of infancy (64 per million).
- Neuroblastomas were by far the most common cancer of infancy, with an incidence rate almost double that of leukemia, the next most common malignancy that occurred during the first year of life.
- Sixteen percent of infant neuroblastomas were diagnosed during the first month following birth and 41% were diagnosed during the first 3 months of life (Figure IV.3).
- Over the 21-year observation period, there was little indication of an increase in the overall incidence of sympathetic nervous system malignancies (Figure IV.4). The estimated annual percent change in age-adjusted incidence rates was 0.4%.

Survival

- For children aged 1 to 4 years at diagnosis, 5-year survival rate improved from 35% during 1975-84 to 55% during 1985-94. Survival at 5 years from diagnosis was essentially unchanged over these time intervals among infants (83%) and children 5 years or older (40%).

Risk factors

- Relatively little is known about the etiology of sympathetic nervous system tumors (Table IV.3). The young age at onset of most cases illustrates the need to investigate exposure events occurring before conception and during gestation.

Table IV.1: Number of cases and age-adjusted* incidence rates per million by ICCC categories of sympathetic nervous system malignancies and sex, age <15, all races, SEER, 1975-95

	Males		Females		Total	
Tumor Type	No.	Rate	No.	Rate	No.	Rate
Neuroblastomas	787	9.4	705	8.9	1492	9.1
Other sympathetic nervous system	28	0.4	22	0.3	50	0.3
Total	815	9.8	727	9.2	1542	9.5

*Adjusted to the 1970 US standard population

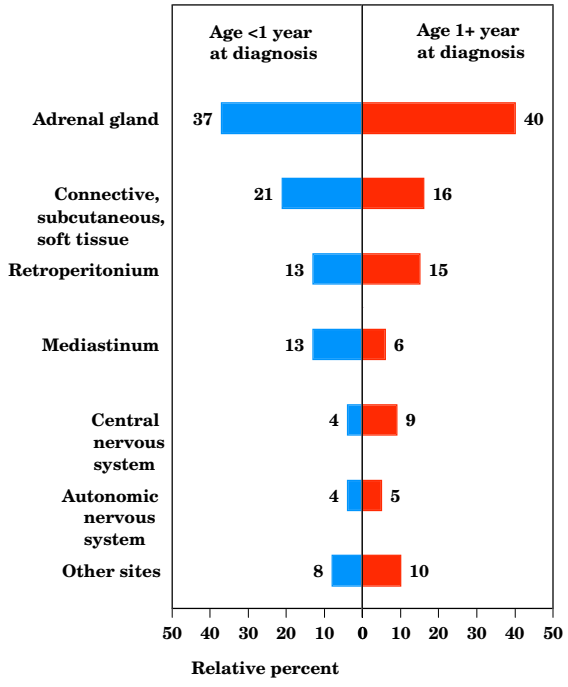
INTRODUCTION

Neuroblastoma is an embryonal malignancy of the sympathetic nervous system that is derived from primordial neural crest cells and occurs almost exclusively in infants and young children [1]. Other childhood malignancies of the sympathetic nervous system include ganglioneuroblastoma, which is a more differentiated variant of neuroblastoma, and the histogenetically related pheochromocytoma [2]. Malignant paragangliomas, medulloepitheliomas, neuroepitheliomas and olfactory neurogenic tumors are also cancers of the sympathetic nervous system, although they are extremely rare in children and will not be emphasized. To follow the convention of the International Classification of Childhood Cancer system [3], data for neuroblastoma and ganglioblastoma are grouped together as one category (henceforth called neuroblastomas), and all other sympathetic nervous system malignancies as a second category. Because of important distinctions in biological characteristics and prognosis of neuroblastomas in infants (less than 1 year at diagnosis) compared with older children (older than 1 year of age at diagnosis) [1], data are provided to highlight the epidemiology of both age groups individually. Additionally, because the occurrence of neuroblastomas and other sympathetic nervous system malignancies are so rare in adolescents, the rate calculations and discussion are limited to children younger than 15 years of age. In the US, approximately 700 children and adolescents younger than 20 years of age are diagnosed with tumors of the sympathetic nervous system each year, of which approximately 650 are neuroblastomas.

INCIDENCE

During the 21-year period from 1975 through 1995, 1,542 children were diagnosed with sympathetic nervous system malignancies in the SEER areas (Table IV.1). This represented 7.8% of all cancer

Figure IV.1 Percent distribution of neuroblastomas by primary site and age, all races, both sexes SEER, 1975-95



in this age group. The majority (97%) of these malignancies were neuroblastomas; only 50 children were diagnosed with any other histological type. Within the neuroblastoma category, ganglioneuroblastomas comprised 15% of tumors (8% among infants and 20% among those 1-14 years of age).

The distribution of neuroblastomas by primary site is shown in Figure IV.1. Regardless of age, neuroblastomas most commonly occurred in the adrenal gland. Mediastinal tumors were more frequent in infants than in older children, while the opposite age pattern was observed for CNS tumors.

Age-specific incidence

The incidence rate for all sympathetic nervous system cancers was 9.5 per million children. The occurrence of sympathetic nervous system malignancies, however, was strongly age-dependent. Figure IV.2 illustrates the incidence rates by single year of age[1] and sex, and shows the predominance of neuroblastomas during infancy. For neuroblastomas alone, the incidence rate for both sexes combined during the second year of life (29 per million) was less than half that of infancy (64 per million). The rates for sympathetic nervous system tumors other than neuroblastomas were 1.2 per million for infants, and less than 1 per million for all other single years of age.

Figure IV.2: Sympathetic nervous system age-specific incidence rates by sex, all races SEER, 1976-84 and 1986-94

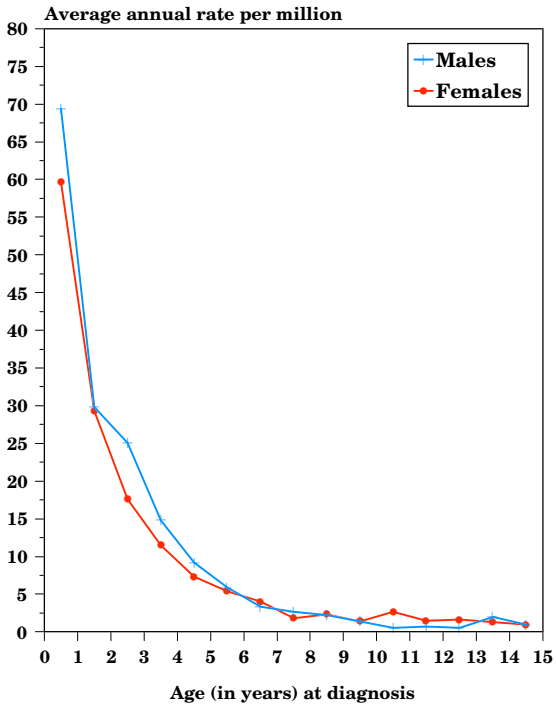
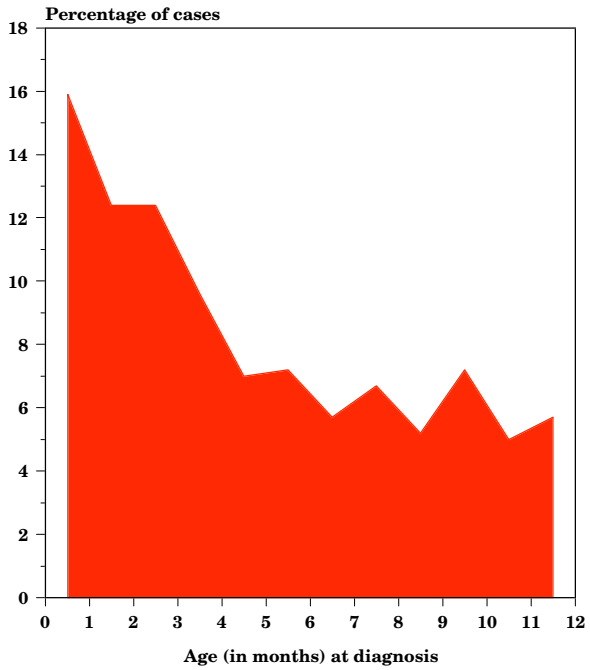


Figure IV.3: Percent distribution of infant neuroblastomas by month of age, all races, both sexes, SEER, 1975-95



Neuroblastomas were by far the most common cancer of infancy with an incidence rate almost double that of leukemia, the next most common malignancy that occurs during the first year of life [4]. As shown in Figure IV.3, 16% of infant neuroblastomas were diagnosed during the first month following birth and 41% were diagnosed during the first 3 months of life.

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

Table IV.2: Average annual age-specific incidence rates per million for all sympathetic nervous system tumors by age, sex, and race SEER 1975-95

		Males			Females	
Age (in years) at diagnosis	White	Black	All	White	Black	All
<1	83.6	50.5	69.3	74.1	38.4	59.6
1-14	8.2	7.4	7.3	7.6	6.5	6.5
<15*	10.1	8.8	9.8	9.6	8.6	9.2

* Adjusted to the 1970 US standard population

Sex and race-specific incidence

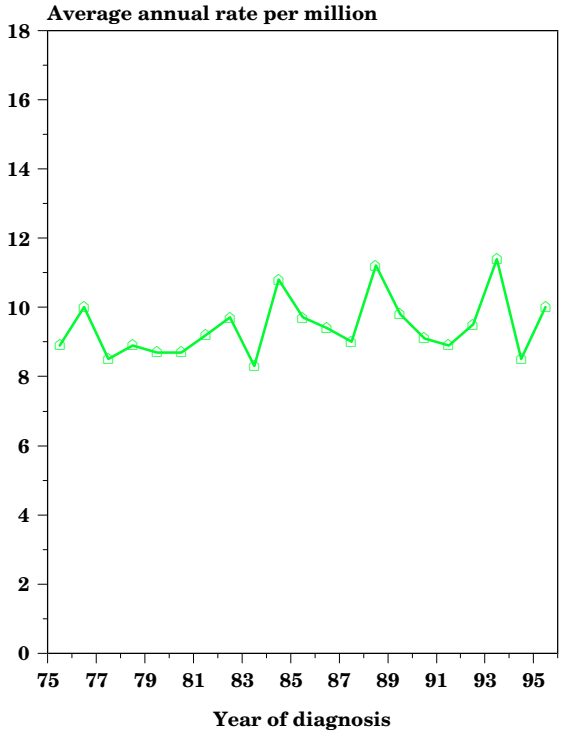
Figure IV.2 also demonstrates that the incidence of sympathetic nervous system cancer was slightly higher among males than females. For neuroblastomas, overall male rates (9.8 per million) were 6.5% higher than female rates (9.2 per million) with the greatest difference occurring during infancy (69.3 per million versus 59.6 per million for males and females, respectively). There was no discernable sex difference for sympathetic nervous system malignancies other than neuroblastomas.

White infants of both sexes had a higher incidence of sympathetic nervous system tumors than did black infants, but little difference by race was observed among older children (Table IV.2). The ratio of white to black incidence rates among infants was 1.7:1 for males and 1:9:1 for females. In Table IV.2, "all races" includes whites, blacks, and children of other identified racial or ethnic backgrounds. There were too few cases of sympathetic nervous system among any other races to calculate reliable incidence rates.

TRENDS

Over the 21-year observation period, there was little indication of a linear trend in the overall incidence of sympathetic nervous system malignancies (Figure IV.4). The estimated annual percent change in age-adjusted incidence rates was 0.37% ($p > 0.05$). Rates, however, have increased somewhat among infants during recent years. Figure IV.5 shows incidence rates of neuroblastomas by year of age at diagnosis for the periods 1976-84 versus 1986-94. Among infants, the rate in the earlier time period was 53 per million compared to 74 per million in the later time period. No differences in rates between the time

Figure IV.4: Trends in sympathetic nervous system age-adjusted* incidence rates by year of diagnosis age <15, all races, both sexes, SEER, 1975-95



*Adjusted to the 1970 US standard population

periods occurred for children either 1 or 2 years of age at diagnosis. Thus, it does not appear that the increase among infants can be explained by a shift towards earlier age at diagnosis. The increase among infants, however may be a result of *de facto* fetal and neonatal screening. Mass screening of infants for neuroblastoma has been evaluated in recent years in Japan, Canada, and some countries in Europe [5,6]. Although systematic screening for neuroblastoma is not conducted in the United States, the awareness of screening in other countries and the recent widespread availability of non-invasive diagnostic tests for neuroblastoma may have resulted in US physicians diagnosing cases of neuroblastoma with minimal clinical symptomatology that previously were undetected. The documented ability of some fetal and infant neuroblastomas to spontaneously regress is consistent with the hypothesis that the increased incidence among infants is the result of detection of cases that were previously not diagnosed [1,9,10]. Also consistent with this hypothesis is the recent widespread use of prenatal ultrasound testing with coincidental detection of adrenal neuroblastomas [7,8].

Figure IV.5: Neuroblastoma age-specifice incidence rates by age, all races, both sexes SEER, 1976-84 and 1986-94

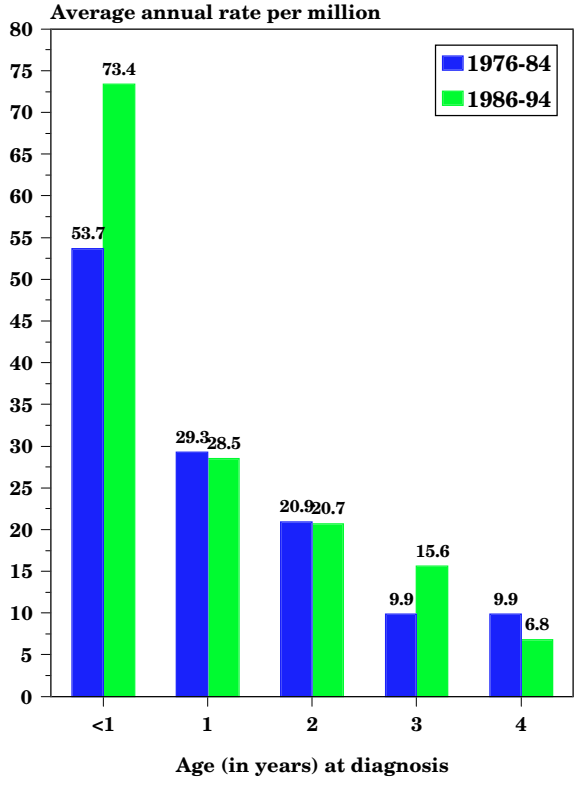
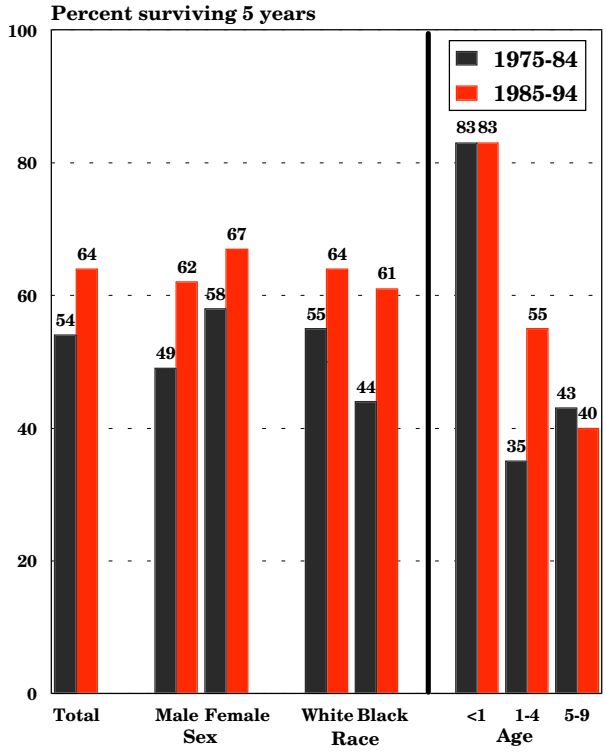


Figure IV.6: Neuroblastoma 5-year relative survival rates by sex, race, age, and time period SEER (9 areas), 1975-84 and 1985-94



SURVIVAL

Prognosis for neuroblastomas is dependent on age, stage of disease, and the molecular biologic and cytogenetic characteristics of the tumor [1]. Figure IV.6 illustrates the more favorable prognosis for infants with neuroblastoma (5-year relative survival rate, 83%) compared to children older than 1 year of age. The favorable outcome for infants with neuroblastoma no doubt reflects the favorable biological

Table IV.3: Current knowledge on causes of neuroblastoma (NB)

Exposure or Characteristic	Comments	References
Factors for which evidence is inconsistent or limited		
Medications	Two studies have reported increased risk when mothers took medications during pregnancy such as amphetamines, diuretics, tranquilizers, or muscle relaxers or for vaginal infection. Other studies have reported an association with maternal phenytoin treatment.	11,12,13
Hormones	Two studies reported that sex hormones were associated with an increase in risk. One of the studies reported a 10-fold increased risk for fertility drug use prior to pregnancy.	12,13,14
Birth characteristics	One study reported increased risk associated with low birth weight and protective effect for preterm delivery. This was not confirmed in two other studies.	13,15,16
Congenital anomalies	A variety of congenital anomalies has been reported to occur with NB in a small number of cases, but no consistent pattern of association has been shown.	11
Previous spontaneous abortion/fetal death	Previous spontaneous abortion was associated with increased risk in one study and decreased risk in another.	13,16
Alcohol	One study reported a dose-response relationship between frequency of alcohol use during pregnancy and NB, but another reported no effect. An association with fetal alcohol syndrome has also been reported.	12,13,17
Tobacco	An early study reported no effect of maternal smoking on risk. However, a later study suggested a weak dose-response relationship between level of maternal smoking during pregnancy and NB risk.	12,13
Paternal occupational exposures	Three studies have reported conflicting results on the risk associated with paternal employment in electronics, agriculture, and packaging and materials handling. Specific associated occupational exposures include electromagnetic fields, pesticides, hydrocarbons, dusts, rubber, paint, and radiation.	18-20

characteristics of neuroblastomas arising in this age group [1]. For children aged 1 to 4 years at diagnosis, the 5-year survival rate improved from 35% during 1975-84 to 55% during 1985-94. Survival was essentially unchanged during these time intervals for children older than 4 years of age (40%). There were no substantive differences in survival by sex or race (Figure IV.6).

RISK FACTORS

Relatively little is known about the etiology of sympathetic nervous system tumors (Table IV.3). The young age at onset of most cases illustrates the need to investigate exposure events occurring before conception and during gestation. The few epidemiological investigations of

neuroblastoma have not had sufficient statistical power or detailed data collection to provide convincing evidence of etiologic risk factors. Medications [11,12,13] and hormones used during pregnancy [12,13,14] are among the most suggestive factors suspected to increase the risk of neuroblastoma. Certain birth characteristics, pesticide exposure, and parental occupational exposure to electromagnetic fields [13,15,16,18-20] have been evaluated, but with conflicting results. In addition, clinical and molecular characteristics, such as amplification of the nmyc oncogene, loss of heterozygosity of the short arm of chromosome 1, and hyperdiploidy, may be useful in establishing homogenous disease subgroups for future epidemiological investigations of neuroblastoma [1].

SUMMARY

Sympathetic nervous system malignancies, of which neuroblastomas comprised 97% of the total, represented 7.8% of cancer in children younger than 15 years of age. The incidence rate was 9.5 per million children, however rates were strongly age-dependent. The incidence rate of sympathetic nervous system malignancies among infants was 65 per million, and the rate dropped by half in the second year of life. Overall, incidence rates did not change substantially during the study period. Among infants, however, there was an increase in incidence rates from 1986-94 compared with the period 1976-84. This increase was not noted in older children, thus excluding earlier age at diagnosis as a likely explanation for the trend. Rather, the increase likely arose from identification of previously undetected cases with minimal clinical symptomatology through widespread application of fetal ultrasound testing and noninvasive diagnostic tests for neuroblastoma. The known propensity of the neuroblastomas of infancy to undergo spontaneous regression supports this explanation. Five-year relative survival of neuroblastomas was 83% for infants, 55% for children 1-4 years of age, and 40% for older children. Unfortunately, there is very little known about why neuroblastoma occurs, or what factors increase risk for occurrence.

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HIGHLIGHTS

Incidence

- Retinoblastoma accounted for approximately 11% of cancers developing in the first year of life, but for only 3% of the cancers developing among children younger than 15 years of age.
- In the US, approximately 300 children and adolescents younger than 20 years of age are diagnosed with retionblastomas each year.
- The vast majority of cases of retinoblastoma occur among young children, with almost two-thirds (63%) of all retinoblastomas occurring before the age of two years and 95% occurring before the age of five years.
- The incidence of bilateral tumors was strongly age dependent with 42% of the retinoblastomas occurring in children less than one year of age being bilateral compared to 21% of those among children aged one year, and only 9% among older children.
- Rates of retinoblastoma were essentially equal among males (3.7 per million) and females (3.8 per million) and among whites (3.7 per million) and blacks (4.0 per million) (Table V.2)
- There was no substantial sustained change in retinoblastoma incidence during the 21-year period, 1975-95 (Figure V.3 and Table V.2).

Survival

- Survival for children with retinoblastoma was quite favorable, with more than 93% alive at five years after diagnosis. Males and females had similar 5-year survival rates for the period 1976-94 (93-94%). Black children had slightly lower 5-year survival rates than white children (89% versus 94%) (Figure V.5).

Risk factors

- A retinoblastoma gene has been identified. Each child of a parent with familial bilateral retinoblastoma has a 50% risk of inheriting the retinoblastoma gene. Some patients develop the gene as the result of a new mutation (sporadic heritable retinoblastoma) and can pass the gene on to their children even though they did not inherit the gene from their parents. Children who inherit the retinoblastoma gene have a 90% risk of developing retinoblastoma. Genetic retinoblastomas are more likely to be bilateral and to occur during the first year of life. Little is know about non-genetic (sporadic) retinoblastomas (Table V.3).

INTRODUCTION

Retinoblastoma is a tumor of childhood which arises in the retina of the eye and extremely rarely in the pineal gland [1]. Two types of retinoblastomas have been described: those linked to genetic mutations and the so-called sporadic retinoblastomas. The genetic-linked retinoblastomas are divided into two groups, those which arise in children who carry the retinoblastoma gene inherited from one or both parents (familial retinoblastoma) and those in which the disease occurs as the result of a new mutation, usually in their father's sperm but sometimes in their mother's egg (sporadic heritable retinoblastoma) [2,3]. Both familial retinoblastomas and sporadic

Table V.1: Number of retinoblastomas by laterality, sex, and race, age <15 SEER, 1975-95

	Total	Unilateral		Bilateral		Unknown	
	No.	No.	%	No.	%	No.	%
Total	625	453	72.5	154	24.6	18	2.9
Males	314	226	72.0	76	24.2	12	3.8
Females	311	227	73.0	78	25.1	6	1.9
Whites	474	341	71.9	116	24.5	17	3.6
Blacks	86	61	70.9	25	29.0	-	-

heritable retinoblastomas are more likely to be bilateral and to occur during the first year of life, while the sporadic retinoblastomas are more likely to be unilateral and occur after the first year of life.

The importance of retinoblastoma to cancer research far exceeds the low incidence of this uncommon tumor, since it was through careful analysis and insightful mathematical modeling of the age distribution of unilateral and bilateral cases that the "tumor suppressor gene" concept was initially developed [4,5]. Subsequent work led to the localization of the gene responsible for retinoblastoma to a small region on the long arm of chromosome 13 [6], and eventually to isolation of the gene itself [7]. The retinoblastoma gene product is now recognized as a critical element in controlling progression through the cell cycle, and abnormalities of the retinoblastoma gene are among the most common occurring in all types of cancer cells [5,8]. In the US, approximately 300 children and adolescents younger than 20 years of age are diagnosed with retionblastomas each year.

INCIDENCE

Table V.1 shows the distribution of retinoblastomas diagnosed among residents of the SEER areas during 1975-95 by laterality, race, and sex. Approximately one-fourth of all retinoblastomas were bilateral. All bilateral disease is hereditary whereas unilateral disease may or may not be hereditary. The percentage of unilateral and bilateral tumors were similar for black children and white children and for males and females.

The vast majority of cases of retinoblastoma occur among young children (Figure V.1), with almost two-thirds (63%)

Figure V.1: Unilateral and bilateral retinoblastoma age-specific incidence rates, all races both sexes, SEER, 1976-84 and 1986-94

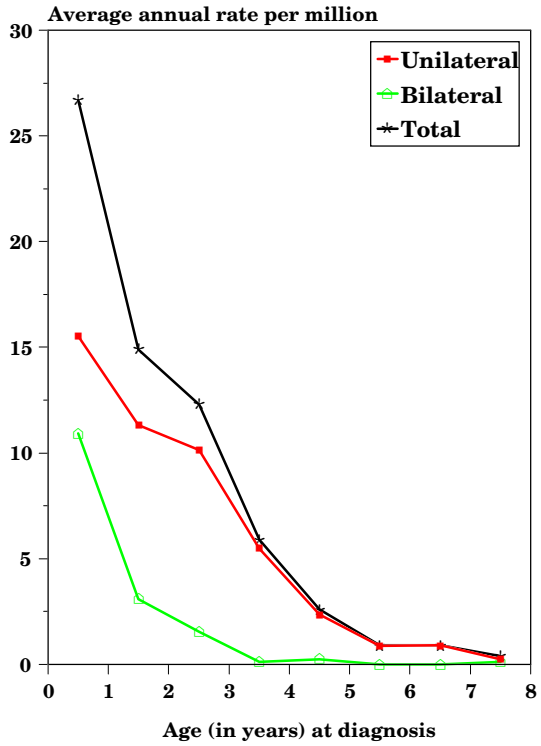
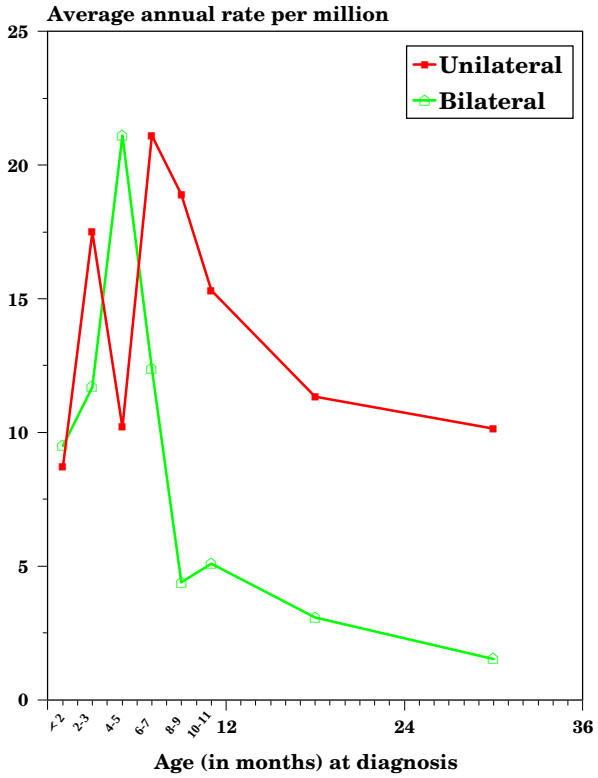


Figure V.2: Unilateral and bilateral retinoblastoma age-specific incidence rates, age <3, all races both sexes,SEER, 1976-84 and 1986-94



of all retinoblastomas diagnosed between 1975-95 among children residing in the SEER areas occurring before the age of two years and with 95% occurring before the age of five years. Since retinoblastoma was extremely rare after the age of five years (only 28 childhood retinoblastomas reported to SEER areas as having been diagnosed younger than 20 years of age occurred in children aged 15-19 years in comparison to 625 cases in children younger than 15 years of age), information presented in this chapter will be limited to children younger than 15 years of age.

The incidence of bilaterality was strongly age dependent, with 42% (103/248) of the retinoblastomas occurring in children less than one year of age being bilateral compared to 21% (31/147) of those among children aged one year, and only 9% (20/230) among older children. The incidence rates for both unilateral and bilateral retinoblastoma decrease as age increases. The incidence rate for bilateral retinoblastoma drops to almost zero after age 2, while the rate for unilateral retinoblastoma remains higher until after age 7 (Figure V.1). Figure V.2 provides a more detailed view of incidence in the first 3 years of life, with incidence for the first year of life being estimated by two month age intervals. For bilateral tumors, the peak incidence is at 4-5 months of age, with a sharp decline thereafter and with very low rates by the third year of life. For unilateral tumors, peak incidence is also in the first year of life (at 6-7 months), but the decline in incidence with increasing age is much more gradual than for bilateral tumors, with rates remaining above 10 per million children for the first 3 years of life.

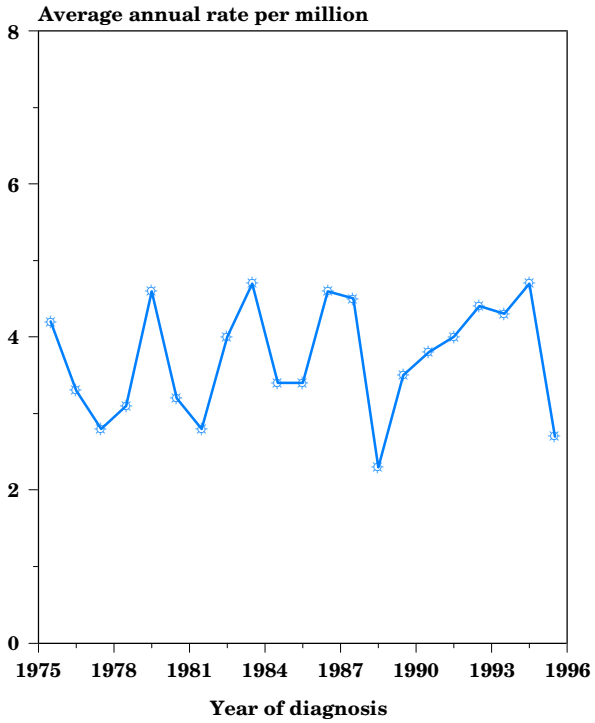
The incidence rate of retinoblastoma for the period 1975-95 was 3.8 per million (Table V.2). Retinoblastoma accounted for approximately 11% of the cancers developing in the first year of life, but for only 3% of the cancers developing among children younger than 15 years of age. Rates of retinoblastoma among males (3.7 per million) and females (3.8 per million) were essentially equal. Rates for whites (3.7 per million) and blacks (4.0 per million) were also similar.

Table V.2: Average annual age-adjusted* incidence rates per million of retinoblastoma, by time period, race, and sex, age <15 SEER, 1975-95

	1975-95	1975-79	1980-84	1985-89	1990-95
All races, Both sexes	3.8	3.6	3.6	3.7	4.0
Male	3.7	3.6	3.3	3.4	4.2
Female	3.8	3.6	4.0	4.0	3.8
White	3.7	3.3	3.5	3.7	4.0
Black	4.0	4.6	4.0	3.7	3.8

* Adjusted to the 1970 US standard population

Figure V.3: Trends in retinoblastoma age-adjusted* incidence rates, age <15, all races both sexes, SEER 1975-1995



*Adjusted to the 1970 US standard population

TRENDS

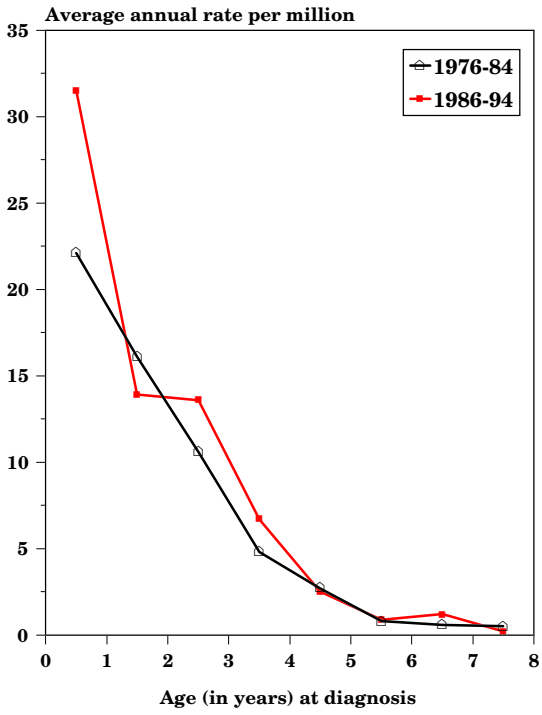
Figure V.3 shows the incidence for retinoblastoma among children younger than 15 years of age for 1975-95. Because of the relatively small numbers of children with retinoblastoma diagnosed in SEER areas annually (approximately 20 per year), there was considerable variability in the year-to-year rates. There was no substantial sustained change in retinoblastoma incidence during this 21 year period.

Table V.2 shows the incidence rate for retinoblastoma among children younger than 15 years of age for four specific time periods between 1975-95 by sex and race. Rates were slightly higher in the last time period for males and for whites. The estimated overall annual percent change was about one-half of one percent per year (0.6%). The change was greater for males (1.2%) than for females (0.2%), but neither change was significant. The rates for blacks were higher than whites for the earlier time period but by the late 1980s were similar. Figure V.4 shows the incidence of retinoblastoma by year of age for an early time period (1976-84) and for a recent time period (1986-94) and illustrates that the small increase that did occur between these two time periods was primarily the result of increased diagnosis of retinoblastoma in the first year of life.

SURVIVAL

Figure V.5 shows that survival for children diagnosed with retinoblastoma in the period 1975-94 was quite favorable, with more than 93% alive at five years after diagnosis. Males and females had similar 5-year survival rates for the period 1975-94 at 93-94%, while black children had slightly lower 5-year survival rates than white children (89% versus 94%).

Figure V.4: Retinoblastoma age-specific incidence rates by time period, all races, both sexes SEER, 1976-84 and 1986-94



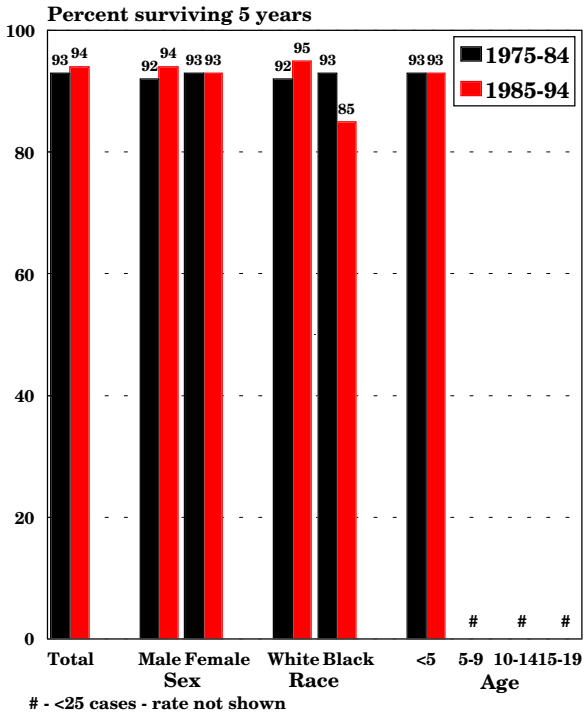
RISK FACTORS

While the genetics of retinoblastoma are well understood, there is much less known about the role of non-genetic factors in retinoblastoma (Table V.3). Each child of a parent with familial bilateral retinoblastoma has a 50% risk of inheriting the retinoblastoma gene. Patients with sporadic heritable retinoblastoma carry the gene for retinoblastoma and can also pass the gene on to their children even though they did not inherit the gene from their parents. Children who inherit the retinoblastoma gene have a 90% risk of developing retinoblastoma. Sporadic (nonheritable) retinoblastoma results from post-conception events and has been associated in a single study with parental occupation (Table V.3) [9].

SUMMARY

Retinoblastomas occur among very young children, usually before the age of five years. The incidence is about equal among males and females and among black children and white children. Rates have changed little over the 21-year period,

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



- <25 cases - rate not shown

Table V.3: Current knowledge of causes of retinoblastoma

Exposure or Characteristic	Comments	References
Known risk factors		
Parent with history of bilateral retinoblastoma	Each child has a 50% risk of inheriting the retinoblastoma gene. If the gene is inherited, the risk of retinoblastoma is over 90%. A small proportion of unilateral patients also carry the gene and can pass it on to their children.	4,10
13q deletion syndrome	Recognition of this syndrome led to the identification of the retinoblastoma gene.	10
Factors for which evidence is inconsistent or limited		
Paternal occupation	There is a single report of association with employment in the military, metal manufacturing, and as welder, machinist, or related occupation.	9

1975-95. Familial and sporadic heritable retinoblastomas are caused by genetic mutations and both usually result in the bilateral form of the disease. Little is known about the causes of sporadic non-heritable retinoblastomas. Survival rates are greater than 90% for children with retinoblastoma.

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HIGHLIGHTS

Incidence

- Malignancies of the kidney (renal cancers) represented 6.3% of cancer diagnoses among children younger than 15 years of age (incidence 7.9 per million) (Table VI.2) and 4.4% of cancer diagnoses for children and adolescents younger than 20 years of age (incidence of 6.2 per million).
- In the US approximately 550 children and adolescents younger than 20 years of age are diagnosed with renal tumors each year, of which approximately 500 are Wilms' tumor.
- Wilms' tumor was by far the most common form of renal cancer in children younger than 15 years of age, representing approximately 95% of diagnoses (Tables VI.1 and VI.2). Much less common were rhabdoid tumors of the kidney (1% of renal cancers) and clear cell sarcoma of the kidney (1.6% of renal cancers). Renal carcinomas, the most common form of renal cancer in adults, represented only 2.6% of renal cancers in children younger than 15 years of age.
- Wilms' tumor occurred most commonly among children younger than 5 years of age (Figure VI.1), with very low incidence for 10-14 and 15-19 year olds. The highest incidence for Wilms' tumor was in the first 2 years of life, followed by steadily decreasing rates with increasing age (Figure VI.2).
- Rhabdoid tumor of the kidney was diagnosed primarily in infants, while clear cell sarcoma of the kidney was diagnosed primarily during the first 4 years of life. Renal carcinomas, by contrast, occurred with highest incidence among 15-19 year olds (Figure VI.1).
- Females had slightly higher incidence than males for Wilms' tumor during the period 1975-95 (Table VI.3). For the recent period of 1990-95, however, incidence rates were similar by sex (Figure VI.3).
- Black children had somewhat higher incidence for Wilms' tumor than white children for the period 1975-95. For the time periods 1986-89 and 1990-95, however, incidence rates by race were similar (Figure VI.4).
- Incidence of Wilms' tumor showed neither substantial increases nor decreases during the 21-year period from 1975 to 1995 (FigureVI.5).

Survival

- The overall relative 5-year survival rate for children with Wilms' tumor was approximately 92% for cases diagnosed from 1985-94 (Figure VI.6), an improvement from the 81% survival rate for cases diagnosed from 1975-84. Relative survival rates were slightly higher for females than males and slightly higher for black children than for white children (Figure VI.6).

Risk factors

- Certain congenital anomalies and genetic conditions increase susceptibility for Wilms' tumor (Table VI.4). Suggestive, although not conclusive, data indicate that certain paternal occupations may be associated with increased Wilms' tumor risk.

INTRODUCTION

Renal tumors occurring in children comprise a spectrum of morphologic subtypes, including some with benign histopathology. Wilms' tumor (also called nephroblastoma or renal embryoma) is by far the most common form of renal cancer in children. Other rarer forms of childhood renal cancers are: clear cell sarcoma of the kidney, rhabdoid tumor of the kidney, congenital mesoblastic nephroma, multilocular cystic renal tumor, renal cell carcinoma, and angiomyolipoma [1,2]. During 1975-95 in regions covered by SEER cancer registries, malignant forms of renal tumors represented 6.3% of total cancer diagnoses among children younger than 15 years of age and 4.4% for the younger than 20 years old population. The contribution of renal cancers to the overall childhood cancer burden was notably age-dependent, with renal cancers representing 9.7% of total incident malignancies diagnosed among children younger than 5 years of age, 5.4% in children 5-9 years of age, 1.1% in children 10-14 years of age, and only 0.6% in adolescents 15-19 years of age.

Wilms' tumor is believed to arise from primitive metanephric blastema (*i.e.*, the tissue from which the normal kidney arises), though this tumor type often contains tissues not occurring in the developing kidney, including skeletal muscle, cartilage, and squamous epithelium [3]. Wilms' tumor usually arises in only one of the affected child's kidneys, although approximately 12% of affected children may be diagnosed with Wilms' tumor that is multicentric in origin [4]. Approximately 7% of children with Wilms' tumor have involvement of both kidneys. Patients with bilateral forms are generally diagnosed at younger ages and are more likely to have associated developmental abnormalities than patients with unilateral forms [4]. In the US approximately 550 children and adolescents younger than 20 years of age are diagnosed with renal tumors each year, of which approximately 500 are Wilm's tumor.

Classification System

The International Classification for Childhood Cancers (ICCC) Group VI of Renal Cancers divides malignant neoplasms into three subgroups [5]:

a. Wilms' tumor, rhabdoid tumor of the kidney, and clear-cell sarcoma of the kidney
b. Renal carcinoma
c. Unspecified malignant renal tumors.

Table VI.1: Number of cases and percent distribution of renal cancers by histologic subtype and age group, all races, both sexes, SEER, 1975-95

Age (in years) at diagnosis	<5	5-9	10-14	15-19	<15	<20
Wilms' tumor	880 (96.2%)[1]	260 (95.9%)	39 (66.1%)	21 (35.0%)	1,179 (94.7%)	1,200 (92.0%)
Rhabdoid tumor of the kidney	12 (1.3%)	*	*	*	12 (1.0%)	12 (0.9%)
Clear cell sarcoma of the kidney	16 (1.8%)	*	*	*	19 (1.6%)	19 (1.6%)
Renal carcinoma	6 (0.7%)	7 (2.6%)	19 (32.2%)	38 (63.3%)	32 (2.6%)	70 (5.4%)
Unspecified renal cancer	*	*	*	*	*	*
Total renal cancers	915	271	59	60	1,245	1,305

[1] Number in parenthesis represents the percentage of all renal cancers for the age group that are represented by the histologic category.
*Less than 5 cases.

Table VI.2: Age-adjusted* incidence rates for renal cancer by race and sex, age <15, SEER, 1975-95

	Both sexes	Males	Females
Renal cancers (VI)			
All races	7.9	7.4	8.4
Whites	8.0	7.4	8.6
Blacks	9.5	9.5	9.6
Wilms' tumor (VIa)			
All races	7.6	7.1	8.1
Whites	7.9	7.3	8.4
Blacks	8.7	8.4	9.0

*Adjusted to the 1970 US standard population

The numbers of cases of these histologic diagnoses among children residing in the SEER areas for the period 1975-95 are shown in Table VI.1. Malignant forms of renal tumors were diagnosed in 1,245 children younger than 15 years of age and in 1,305 children younger than 20 years of age. Wilms' tumor was by far the most common form of renal cancer, accounting for 94.7% of the 1,245 renal cancers in children younger than 15 years of age and 92.0% of the 1,305 renal cancers among the younger than 20 year olds. Occurring much less commonly among the total 1,245 cases of renal cancer in children younger than 15 years of age were rhabdoid tumor of the kidney (12 cases representing 1.0% of renal cancers) and clear cell sarcoma of the kidney (19 cases representing 1.6% of renal cancers). For renal cell carcinoma, there were 32 cases among children younger than 15 years of age (2.6% of renal cancers) and 70 cases among children younger than 20 years of age (5.4% of renal cancers).

Wilms' tumor, rhabdoid tumor of the kidney, and clear cell sarcoma of the kidney are classified together in the ICCC category VIa, while the renal carcinomas are grouped together in the ICCC category VIb. In presenting incidence data, the ICCC category VIa (for which Wilms' tumor represents greater than 95% of cases for all age groups) is designated Wilms' tumor (ICCC VIa), since the incidence patterns and trends for this subcategory are largely determined by cases of Wilms' tumor. When Wilms' tumor is discussed as a single diagnosis, the term Wilms' tumor without any parenthetic modifier is used. Additionally, since incidence rates for renal cancers were low and based on very small numbers in children ages 15-19 (a total of 60 incident cases diagnosed in the SEER areas during 1975-95), presentation of incidence data are generally restricted to renal cancers diagnosed among children younger than 15 years of age.

INCIDENCE

The average annual age-adjusted incidence rates of renal cancer for the years 1975-95 was 7.9 per million for children younger than 15 years of age (Table VI.2) and 6.2 per million for children younger than 20 years of age in the SEER areas. As discussed in greater detail in subsequent paragraphs, incidence rates for renal cancers *in toto* and for Wilms' tumor (ICCC VIa) for the period 1975-95 were slightly higher for females than males and for black children compared to white children. However, for the most recent time period (1990-95), rates were similar for both sexes and for black children and white children.

Age-specific incidence

Age-specific incidence rates of renal cancers in 5-year age groups were highest among children younger than 5 years of age

Table VI.3: Age-specific incidence rates per million for renal cancer by age and race, SEER, 1975-95

	All races	Whites	Blacks
Males			
<5 years	17.8	18.2	21.5
5-9 years	4.9	4.9	6.7
10-14 years	1.2	1.1	2.2
Females			
<5 years	19.1	19.6	21.4
5-9 years	6.6	6.8	7.8
10-14 years	1.2	1.3	1.6

(Table VI.3). Incidence declined markedly with increasing age. The age-incidence pattern for renal cancer in children was driven by that for Wilms' tumor (ICCC VIa), as illustrated in Figure VI.1. Renal cell carcinomas (ICCC VIb) occurred very infrequently among each 5-year age group younger than 15 years of age, but for 15-19 year olds the incidence rate was higher (though still only 0.7 per million) (Figure VI.1). Among the 15-19 year old population, renal carcinomas represented the majority (63%) of cases of renal cancer.

Average annual incidence rates for Wilms' tumor by single year of age are presented in Figure VI.2 for the time periods 1976-84 and 1986-94.[1] The age-specific incidence rates were highest in the first two years of life at 21 per million, with incidence rates subsequently declining to levels less than 2 per million for children older than 9 years of age. Age-specific rates for the other renal cancers were much lower than those for Wilms' tumor. Rhabdoid tumors of the kidney was present almost exclusively in the first 2 years of life, with a peak in infancy of 1.0 per million. Clear cell sarcoma of the kidney also occurred much less frequently than Wilms' tumor, with age-specific incidence in the first 4 years of life ranging between 0.4 and 0.6 per million, and with very few cases occurring among children older than 3 years of age. Renal cell carcinoma was also uncommon among children of any age, with most cases occurring in adolescents 15-19 years of age, for which age-specific incidence rates varied between 0.5 and 0.9 per million.

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

Sex-specific incidence

For the 21 year period from 1975 to 1995, renal cancer incidence rates among children younger than 15 years of age were minimally higher for females compared to males (13 percent higher among females) (Table VI.2). For Wilms' tumor (ICCC VIa), there was also a slight female predominance when the overall period 1975-95 was considered. However, incidence rates for Wilms' tumor (ICCC VIa) were the same for males and females for the most recent period evaluated (1990-95) (Figure VI.3). As illustrated in Figure VI.2, females had slightly higher rates of Wilms' tumor than males in infancy (22.6 per

Figure VI.1: Renal cancer age-specific incidence rates by ICCC subcategory, all races, both sexes, SEER, 1975-95

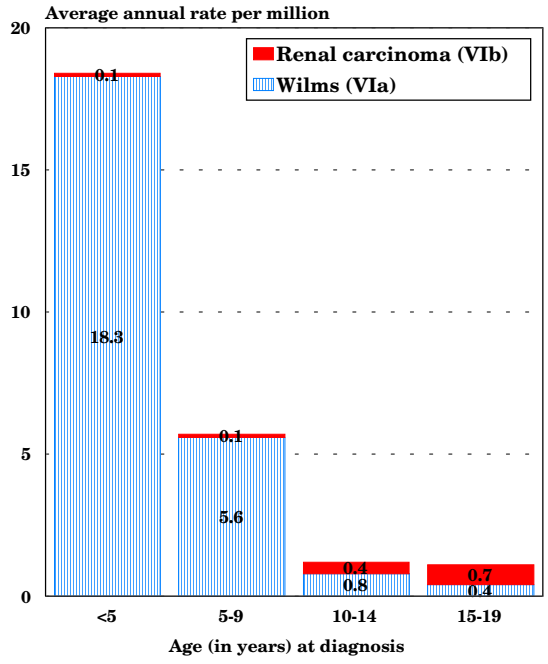


Figure VI.2: Wilms' tumor (VIa) age-specific incidence rates by sex, all races, SEER, 1976-84 and 1986-94

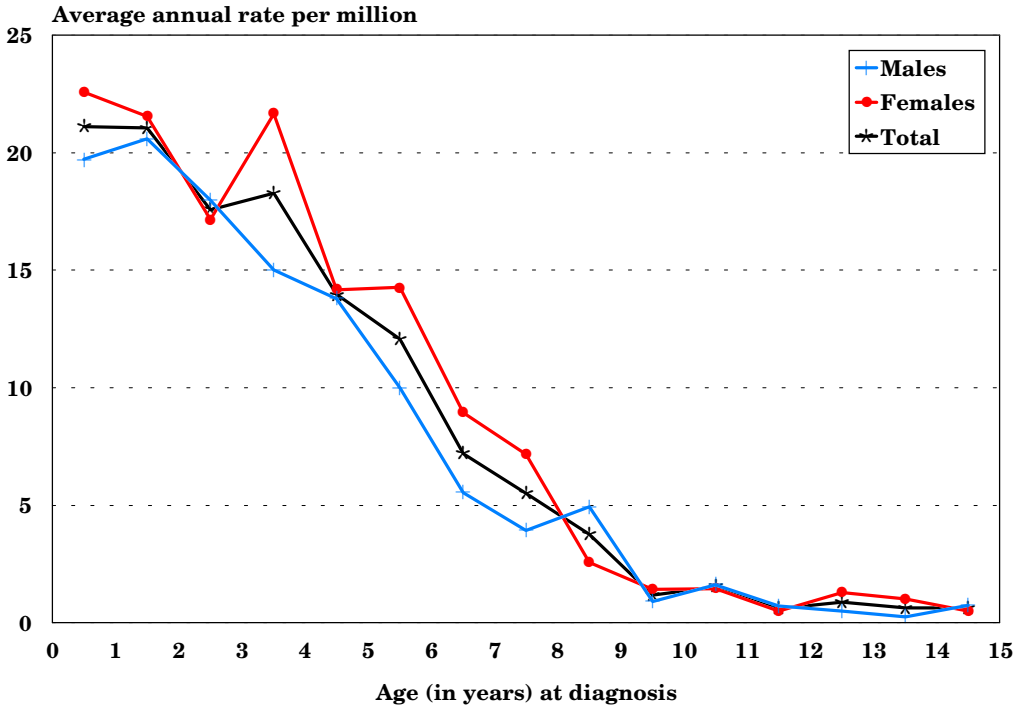
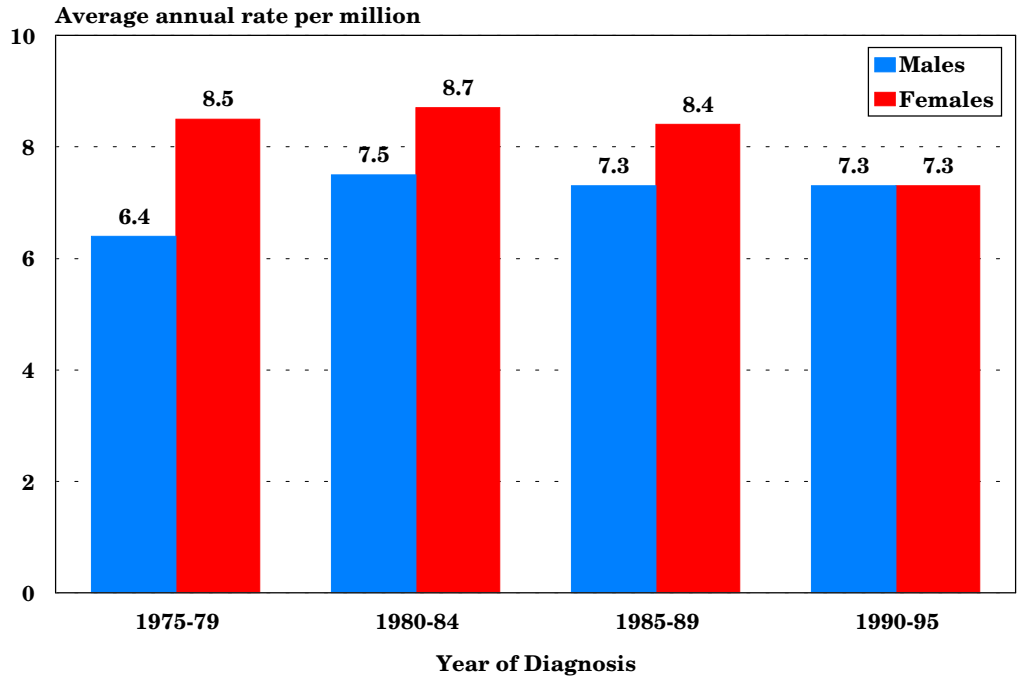
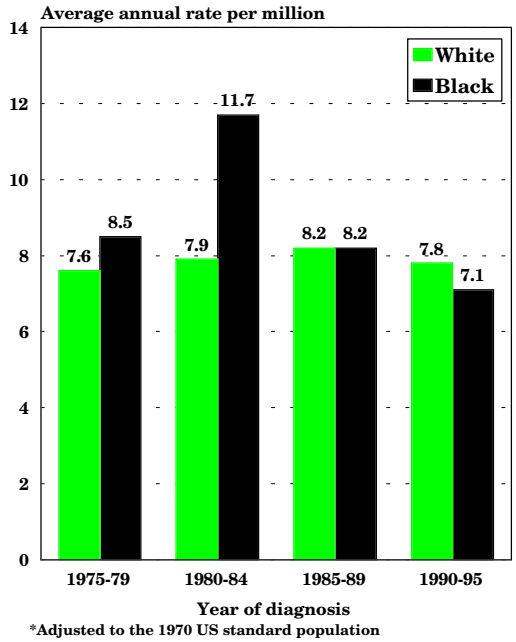


Figure VI.3: Wilms' tumor (VIa) age-adjusted* incidence rates by sex and year of diagnosis, age <15 all races, both sexes, SEER 1975-95



*Adjusted to the 1970 US standard population

Figure VI.4: Wilms' tumor (VIa) age-adjusted* incidence rates by race and year of diagnosis, age <15 both sexes, SEER, 1975-95



million versus 19.7 per million, respectively). Among children 3-8 years old, the age-specific incidence rates for females were generally equal to or greater than rates for males. For females, but not for males, the steady decline in Wilms' tumor incidence rates with increasing age after infancy was apparent except in the fourth year of life during which rates increased in females to levels approaching those seen in infancy, then subsequently declined linearly.

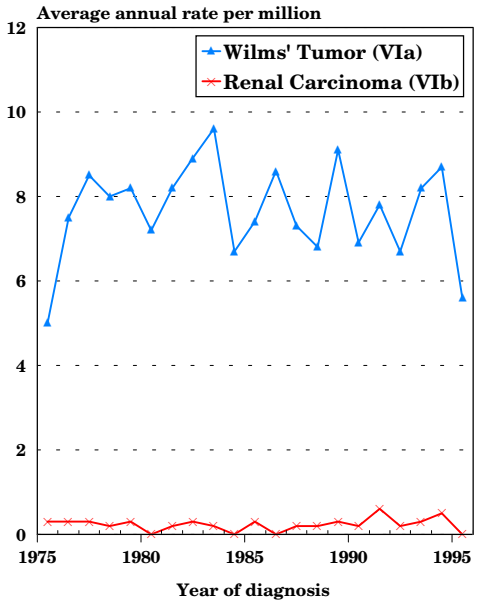
Black-white differences in incidence

Renal cancer and Wilms' tumor (ICCC VIa) incidence rates for the overall period 1975-95 were somewhat higher for black children than for white children (Table VI.2). For the two most recent five year periods (1985-89 and 1990-95), however, incidence rates for Wilms' tumor were similar for black children and white children (Figure VI.4).

TRENDS

The age-adjusted incidence rates for childhood renal cancers did not change significantly during the period 1975-95. Incidence rates for Wilms' tumor (ICCC VIa) varied from year to year (Figure VI.5), but there was no trend for increase or decrease during the 21-year period (estimated annual percentage change = -0.03%). The incidence of renal carcinoma was very low throughout the period (Figure VI.5). For the years 1975-79, Wilms' tumor (ICCC VIa) incidence rates for females (8.5 per million) were higher than for males (6.4 per million) (Figure VI.3). However, rates for males rose between 1975-79 and 1980-84 to 7.5 per million, and thereafter remained fairly stable. Rates for females declined, particularly between 1985-89 and 1990-95, so that females and males had the same incidence rate (7.3 per million) during 1990-95 (Figure VI.3). Incidence rates for Wilms' tumor (ICCC VIa) for white children did not vary much between each 5-6 year time period from 1975 to 1995. Black

Figure VI.5: Trends in renal cancer age-adjusted* incidence rates by type, age <15 all races, both sexes, SEER, 1975-95



children had higher incidence rates for Wilms' tumor (ICCC VIa) in 1975-79 and 1980-84 (8.5 and 11.7 per million, respectively), but the rates dropped for the years 1985-89 and 1990-95 (8.2 and 7.1 per million, respectively) to levels very similar to those for white children (Figure VI.4).

SURVIVAL

For children of all ages, both sexes, and all racial/ethnic groups residing in the SEER areas, the relative 5-year survival rate for children diagnosed with Wilms' tumor younger than 15 years of age during 1985-94 was 92%, compared with a rate of 81% among children diagnosed with this malignancy during 1975-84. Among cases diagnosed during 1985-94, 5-year survival was slightly better for females (94%) than males (91%). For 1985-94, black children had somewhat better outcome than white children (95% versus 92% 5-year survival) (Figure VI.6). Children with rhabdoid tumor are known to have a much poorer outcome than children with Wilms' tumor [44], and among the small number of children with rhabdoid tumor of the kidney followed for survival in SEER areas (n = 8), all either died (6) or were lost to follow-up (2). Children with clear cell sarcoma of the kidney are known to have a somewhat poorer prognosis than children with Wilms' tumor, with 6-year relapse-free survival rates of slightly above 60% based on data from the US National Wilms' Tumor Study Group [45,46]. There were only 13 children with clear cell sarcoma of the kidney evaluable for survival from the SEER areas for the time period 1975-94, and their relative 5-year survival rate was 84%. For children and adolescents with renal carcinomas, 5-year relative survival rates increased from 48% for cases diagnosed in 1975-84 to 83% for cases diagnosed in 1985-94 (although these estimates are

Figure VI.6: Wilms' tumor 5-year relative survival rates by race and sex, age <15, SEER (9 Areas), 1975-84 and 1985-94

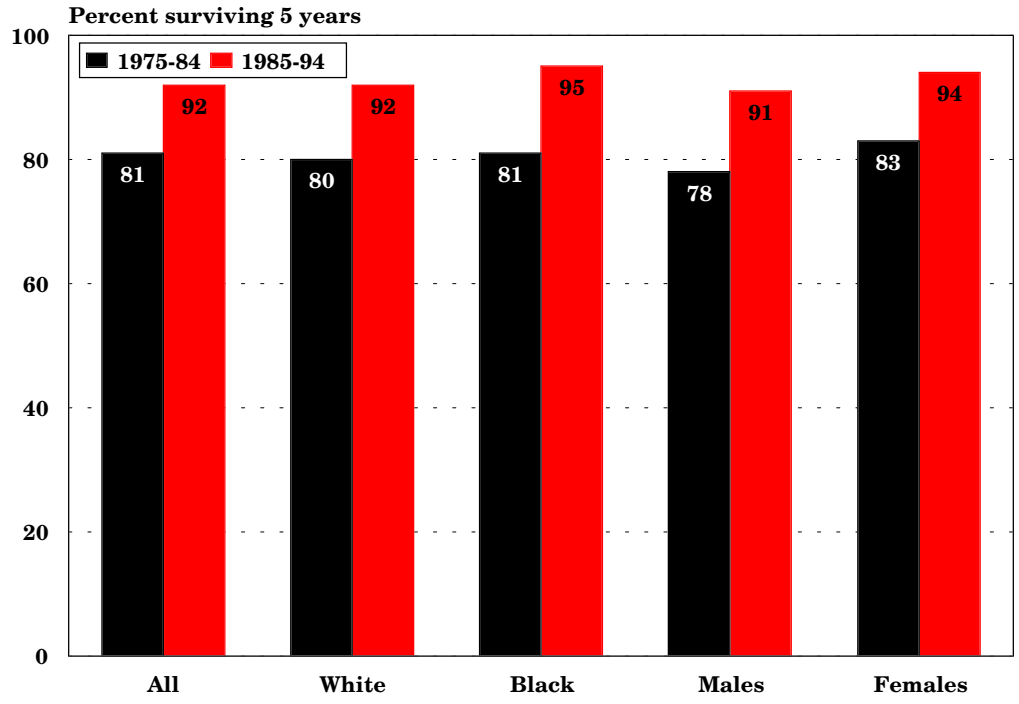


Table VI.4: Current knowledge on causes of Wilms' Tumor (WT)

Exposure or Characteristic	Comments	References
Known risk factors		
Race	Incidence in Asians is about half that in blacks and whites.	10,11
Aniridia, genitourinary anomalies, WAGR syndrome (Wilms' tumor, aniridia, genitourinary abnormalities, mental retardation), Beckwith-Wiedemann syndrome, Perlman syndrome, Denys-Drash syndrome, Simpson-Golabi-Behmel syndrome	Risk is increased in children with these congenital anomalies and genetic conditions. The study of children with WAGR led to the identification of one of the WT genes.	12-22
Factors for which evidence is suggestive but not conclusive		
Paternal occupation	An increased risk for fathers employed as a welder or mechanic has been reported in several studies.	13,26,28
Factors for which evidence is inconsistent or limited		
High birth weight	Association with birth weight over 4,000 grams has been reported in some studies.	13,29,30
Parental exposure to pesticides	One study found an increased risk for parental occupational exposure to pesticides. Another study found an association with household insect extermination.	13,27,31-33
Ionizing radiation (in utero)	Prenatal diagnostic x-ray was associated with increased risk in one study.	34
Maternal consumption of coffee and tea during pregnancy	Three studies reported association with coffee and/or tea; another did not replicate this finding.	31,35,36
Maternal hair dye use during pregnancy	Use was associated with risk in one study, but not in others.	31,36
Maternal medication use during pregnancy	Studies reported associations with various drugs including hormones, antibiotics, dipyrone, metoclopramide, pethrane anesthesia during delivery. Most of these results were found in only a single study.	13,37,38
Maternal occupation	One study found an association with job groupings that included hairdressers, electronic and clothing manufacturing workers, laboratory workers, dental assistants.	26,39

based on only 23 and 29 cases, respectively, from these two time periods).

RISK FACTORS

Despite the rarity of renal cancer in children, a substantial body of epidemiologic, genetic, and molecular studies have contributed important insights to understanding its pathogenesis [3,6,7]. Historically, Wilms' tumor was thought to vary little in incidence throughout the world and was therefore proposed as an "index tumor" of childhood cancer [8]. However, international comparisons based on data through the 1980s showed a greater than threefold difference in age-adjusted incidence rates among populations, with highest rates observed in US and Nigerian blacks, followed by somewhat lower rates in Sweden and US whites, and lowest rates in Chinese and other Asians [9,10]. Data for the years 1973-88 from the US showed similar ethnic variation, with incidence in Asians about half that in blacks, and rates for blacks slightly higher than rates for whites [11] (Table VI.4).

A small proportion of Wilms' tumor cases appear to be heritable including: those patients with bilateral tumors, those occurring in association with aniridia and other congenital anomalies, and those few cases arising in the small number of families with one or more additional cases of Wilms' tumor in close family members [12,13]. Approximately 1.5% of patients in a large series had one or more family members (usually siblings or cousins) with Wilms' tumor based on interview data [14]. Congenital disorders that have been linked with Wilms' tumor include: the Beckwith-Wiedemann syndrome (an overgrowth syndrome associated with macrosomia, omphalocele, macroglossia, and visceromegaly and believed to be linked to an as yet unidentified gene(s) at chromosome region 11p15) [14,15]; the Simpson-Golabi-Behmel syndrome (an X-linked fetal overgrowth disorder caused by mutations in the glypican 3 gene) [15,16]; hemihypertrophy as an isolated abnormality; the Perlman and Sotos syndromes [17-19]; the Denys-Drash syndrome (associated with mutations of the Wilms' tumor suppressor gene WT1) [20-22]; and the WAGR syndrome (Wilms' tumor, aniridia, genitourinary malformations, and mental retardation) that results from deletion of a number of contiguous genes on chromosome 11 including the aniridia gene PAX6 and the WT1 gene [12]. In addition to the heritable conditions cited above, inherited predisposition genes associated with some familial Wilms' tumor cases appear to exist at two other loci (and possibly others not yet identified) [23,24]. However, survivors of Wilms' tumor that is unilateral at diagnosis are at low risk for having children with Wilms' tumor [25].

Most of the analytical and epidemiologic investigations of childhood renal cancer have focused on Wilms' tumor, and very little is known about risk factors for childhood renal carcinoma or the other rarer childhood renal cancer subtypes. Several epidemiological studies have investigated occupational, environmental, and lifestyle characteristics as potential risk factors for Wilms' tumor, but findings to date have been inconsistent [13,26,27]. A few studies have suggested that children of fathers employed as welders or mechanics have increased risk of Wilms' tumor [13,28], but occupational exposure assessment was insufficient to draw firm conclusions [26]. Limited evidence implicates high birth weight in the etiology [29,30]. Parental and postnatal exposures to pesticides have also been linked with increased risk [27,31-33], but these associations were derived from interview data only and have not been confirmed with studies utilizing measurements. A large study in the United Kingdom has reported an association of Wilms' tumor with exposure of the mother to ionizing radiation from diagnostic x-rays

during pregnancy [34.] Some [31,32,35], but not all [36] investigations have found associations between maternal consumption of coffee and tea during pregnancy and risk of Wilms' tumor in offspring. Inconsistent reports have also implicated maternal hair dye use and various types of medications taken or anesthetics to which mothers have been exposed during pregnancy [13,37,38]. The role of maternal occupational exposures has received limited evaluation [26,39].

Most of the reported associations described in the preceding paragraph have not been consistently replicated in multiple, high quality studies in different populations. Future epidemiologic studies may benefit from more detailed exposure assessment, validated by environmental and biologic measurements. In addition, the role of genetic susceptibility and assessment of gene-environment interaction should be considered by evaluation of appropriate molecular markers to better define etiologic pathways for Wilms' tumor.

Recurring molecular abnormalities have been identified in the tumor cells of two of the uncommon renal cancers that occur in young children, rhabdoid tumor of the kidney and congenital mesoblastic nephroma. Rhabdoid tumor, which can develop in the central nervous system and extrarenal sites as well as in the kidney, is associated with tumor cell mutations in the INI1 gene located on chromosome 22 [40,41]. Evaluation of some children with rhabdoid tumors has revealed germline mutations of the INI1 gene [41]. Congenital mesoblastic nephroma is an infantile spindle cell tumor of the kidney with low malignant potential that is virtually identical morphologically to congenital fibrosarcoma [42]. The tumor cells of both of these tumors of infancy have been found to possess fusions of the ETV6 gene (also known as TEL) on chromosome 12 to the NTRK3 gene on chromosome 15 [42,43].

SUMMARY

The descriptive epidemiologic features of Wilms' tumor have been known for a number of years. Associated congenital anomalies and genetic factors have also been subject of much interest. More recent studies have further characterized the specific genetic loci and molecular alterations involved in the development of Wilms' tumor. Several epidemiologic studies have investigated occupational, environmental, and lifestyle factors as risk factors for Wilms' tumor. A number of parental and childhood exposures have been found to be associated with an increased risk of Wilms' tumor. Most of these associations have not been replicated in multiple high quality studies. However, some warrant further evaluation including paternal occupational exposures, pesticide exposure, and certain maternal exposures during pregnancy. Future epidemiologic studies may benefit from the inclusion of molecular markers that may better define etiologic pathways for Wilms' tumor.

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HIGHLIGHTS

Incidence

- Primary neoplasms of the liver are rare in children, comprising only 1.1% of malignancies for children younger than 20 years of age. In the US, 100-150 children are diagnosed with liver cancer each year.
- Primary liver cancer is subdivided into the following histologic subtypes: hepatoblastoma comprises over two-thirds of the malignant tumors of the liver in children and adolescents (79% <15 years of age; 66% <20 years of age) and hepatocellular carcinoma accounts for most of the remaining cases. Hepatoblastoma occurs primarily in children younger than 5 years of age while hepatocellular carcinoma occurs primarily after 10 years of age (Figure VII.2).
- The rate of hepatoblastoma was highest among infants with rates rapidly declining with increasing age (Figure VII.3). In contrast, the incidence of hepatocellular carcinoma increased as age increased (Figure VII.2).
- For those younger than 20 years of age, there was little change in liver cancer incidence during the 21-year period, with rates between 1.4 and 1.6 per million throughout the time period (Table VII.1).
- The incidence of hepatoblastoma for children younger than 15 years of age increased during the 1975-95 period while the incidence of hepatocellular carcinoma decreased during the same period (Figure VII.4).

Survival

- Five-year survival rates for children with hepatoblastoma improved from 51% to 59% between 1976-84 and 1985-94 (Figure VII.5). Survival rates were substantially lower for children and adolescents with hepatocellular carcinoma, with an improvement in 5-year survival rates from 31% for the years 1976-84 to 42% for the years 1985-94 (Figure VII.5).

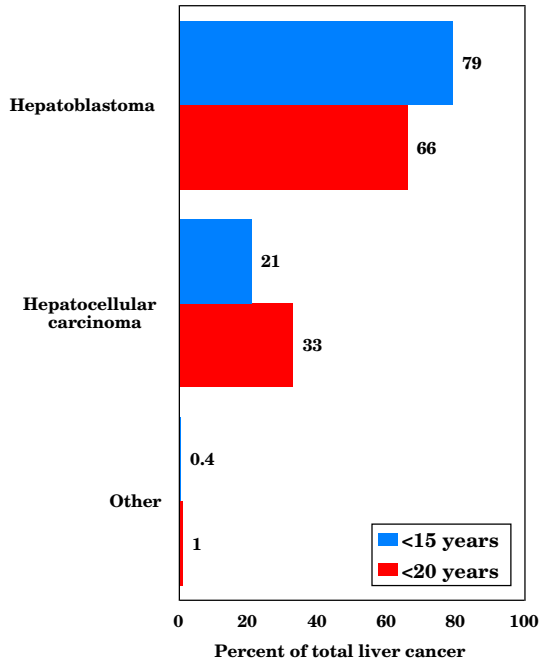
Risk factors

- The etiology of hepatoblastoma is as yet unknown but there are some tantalizing clues (Table VII.2).

INTRODUCTION

Primary neoplasms of the liver are rare in children, comprising only 1.1% of malignancies in SEER areas for children younger than 20 years of age. The ICCC category for liver cancers (VII) is subdivided into the following histologic subtypes: hepatoblastoma (VIIa), hepatic carcinomas (hepatocellular carcinoma) (VIIb), and "unspecified" tumors of the liver (VIIc) [1]. In the US, 100-150 children younger than 20 years of age are diagnosed with hepatic tumors each year. Hepatoblastoma comprises over two-thirds of the malignant tumors of the liver in children (79% younger than 15 years of age; 66% younger than 20 years of age) and hepatocellular carcinoma accounts for most of the remaining cases. Most patients with hepatoblastoma are younger than 4 years of age at diagnosis, while hepatocellular carcinoma occurs primarily after 10 years of age.

Figure VII.1: Distribution of liver cancer by histology and age, all races both sexes, SEER 1975-95



INCIDENCE

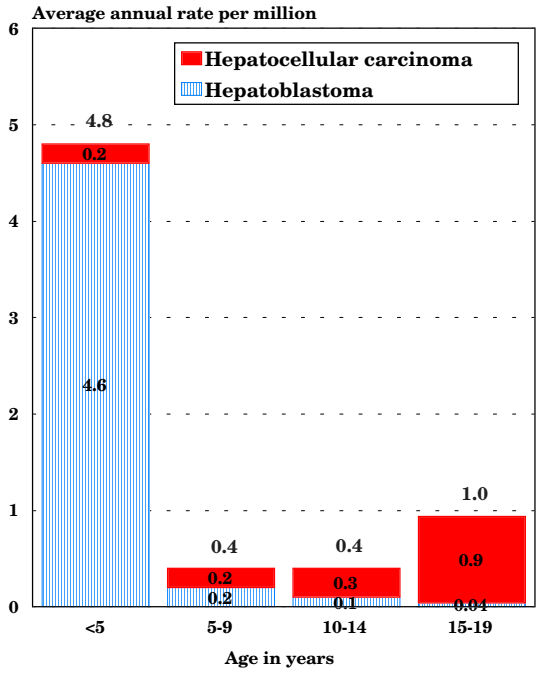
During the 21-year period from 1975 through 1995, there were 316 children younger than 20 years of age in SEER areas who were diagnosed with a primary liver cancer, with 262 (83%) of these children being younger than 15 years of age at the time of diagnosis. Figure VII.1 shows that the majority of these cancers were hepatoblastomas, with the remainder being almost exclusively hepatocellular carcinomas. For the entire 21-year period, hepatoblastoma represented 79% of the liver cancers for the younger than 15 year age group, although for the most recent 6-year period (1990-95) hepatoblastoma accounted for an even higher proportion (90%) of childhood liver cancers.

Age-specific incidence

The incidence rates for hepatoblastoma and hepatocellular carcinomas were very age-dependent. Among children younger than 5 years of age, over 95% of liver cancers were hepatoblastoma, whereas hepatoblastoma was distinctly uncommon for older age groups (Figure VII.2). Within the younger than 5-year age group, the rate of hepatoblastoma was highest among infants with rates rapidly declining with increasing age (Figure VII.3).[1] During the most recent period (1986-94), the incidence rate during infancy was approximately 11.2 per million. In contrast to the age-incidence relationship for hepatoblastoma, the incidence of hepatocellular carcinoma increased with each successive 5-year age group, with rates for 15-19 year olds (0.9 per million) being substantially higher than for any of the younger age groups (Figure VII.2).

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

Figure VII.2: Liver cancer age-specific incidence rates by histology and age all races, both sexes, SEER, 1986-95



Sex and race-specific incidence

For children younger than 15 years of age, the incidence of liver cancers was slightly higher in males than females (male:female ratio = 1.2) and somewhat lower in black children compared with white children (1.3 per million versus 1.6 per million). For children younger than 20 years of age, incidence rates were similar for blacks and whites (1.4 per million versus 1.5 per million) and were slightly higher for males than females (male:female = 1.2). The incidence of hepatoblastoma was slightly higher in males than females (male:female = 1.2), while the incidence of hepatocellular carcinoma was similar in both sexes (male:female = 1).

TRENDS

The incidence for total liver cancers in children younger than 15 years of age increased slightly from 1975 to 1995. The rate was 1.4 per million for 1975-79 and increased to 1.7 per million for 1990-95 (Table VII.1). For children younger than 20 years of age, there was little change in liver cancer incidence during the 21-year period, with rates between 1.4 and 1.6 per million throughout the time period (Table VII.1).

The incidence of hepatoblastoma increased markedly during the 1975-95

Figure VII.3: Hepatoblastoma and hepatocellular carcinoma age-specific incidence rates all races, both sexes SEER, 1976-84, 1986-94

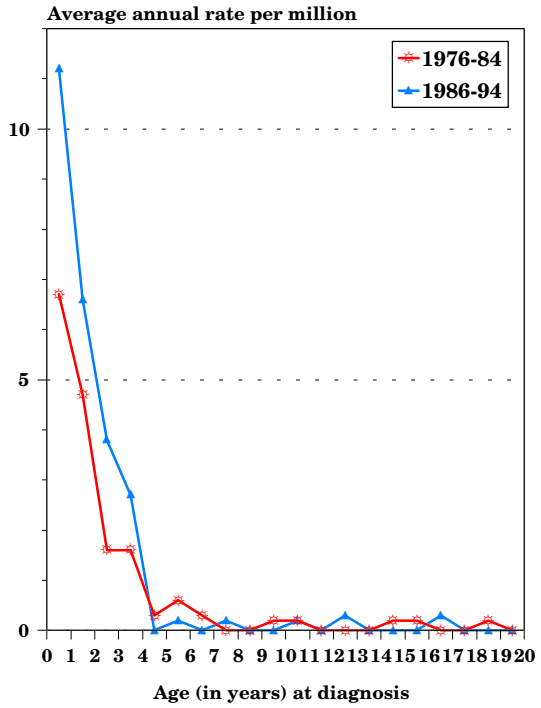


Table VII.1: Age-adjusted* incidence rates per million of liver cancers by age group, type, and time period, all races, both sexes, SEER, 1975-95

<15 Years

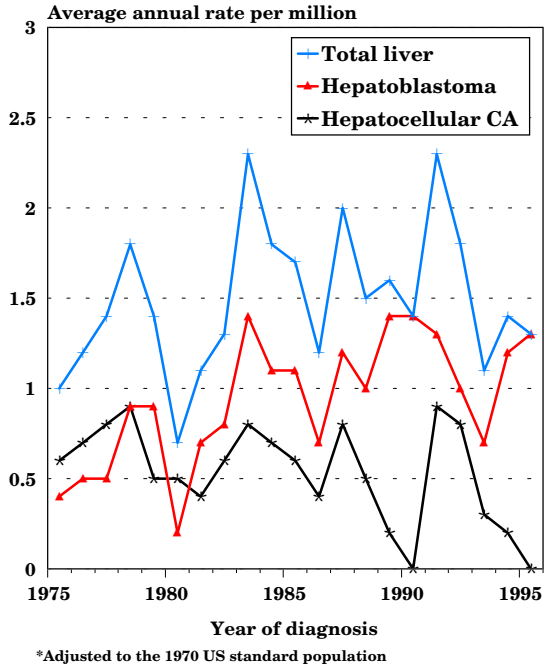
Diagnosis	ICCC Category	1975-79	1980-84	1985-89	1990-95	1975-95
Hepatic tumors (total)	VII(total)	1.4	1.6	1.7	1.7	1.6
Hepatoblastoma	VIIa	0.8	1.1	1.4	1.5	1.3
Hepatocellular carcinoma	VIIb	0.6	0.5	0.3	0.2	0.4

<20 Years

Diagnosis	ICCC Category	1975-79	1980-84	1985-89	1990-95	1975-95
Hepatic tumors (total)	VII(total)	1.4	1.4	1.6	1.5	1.5
Hepatoblastoma	VIIa	0.6	0.9	1.1	1.1	1.0
Hepatocellular carcinoma	VIIb	0.7	0.6	0.5	0.4	0.5

*Adjusted to the 1970 US standard population

Figure VII.4: Trends in liver cancer age-adjusted* incidence rates by histology, age <20 all races, both sexes, SEER, 1975-95



*Adjusted to the 1970 US standard population

period (Figure VII.4). The incidence rate for children younger than 15 years of age from 1975-79 was 0.8 per million and increased to 1.5 per million for 1990-95 (Table VII.1). The incidence of hepatocellular carcinoma decreased during the period 1975-95, in contrast to the increase observed for hepatoblastoma (Figure VII.4). For children younger than 15 years of age, the rate decreased from 0.6 per million in 1975-79 to 0.2 per million for 1990-95 (Table VII.1). Possible changes over time in the assignment by histologic category could only account for a small portion of the observed opposite trends in incidence for hepatoblastoma and hepatocellular carcinoma.

SURVIVAL

Five-year survival rates for children with hepatoblastoma improved from 51% to 59% between 1975-84 and 1985-94 (Figure VII.5). Survival rates were substantially lower for children and adolescents with hepatocellular carcinoma, with an improvement in 5-year survival rates from 31% for the years 1975-84 to 42% for the years 1985-94 (Figure VII.5).

RISK FACTORS

Table VII.2 briefly summarizes current knowledge on causes of hepatoblastoma. The etiology of hepatoblastoma is as yet unknown but there are some tantalizing clues. One case-control study reported elevated odds ratios with specific parental occupational exposures, including maternal exposures to metals, petroleum products, and paints, and paternal exposures to metals [2]. There have also been isolated case reports of hepatoblastoma occurring in association with fetal alcohol syndrome [3], oral contraceptive use during pregnancy [4], hormonal treatment for sterility [5], and liver transplantation in the mother combined with immunosuppressive treatment throughout pregnancy [6]. Investiga-

Figure VII.5: Hepatoblastoma and hepatocellular carcinoma 5-year relative survival rates age <20, all races, both sexes SEER (9 areas), 1975-84 and 1985-94

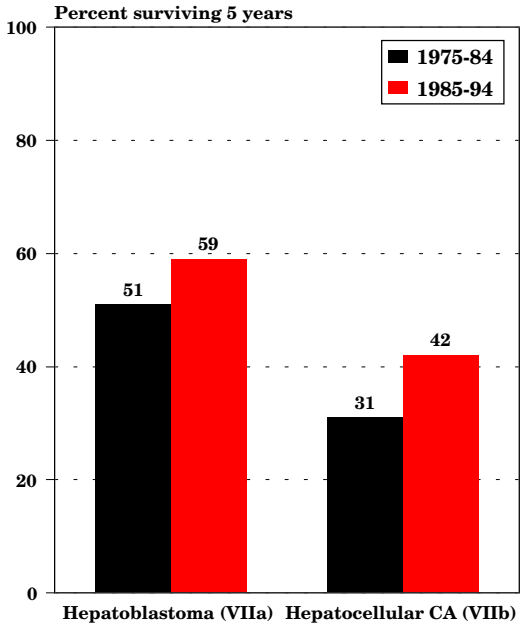


Table VII.2: Current knowledge on causes of hepatoblastoma

Exposure or Characteristic	Comments	References
Known risk factors		
Beckwith-Wiedemann syndrome, hemihypertrophy	Hepatoblastoma, Wilms' tumor and adrenocortical carcinoma are associated with these syndromes that involve organomegaly.	11,20,21
Family history of familial adenomatous polyposis and Gardner's syndrome	Both these syndromes involve multiple colonic polyps, have an autosomal dominant inheritance, and are caused by mutations in the APC gene.	10,22-24
Factors for which evidence is inconsistent or limited		
Parental occupational exposures	Associations with metals, petroleum products, paints and pigments were reported from the only case-control study done to date.	2

tors in Japan recently noted that hepatoblastoma accounted for more than 50% of early malignancies among Japanese children who were of extremely low birth weight (<1000gm) [7,8]. This finding raises the possibility that factors associated with prematurity and its treatment may play a role in the occurrence of hepatoblastoma. As a result, the marked improvement in survival in recent years of extremely low birth weight infants could in part be responsible for a notable increase in hepatoblastoma rates in the United States [9].

Hepatoblastoma has been associated with familial adenomatous polyposis as well as with syndromes involving organomegaly (e.g., Beckwith-Wiedemann syndrome and isolated hemihypertrophy) [10,11]. Genes that are altered in the tumor cells from some cases of hepatoblastoma and that likely play an important role in the pathogenesis of hepatoblastoma include the APC gene (which is responsible for familial adenomatous polyposis) and the b-catenin gene [12]. Another molecular abnormality observed in some cases of hepatoblastoma is loss of heterozygosity in the region of chromosome 11 that is associated with Beckwith-Wiedemann syndrome [13].

Hepatocellular carcinoma in children is most common in regions of the world where adult hepatocellular carcinoma is also highly prevalent, for instance in sub-Saharan Africa and Eastern Asia [1] and among Alaskan Natives [14]. Chronic infection with hepatitis B virus has been implicated as the leading cause of hepatocellular carcinoma in children and young adults. Universal hepatitis B immunization will prevent the carrier state in children and will lead to a dramatic reduction in hepatocellular carcinoma, as demonstrated during the past decade in Taiwan [15]. Chronic infection with hepatitis C virus (e.g., among hemophiliac males) is an emerging risk factor for hepatocellular carcinoma during adolescence [16]. Genes that are altered in the tumor cells from some cases of hepatocellular carcinoma and that may play a role in its pathogenesis include the β-catenin gene [17,18] and the MET protooncogene [19].

SUMMARY

Liver cancers are uncommon in children and represented only 1.1% of malignancies in SEER areas for children younger than 20 years of age, with an annual incidence rate of 1.5 per million (1975-95). Hepatoblastoma was the most common malignancy of the liver in children and its incidence was highest during the first year of life and decreased rapidly with increasing age. Hepatocellular carcinoma was the second most common malignancy of the liver and occurred primarily among adolescents. While the incidence of hepatoblastoma increased from 1975-95, the incidence of hepatocellular carcinoma decreased.

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HIGHLIGHTS

Incidence

- Malignancies of the bone, with an average annual incidence rate of 8.7 per million children younger than 20 years of age, comprised about 6% of childhood cancer reported by SEER areas from 1975-95.
- In the US, 650-700 children and adolescents younger than 20 years of age are diagnosed with bone tumors each year of which approximately 400 are osteosarcoma and 200 are Ewing's sarcoma.
- The two types of malignant bone cancer that predominated in children were osteosarcomas and Ewing's sarcomas, about 56% and 34% of the malignant bone tumors, respectively.
- Osteosarcomas derive from primitive bone-forming mesenchymal stem cells and most often occur near the metaphyseal portions of the long bones. The Ewing's sarcomas are believed to be of neural crest origin and occur roughly evenly between the extremities and the central axis.
- For all bone cancer combined, a steady rise in incidence rates occurred with increasing age between ages 5 and 10, and a steeper rise began at age 11 until age 15 coinciding with the adolescent growth spurt. The peak incidence of bone cancer (19 per million) occurred at age 15, after which rates showed a decline (Figure VIII.2).
- Rates did not differ much by sex among younger children, but males had higher incidence than females during adolescence (Figure VIII.4).
- For osteosarcoma, black children had a higher overall rate than did white children (Figure VIII.7). For Ewing's sarcoma the racial variation in rates was dramatic: white children had an approximate 6-fold higher incidence rate than black children (Figure VIII.8).
- The most frequent site of bone cancer development was the long bones of the lower limbs for osteosarcomas and the central axis for Ewing's sarcomas (Figure VIII.9).

Survival

- The 5-year relative survival for children with bone cancer improved from 49% in the period 1975-84, to 63% in the period 1985-94. The survival rates improved between the two time periods for both osteosarcoma (Figure VIII.11) and Ewing's sarcoma (Figure VIII.12).
- Survival rates for osteosarcoma were higher than those for Ewing's sarcoma especially in the earlier time period (Figures VIII.11 and VIII.12).

Risk factors

- Although directed ionizing radiation exposure and a few genetic susceptibility syndromes are associated with increased risk of osteosarcoma, to date no factor has emerged to explain even a modest proportion of cases (Table VIII.2). Other than the important racial difference in incidence between black and white children, no environmental factor or other characteristic has yet been shown to be a strong risk factor for Ewing's sarcoma (Table VIII.3).

INTRODUCTION

This chapter describes the descriptive epidemiology of childhood bone cancer, including short discussions on survival and risk factors for occurrence. Sarcomas of the bone and cartilage are a diverse group of tumors comprising about 0.5% of all malignancies in humans. The relative magnitude of bone cancer, however, is considerably higher in children than in adults [1].

About half of bone tumors that occur among children are of nonmalignant histopathology [2]. Because SEER case reporting is limited to primary malignant neoplasms, the information presented in this report will refer only to malignancies of the bone (bone cancer). In the International Classification of Childhood Cancer (ICCC) classification system, bone cancers are categorized as osteosarcomas, Ewing's sarcomas, chondrosarcomas, 'other specified malignant bone tumors' and 'unspecified malignant bone tumors' [3]. The two types of bone cancer that predominate in children are osteosarcomas and Ewing's sarcomas. For the 21-year period of 1975-95, there were 1,657 children younger than 20 years of age in the SEER areas who were diagnosed with a primary bone malignancy. Osteosarcomas represented about 56% of these tumors and Ewing's sarcomas an additional 34%. In the US, 650-700 children and adolescents younger than 20 years of age are diagnosed with bone tumors each year of which approximately 400 are osteosarcoma and 200 are Ewing's sarcoma.

Osteosarcomas derive from primitive bone-forming mesenchymal stem cells and most often occur near the metaphyseal portions of the long bones [3]. There is a bimodal age distribution of osteosarcoma incidence, with peaks in early adolescence and in adults older than 65 years of age [1]. The Ewing's sarcomas, which include Ewing's, atypical Ewing's, and the peripheral primitive neuroectodermal tumor of bone, are believed to be of neural crest

Figure VIII.1: Percent distribution of bone cancers by histology and age group, all races, both sexes, SEER, 1975-95

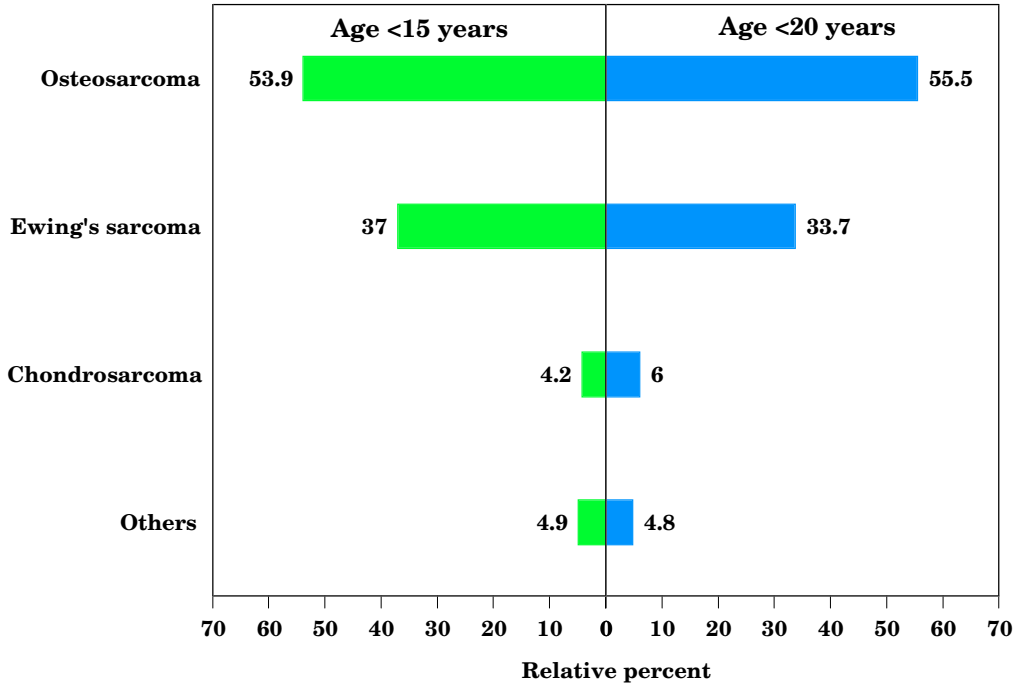
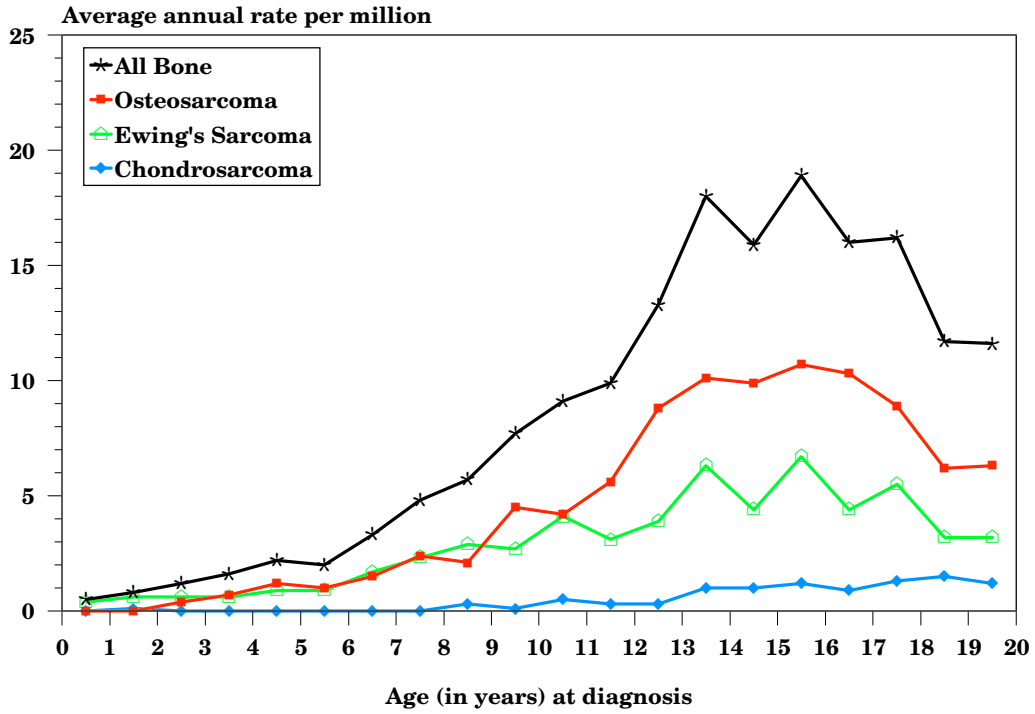


Figure VIII.2: Bone cancer age-specific incidence rates by histology all races, both sexes, SEER, 1976-84 and 1986-94 combined



origin and occur roughly evenly between the extremities and the central axis [5]. Ewing's sarcoma is a disease primarily of childhood and young adults; occurrence in older adults is extremely rare [1]. Chondrosarcomas, which after osteosarcomas are the most common of the bone malignancies among adults [1], are very rare in children. Figure VIII.1 presents the relative distribution of bone cancer by histologic types, both for children younger than 15 years of age and younger than 20 years of age.

INCIDENCE

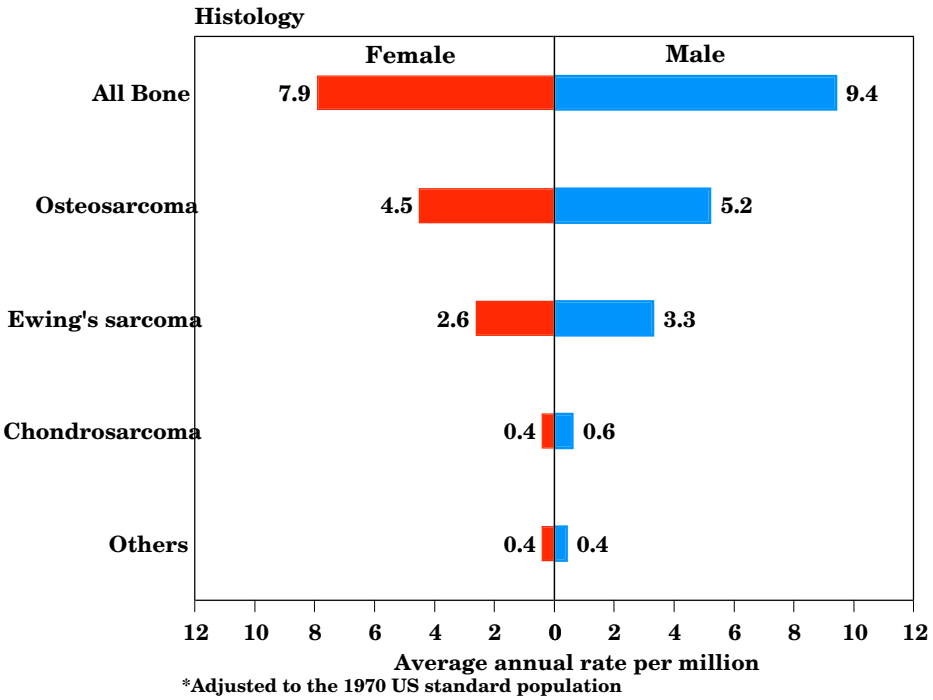
Malignancies of the bone, with an average annual incidence rate of 8.7 per than 20 years, unless otherwise noted). The histology-specific rates were 4.8 per million for osteosarcoma, 2.9 per million for Ewing's sarcoma and 0.5 per million for chondrosarcoma.

Age-specific incidence

Bone cancer represented only 0.5% of all malignancies among children younger than 5 years, compared with 5% for those 5-9 years, 11% for those 10-14 years, and 8% for adolescents 15-19 years. Figure VIII.2 shows 1-year age-specific rates for all bone cancer combined and for specific histologic subtypes. [1] For all bone cancer combined, a steady rise in rates occurred from ages 5 through 10, and a steeper rise began at age 11. The increase in rates among older children appeared to coincide with the adolescent growth spurt. The peak incidence of bone cancer (19 per million) occurred at age 15, after which rates showed a decline. Incidence of chond-

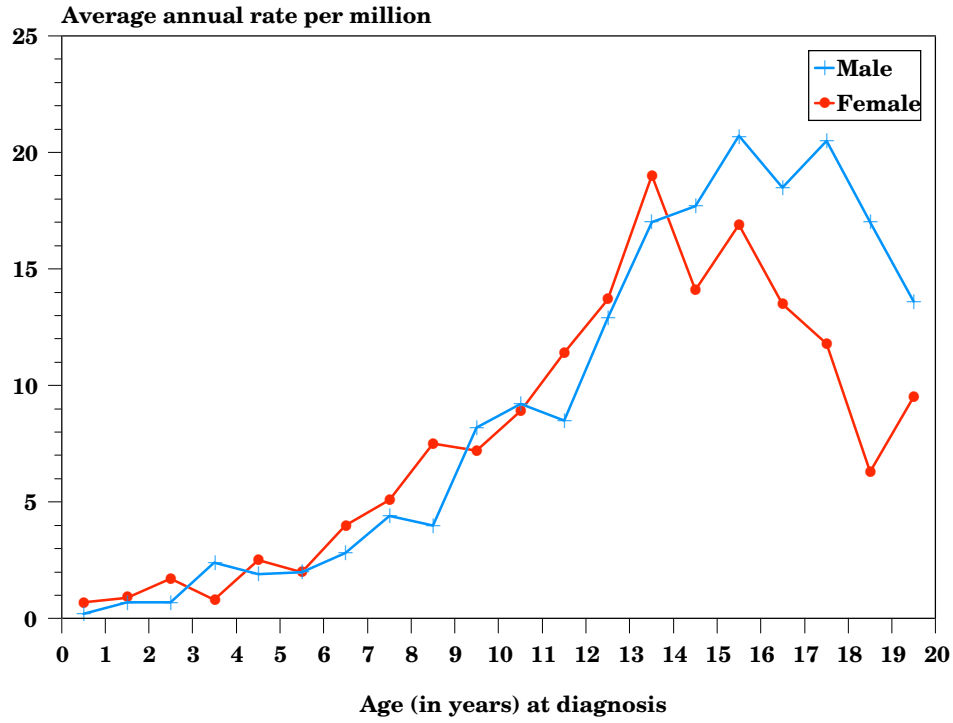
[1] Enumeration of the population at risk by single years of age was available only for the census years 1980 and 1990. The US Bureau of the Census provides intercensal population estimates by 5-year age groups, but not by single years of age. Therefore, the population estimates for 1980 were used in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

Figure VIII.3: Bone cancer age-adjusted incidence* rates by type and sex, age <20, all races, SEER, 1975-95



*Adjusted to the 1970 US standard population

Figure VIII.4: Bone cancer age-specific incidence rates by sex, all races, SEER, 1976-84 and 1986-94

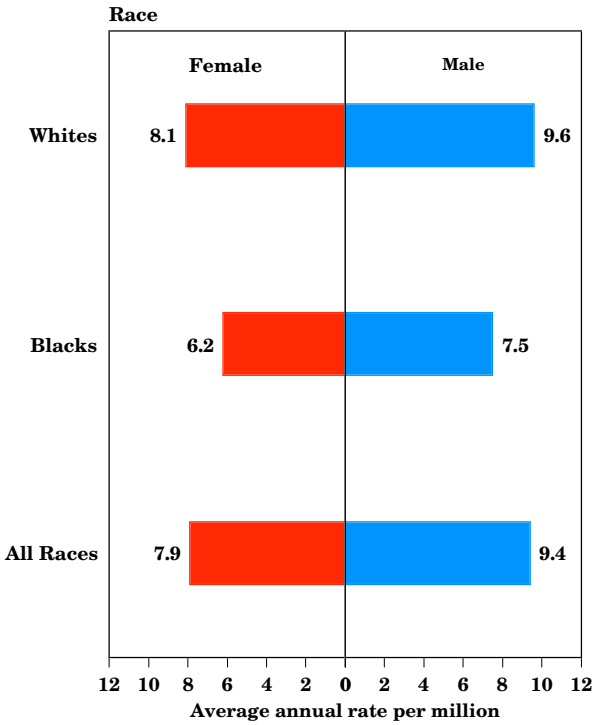


rosarcoma was very low at all ages. Rates of osteosarcoma and Ewing's sarcoma were similar until about age 10, when substantially higher rates of osteosarcoma became apparent.

Sex-specific incidence

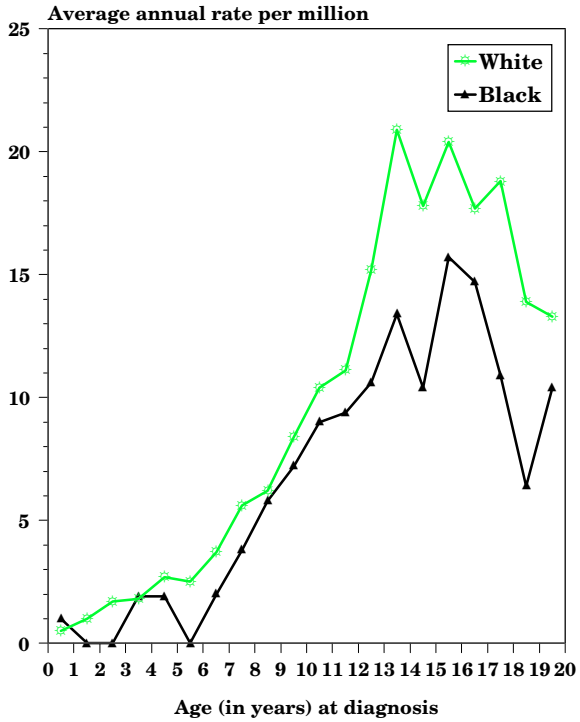
The incidence rates of osteosarcoma and Ewing's sarcoma were slightly higher for males relative to females, albeit the absolute differences in rates were quite small (Figure VIII.3). Figure VIII.4 presents 1-year age and sex specific incidence rates for all bone cancer combined. The incidence pattern by age is similar for males and females, although from age 14 through 19 male rates are higher than female rates. For females, rates of bone cancer peaked at age 13, while the highest rates for males occurred from ages 15 through 17.

Figure VIII.6: Bone cancer age-adjusted* incidence rates by race and sex, age <20, SEER, 1975-95



*Adjusted to the 1970 US standard population

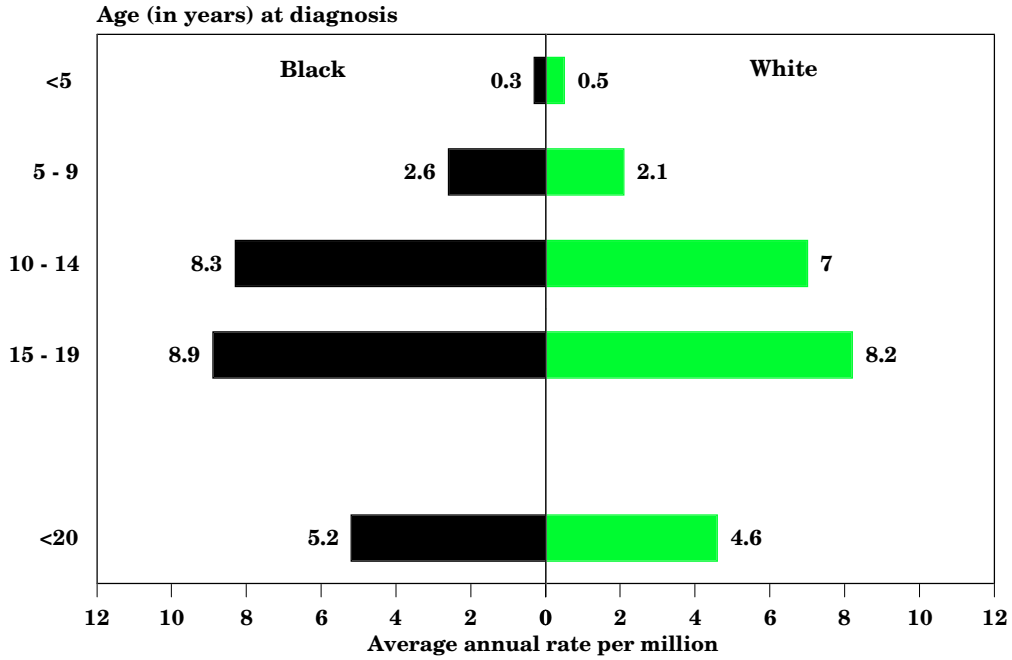
Figure VIII.5: Bone cancer age-specific incidence rates by race, both sexes, SEER, 1976-84 and 1986-94 combined



Black-white differences in incidence

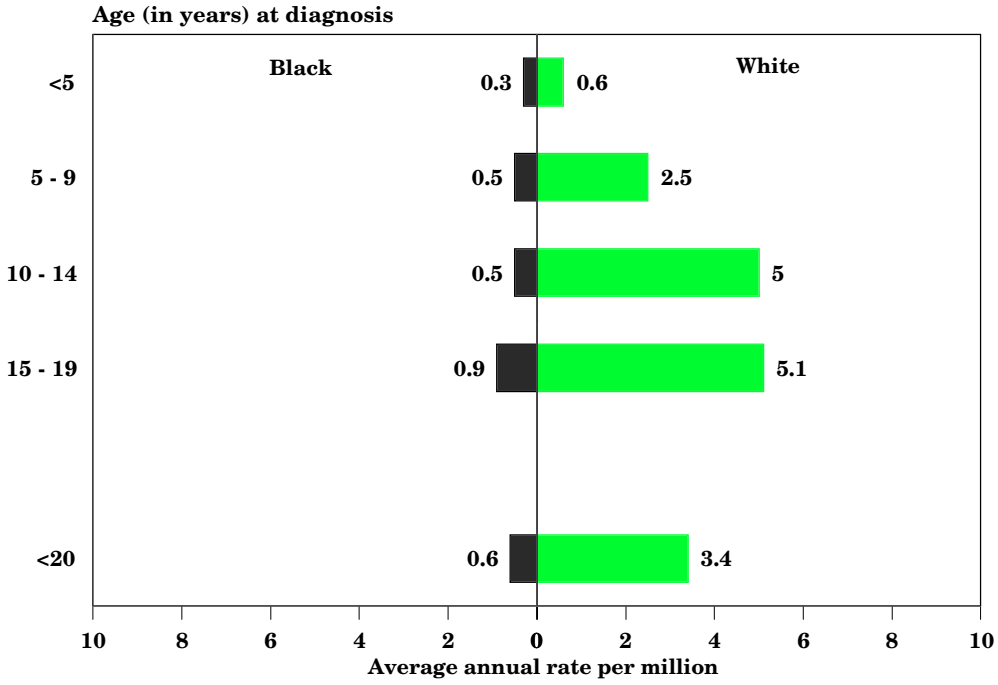
One-year age specific incidence rates of bone cancer are shown in FigureVIII.5 for white and black children. The age pattern of bone cancer incidence was quite similar by race, although higher rates among whites were seen at virtually all ages. The overall incidence rate among white children was 8.8 per million compared with 6.8 per million for black children. Figure VIII.6 shows that both white males and females had higher rates than blacks of the same sex, at about the same ratios. This racial disparity in bone cancer incidence was not consistent across histologic subtypes. For osteosarcoma, black children had a higher overall rate than did white children (Figure VIII.7). Rates were slightly higher in blacks than in whites for each age group except for those younger than 5 years of age. For Ewing's sarcoma the racial varia-

Figure VIII.7: Osteosarcoma age-adjusted* incidence rates by age group and race, both sexes, SEER, 1975-95



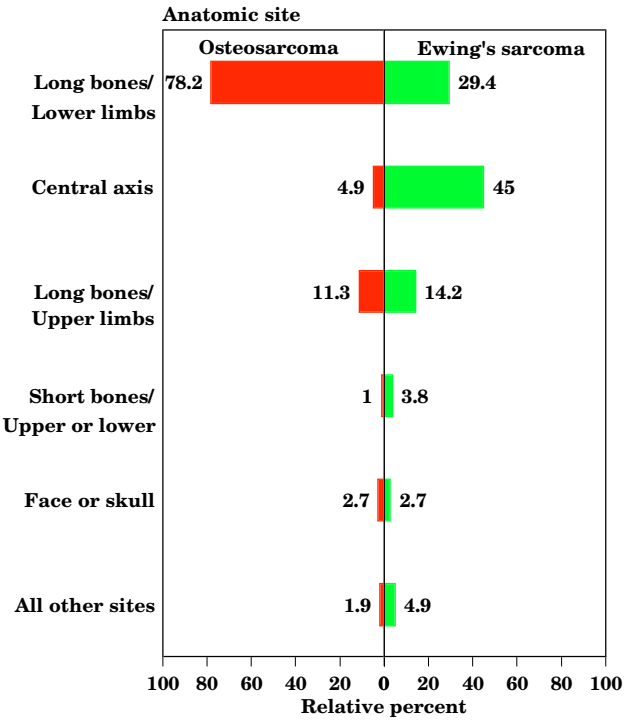
*Adjusted to the 1970 US standard population

Figure VIII.8: Ewing's sarcoma age-adjusted* incidence rates by age group and race, both sexes, SEER, 1975-95



*Adjusted to the 1970 US standard population

Figure VIII.9: Anatomic site distribution of bone cancer by histology, age <20, all races, both sexes SEER, 1975-95



tion in rates was dramatic: white children had an approximate 6-fold higher incidence rate than black children (Figure VIII.8), thus entirely accounting for the white preponderance in overall bone cancer rates. This strong racial difference was apparent in all age groups. The fact that black children in the US rarely develop Ewing's sarcoma has been observed for many years, but the protective etiology has yet to be elucidated. It is interesting to note that in several African countries the ratio of Ewing's sarcoma to osteosarcoma is very similar to that of US blacks [6].

Bone cancer location

The most frequent site of bone cancer development (57%) was the long bones of the lower limbs. The site distribution of Ewing's sarcomas, however, differed substantially from that of osteosarcomas (Figure VIII.9). The long bones of the lower limb were the site of 78% of osteosarcomas, but only 29% of Ewing's sarcomas. The central axis (vertebral column; rib, sternum, and clavicle; pelvic, sacrum, and coccyx) was the most frequent site for Ewing's sarcomas (45%), where osteosarcomas are relatively unusual.

Table VIII.1: Average age-adjusted* incidence rates per million children for bone cancer all races, both sexes, age<20, SEER 1975-95

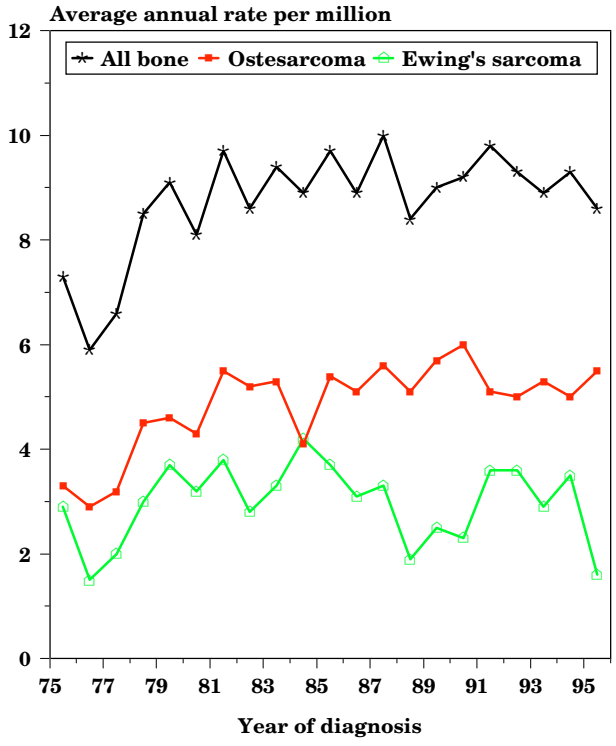
	1975-79	1980-84	1985-89	1990-95
Osteosarcoma	3.7	4.9	5.4	5.3
Ewing's Sarcoma	2.6	3.4	2.9	2.9
All Bone Cancer	7.4	9.0	9.2	9.2

*Adjusted to the 1970 US standard population

Trends in incidence rates

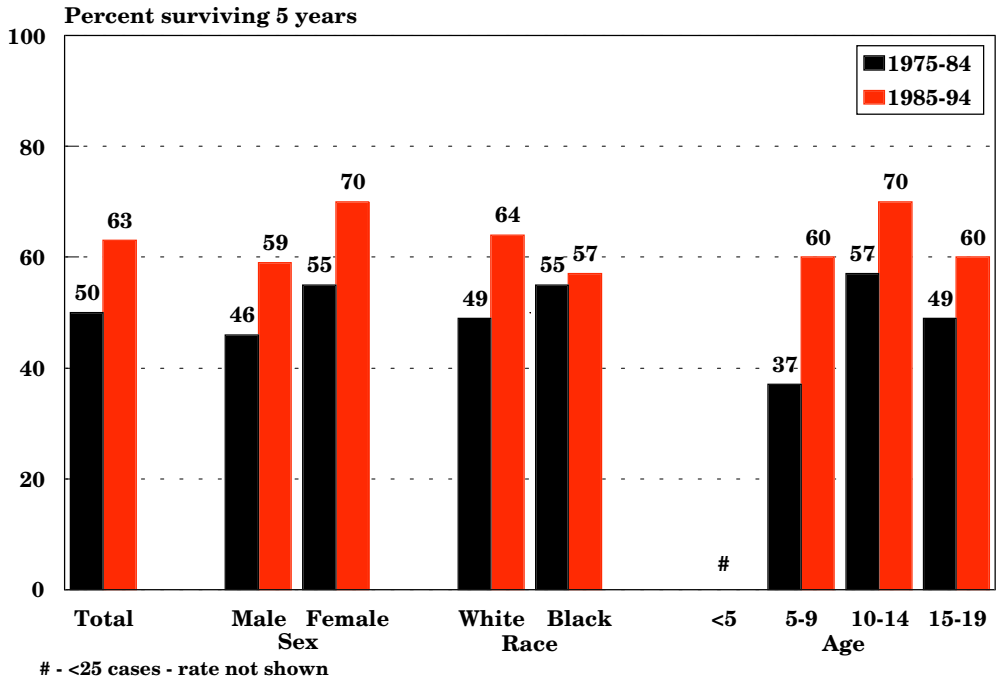
Figure VIII.10 shows histology-specific incidence rates by single year of diagnosis from 1975-95. It is unclear why rates of both osteosarcoma and Ewing's sarcoma were lower from 1975-78 than in later years. Table VIII.1 shows the average rates of bone cancer during the time periods of this study.

Figure VIII.10: Trends in bone cancer age-adjusted* incidence rates by histology, age <20 all races both sexes, SEER, 1975-95



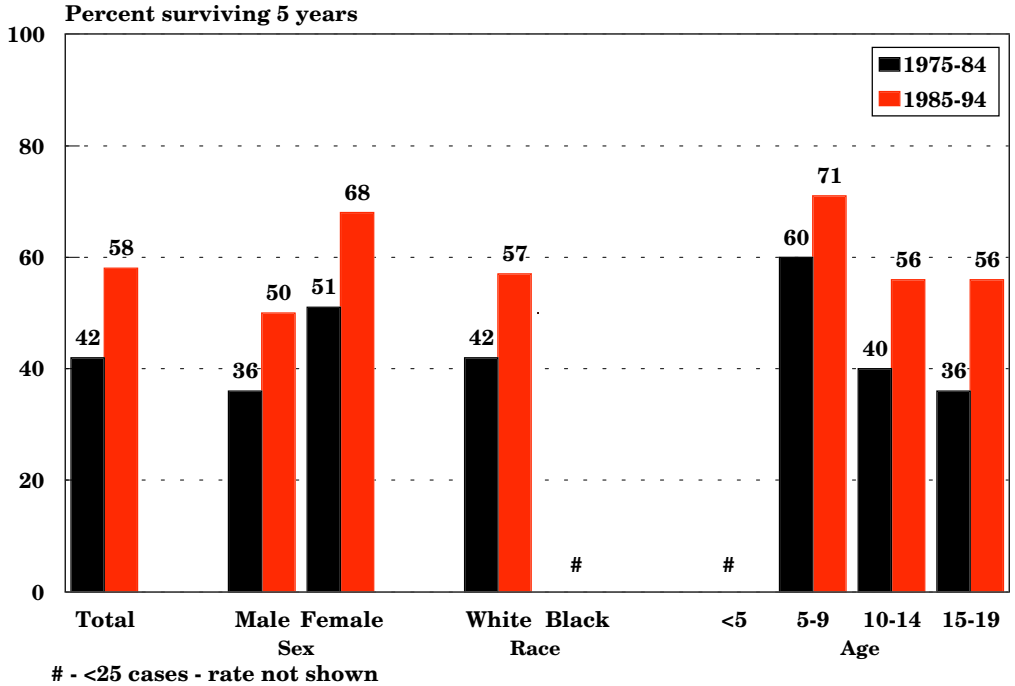
*Adjusted to the 1970 US standard population

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



- <25 cases - rate not shown

Figure VIII.12: Ewing's sarcoma 5-year relative survival rates by sex, race, age and time period, SEER (9 areas), 1975-84 and 1985-94



- <25 cases - rate not shown

SURVIVAL

The 5-year relative survival for children with bone cancer improved from 49% in the period 1975-84, to 63% in the period 1985-94. The time period for relative survival is 1985-94 unless otherwise noted. Females had better 5-year survival probability (70%) than males (59%) and there was only a slight difference in survival between blacks (60%) and whites (63%). No notable survival differences were observed across 5-year age groups. For osteosarcoma the 5-year relative survival was 63% (59% for males, 70% for females). Prognosis for Ewing's sarcoma was somewhat poorer than for ostoesarcoma. The overall 5-year relative survival for Ewing's sarcoma was 58%, and again there was a notable difference by sex (50% for males, 68% for females). Although survival did not differ substantially by tumor site for osteosarcoma, children with Ewing's sarcoma of the pelvic, sacrum, or coccyx has survival probabilities of under 35%.

Table VIII.2: Current knowledge on causes of osteosarcoma

Exposure or Characteristic	Comments	References
Known risk factors		
Prior treatment for childhood cancer with radiation therapy and/or chemotherapy	There is an increased risk following radiotherapy for childhood cancer. Independent of radiotherapy, treatment with alkylating agents increases the risk of developing osteosarcoma.	7-9
Hereditary retinoblastoma, Li-Fraumeni syndrome, and Rothmund-Thomson syndrome	Increased risk is well documented for these genetic conditions.	10-13
Radium	High doses of the radioisotope radium are known to cause osteosarcoma in adults. Whether the low levels sometimes found in drinking water confer risk to children or adults is unknown.	1,14
Factors for which evidence is limited or inconsistent		
Growth and development	There has been some suggestion that taller stature is associated with an increased risk, but the results of more recent studies do not support this finding. One study showed an association with earlier age at onset of secondary sex characteristics in females and lower weight gain during pubertal growth spurt in males.	15-19
Prior trauma to tumor site	One study found a small positive association between damage to the tumor site and increased risk of osteosarcoma.	16
Prenatal exposure and development	Short birth length and fetal x-rays were associated with an increased risk in a single study.	16
Parental exposures	An association with chicken farming and another with gardening with fertilizer, herbicides or pesticides have been reported in single studies.	20-21
Fluoride in drinking water	The few epidemiologic studies as well as ecologic and time trend analyses suggest that fluoride is unlikely to cause osteosarcoma.	22-25

Table VIII.3: Current knowledge on causes of Ewing's Sarcoma (ES)

Exposure or Characteristic	Comments	References
Known risk factors		
Race	ES is almost exclusively a disease of white children. Rates in whites are approximately 9 times those in blacks.	18,26,27
Risk factors for which evidence is limited or inconsistent		
Growth	As for osteosarcoma, recent studies have not found a consistent association with increased height or weight, or age at pubertal growth spurt.	15,18,27-30
Hernia	An association was found between hernias and increased risk in one study.	29
Paternal occupation	Paternal occupation in agriculture has been associated with increased risk in two studies, although only in one were the results statistically significant.	29,30
Ingestion of poison or overdose of medication	A prior poisoning episode was more common among cases than controls in a single study.	30
Family history of cancer	ES has been reported in several pairs of siblings. However, more than one family member with ES is rare. In a study of over 200 cases, none had a relative with ES. Unlike osteosarcoma, ES is not part of the Li-Fraumeni syndrome.	12,31-32

RISK FACTORS

Unfortunately, the current state of knowledge regarding the causes of bone cancer is limited. Table VIII.2 briefly summarizes results from a number of epidemiologic studies that have been conducted on children with osteosarcoma. Although directed ionizing radiation exposure and a few genetic susceptibility syndromes are associated with increased risk of osteosarcoma, to date no factor has emerged to explain even a modest proportion of cases. The same is true for Ewing's sarcoma. Other than the important racial difference in incidence between black and white children, no environmental factor or other characteristic has yet been shown to be a strong risk factor for Ewing's sarcoma (TableVIII.3).

SUMMARY

In this descriptive analysis of the population-based SEER data, bone cancer represented about 6% of malignancies in children younger than age 20 years, with an average annual incidence rate of 8.7 cases per million children from 1975-95 (9.2 per million from 1990-95). Incidence increased with increasing age until late adolescence. Rates did not differ much by sex among younger children, but males had higher incidence than females during adolescence. Osteosarcoma and Ewing's sarcomas were the most common malignancies of bone in children. Black children had slightly higher rates of osteosarcoma relative to white children, while incidence of Ewing's sarcoma was dramatically higher among white compared with black children. The most common site for development of

osteosarcoma was the long bones of the lower limbs, while Ewing's sarcoma most frequently developed in bones of the central axis. Except for the first few years of the data collection, incidence rates of bone cancer have been stable. The etiology of bone cancer remains uncertain and the few risk factors that have been identified explain only a very small proportion of the incidence of these diseases. The 5-year relative survival for children with bone cancer improved from 49% in the period 1975-84, to 63% in the period 1985-94. In general, 5-year relative survival for osteosarcoma was slightly better than for Ewing's sarcoma. For both diseases, however, females had notably better survival than males.

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HIGHLIGHTS

Incidence

- The soft tissue sarcomas of children and adolescents arise primarily from the connective tissues of the body, such as fibrous tissue, adipose tissue, and muscle tissue. The sarcomas that arise from bone are discussed separately in the bone tumor chapter.
- In the US, 850-900 children and adolescents younger than 20 years of age are diagnosed with soft tissue sarcomas each year, of which approximately 350 are rhabdomyosarcomas.
- The incidence of soft tissue sarcomas for children and adolescents younger than 20 years of age was 11.0 per million (Table IX.2), representing 7.4% of cancer cases for this age group.
- Rhabdomyosarcoma was the most common soft tissue sarcoma among children 0-14 years, representing nearly 50% of soft tissue sarcomas for this age range (Figure IX.1) with an incidence rate of 4.6 per million (Table IX.2).
- There are two major types of rhabdomyosarcoma: embryonal (about 75% of rhabdomyosarcoma cases) and alveolar. These two subtypes tended to occur at different body sites (Figure IX.3) and had different age patterns (Figure IX.2). The incidence of embryonal rhabdomyosarcoma was higher among children 0-4 years, while the incidence of alveolar rhabdomyosarcoma was similar throughout childhood (Figure IX.2).
- Other types of soft tissue sarcomas are rare and the incidence is higher in adolescents compared to younger children. Among these are the fibrosarcomas, malignant fibrous histiocytoma, synovial sarcoma, leiomyosarcoma, liposarcoma, and others (Table IX.2).
- For infants, the most common soft tissue sarcoma was embryonal rhabdomyosarcoma. However, a distinctive set of other soft tissue sarcomas can develop in infants (e.g., infantile fibrosarcoma and malignant hemangiopericytoma). These tumors are different from the types of soft tissue sarcomas that arise in adolescents (Table IX.2).
- Males had slightly higher incidence rates for soft tissue sarcomas than females for the period 1975-95 (Table IX.3).
- Black children had slightly higher incidence rates for soft tissue sarcomas than white children (Table IX.3), with the largest difference observed among 15-19 year olds.
- The incidence of soft tissue sarcomas among those younger than 20 years of age has not changed much between 1975-79 (10.2 per million) and 1990-95 (11.3 per million) (Table IX.4 and Figure IX.5).

Survival

- The overall 5-year survival rate for children with rhabdomyosarcoma was approximately 64% for cases diagnosed from 1985-94 (Figure IX.7). Younger children had higher survival rates than older children and adolescents, and children with embryonal rhabdomyosarcoma had a more favorable prognosis than children with alveolar rhabdomyosarcoma (Figure IX.7).

Risk factors

- Congenital anomalies and genetic conditions are the only known risk factors for soft tissue (Table IX.5).

INTRODUCTION

The soft tissue sarcomas of childhood are a heterogeneous group of malignancies primarily of mesenchymal cell origin that develop at primary sites throughout the body [1]. Mesenchymal cells normally mature into skeletal muscle, smooth muscle, fat, fibrous tissue, bone and cartilage. The malignant counterparts of normal soft tissue cells include: fibrosarcomas (fibrous tissue), liposarcomas (adipose tissue), leiomyosarcomas (smooth muscle), rhabdomyosarcomas (striated muscle), angiosarcomas and malignant hemangiopericytoma (blood vessels), synovial sarcomas (synovial tissue), and chondrosarcomas (cartilage) [1]. Tumors derived from peripheral nervous system tissues are also included within the soft tissue sarcoma category, including malignant peripheral nerve sheath tumors (also termed malignant schwannoma and neurofibrosarcoma),and extraosseous Ewing's sarcoma [1,2]. The sarcomas of bone are not included in this discussion, but are considered within the bone tumor chapter of this monograph.

In the US, 850-900 children and adolescents younger than 20 years of age are diagnosed with soft tissue sarcomas each year, of which approximately 350 are rhabdomyosarcomas. In children, soft tissue sarcomas generally are classified as either rhabdomyosarcomas (RMS) or non-rhabdomyosarcomas (non-RMS) [1,3,4], with the non-RMS being further divided into multiple histologic subtypes such as those listed in the preceding paragraph [5-8]. The International Classification of Childhood Cancer (ICCC) partitions soft tissue sarcomas into 5 subcategories [9]: a) the rhabdomyosarcoma subcategory (including embryonal and alveolar); b) the fibrosarcoma subcategory (fibromatous malignancies and malignant nerve sheath tumors); c) Kaposi's sarcoma; d) the "other specified" soft tissue sarcoma subcategory (including synovial malignancies; blood vessel malignancies; myomatous malignancies; lipomatous malignancies; and soft tissue (extraosseous) Ewing's sarcoma and peripheral neuroectodermal tumors) and, e) the "unspecified" soft tissue sarcoma subcategory. Individual characteristics of each subcategory are discussed in more detail in the sections that follow.

The various soft tissue sarcomas are associated with distinctive chromosomal alterations that can be used in some instances to support or confirm a specific diagnosis [10,11] (Table IX.1). Embryonal RMS tumor cells often show extra chromosome copies (hyperdiploidy) and loss of heterozygosity involving a specific site on the short arm of chromosome 11 [11]. Alveolar RMS tumors cells have translocations involving the FKHR gene on the long arm of chromosome 13 with genes of the PAX family on either chromosome 2 (PAX3) or chromosome 1 (PAX 7) [11]. Many of the non-RMS also show characteristic chromosome translocations. Of note, infantile fibrosarcoma tumor cells contain the same chromosomal abnormalities as the tumor cells of congenital mesoblastic nephroma, with both possessing t(12;15)(p13;q25)-associated ETV6-NTRK3 gene fusions [12]. Synovial sarcomas are virtually always associated with translocations that fuse the SYT gene on chromosome 18 with the SSX-1 or SSX-2 genes on the X chromosome [13-15]. Extraosseous Ewing's sarcoma and peripheral neuroectodermal tumors have translocations involving the EWS gene on chromosome 22 and either the FLI1 gene on chromosome 11 or the ERG gene on chromosome 21 [16]. Malignant peripheral nerve sheath tumors (also known as neurofibrosarcomas, malignant schwannomas, and neurogenic sarcomas) are associated with neurofibromatosis 1 (NF1) [17], the gene for which is located on the long arm of chromosome 17 [18]. The occurrence of characteristic chromosomal translocations among many of the soft

Table IX.1: Molecular characterization of soft tissue sarcomas

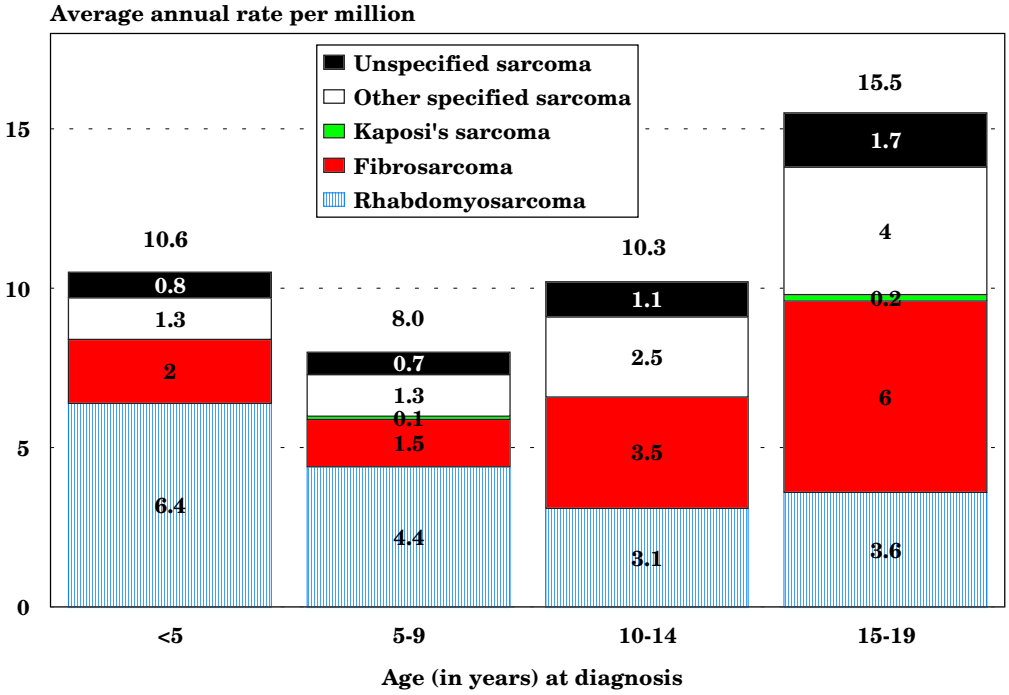
Diagnosis	Chromosomal Abnormality	Genes Involved
Rhabdomyosarcoma, Embryonal [11]	Hyperdiploidy, and loss-of-heterozygosity at chromosome 11p15	Unidentified gene at chromosome band 11p15
Rhabdomyosarcoma, Alveolar [11]	t(2;13) or t(1;13)	FKHR on chromosome 13 and PAX 3 (chromosome 2) or PAX7 (chromosome 1)
Infantile fibrosarcoma [22,23]	t(12;15)	TEL (ETV6) gene on chromosome 12 and NTRK3 (TRKC) on chromosome 15.
Dermatofibrosarcoma protuberans [24,25]	t(17;22)	Platelet-derived growth factor b-chain (PDGFB) gene on chromosome 17 and collagen type I alpha 1 (COL1A1) on chromosome 22
Malignant peripheral nerve sheath tumors (also known as neurofibrosarcomas and malignant schwannomas) [26,27]	Abnormalities of Chromosome 17	Neurofibromatosis 1 (NF1) gene
Synovial sarcoma [13-15]	t(X;18)	SYT on chromosome 18 and SSX-1 or SSX-2 on the X chromosome
Liposarcoma [28-30]	t(12;16),	FUS gene on chromosome 16 and CHOP gene on chromosome 12
Chondrosarcoma, Myxoid [31,32]	t(9;22)	EWS gene on chromosome 22 (also associated with Ewing's sarcoma) and TEC gene on chromosome 9
Extra-osseuous Ewing's sarcoma and peripheral neuroectodermal tumor (PNET) [33]	t(11;22)	EWS gene on chromosome 22 and FLI gene on chromosome 11.
Alveolar soft part sarcoma [34,35]	t(X; 17)	Unidentified gene at chromosome band 17q25

tissue sarcomas of children and adolescents is in contrast to the rarity of such translocations among the epithelial solid tumors that predominate among adults, with the reason(s) for this difference not understood.

INCIDENCE

From 1975-95 in SEER areas, 2,182 neoplasms in children younger than 20 years of age were classified into the ICCC soft tissue sarcoma diagnostic category. The ICCC soft tissue sarcoma category is primarily based on histology and not anatomic site. Thus, nearly one-half of the cases (974) occurred at anatomic sites other than connective tissue, with RMS showing a particular propensity for arising at anatomic sites throughout the body (see RMS discussion below). Conversely, there were 512 cancers among children arising in anatomic sites coded as connective tissues

Figure IX.1: Soft tissue sarcoma age-specific incidence rates by ICCC subcategory, all races, both sexes, SEER, 1975-95



that were not included in the ICCC soft tissue sarcoma category (including 373 classified in the ICCC sympathetic nervous system tumor category and 77 classified in the ICCC category germ cell, trophoblastic, and other gonadal tumor category). These cases have been included in the appropriate chapters in the monograph.

Average annual incidence rates of soft tissue sarcomas are shown in Table IX.2. Overall, the age-adjusted rate of soft tissue sarcomas was 11.0 per million children younger than 20 years of age, which represented 7% of all primary malignancies for this population. Of these, 40% were RMS, 29% were in the ICCC fibrosarcoma subcategory, 21% were in the "other specified" soft tissue sarcoma subcategory, and 10% were unspecified soft tissue sarcomas. Kaposi's sarcoma, a disease associated with AIDS, was extremely rare in this population, with only 18 cases reported to SEER areas during 1975-95.

Histology-specific incidence

Table IX.2 provides the incidence of specific diagnoses within each of the ICCC soft tissue sarcoma subcategories. The incidence of soft tissue sarcoma subtypes differed notably by age as illustrated in Figure IX.1. RMS represented 60% of soft tissue sarcomas for children younger than 5 years of age, but the relative frequency of RMS decreased with each successive 5-year age group; RMS accounted for only 23% of soft tissue sarcomas among the 15-19 year-old group. The opposite pattern occurred for the non-RMS subcategories, which represented 40% of soft tissue sarcomas among children younger than 5 years of age, but 77% of these tumors among 15-19 year-olds. The primary diagnoses for each subcategory are listed and briefly described below.

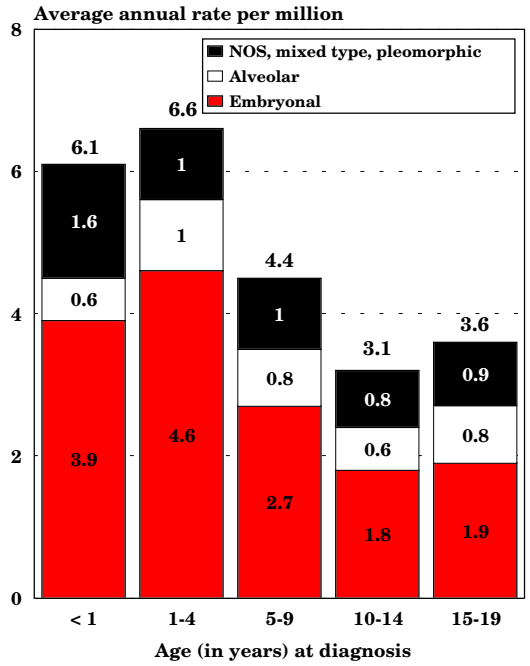
The RMS subcategory (ICCC IXa) is comprised of embryonal and alveolar RMS,

Table IX.2: Age-specific and age-adjusted incidence rates per million of soft tissue sarcomas by ICCC group and subcategory, all races, both sexes, SEER 1975-95

		Age (in years) at diagnosis					
	ICD-O-2 Codes	<5	5-9	10-14	15-19	Total* <15	Total* <20
Soft Tissue Sarcomas (IX)		**10.6**	**8.0**	**10.3**	**15.5**	**9.6**	**11.0**
Rhabdomyosarcoma Subcategory (IXa)		**6.4**	**4.4**	**3.1**	**3.6**	**4.6**	**4.3**
Embryonal rhabdomyosarcoma	8910	4.4	2.7	1.6	1.8	3.0	2.6
Alveolar rhabdomyosarcoma	8920	0.8	0.8	0.6	0.8	0.7	0.7
Rhabdomyosarcoma, NOS, pleomorphic, etc.	8900-8902, 8991	1.2	0.9	0.9	0.9	1.0	1.0
Fibrosarcoma Subcategory (IXb)		**2.0**	**1.5**	**3.5**	**6.0**	**2.3**	**3.2**
Fibrosarcoma	8810	0.3	0.3	0.5	1.1	0.4	0.6
Infantile fibrosarcoma	8814	0.7	0.0	0.0	0.0	0.2	0.2
Malignant fibrous histiocytoma	8830	0.4	0.4	0.7	1.7	0.5	0.8
Dermatofibrosarcoma	8832	0.2	0.5	1.2	1.9	0.7	1.0
Malignant peripheral nerve sheath tumor	9540,9560	0.2	0.2	0.8	1.2	0.4	0.6
Kaposi's sarcoma (IXc)	9140	**0**	**0.1**	**0**	**0.2**	**0**	**0.1**
Other specified STS Subcategory (IXd)		**1.3**	**1.3**	**2.5**	**4.0**	**1.8**	**2.3**
Liposarcoma	8850,8852,8854	0.1	0.0	0.1	0.4	0.1	0.1
Leiomyosarcoma	8890, 8891	0.1	0.2	0.2	0.7	0.2	0.3
Malignant mesenchymoma	8990	0.3	0.2	0.1	0.1	0.2	0.2
Synovial sarcoma	9040, 9041 9043	0.1	0.3	0.8	1.4	0.4	0.7
Hemangiosarcoma & Malignant Hemangioendothelioma	9120, 9130, 9133	0.1	0.1	0.1	0.3	0.1	0.2
Hemangiopericytoma, malignant	9150	0.2	0.1	0.1	0.1	0.1	0.1
Alveolar soft part sarcoma	9581	0.1	0.1	0.1	0.1	0.1	0.1
Chondrosarcoma	9231, 9240	0.0	0.0	0.2	0.0	0.1	0.1
Ewing's (extraosseous) Family	9364, 9260	0.2	0.3	0.4	0.6	0.3	0.4
Unspecified Subcategory (IXe)	8800-8804	**0.8**	**0.7**	**1.1**	**1.7**	**0.9**	**1.1**

* Adjusted to the 1970 US standard population

Figure IX.2: Rhabdomyosarcoma (RMS) age-specific incidence rates by subtype and age group all races, both sexes, SEER, 1976-84 and 1986-94 combined

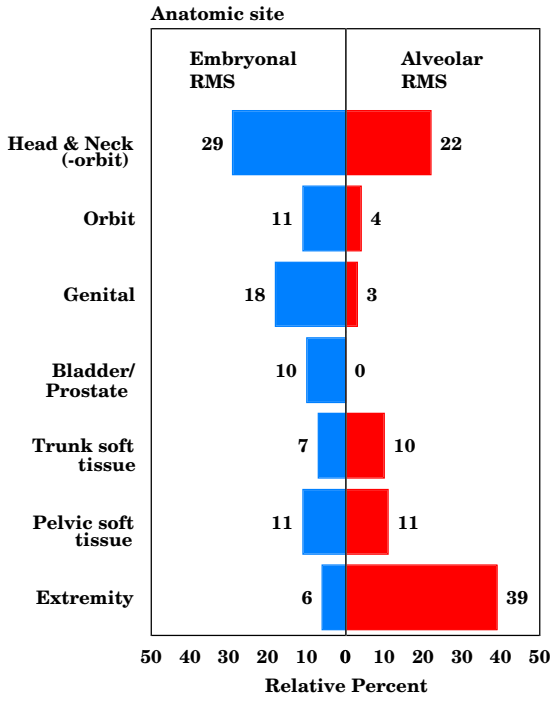


as well as "not otherwise specified" RMS, pleomorphic RMS, mixed-type RMS, and embryonal sarcoma. RMS 'not otherwise specified' (NOS) represented 17% of all RMS in SEER areas for 1975-95. Embryonal RMS was the most common type of RMS at all ages and accounted for 75% of cases for those younger than 20 years of age with a specific RMS diagnosis (i.e., excluding the NOS category). However, as shown in Figure IX.2, the incidence of embryonal RMS varied by age. The relative percentage of RMS decreased with increasing age, from 83% of cases with a specific RMS diagnosis among children younger than 5 years of age to 64% of cases among 15-19 year olds. The relative percentage of alveolar RMS showed a corresponding increase, from 15% of cases with a specific RMS diagnosis among children younger than 5 years of age to 30% of cases among 15-19 year olds. Pleomorphic (1.5%) and mixed type RMS (1.0%) comprised only a small percentage of total RMS.

Embryonal RMS occurred at sites throughout the body (Figure IX.3), with the head and neck region (excluding the orbit) being most common (29% of cases). RMS arising in the orbit, which is known to have an especially favorable prognosis [19], represented an additional 11% of embryonal RMS cases. Genital and urinary organ sites were also common locations of RMS development (18% and 10% of embryonal RMS cases, respectively), while the extremities were an uncommon site for embryonal RMS (only 6% of embryonal RMS cases). By comparison, alveolar RMS occurred most commonly at extremity sites (39% of alveolar RMS cases) and occurred infrequently at genitourinary sites (3% of cases).

The fibrosarcoma subcategory (ICCC IXb) includes the following diagnoses (incidence rates for the younger than 20 year old population are provided in parentheses): dermatofibrosarcoma (1.0 per million), malignant fibrous histiocytoma (0.8 per million), fibrosarcoma (0.6 per

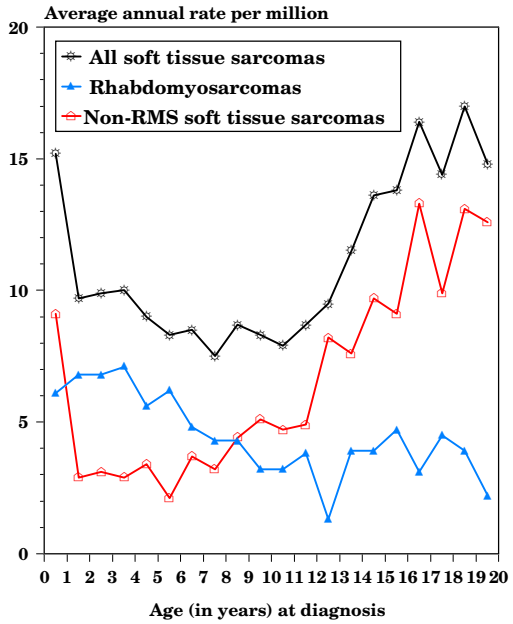
Figure IX.3: Percent distribution of embryonal and alveolar rhabdomyosarcoma (RMS) by anatomic site age <20, all races, both sexes, SEER, 1975-95



million), malignant peripheral nerve sheath tumor (0.6 per million), and infantile fibrosarcoma (0.2 per million). Each of these soft tissue sarcomas, save infantile fibrosarcoma, occurs in adults as well as in children [7,20]. With the exception of infantile fibrosarcoma, each of these diagnoses occurred at higher incidence among the 15-19 year old population than among any of the younger age groups (Table IX.2). Infantile fibrosarcomas, which are known for their excellent outcome with surgery alone [7], occurred only in the younger than 5-year age group.

For the "other specified" soft tissue sarcoma subcategory (ICCC IXd), synovial sarcoma was the most common subtype (0.7 per million), followed by the Ewing's (extraosseous) family of tumors (0.4 per million) and leiomyosarcoma (0.3 per million) (Table IX.2). Blood vessel tumors (e.g., hemangiosarcomas and malignant hemangiopericytoma), liposarcomas, and alveolar soft part sarcomas occurred less commonly. As with the ICCC fibrosarcoma subcategory, most diagnoses occurred at higher rates among the 15-19 year old group than among younger age groups. Exceptions were malignant mesenchymoma and malignant hemangiopericytoma, which developed most frequently in the first five years of life.

Figure IX.4: Soft tissue sarcoma age-specific incidence rates by histology, all races, both sexes SEER, 1976-84 and 1986-94 combined



Age-specific incidence

Figure IX.4 shows incidence rates for soft tissue sarcomas by single year of age[1]. Incidence rates were highest among young children during infancy. Rates dropped in the second year of life, and remained fairly stable through age 10 years. After age 10 years, incidence rates began to rise again as a result of increasing rates for the non-RMS soft tissue sarcomas. Among infants, the overall incidence was 15.2 per million, compared to approximately 10 per million for children ages 1-4 years. Non-RMS tumors strongly contributed to the peak in soft tissue sarcoma incidence during infancy. While RMS accounted for approximately 40% of soft tissue sarcomas among infants, RMS occurred at a similar rate among children 1-4 years. The non-RMS diagnoses that occurred more commonly in the first year of life than in the succeeding 4 years included: infantile fibrosarcoma and fibrosarcoma, NOS (22% of infant soft tissue sarcomas); malignant hemangiopericytoma (5% of infant soft tissue sarcomas), and malignant mesenchymoma (5% of infant soft tissue sarcomas).

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

Table IX.3: Age-specific and age-adjusted incidence rates per million of soft tissue sarcomas, by race and sex, SEER, 1975-95

	Age (in years) at Diagnosis					
ICCC Group	**<5**	**5-9**	**10-14**	**15-19**	**<15***	**<20***
All races/Both sexes	10.6	8.0	10.3	15.5	9.6	11.0
Whites	10.5	7.8	9.9	14.2	9.4	10.6
Blacks	9.6	9.0	11.8	18.9	10.2	12.4
Males	11.2	9.0	10.7	16.2	10.3	11.8
Females	9.9	6.9	9.8	14.7	8.8	10.3

* Adjusted to the 1970 US standard population

Sex-specific incidence

Incidence rates for males and females are also shown in Table IX.3. Rates among males tended to be higher than rates for females within all age groups, although the overall difference was slight (11.8 per million males versus 10.3 per million females for the younger than 20 year old population). The pattern of rates by age and histologic subgroups were essentially the same for males and females.

Black-white differences in incidence

Table IX.3 shows incidence rates by 5-year age groups for both white and black children. Black children had slightly higher incidence rates overall than white children. Although rate differences were slight within all age groups, the largest difference occurred among those 15-19 years of age. To the extent that numbers allowed reliable comparisons, there were no notable racial differences in soft tissue sarcoma rates by histologic subgroups.

TRENDS

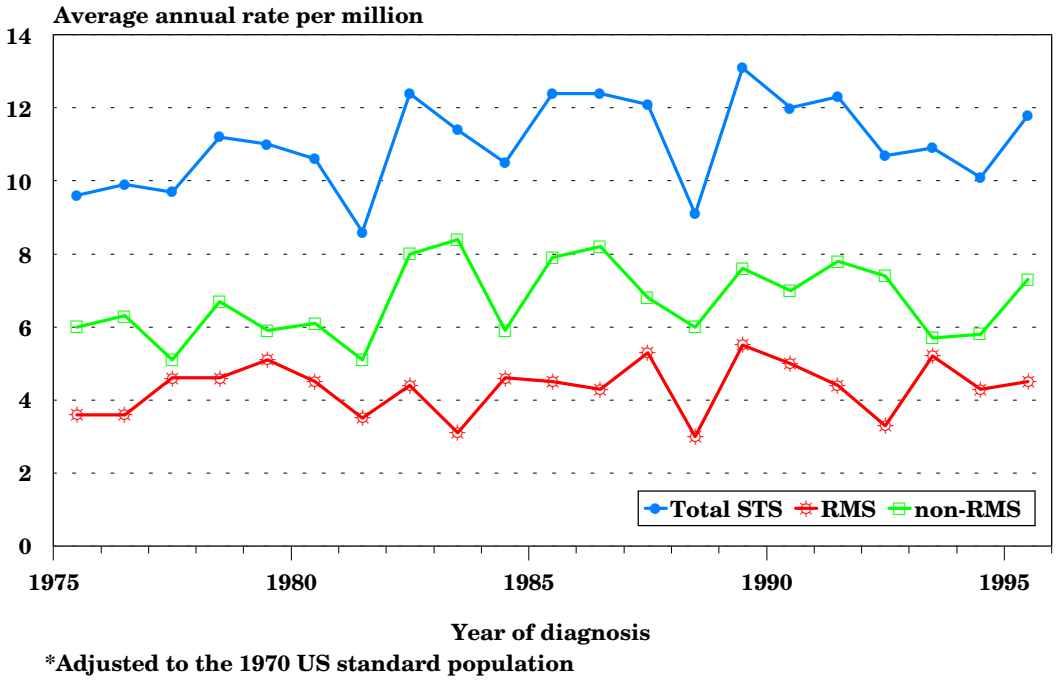
Average annual age-adjusted incidence rates across 5-year time periods (6 years for the last period) are shown in Table IX.4. Overall rates for soft tissue sarcomas increased slightly over the first three time periods from 10.2 to 11.8 per million, and then dropped a small amount in the 1990-95 period to 11.3 per million. Figure IX.5 shows the incidence rates for individual years from 1975-95 for total soft tissue sarcomas, RMS, and non-RMS soft tissue sarcomas. This figure illustrates the small changes in incidence during this period; RMS incidence was fairly stable at 4 per million and non-RMS soft tissue sarcoma incidence varied between 6 and 8 per million.

Table IX.4: Age-adjusted* incidence rates per million of soft tissue sarcomas by time period, race, and sex, age <20, SEER, 1975-95

	1975-79	**1980-84**	**1985-89**	**1990-95**
All races/Both sexes	10.2	10.7	11.8	11.3
Whites	10.1	10.4	11.5	10.4
Blacks	10.2	10.5	14.5	13.9
Males	11.0	10.6	13.1	12.2
Females	9.5	10.7	10.5	10.3

*Adjusted to the 1970 US standard population

Figure IX.5: Trends in total soft tissue sarcoma, rhabdomyosarcoma(RMS) and non-RMS age-adjusted* incidence rates, age <20, all races, both sexes SEER 1975-95



*Adjusted to the 1970 US standard population

SURVIVAL

Figure IX.6 shows survival rates for the time periods 1975-84 and 1985-94. The 5-year relative survival rate for all soft tissue sarcomas combined was 71% from 1985-1994, with little change from the earlier period of 1975-84. Survival rates were higher for the non-RMS fibrosarcoma subcategory and the "other specified" soft tissue sarcoma subcategory than for rhabdomyosarcoma. A small survival improvement in RMS occurred from the earlier to the later period (59% to 64% 5-year survival), but no difference between the two time periods was observed for either the fibrosarcoma subcategory (82% 5-year survival) or for the "other specified" soft tissue sarcoma subcategory (74% 5-year survival).

Figure IX.6: Soft tissue sarcoma 5-year relative survival rates, age <20, all races both sexes, SEER, 1975-84 and 1985-94

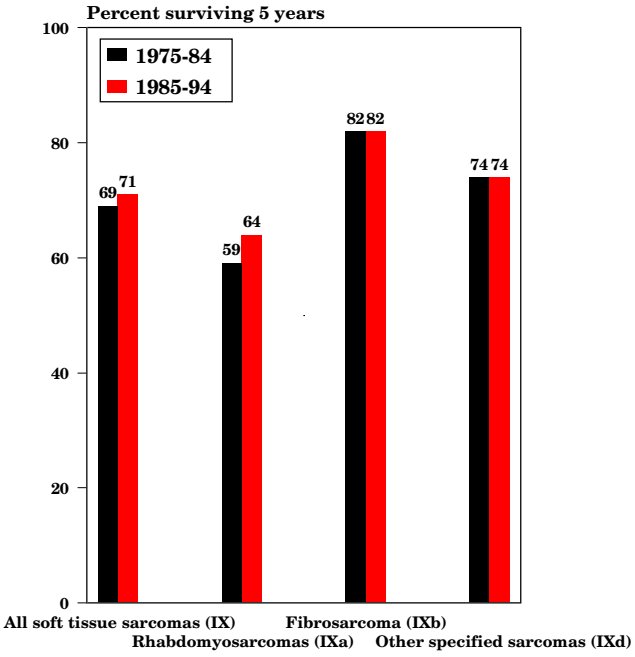
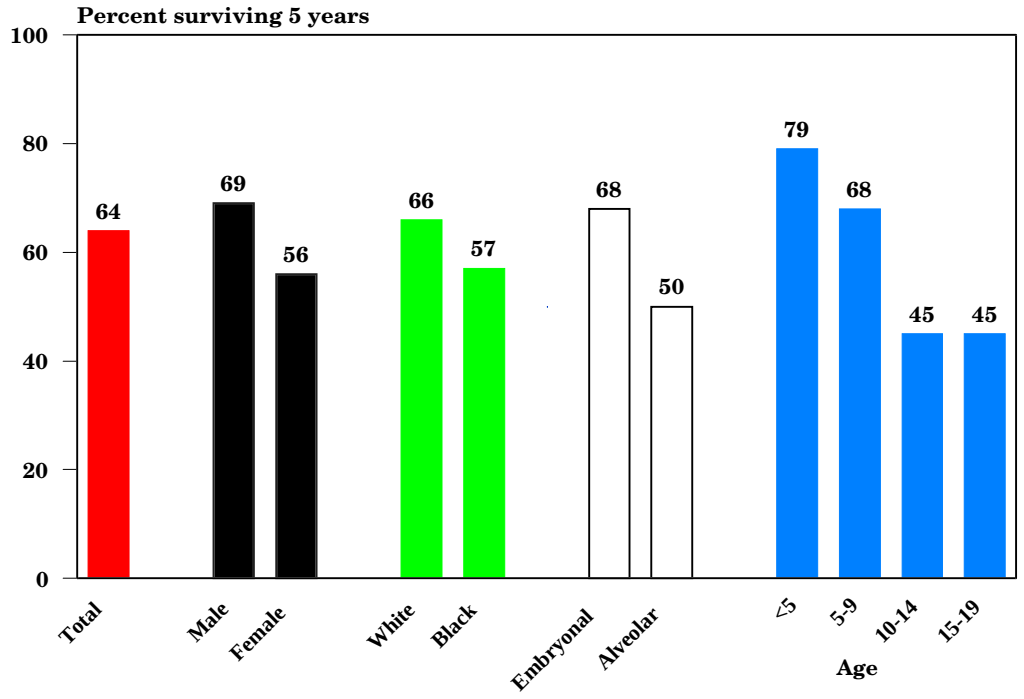


Figure IX.7: Rhabdomyosarcoma 5-year relative survival rates by sex, race, subtype, and age, SEER 1985-94



Additional data on 5-year relative survival of RMS are shown in Figure IX.7. Survival among males with RMS was better than that of females, and survival was somewhat higher for white children than for black children. Figure IX.7 also demonstrates the important prognostic advantage of younger age. Children younger than 5 years of age had much higher 5-year survival rates than 15-19 year olds (79% versus 45%). The prognostic advantage associated with younger age may be partially explained by the higher percentage of embryonal cases among young children, since RMS cases with embryonal histology are associated with superior outcome compared to cases with alveolar histology (Figure IX.7).

RISK FACTORS

Very little population-based research has been conducted on potential causes of RMS or other soft tissue sarcomas in children. Table IX.5 provides a brief summary of risk factors that have been explored. Certain congenital anomalies and genetic conditions are the strongest known risk factors, although they explain only a small proportion of cases. While the overwhelming majority of RMS occurs sporadically, a small proportion of RMS is associated with Li-Fraumeni cancer susceptibility syndrome (21), and probably neurofibromatosis type I (3).

SUMMARY

Soft tissue sarcomas accounted for 7% of all primary malignancies in SEER areas for children younger than 20 years of age from 1975-95. RMS represented approximately 40% of soft tissue sarcomas, with the remaining non-RMS cases being spread among multiple diagnoses primarily within the ICCC fibrosarcoma subcategory and the "other specific" soft tissue sarcomas subcategory. The average age-adjusted incidence

Table IX.5: Risk factors for soft tissue sarcomas in children

Exposure or Characteristic	Comments	References
Known risk factors		
Congenital anomalies	There is some concordance with the anatomic location of RMS and major birth defects. One autopsy study showed 32% of 115 children and adolescents with RMS to have at least one congenital anomaly.	36,37
Genetic conditions	Li-Fraumeni syndrome (associated with p53 mutations), and neurofibromatosis (associated with NF1 mutations)	21,38,39
Factors for which evidence is inconsistent or limited		
Socioeconomic status	Low socioeconomic status is associated with increased risk.	40
Ionizing radiation (in utero)	Diagnostic x-rays during pregnancy were associated with 2-fold increase in risk in one study.	41
Parental use of recreational drugs	Parents use of marijuana and cocaine during the pregnancy was associated with increased risk in one study.	37,42

rate of all soft tissue sarcomas combined was 11 per million children younger than 20 years of age. While RMS was the most common soft tissue sarcoma in children, especially in young children, in older adolescents the non-RMS tumors were more common than RMS, although no single non-RMS diagnosis accounted for more than 15% of all cases. There have been very few population-based studies to evaluate risk factors for soft tissue sarcoma occurrence; factors have been identified that explain only a very small proportion of cases. Five-year survival rates of soft tissue sarcomas improved only slightly from the period 1975-84 (69%) to 1985-94 (71%). Children with RMS had a somewhat poorer 5-year survival (64%) than did children with non-RMS in the fibrosarcoma subcategory (82%) and the "other specified" soft tissue sarcoma subcategory (74%). Males tended to have slightly better survival rates than females, and white children tended to fare better than black children. Younger children with RMS had better outcome than did older children (Figure IX.7).

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HIGHLIGHTS

Incidence

- While germ cell, trophoblastic and other gonadal (GCTOG) tumors represented 16% of all cancers among adolescents between 15 and 19, they represented only 7% of cancer diagnoses among children younger than 20 (incidence 12.0 per million) and 3.5% of cancer diagnoses for children younger than 15 (incidence 5.4 per million) (Table X.4).
- In the US, approximately 900 children and adolescents younger than 20 years of age are diagnosed with germ cell tumors each year.
- The majority (61%) of GCTOG tumors occurring among children younger than 20 years are gonadal (ovarian or testicular) germ cell tumors (Table X.1). However, when only children younger than 15 years of age are considered, non-gonadal germ cell tumors are more common than gonadal germ cell tumors (Table X.4).
- For males, the incidence rates of testicular (Xc) and non-CNS extragonadal (Xb) germ cell tumors were similar during the first year of life at approximately 9 per million, and then declined to very low levels by age 4. Between ages 4 and 15 the rates of testicular germ cell tumors remained very low, but between ages 15 and 19 years of age, the incidence rates increased dramatically (Figure X.2).
- For females, ovarian (gonadal) germ cell tumors (Xc) began to increase in incidence at age 8-9 years and peaked at age 18 (20 per million) (Figure X.3). For males, the rate of testicular germ cell tumors (Xc) at age 19 was substantially higher than that observed for ovarian germ cell tumors among 19 year old females (44.5 versus 10.4 per million).
- White males younger than age 20 had much higher rates of testicular germ cell tumors (9.1 per million) than blacks males (1.2 per million). In contrast, white females younger than age 20 had slightly lower rates (4.5 per million) than black females (5.6 per million) for ovarian germ cell tumors (Table X.3).

Survival

- For patients younger than 20 years of age, females had slightly higher 5-year survival rates than males, and whites had somewhat higher 5-year survival rates than blacks for GCTOG tumors (Figure X.6).
- Increasing survival rates were observed between 1975-84 and 1985-94 for each subgroup of the ICCC for patients younger than 20 (Figure X.7). The overall 5-year relative survival rate for all subgroups combined increased from 77% to 87% (Figure X.6).
- The increase in survival between 1975-84 and 1985-94 was similar for ovarian and testicular germ cell tumors. Both increased from 82% to 93-94% (Figure X.7). Young males (<5 years) survived better than males aged 15-19.

Risk factors

- The etiology of malignant germ cell tumors is poorly understood. Cryptorchidism is the only confirmed risk factor for testicular germ cell tumors (see Table X.5 for references).

INTRODUCTION

Germ cell tumors are biologically diverse and histologically heterogeneous [1-3], with a substantial proportion having benign rather than malignant behavior (particularly among young children). Germ cell tumors originate in primordial germ cells, which may undergo germinomatous or embryonic differentiation. Primordial germ cells are initially detectable in the yolk sac of the four week embryo, and their migratory route during embryogenesis from the yolk sac to the gonads (either the testes or ovaries) may account for the primarily midline location of most extragonadal germ cell tumors [1].

Germ cell tumors are grouped together with trophoblastic and other gonadal neoplasms in the International Classification of Childhood Cancer (ICCC) [4]. For shorthand notation this entire group, ICCC X, will be abbreviated as GCTOG tumors. This diagnostic group is categorized into five subgroups according to the cells of origin of the cancer (germ cells, trophoblastic cells or other cells) and the location in the body of the cancer (gonads: testes or ovaries; central nervous system; or elsewhere) (see Table X.1).

In the US, approximately 900 children and adolescents younger than 20 years of age are diagnosed with germ cell tumors each year. Essential for understanding the incidence patterns for germ cell tumors of children and adolescents is recognition that the germ cell tumors of infancy and early childhood are biologically distinctive from those that arise in older children and adolescents [2,3]. Thus, tumors in the same ICCC subgroup may have very different biological characteristics and clinical behavior (Table X.2. [5]). The categorization of germ cell tumors in Table X.2 provides a

Table X.1: Average annual age-adjusted* incidence rates per million for germ cell trophoblastic and other gonadal cancers by sex and subtype, age <20 all races, SEER, 1986-95

ICCC Group X	Description	Total	Males	Females
X a-e	Germ cell, trophoblastic and other gonadal tumors	11.6	12.0	11.1
Xa	Intracranial and intraspinal germ cell tumors	1.6	2.3	0.9
Xb	Other and unspecified non-gonadal germ cell tumors. (This category includes the tumors of infants and young children that originate in the sacrococcygeal region, as well as mediastinal tumors primarily developing in older children.)	1.6	1.5	1.8
Xc	Gonadal germ cell tumors	6.7	8.0	5.3
	Testis	4.1	8.0	-
	Ovary	2.6	-	5.3
Xd	Gonadal carcinoma	1.4	0.1	2.9
	Ovary	1.3	-	2.6
	Other	0.1	0.1	0.3
Xe	Other and unspecified malignant gonadal tumors	0.2	0.1	0.3

*Adjusted to the 1970 US standard population

Table X.2: GCTOG tumors by sub-group, age and biological characteristics [5]

GCTOG TUMORS (ICCC X)	Site	Age	Characteristics
Intracranial and intraspinal germ cell tumors (ICCC Xa)	Intracranial (especially pineal region) [2]	Older children, adolescents and adults	Some, though not all, of these tumors have biological characteristics similar to those of testicular germ cell tumors in adolescents and young adults (e.g., an isochromosome of the short of chromosome 12 as discussed below) [6-9].
Non-CNS, Non-gonadal germ cell (ICCC Xb)	Sacrococcygeal/pelvic region [2]	Infants and young children	The biological characteristics of these tumors is similar to those of testicular germ cell tumors in young boys (see below), but different from those of testicular germ cell tumors in adolescents and young adults (see below).
"	Mediastinum [2]	Older children, adolescents and adults	Some, though not all, mediastinal germ cell tumors have biological characteristics similar to those of testicular germ cell tumors in adolescents and young adults (e.g., an isochromosome of the short of chromosome 12 as discussed below) [10,11].
Gonadal germ cell (ICCC Xc)	Testicular	Infants and young boys	The biological characteristics of these tumors are distinctive from those of testicular germ cell tumors in adolescents and young adults (see below). The tumors primarily show yolk sac tumor (endodermal sinus tumor) histology and are generally diploid or tetraploid. Recurring chromosomal abnormalities include deletions of chromosome 1p and 6q, but not isochromosome of the short arm of chromosome 12 [12-15].
"	Testicular	Adolescents and young adults	These typically possess an isochromosome of the short arm of chromosome 12 [5,16-19] and are aneuploid [12,19]
"	Ovary	Adolescents and adults	These show greater biological diversity than do germ cell tumors arising in the testes, and include malignant teratomas and other malignant germ cell tumors (e.g., dysgerminomas, yolk sac tumors, and mixed germ cell tumors). Like their testicular counterparts, they commonly show increased copies of the short arm of chromosome 12 [5].
Gonadal carcinomas (Xd)	Ovary	Adolescents and adults	These carcinoma tumors are not biologically related to the germ cell tumors and develop almost exclusively in the ovary.

basis for understanding the incidence patterns and trends of germ cell tumors in children.

A total of 2,065 children younger than 20 years of age were diagnosed with GCTOG tumors during the period 1975 through 1995 in the SEER areas. This represents 7% of all neoplasms diagnosed among children younger than 20 years of age: 3.5% of all neoplasms for children younger than 15 years of age and a much higher proportion, 13.9%, for 15-19 year olds. The majority (1,260 or 61%) of GCTOG tumors occurring among children younger than 20 years of age are gonadal (ovarian or testicular) germ cell tumors (Xc). However, when only children younger than 15 years of age are considered, non-gonadal germ cell tumors (Xa and Xb) are more common than gonadal germ cell tumors.

The GCTOG tumor group (ICCC X) includes 94% of the malignant testicular tumors and 99% of the ovarian tumors among children and adolescents. Six percent of malignant testicular tumors and less than 1% of ovarian tumors are sarcomas and are grouped under ICCC IX (soft tissue sarcomas). Excluding the sarcomas, nearly all of the testicular tumors in male children and adolescents were germ cell tumors, 98%. Excluding the small number of ovarian sarcomas, the histologic types of ovarian tumors in female children and adolescents were 64% germ cell (Xc), 33% carcinomas (Xd), and 3% other and unspecified (Xe).

INCIDENCE

Sex-specific incidence

Table X.1 shows the incidence of GCTOG tumors by sex for children younger than 20 years of age for the years 1986 to 1995. The incidence for males (12.0 per million) slightly exceeded that for females (11.1 per million). For males, the subgroup with the highest incidence was testicular germ cell tumors (8.0 per million). For females, ovarian germ cell tumors had the highest rate (5.3 per million). Intracranial and intraspinal germ cell tumors (ICCC Xa) were more common in males (2.3 per million) than in females (0.9 per million), and accounted for about 14 percent of all GCTOG tumors among those younger than 20 years of age. Non-gonadal germ cell tumors arising outside of the central nervous system (CNS), ICCC Xb, occurred with similar frequency among males and females. In contrast gonadal carcinomas were almost exclusively seen among females and most of these were ovarian gonadal carcinomas.

Table X.3: Average annual age-adjusted* incidence rates per million for germ cell trophoblastic and other gonadal cancers by race, sex, and subtype age <20, SEER, 1975-95

ICCC Group X	ICCC Germ Cell Tumor Category	White Male	Black Male	White Female	Black Female
X a-e	All	12.3	3.2	9.0	10.8
Xc	Gonadal germ cell tumors	9.1	1.2	4.5	5.6
	Testis	9.1	1.2	-	-
	Ovary	-	-	4.5	5.6
X a,b,d,e	Other than gonadal germ cell tumors	3.2	2.0	4.5	5.2

*Adjusted to the 1970 US standard population

Black-white differences in incidence

Black children had a lower incidence of germ cell tumors than white children (7.0 vs. 10.7 per million). This difference was primarily the result of a lower rate of gonadal germ cell tumors among blacks than whites. Table X.3 shows the incidence rates for gonadal germ cell tumors for children younger than 20 years of age for the years 1975 to 1995 by race and sex. Remarkably, the lower rates of gonadal germ cell tumors among black children were restricted to males. For children younger than 20 years of age, black males had a rate of testicular germ cell tumor that was only one-seventh that for white males (1.2 versus 9.1 per million), while black females had slightly higher rates of ovarian germ cell tumors than white females (5.6 versus 4.5 per million). The low rate of testicular germ cell tumors observed among young black males is consistent with the reported low incidence for testicular cancer among adult black males [20-22].

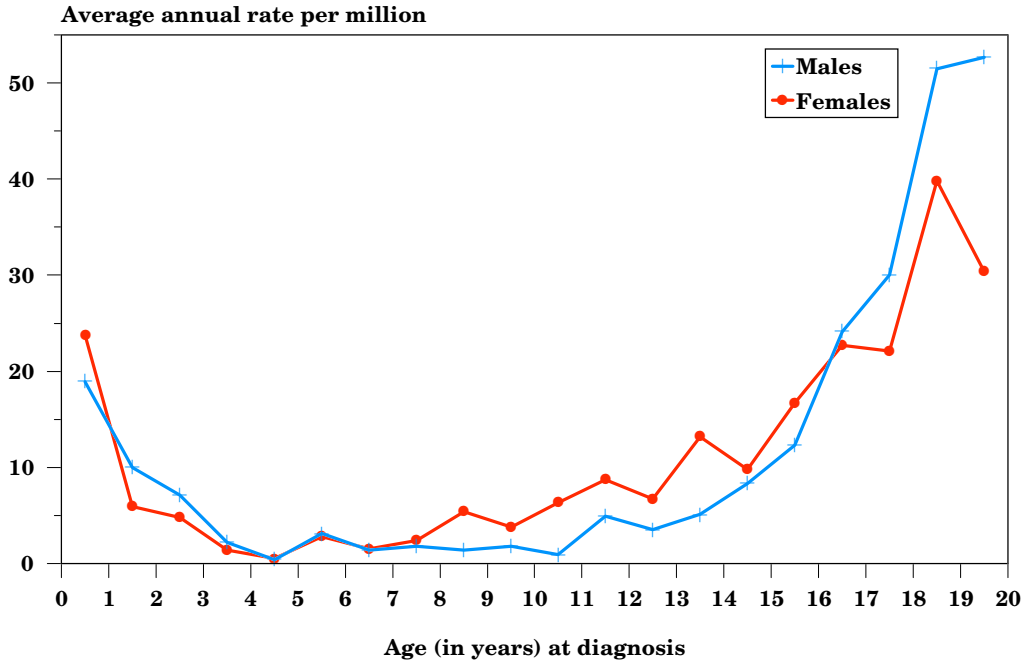
Age-specific incidence

Figure X.1 shows the age-specific incidence of GCTOG tumors by single year of age and sex.[1] Rates were relatively high in the first year of life and then declined to very low levels before increasing at age 8-12 years for females and at age 11-14 years for males. Incidence continued to increase for both males and females up through age 19. The distribution of tumor types by age was distinctive for males and females.

For males, the incidence rates of testicular (Xc) and non-CNS extragonadal (Xb) germ cell tumors were similar during the first year of life at approximately 9 per

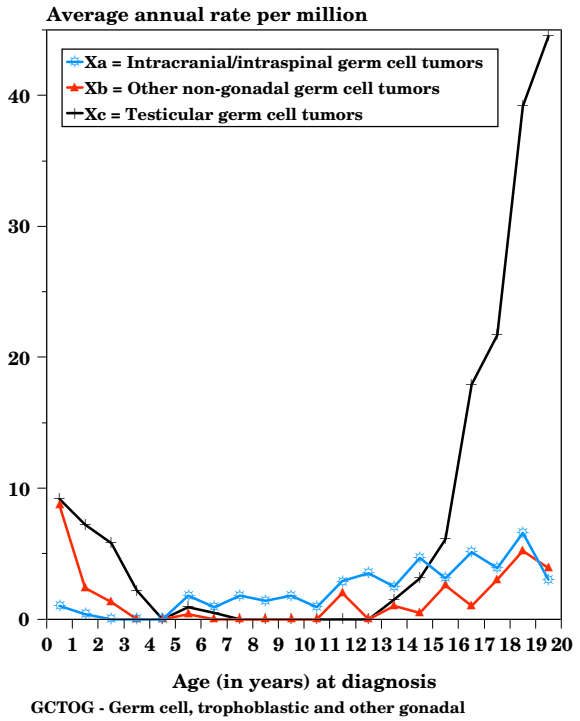
[1] Enumeration of the population at risk by single years of age was available only for the census year 1990. The US Bureau of the Census provides intercensal population estimates by 5-year age groups, but not by single years of age. Therefore, the population estimates for 1990 were used in rate calculations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

Figure X.1: GCTOG age-specific incidence rates by sex, all races, SEER, 1986-94



GCTOG - Germ cell, trophoblastic and other gonadal

Figure X.2: GCTOG age-specific incidence rates by selected ICCC subgroups, males all races, SEER, 1986-94



million, and then declined to very low levels by age 4 years (Figure X.2). Between ages 4 and 15 the rates remained very low, but between ages 15 and 19 years of age, the incidence rates increased dramatically.

For females, non-CNS extragonadal germ cell tumors (Xb) accounted for the vast majority of cases in the first year of life, with ovarian germ cell tumors (Xc) being extremely rare (Figure X.3). Most of the extragonadal germ cell tumors arising in the first year of life occurred in pelvic soft tissue (e.g., the sacrococcygeal region) and in the retroperitoneum. Gonadal germ cell tumors (Xc) began to increase in incidence for females at age 8-9 years, while gonadal carcinomas (Xd) began to increase after age 12. By age 19, the rate of gonadal carcinomas (Xd) was similar to ovarian germ cell tumors (Xc) in females. For males, the rate of testicular germ cell tumors (Xc) at age 19 was substantially higher than that observed for ovarian germ cell tumors among 19 year old females (44.5 versus 10.4 per million for age 19).

TRENDS

The age-adjusted incidence rates for GCTOG tumors increased between 1975-79 and 1990-95 from 3.7 to 5.4 per million for children younger than 15 years of age and from 8.5 to 12.0 per million for those younger than 20 years of age (Table X.4). For both males and females younger than 15 years of age, the increase in incidence primarily resulted from higher rates for intracranial and intraspinal germ cell tumors (Xa) and for non-CNS extragonadal germ cell tumors (Xb), while the rates of gonadal germ cell tumors (Xc) did not increase. The increased incidence of non-CNS extragonadal tumors (Xb) for both males and females was due in large measure to an increase in incidence in the first

Figure X.3: GCTOG age-specific incidence rates by selected ICCC subgroups females, all races, SEER, 1986-94

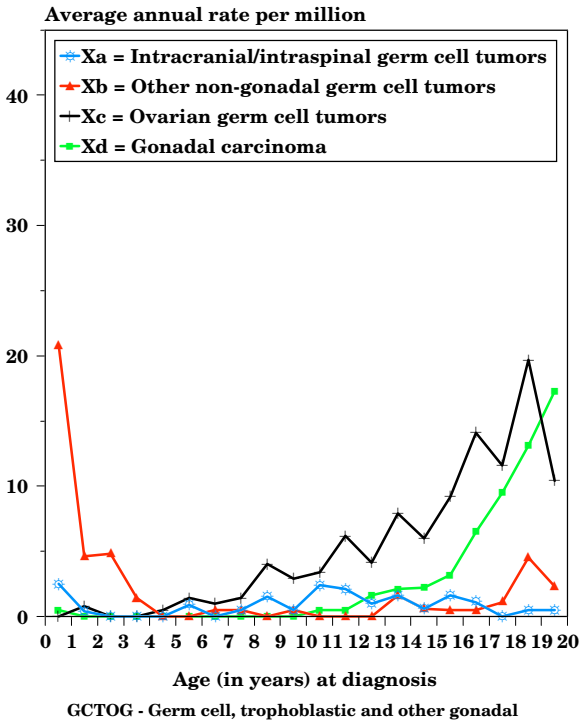


Table X.4: Average annual age-adjusted[1] incidence rates per million for germ cell trophoblastic, and other gonadal cancers by sex, age, subtype, and time period, all races, SEER, 1975-95

Sex/Age Group	Years	X(total)	Xa[2]	Xb[2]	Xc[2]	Xd[2]	Xe[2]
Total <15	1975-79	3.7	0.5	0.7	2.2	0.1	0.2
	1980-84	4.8	0.9	1.1	2.6	0.1	0.1
	1985-89	4.8	0.7	1.3	2.7	0.1	0.1
	1990-95	5.4	1.5	1.4	2.1	0.3	0.0
Males <15	1975-79	3.1	0.5	0.6	1.8	0.1	0.1
	1980-84	4.1	1.2	0.9	2.0	0.0	0.0
	1985-89	4.1	1.1	0.8	2.2	0.0	0.1
	1990-95	4.4	1.9	1.1	1.4	0.0	0.0
Females <15	1975-79	4.3	0.4	0.8	2.6	0.2	0.4
	1980-84	5.5	0.6	1.3	3.3	0.2	0.2
	1985-89	5.6	0.4	1.8	3.2	0.1	0.1
	1990-95	6.4	1.2	1.9	2.7	0.7	0.0
Total <20	1975-79	8.5	0.6	1.4	5.4	0.8	0.3
	1980-84	9.6	0.9	1.5	6.4	0.7	0.2
	1985-89	10.7	1.1	1.7	6.6	1.1	0.2
	1990-95	12.0	1.9	1.6	6.8	1.6	0.2
Males <20	1975-79	9.1	1.0	1.2	6.9	0.1	0.1
	1980-84	11.0	1.2	1.5	8.1	0.1	0.1
	1985-89	11.4	1.7	1.6	7.8	0.1	0.1
	1990-95	12.2	2.6	1.3	8.1	0.1	0.1
Female <20	1975-79	7.8	0.3	1.6	3.9	1.5	0.6
	1980-84	8.1	0.6	1.5	4.5	1.3	0.3
	1985-89	10.0	0.4	1.8	5.3	2.2	0.3
	1990-95	11.7	1.1	1.8	5.3	3.2	0.3

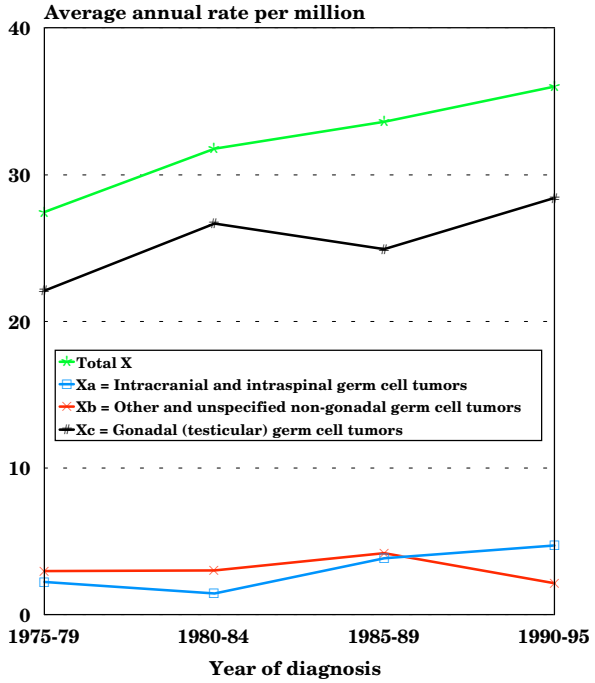
[1] Adjusted to the 1970 US standard population

[2] Xa = Intracranial and intraspinal germ cell tumors; Xb = Other and unspecified non-gonadal germ cell tumors; Xc = Gonadal (ovarian and testicular) germ cell tumors; Xd = Gonadal carcinoma; Xe = Other and unspecified malignant gonadal tumors.

year of life. This increase in non-CNS extragonadal malignant tumors among infants must be interpreted with caution, because non-malignant sacrococcygeal teratomas diagnosed in the newborn period outnumber malignant teratomas [3,23-25], and because careful inspection of mature and immature sacrococcygeal teratomas may show microscopic foci of yolk sac tumor [26,27]. Since nonmalignant sacrococcygeal teratomas are not reported and yolk sac tumors are reported, the increase in incidence in the first year of life may be the result of increasing recognition by pathologists of the need for careful scrutiny of apparently non-malignant sacrococcygeal teratomas. Almost all of the increase in the first year of life for females was in malignant teratomas/embryonal teratomas.

An increase in the age-adjusted incidence for GCTOG tumors was also observed for both sexes among those younger than 20 years of age. For males younger than 20 years of age, the increase in incidence was from 9.1 to 12.2 per million, with most of the increase attributed to intracranial and intraspinal germ cell tumors (Category Xa) and to testicular germ cell tumors (Category Xc). For females, the increase was from 7.8 to 11.7 per million, with most of the increase attributable to ovarian germ cell tumors

Figure X.4: Trends in GCTOG age-specific incidence rates by selected ICCC subgroups age 15-19, males, all races, SEER 1975-95



GCTOG - Germ cell, trophoblastic and other gonadal

(Category Xc) and to ovarian carcinomas (Category Xd). Because of the larger number of cases in the 15-19 year group compared to the younger than 15 year group, the trends for those younger than 20 years of age are primarily determined by trends for the 15-19 year age group.

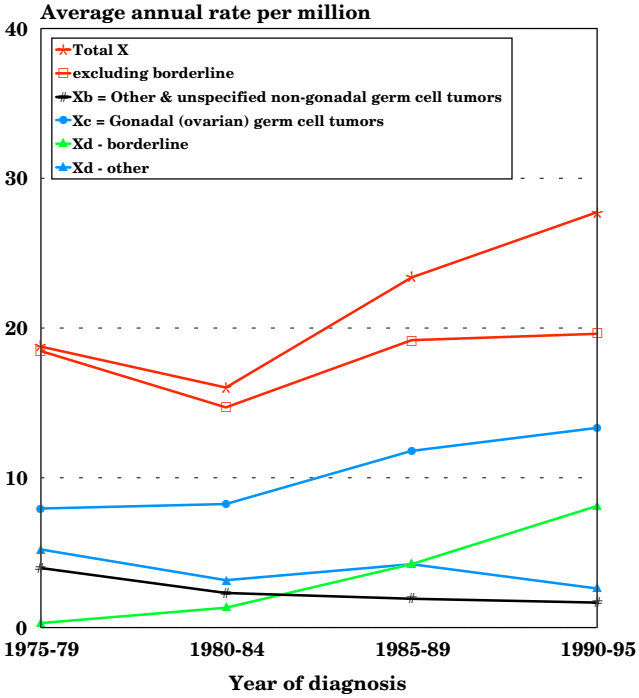
Figure X.4 illustrates the increase in incidence of testicular germ cell tumors (Xc) for the 15-19 year age group between 1975-79 (22 per million) and 1990-1995 (28 per million). The increase in incidence of testicular germ cell tumors for those 15-19 years of age is reminiscent of the increase in testicular cancer among adult males. Over the past 30-40 years, increased rates of testicular cancer have been reported from developed countries throughout the world, including the United States [21,22], European countries [28], Australia [29], and New Zealand [30].

The overall rate of GCTOG tumors for females aged 15-19 increased markedly from 1975-79 to 1990-95 (Figure X.5), but much of the increase was attributable to the inclusion of borderline tumors of the ovary which were not reportable cancers for the entire time period. Figure X.5 shows the overall rate for ICCC X for females both with and without the borderline tumors. With the borderline tumors excluded, the overall rate increased only slightly between 1975-79 and 1990-95 (Figure X.5), and this increase was driven by an increased incidence of ovarian germ cell tumors (8 per million for 1975-79 to 13 per million for 1990-95). An increased incidence for ovarian germ cell tumors in adults has also been reported [31,32].

SURVIVAL

For the period from 1985 to 1994, the 5-year survival rate for patients

Figure X.5: Trends in GCTOG age-specific incidence rates by selected ICCC subgroups age 15-19, females, all races, SEER, 1975-95



GCTOG - Germ cell, trophoblastic and other gonadal

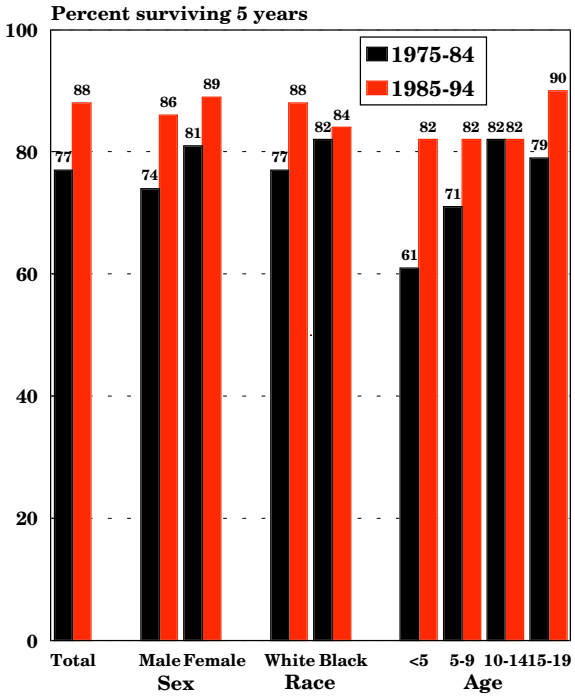
younger than 20 years of age with germ cell tumors was 87% (Figure X.6). Survival rates were better for the 15-19 year olds (5-year survival, 90%) than for the younger than 15 year olds (5-year survival, 84%). Other observations about outcome for children with germ cell tumors are illustrated in Figures X.6 and X.7 and include:

- For those younger than 20 years of age, females had slightly higher 5-year survival rates than males, and whites had somewhat higher 5-year survival rates than blacks (Figure X.6).

- Survival for patients younger than 20 years of age was better for gonadal germ cell tumors (ICCC Xc) than for tumors arising at "other and unspecified" sites (ICCC Category Xb), with 5–year survival rates of 94% and 71%, respectively in 1985-1994. Outcome was similar for patients younger than 20 years of age with intracranial germ cell tumors (ICCC Xa) and with tumors arising at "other and unspecified" sites (ICCC Xb), with both groups having survival rates for 1985-94 of approximately 70% (Figure X.7).

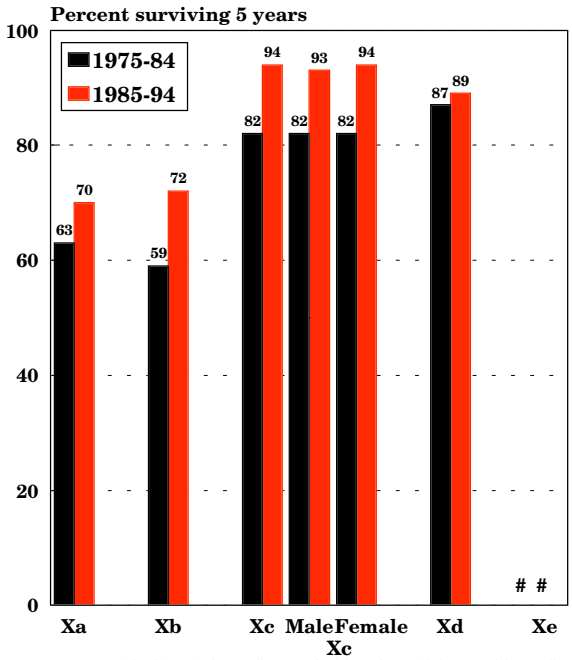
- Increasing survival rates were observed between 1975-84 and 1985-94 for each subgroup of the ICCC for patients younger than 20 years if age. The overall 5-year relative survival rate for all subgroups combined increased from 77% to 87% (Figure X.6). The largest increase in survival was for tumors arising at other and unspecified sites (ICCC Xb): 58 percent compared to 72 (Figure X.7).

Figure X.6: Germ-cell tumor 5-year relative survival rates by sex, race, age, and time period SEER (9 areas), 1975-84 and 1985-94



GCTOG - Germ cell, trophoblastic and other gonadal

Figure X.7: GCTOG tumor 5-year relative survival rates by sub-group, sex and time period, all races SEER (9 areas), 1975-84 and 1985-94



Xa = Intracranial and intraspinal germ cell tumors; Xb = Other and unspecified non-gonadal germ cell tumors; Xc = Gonadal (ovarian and testicular) germ cell tumors; Xd = Gonadal carcinoma; Xe - Other and unspecified malignant gonadal tumors.

GCTOG - Germ cell, trophoblastic and other gonadal # - < 25 cases - rate not shown

Table X.5: Current knowledge on causes of childhood malignant germ cell tumors (MGCT)

Exposure or Characteristic	Comments	References
Known risk factors		
Cryptorchidism	Risk is increased 2.5 - 11-fold. The contralateral as well as ipsilateral testis is at increased risk.	34-36
Factors for which evidence is suggestive but not conclusive		
High maternal hormone levels during pregnancy	Use of oral contraceptives during pregnancy, high pre-pregnancy weight, bleeding, hyperemesis and spotting indicate high hormone levels.	34,35,37-39
Family history of germ cell tumor	When malignant germ cell tumors occur in the same family, they are usually of the same histologic type.	40,41
Hernia	Central nervous system and genitourinary anomalies have also been observed in germ cell tumor patients.	34,35,42
Pre-term birth	Excess risk was not explained by cryptorchidism.	43,44
Trauma	The causality of this association is not clear. Trauma may result in closer scrutiny and earlier detection of an existing tumor.	45-47
Factors for which evidence is inconsistent or limtied		
Virus infection, e.g., mumps, cytomegalovirus, Epstein-B virus, and parvovirus B19		48-52
High birth weight		35,43,44
Prenatal X-ray exposure		43,53
Parental occupation	Associations have been observed with maternal employment in the medical field, paternal employment in service stations and aircraft industry, and paternal exposure to x-rays, maternal exposure to solvents, plastic and resin fumes.	44,54,55
Constitutional chromosome abnormalities, particularly sex chromosome abnormalities (e.g., Klinefelter syndrome (47,XXY), inverted Y)		56-60

The increase in survival for this subgroup, ICCC Xb, was dramatic for children younger than 5 years of age; the survival rate increased from 38% to 86%.

- The increase in survival between 1975-84 and 1985-94 was similar for ovarian and testicular germ cell tumors (Figure X.7). Both increased from 82% to 93-94%.

The improvement in outcome observed in the more recent period for children with germ cell tumors likely represents the widespread application of platinum-based chemotherapy, which is particularly effective against germ cell tumors [33].

RISK FACTORS

The etiology of malignant germ cell tumors is poorly understood. Cryptorchidism is the only confirmed risk factor for testicular germ cell tumors (see Table X.5 for references). Although rare, testicular cancer coincidence in father and son, and in male siblings has been reported, implying a genetic contribution in the disease origination. Suggested risk factors for malignant germ cell tumors, mainly based on findings from studies of testicular cancer among adult populations, include maternal exogenous hormone use and high endogenous hormone level during pregnancy, pre-term birth, high birth weight, hernia, trauma, pre-natal X-ray exposure, virus infection, parental occupation and occupational exposures, and certain constitutional chromosome abnormalities.

SUMMARY

The ICCC Diagnostic Group X for GCTOG tumors represents less than 4% of tumors among children younger than 15 years of age. However, for the 15-19 year age group, these tumors account for a much higher proportion (approximately 16%) of cancer cases. The age-incidence pattern for the group of GCTOG tumors is characterized by relatively high rates in the first year of life, followed by much lower rates until puberty, when incidence begins to increase and reaches rates greater than those in the first year of life. For males, the majority of testicular cancers occurring before age 15 years are diagnosed in the first 4 years of life. However, because the incidence of testicular germ cell tumors increases rapidly after age 15, the vast majority of testicular cancer cases among those younger than 20 years of age develop among 15-19 year olds. Black males have a much lower incidence of testicular germ cell tumors than white males, while black females and white females have similar rates for ovarian germ cell tumors.

The distinctive nature of the germ cell tumors of infants and young children compared to those of adolescents and young adults complicates analyses of trends in incidence for the children younger than 20 years of age. However, over the past 20 years there has been a small absolute increase in incidence for germ cell tumors for children younger than age 15 years, with most of the increase due to higher rates for extragonadal germ cell tumors. Among children younger than 20 years of age, the incidence of GCTOG tumors has increased. The increase has been primarily driven by higher rates for gonadal germ cell tumors among 15-19 year olds and by higher rates for gonadal carcinomas among 15-19 year old females. The latter increase is attributable to changes in reporting of ovarian tumors during this time period, specifically inclusion of borderline tumors of the ovary. The increases in gonadal germ cell tumors for adolescents 15-19 years of age mirrors that observed for young adults with germ cell tumors. The onset of higher rates in males and females at the time of puberty as well as results from epidemiological studies suggest a contributory role

for hormonal influences, although the nature of these influences remains to be elucidated.

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HIGHLIGHTS

Incidence

- Among children, particularly before the adolescent years, carcinomas are very rare.
- In the US, approximately 1,050 children and adolescents younger than 20 years of age are diagnosed with carcinomas each year, of which approximately 350 are thyroid carcinomas and 300-350 are melanomas.
- All of the carcinomas combined comprised 9.2% of cancer in children younger than 20. The majority of the carcinomas were either thyroid carcinomas (35.5%) or melanomas (30.9%). Adrenocortical carcinomas (1.3%), nasopharyngeal carcinomas (4.5%), and other skin carcinomas (0.5%) combined for only a small proportion of the total, while other and unspecified carcinomas comprised 27.3%.
- The incidence rates for thyroid carcinoma were highest among the 15-19 year olds and much higher among females (24.4 per million) than males (4.7 per million) (Table XI.2).
- The incidence rates for malignant melanoma were highest among the 15-19 year olds and higher among females (16.5 per million) than males (10.0 per million) (Table XI.2).

Survival

- The 5-year survival rate was 99% for thyroid carcinomas. Males had a slightly lower survival rate than females (Table XI.4).
- The 5-year survival rate was 91% for malignant melanoma. Females had a 93% survival rate compared to males with an 87% survival rate (Table XI.4).

Risk factors

- The most well established risk factor for thyroid carcinoma is ionizing radiation exposure, from both environmental and therapeutic sources.
- The primary risk factors for melanoma are sun exposure and number of melanocytic and dysplastic nevi.

INTRODUCTION

Carcinomas are malignancies that originate in epithelial tissues. Epithelial cells cover the external surface of the body, line the internal cavities, and form the lining of glandular tissues [1,2]. Cancers that originate from epithelial cells, including those of the breast, lung, prostate, and colon, are by far the most common types of cancer in adults. Among children, however, particularly before the adolescent years, carcinomas are very rare. Leukemias, central nervous system cancer, lymphomas, sarcomas, and the embryonal cancers such as neuroblastoma, retinoblastoma and Wilms' tumor, represent a far greater burden to young children than does any specific epithelial cancer. Nevertheless, a variety of carcinomas do occur in children, especially during late adolescence, and in this report we provide descriptive epidemiologic data to characterize their occurrence. In the US, approximately 1,050 children and adolescents younger than 20 years of age are diagnosed with carcinomas each year, of which approximately 350 are thyroid carcinomas and 300-350 are melanomas.

Classification system

Although other classification systems exist [2], the diverse types of epithelial malignancies that are called 'carcinomas and other malignant epithelial neoplasms' by the ICCC system are classified into six broad subgroups [3]:

a. adrenocortical carcinoma
b. thyroid carcinoma
c. nasopharyngeal carcinoma
d. malignant melanoma
e. skin carcinoma other than melanoma
f. other and unspecified carcinomas

All of the malignancies within the group 'other and unspecified carcinomas' are very rare in children. Neoplasms of the salivary gland, colon, appendix, lung and bronchus, uterine cervix, and urinary bladder account for most of this group. Likewise, the adrenocortical, nasopharyngeal, and skin carcinomas (other than melanoma) rarely occur in children. Because thyroid carcinomas and malignant melanoma (henceforth called melanoma) are the only epithelial malignancies that occur with any significant frequency in children, we will focus primarily on these two cancers in this report. It should be noted that the ICCC system includes germ cell carcinomas within 'germ cell, trophoblastic, and other gonadal neoplasms', rather than 'carcinomas and other malignant epithelial neoplasms'. The incidence rate of gonadal carcinomas for children younger than 20 years of age is only 1.0 per million, so this omission will not appreciably influence our results. Please note also that we have calculated frequencies and rates from SEER data for the years 1975 through 1995, and, unless otherwise specified, we report incidence rates as average annual rates per million children younger than 20 years of age, adjusted to the 1970 US standard population.

Thyroid carcinomas are endocrine tumors, although they do not necessarily exhibit hormonal activity. There are four types of thyroid carcinomas: papillary, follicular, medullary and anaplastic. In children, papillary tumors represent greater than 70% of thyroid carcinomas, and follicular tumors another 20%. Only a small proportion of thyroid carcinomas are medullary (5-10%), or anaplastic (extremely rare). The vast majority of childhood thyroid carcinomas are well differentiated tumors, and despite their malignant pathology, the clinical course of most thyroid carcinomas is relatively benign [4-6].

Malignant cutaneous melanomas arise from epidermal melanocytes and are often classified into one of three histopathological types according to the presence and pattern of intraepidermal growth: superficial spreading melanoma, nodular melanoma, and lentigo maligna melanoma. Melanomas occur most frequently on the trunk in white males, the lower limbs in white females, and the soles of the feet in blacks [7,8].

INCIDENCE

All of the carcinomas combined comprised 9.2% of cancer in children during the time period of this study. The majority of the 2,735 epithelial cancers were either thyroid carcinomas (35.5%) or melanomas (30.9%). Adrenocortical carcinomas (1.3%), nasopharyngeal carcinomas (4.5%), and other skin carcinomas (0.5%) combined for only a small proportion of the total, while other and unspecified carcinomas comprised 27.3%. Nearly 75% (2,047) of the childhood carcinomas occurred in adolescents 15-19 years of age, including 75% of the thyroid carcinomas, 80% of the melanomas, 63% of the nasopharyngeal carcinomas, and 74% of the other and unspecified carcinomas. Although there were only 36 adrenocortical carcinomas reported to

SEER areas, 18 of them occurred in children younger than 5 years of age.

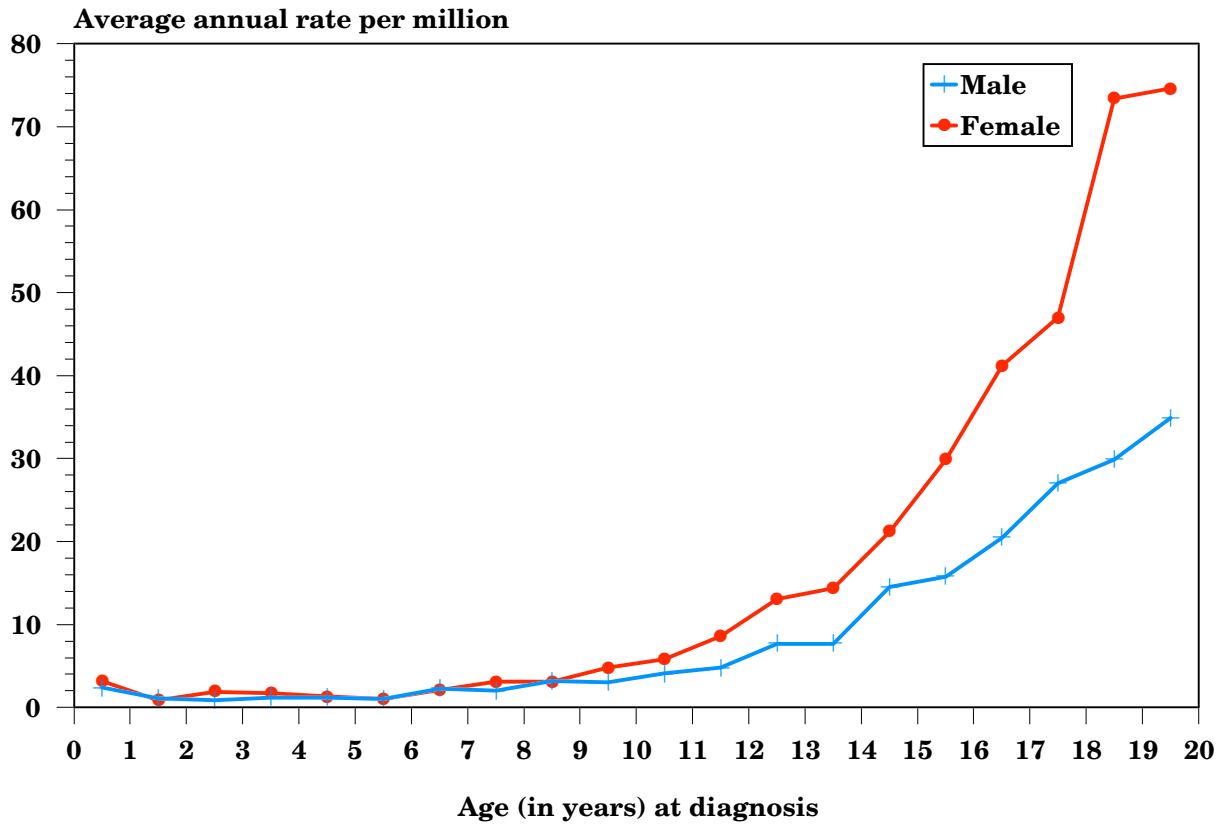
Age-specific incidence

The impressive age differences in incidence rates of carcinomas are shown in Table XI.1. Incidence rates of thyroid carcinoma and melanoma were practically negligible in very young children. Among 15-19 year olds, however, both melanoma and thyroid cancer substantially increased in occurrence over younger ages, particularly for females. The male-to-female ratios

Table XI.1: Average annual age-specific incidence rates per million by histology and sex, all races, SEER, 1975-95

Tumor type	Age	Total	Females	Males	F/M Ratio
All carcinomas	0-4	1.6	1.9	1.3	1.5
	5-9	2.7	3.1	2.3	1.3
	10-14	10.0	12.1	8.0	1.5
	15-19	40.3	55.5	25.9	2.1
Adrenocortical carcinoma	0-4	0.4	0.5	0.3	1.7
	5-9	0.1	0.1	0	
	10-14	0.1	0.1	0.1	1.0
	15-19	0.2	0.2	0.1	2.0
Thyroid carcinoma	0-4	0.1	0.2	0	
	5-9	1.0	1.3	0.8	1.6
	10-14	3.9	6.0	1.8	3.3
	15-19	14.4	24.4	4.7	5.2
Nasopharyngeal carcinoma	0-4	0.1	0	0.1	
	5-9	0.1	0	0.1	
	10-14	0.8	0.3	1.30	0.2
	15-19	1.5	1.2	1.8	0.7
Malignant melanoma	0-4	0.7	0.7	0.7	1.0
	5-9	0.7	0.8	0.7	1.1
	10-14	2.2	2.5	1.9	1.3
	15-19	13.2	16.5	10.0	1.7
Skin carcinoma other than melanoma	0-4	0	0	0	
	5-9	0	0	0	
	10-14	0.1	0.1	0.1	1.0
	15-19	0.2	0.2	0.1	2.0
Other and unspecified carcinomas	0-4	0.4	0.5	0.3	1.7
	5-9	0.8	0.9	0.6	1.5
	10-14	2.8	3.0	2.7	1.1
	15-19	11.0	12.8	9.2	1.4

Figure XI.1: Total carcinoma age-specific incidence rates by sex, all races, SEER, 1976-84 and 1986-94



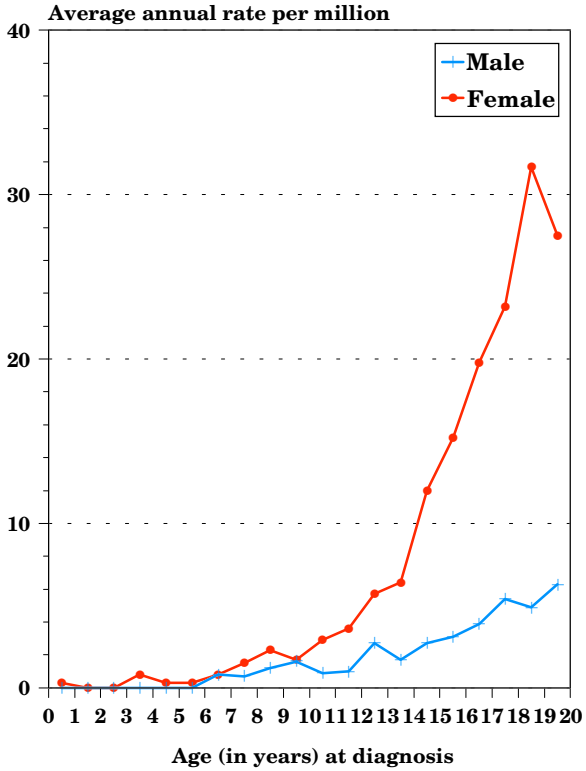
in rates were greatest among adolescents 15-19 years, and the sex difference was most pronounced for thyroid carcinoma. Figure XI.1 provides greater detail on the age-specific patterns of incidence for all carcinomas combined[1]. Carcinoma incidence was quite low through age 10 years, but the rates increased dramatically in older children. At age 19, incidence rates were 35 per million males and 75 per million females. For thyroid carcinoma (Figure XI.2), the age-specific incidence rates for males and females began to diverge at age 10 years. Beginning at age 13, the rates increased substantially for females, while the increase in male rates was more modest. Incidence rates of melanoma are shown in Figure XI.3. Rates differed minimally by sex until age 16, when the rates for females became greater than those for males.

Sex-specific and race-specific incidence

As shown in Table XI.2, the incidence rate of all childhood carcinomas combined was 13.8 per million. The ratio of white to black rates was 1.5 to 1. The magnitude of this racial difference is explained by the 2.5 to 1 ratio for thyroid cancer and the dra-

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

Figure XI.2: Thyroid carcinoma age-specific incidence rates, by sex, all races SEER, 1976-84 and 1986-94



matic 16 to 1 ratio for melanoma. The variation in carcinoma rates between whites and blacks was greater among females than males.

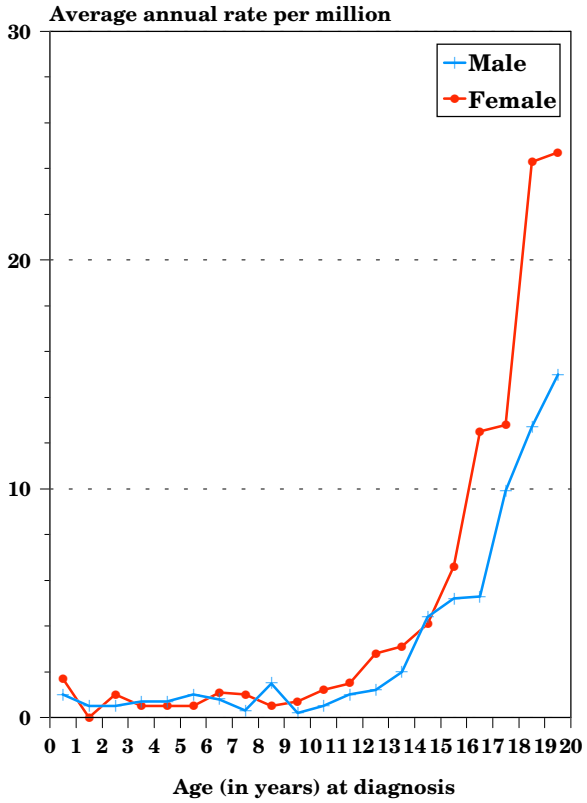
Table XI.2 further illustrates that incidence rates of thyroid carcinoma were over 4-fold higher in females than males for both white and black children. Among whites, melanoma was more common in females than males, but not nearly to the extent that was observed for thyroid cancer. In fact, among whites, male rates of melanoma were higher than male rates of thyroid cancer. As is well known, occurrence of melanoma in blacks is extremely unusual. Although not shown in the table, black children had a slightly higher rate of other and unspecified carcinomas than white children (4.7 versus 3.6 per million, respectively).

Table XI.2: Average annual age-adjusted* incidence rates per million by histology, race, and sex, age <20, SEER, 1975-95

Tumor type	Race	Total	Females	Males	F/M Ratio
All carcinomas	All races	13.8	18.2	9.5	1.9
	Whites	14.2	19.3	9.4	2.1
	Blacks	9.3	10.7	7.8	1.4
Thyroid carcinoma	All races	4.9	8.1	1.9	4.3
	Whites	5.2	8.6	2.0	4.3
	Blacks	2.1	3.4	0.7	4.9
Malignant melanoma	All races	4.2	5.1	3.3	1.5
	Whites	4.8	5.8	3.8	1.5
	Blacks	0.3	0.2	0.3	0.7

* Adjusted to the 1970 US standard population

Figure XI.3: Malignant melanoma age-specific incidence rates, by sex, all races SEER, 1976-84 and 1986-94



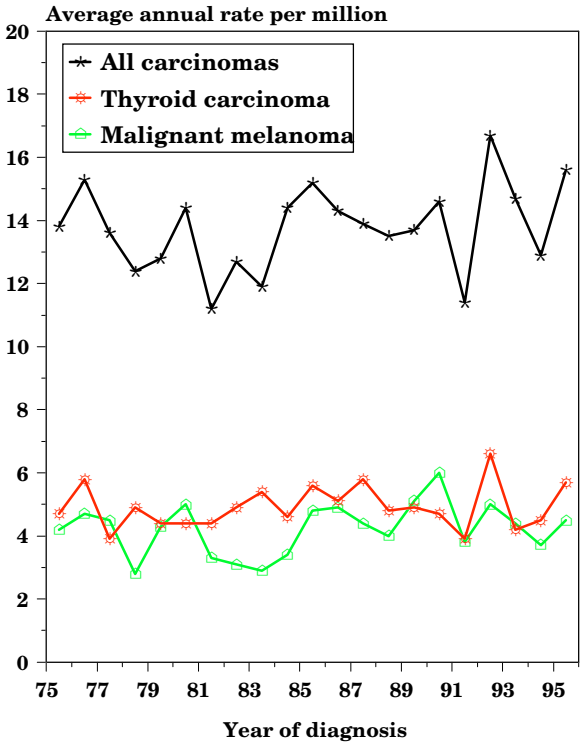
TRENDS

Figure XI.4 illustrates yearly rates of carcinomas from 1975-95. Age-adjusted incidence rates did not increase appreciably over this time frame for either melanoma or thyroid carcinoma. Incidence rates over time are further illustrated in Table XI.3, where rates by sex are shown within specific time periods.

SURVIVAL

Survival probability is excellent for children with either thyroid carcinoma or melanoma. Table XI.4 provides 5-year relative survival probabilities for both major types of childhood carcinoma, as well as for all carcinomas combined. Virtually no change in survival was observed for thyroid carcinoma over the time periods 1975-84 versus 1985-94 (Figure XI.5). Survival improved slightly for melanoma, from 85% for those diagnosed during 1975-84, to 91% during 1985-94 (Figure XI.6).

Figure XI.4: Trends in carcinoma age-adjusted* incidence rates, by histology, age <20 all races, both sexes, SEER 1975-95



*Adjusted to the 1970 US standard population

Table XI.3: Trends in average annual age-adjusted* incidence rates per million, by histology and sex, age <20, all races SEER, 1975-95

Tumor type	Year of diagnosis	Total	Females	Males
All carcinomas	1975-79	13.6	18.7	8.7
	1980-84	12.9	16.1	9.4
	1985-89	14.1	18.4	10.1
	1990-95	14.3	19.3	9.7
Thyroid carcinoma	1975-79	4.8	7.8	1.8
	1980-84	4.7	7.2	2.4
	1985-89	5.2	8.8	1.8
	1990-95	4.9	8.6	1.5
Malignant melanoma	1975-79	4.1	5.1	3.1
	1980-84	3.6	4.4	2.8
	1985-89	4.6	5.5	3.9
	1990-95	4.6	5.6	3.6

* Adjusted to the 1970 US standard population

For each type of carcinoma shown, females had slightly better survival probabilities than males. Black children appeared to fare worse than white children for all carcinomas combined, however there were only 29 black males and 34 black females during the time period, so the results should be viewed very cautiously. Similarly, there were too few black children with either thyroid carcinoma or melanoma on whom to base relative survival rates.

RISK FACTORS

Risk factors for thyroid carcinoma have been reviewed in several previous reports [9-15] and will only be briefly summarized here. The most well established risk factor for thyroid carcinoma is ionizing radiation exposure, from both environmental and therapeutic sources. Irradiation treatment for conditions such as tinea capitis, enlarged thymus, acne, and cancer have clearly been shown to increase risk for thyroid carcinoma development. Other than cancer treatment, however, these causes are primarily of historical concern. Environmental exposures to ionizing radiation from the atomic bombings in Japan and from the nuclear disaster at Chernobyl also have definitively been shown to cause substantial increases in thyroid carcinoma. The preponderance of thyroid cancer in females suggests that hormonal factors may mediate disease occurrence. Other potential etiologic factors include benign thyroid diseases and certain inherited cancer susceptibility syndromes, such as familial adenomatous polyposis, and multiple endocrine neoplasia (MEN) types I, IIA and IIB.

The primary risk factors for melanoma are sun exposure and number of melanocytic and dysplastic nevi. An extensive review of studies related to sun expo-

Table XI.4: Five-year relative survival rates by histology, race and sex age <20, SEER, 1985-94

Tumor type	Total	Females	Males
	Percent	Percent	Percent
All carcinomas			
All races	89	93	83
White	91	93	86
Black	77	85	65
Thyroid carcinoma			
All races	99	99	95
White	98	99	94
Black	*	*	*
Malignant melanoma			
All races	91	93	87
White	91	93	88
Black	*	*	*

*Less than 25 cases.

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

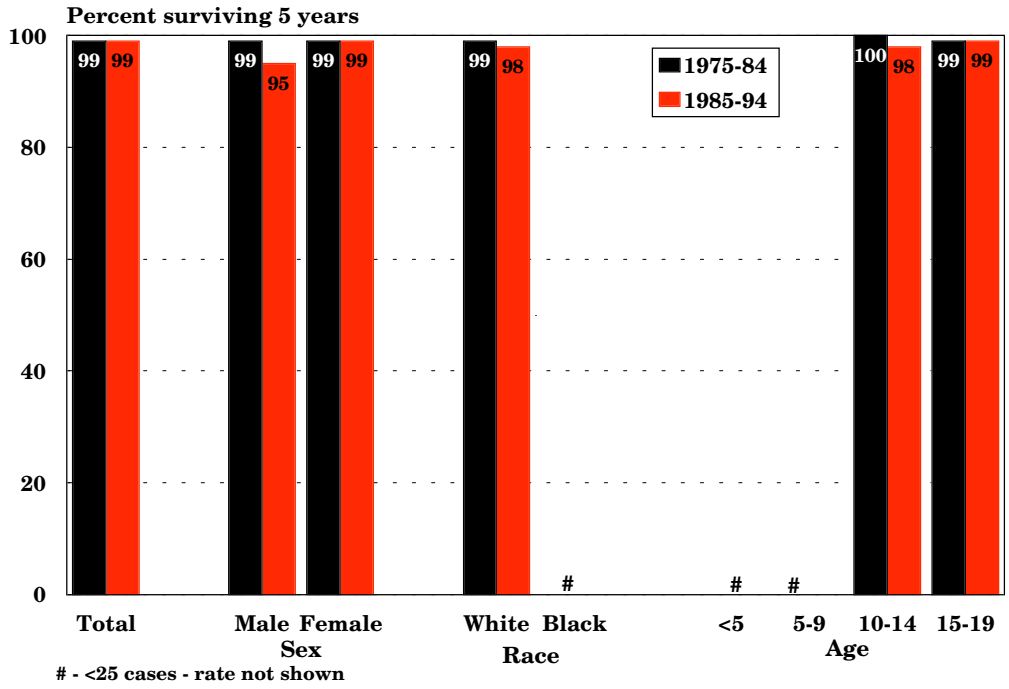
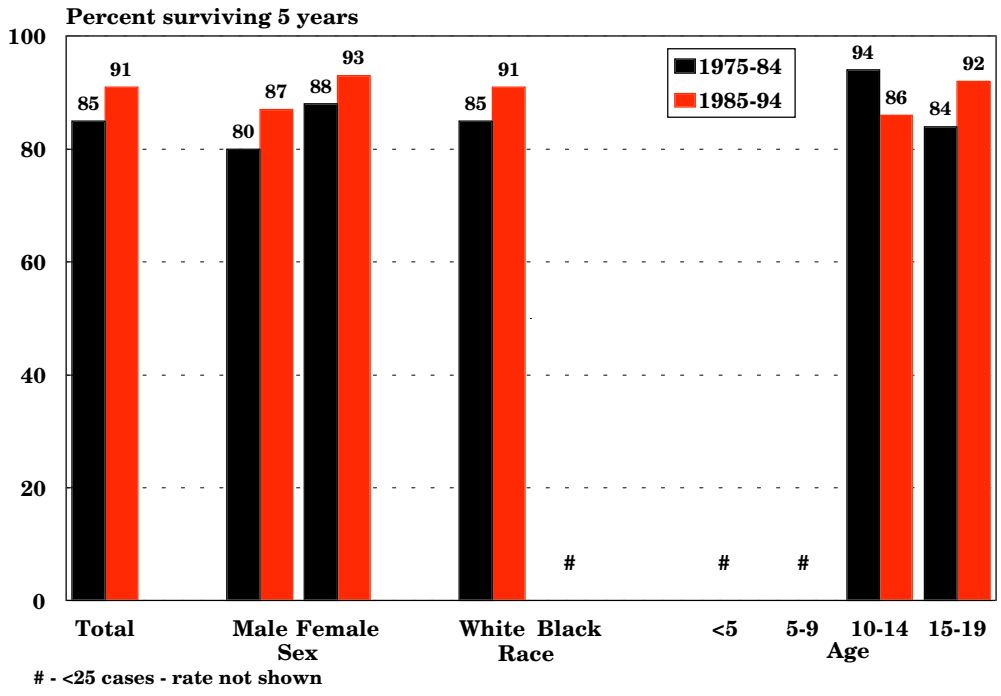


Figure XI.6: Malignant melanoma 5-year relative survival rates by sex, race, age and time period, SEER (9 areas), 1975-84 and 1985-94



sure, nevi, and other potential risk factors can be found in reference 6.

SUMMARY

In stark contrast to cancer incidence in adults, carcinomas were very rare in children, especially those younger than 15 years of age. Rates increased quite substantially with increasing age, however, particularly among females aged 10-19 years. The most common types of epithelial cancer in children were thyroid carcinomas (4.9 per million younger than 20 years of age) and melanomas (4.2 per million younger than 20 years of age). Females, however, had 4 times the thyroid cancer rate observed for males. Additionally, white children had 2.5 times the thyroid cancer rate and 16 times the melanoma rate observed for black children. From 1975-95 incidence rates of both thyroid cancer and melanoma remained fairly stable. The strongest known risk factor for thyroid carcinoma is ionizing radiation exposure. Sun exposure and number of nevi are the best described risk factors for melanoma occurrence. Fortunately, 5-year survival probability is excellent for both thyroid cancer (99%) and melanoma (91%).

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HIGHLIGHTS

Incidence

- The age of peak cancer incidence among children occurred during the first year of life (Figure XII.1).
- Malignancies of infancy represented 10% of all cancer that was diagnosed among children younger than 15 years of age. The average annual incidence rate of all infant cancer combined was 233 per million infants, which was 12% higher than the age (2 years) with the next highest incidence.
- The rate among females (234 per million infants) was essentially the same as that in males (232 per million infants). This is notable because infancy was the only age among children younger than 15 years of age in which female rates were not lower than male rates.
- Neuroblastoma comprised 28% of infant cancer cases and was the most common malignancy among these young children (65 per million infants).
- The leukemias as a group (41 per million infants) represented the next most common type of cancer, comprising 17% of all cases (Figure XII.2).
- Central nervous system malignancies comprised 13% of infant cancer, with an average annual incidence rate of nearly 30 per million infants.
- The average annual incidence rates for malignant germ cell and malignant soft tissue tumors were essentially the same at 15 per million infants. Each comprised about 6% of infant cancer (Figure XII.2).
- Leukemias accounted for a substantial proportion of the racial difference, in that the average annual rate for white infants (48.7 per million) was 66% higher than for black infants (29.4 per million).

Survival

- The prognosis for infants with cancer is often worse than in children of older ages, even when comparing the same histologic diagnosis. For instance, the 5-year relative survival for children younger than 15 years of age who were diagnosed with acute lymphoid leukemia from 1975-94 was well over 70%, but for infants the survival rate was 33%.
- Over 80% of children diagnosed with neuroblastoma during infancy were alive 5 years following diagnosis. In contrast, for children diagnosed with neuroblastoma at age 1 year or older, the 5-year relative survival was about 45%.

INTRODUCTION

Adult cancers usually form in epithelial tissues and are believed often to be the result of a long biological process related to the interaction of exogenous exposures with genetic and other endogenous characteristics among susceptible people. However, in young children, particularly infants, the aberrant genetic processes that fail to safeguard against the clonal proliferation of cells with unregulated growth potential occur very early in life and progress very quickly. Due to the unique clinical, genetic, and epidemiologic characteristics of cancers in infants [1,2], it is becoming increasingly

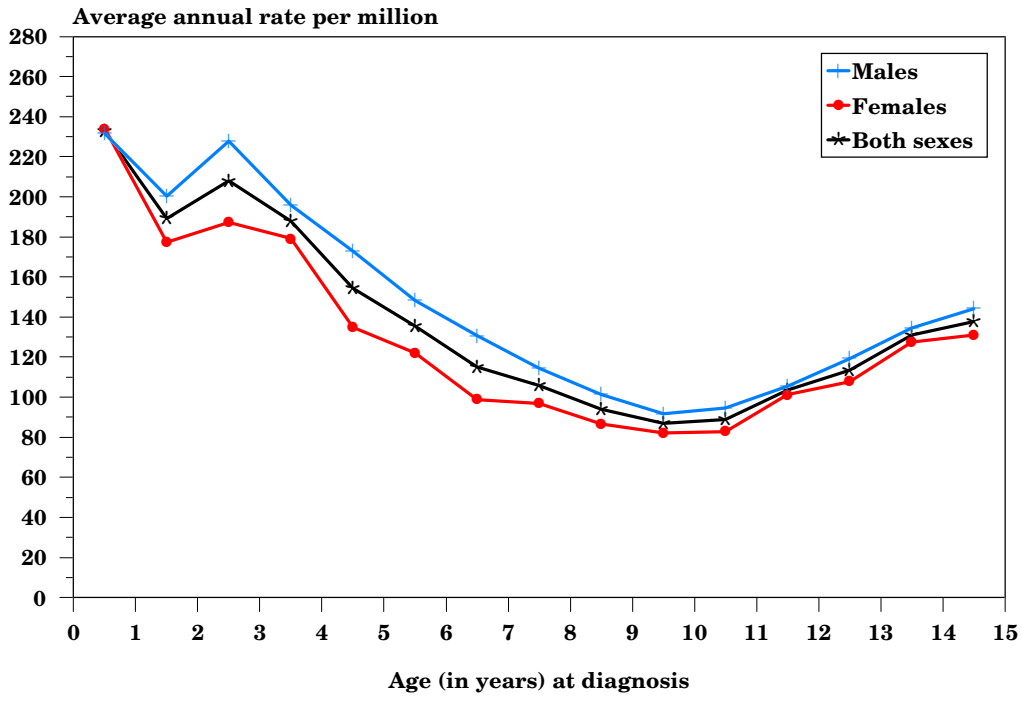
apparent that the study of infant cancer may lead to further understanding of the mechanisms of carcinogenesis. With that in mind, this chapter will briefly summarize and discuss data on cancer that occurs among children who are diagnosed within the first year of life.

INCIDENCE

The cancer cases used to calculate incidence rates in this discussion were limited to primary malignancies that were registered in SEER areas of the United States during the time periods 1976-84 and 1986-94. This time restriction was imposed because enumeration of the population at risk by single years of age was available only for the census years of 1980 and 1990. The US Bureau of the Census provides intercensal population estimates by 5-year age groups, but not by single years of age. Therefore, the population estimates for 1980 were used in rate calculations for cases diagnosed from 1976-84, and the 1990 estimates were used for cases diagnosed from 1986-94.

The age of peak cancer incidence among children occurred during the first year of life, as shown in Figure XII.1. Malignancies of infancy represented 10% of all cancer that was diagnosed among children younger than 15 years of age. The incidence rate of all infant cancer combined was 233 per million infants, which was 12% higher than the age (2 years) with the next highest incidence. The rate among females (234 per million infants) was essentially the same as that in males (232 per million infants). This is notable because infancy was the only age among children younger than 15 years of age in which female rates were not lower than male rates. Differences in rates by sex will be discussed in more detail below.

Figure XII.1: Total childhood cancer age-specific incidence rates by sex, all races, SEER, 1976-84 and 1986-94 combined



Histology-specific incidence

Figure XII.2 illustrates the incidence rate for the most predominant types of infant cancer. Although neuroblastoma represented less than 8% of cancer cases among children younger than 15 years of age, neuroblastoma comprised 28% of infant cancer cases and was the most common malignancy among these young children (65 per million infants). The leukemias as a group (41 per million infants) represented the next most common type of cancer, comprising 17% of all cases. As with older children, acute lymphoid leukemia was the most frequently occurring leukemia. The average annual incidence rate of acute lymphoid leukemia was 21 per million infants, while the rate for the acute non-lymphoid leukemias was 11 per million infants. For juvenile chronic myeloid leukemia, which by international consensus is now called juvenile myelomonocytic leukemia (JMML), the average annual incidence rate was 3 per million infants. The combined rate for other and unspecified leukemias was about 5 per million infants.

Central nervous system malignancies comprised 13% of infant cancer, with an incidence rate of nearly 30 per million infants. Astrocytomas and other gliomas (combined) accounted for half of the CNS malignancies (15 per million), followed by primitive neuroectodermal tumors/medulloblastomas (PNET, 9 per million infants) and ependymomas (5 per million). Retinoblastoma and Wilms' tumor followed CNS cancer in order of occurrence among infants. Retinoblastoma accounted for about 12% of infant cancer and Wilms' tumor an additional 9%.

The incidence rates for malignant germ cell tumors (including intracranial) and malignant soft tissue tumors were essentially the same at 15 per million infants.

Figure XII.2: Infant age-specific incidence rates by type, all races, both sexes, SEER, 1976-84 and 1986-94 combined

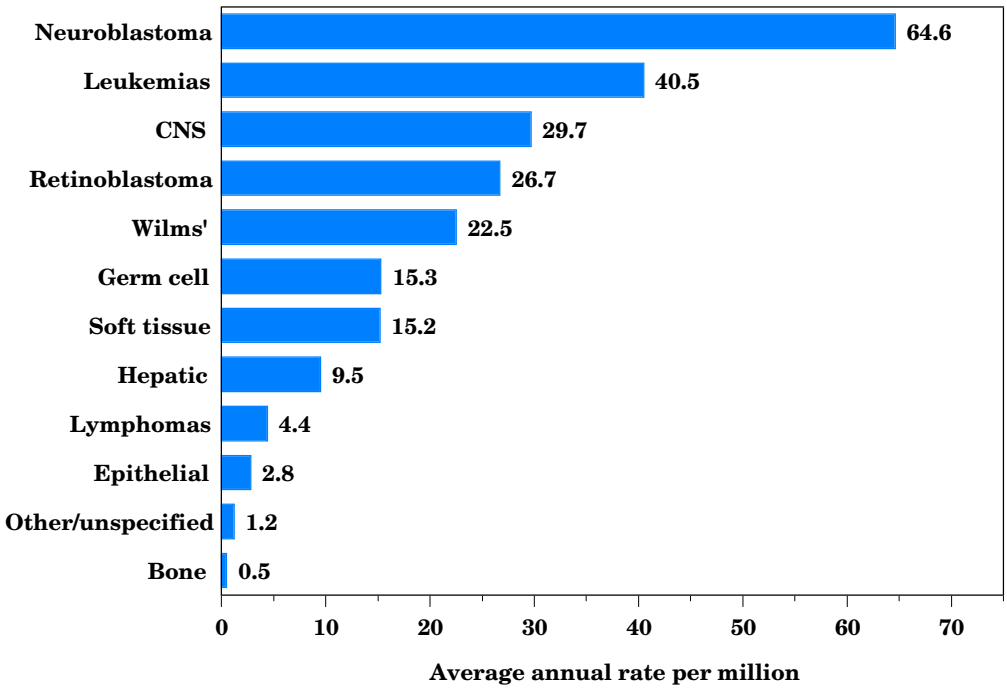
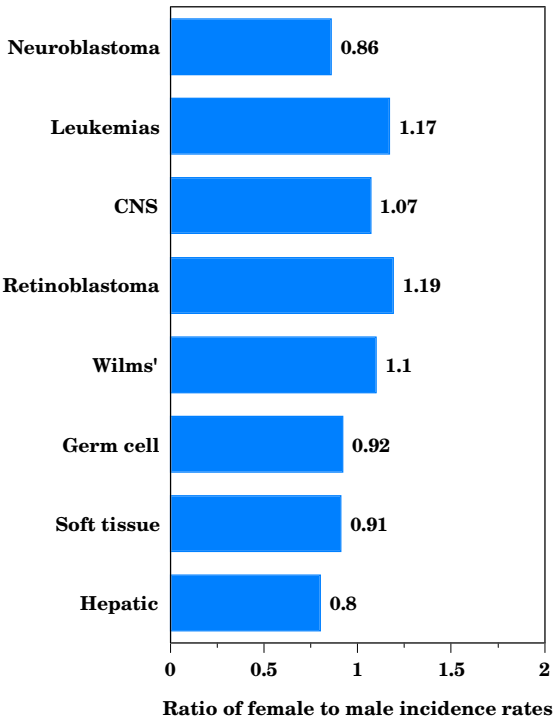


Figure XII.3: Ratios of female to male cancer incidence rates among infants by type, all races SEER, 1976-84 and 1986-94 combined

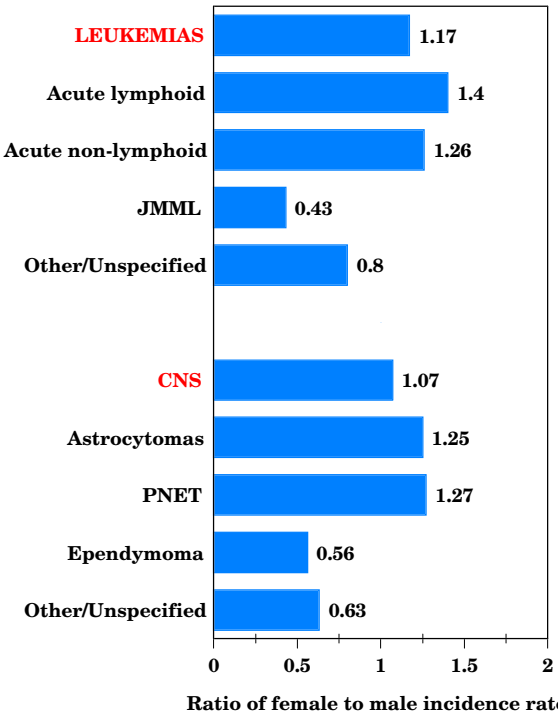


Each comprised about 6% of infant cancer. About 29% of the germ cell malignancies diagnosed during infancy were gonadal, which is half the percentage that occurs overall in children younger than 15 years of age. Unlike soft tissue tumors in older children, the rate of fibrosarcomas (5 per million infants) was similar to that of rhabdomyosarcomas (6 per million infants). This contrasts with the rhabdomyosarcoma and fibrosarcoma rates among children younger than 15 years of age of 4.6 per million and 2.3 per million, respectively. The rate for malignancies of the liver, almost exclusively hepatoblastoma, was 9.5 per million infants. Hepatoblastoma is similar to neuroblastoma, retinoblastoma, and Wilms' tumor (nephroblastoma) in that it is an embryonal malignancy with the age of peak incidence occurring during very early childhood. Lymphomas and especially bone cancers, which are quite important cancers among adolescents, are extremely rare in infants.

Sex-specific incidence

The female to male ratios of incidence rates for selected cancer types are illustrated in Figure XII.3. None of the sex differences were very pronounced. For leukemias and CNS cancer, however, the sex ratios differed by histologic subtype. Figure XII.4 provides female to male ratios for major subgroups of leukemia and CNS cancer. This illustration reveals that most types of infant leukemia and CNS cancer were more common in females than males, but JMML and ependymoma were notable exceptions. For both types of neoplasms, there is around a 2-fold higher average annual incidence in males than in females. The JMML rates were 4.0 per million male infants compared with 1.7 per million female infants. The ependymoma rates

Figure XII.4: Ratios of female to male cancer incidence rates among infants by type, all races SEER, 1976-84 and 1986-94 combined



were 6.2 per million male infants compared with 3.5 per million female infants.

Black-white differences in incidence

Figure XII.5 demonstrates the substantial discrepancy in black-white cancer incidence rates among children, especially young children. During infancy this racial variation is quite pronounced, in that white children (275 per million white infants) had a 40% higher malignancy rate than black children (196 per million black infants). This difference does not appear to be a result of earlier diagnosis for white children, based on the similar age pattern of incidence that is illustrated in Figure XII.5. The ratios of incidence rates for white relative to black infants are shown for selected cancer types in Figure XII.6. Leukemias accounted for a substantial proportion of the racial difference, in that the average annual rate for white infants

Figure XII.5: Total childhood cancer age-specific incidence rates by race, both sexes SEER, 1976-84 and 1986-94 combined

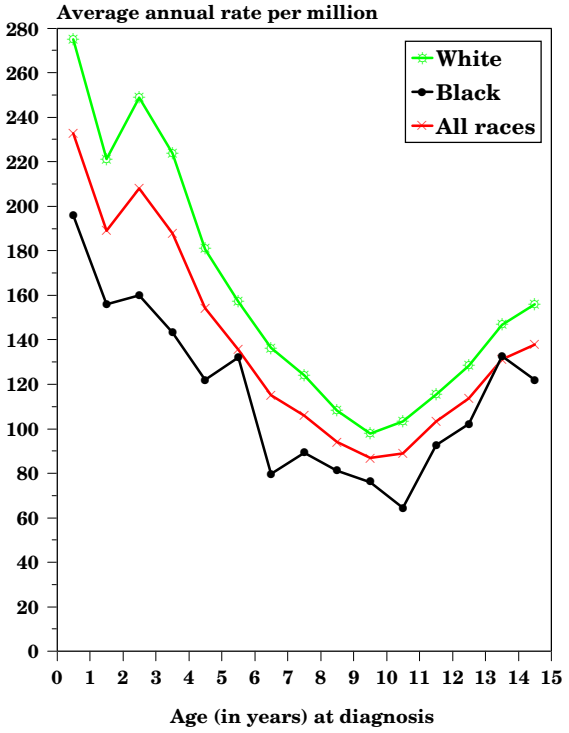
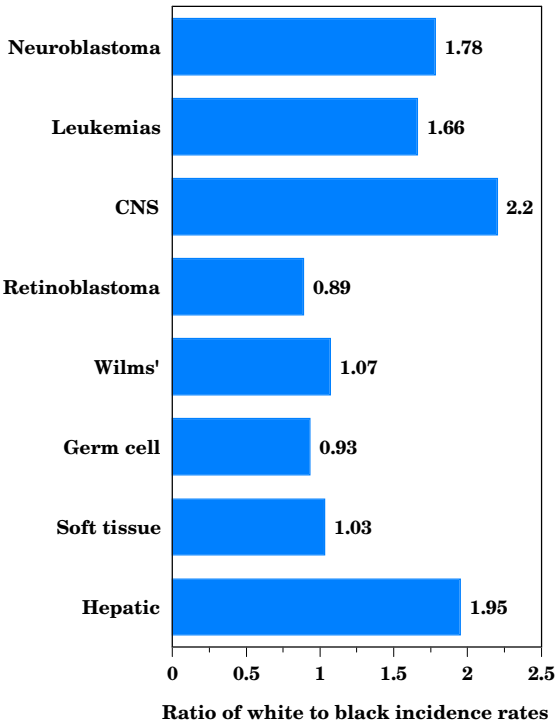


Figure XII.6: Ratios of white to black incidence rates among infants by type, both sexes SEER, 1976-84 and 1986-94 combined



(48.7 per million) was 66% higher than for black infants (29.4 per million). For neuroblastoma, white rates were 78% higher than black rates (79.0 vs. 44.5 per million, respectively). The relative difference was even greater for both liver cancer and CNS cancer. The infant incidence rate for hepatoblastoma was 95% higher in whites than in blacks (11.1 vs. 5.7 per million, respectively) and for CNS malignancies the rate was 120% higher for whites (37.7 per million) than for blacks (17.1 per million). Of the more common infant cancers, only rates of malignant germ cell tumors and retinoblastoma were higher in black infants, and these differences were slight. The small number of cases for black infants precluded reliable subgroup comparisons for the CNS cancers and leukemias.

Distribution by month of age at diagnosis

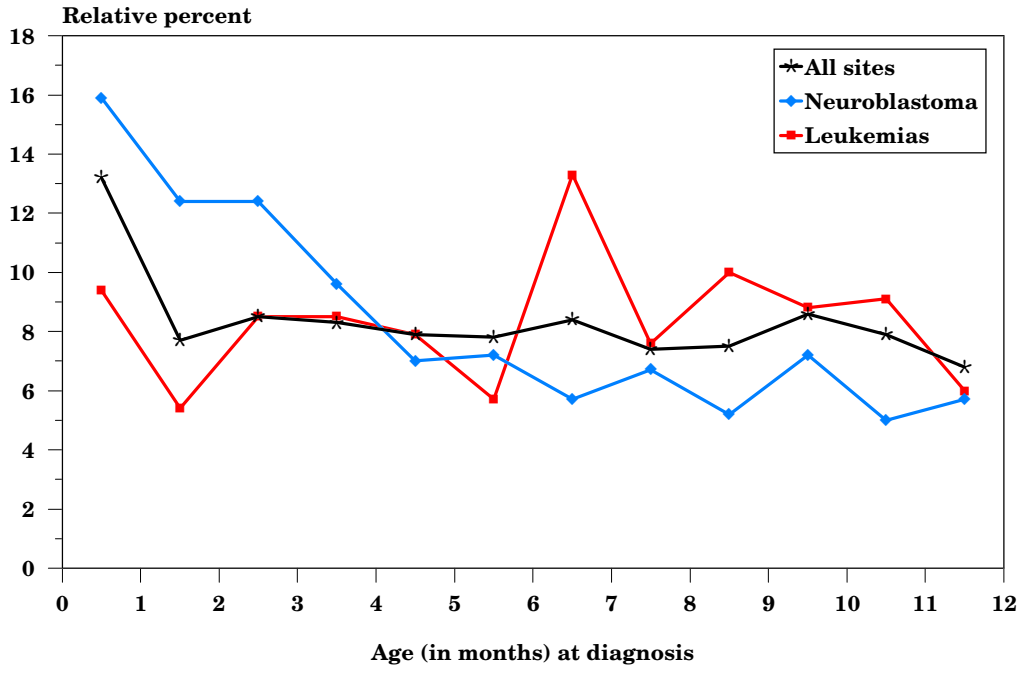
Although we lack a valid denominator (the number of children at risk by month of

age) to accurately calculate month-specific age incidence rates, the percentage of cancer cases (all types combined) by month of age at diagnosis is presented in Figure XII.7. This distribution shows that 13% of the infant malignancies were diagnosed during the first month following birth. Separate distributions for all leukemias combined and for neuroblastoma are also illustrated. Approximately half of neuroblastomas were diagnosed within the first 4 months of life, with 16% diagnosed during the month following birth. In fact, many of these tumors were likely detected *in utero*. Unlike neuroblastoma, the pattern of diagnosis for leukemias shows that the peak month of diagnosis occurred during the latter part of infancy, in the 7th month of life. Although not shown in the figure, the majority of infant germ cell tumors (56%) were diagnosed very soon after birth, before 2 months of age. There was no other cancer type that presented with such a large percentage of cases so early after birth.

TRENDS

As discussed in a previous report of trends in infant cancer [2], considerable caution must be exercised when interpreting temporal changes in rates for a single age group. Any trend analysis of incidence rates may be confounded by changes in population characteristics, the accuracy of census estimates, screening practices, diagnostic technology, morphology classifications, and case ascertainment. One or more of these factors could effectively conspire to show increasing incidence over time that is not reflective of more cancer, but rather of earlier diagnosis or better case identification. Neuroblastoma is an excellent example of this because of the recent introduction of (controversial) screening practices for earlier detection in Japan and Canada [3,4] and because of the

Figure XII.7: Percent distribution of infant cancer cases by month of age at diagnosis and type, all races both sexes, SEER, 1976-84 and 1986-94 combined



fairly recent advent of fetal ultrasound diagnosis [5]. With that caveat in place, a table of incidence rates for two time periods (1976-84 and 1986-94) is presented. (Table XII.1) The percentage change in the incidence rates is also shown.

These data imply that incidence rates of infant cancer were higher during the time period 1986-94 than the time period 1976-84. To what degree these data represent a true increase in cancer incidence in the US, compared with the influence of the potentially misleading factors that were mentioned above, has not been determined and requires more detailed assessment. For instance, the 125% increase in germ cell tumors is largely concentrated among nongonadal malignancies (primarily sacrococcygeal and pelvic) among female infants (see the monograph chapter entitled: "Germ Cell, Trophoblastic and Other Gonadal Tumors" for additional details). While this could indicate a true increase in the incidence of this disease, it is likely that a substantial proportion of the increase reflects changes over time in the identification by pathologists of malignant elements in teratomas with an otherwise benign appearance, leading to increased reporting of malignant teratomas among infants [6]. Likewise, the increase in reported rates of infant neuroblastoma, a disease with an exceptionally high survival rate and with a propensity for spontaneous regression, may reflect increased diagnoses and reporting of tumors that previously regressed before being detected [7].

Table XII.1: Average annual incidence rates per million by type, age <1, all races both sexes, SEER, 1976-84 and 1986-94

Cancer type	1976-84	1986-94	% Change
All cancer	197.9	269.3	36
Neuroblastoma	55.2	74.4	35
All leukemia	35.9	45.4	26
All CNS	23.3	36.5	57
Retinoblastoma	22.1	31.5	43
Wilms'	21.4	23.6	10
Germ cell	9.5	21.3	124
Soft tissue	13.6	16.6	22
Hepatic	7.6	11.4	50
Lymphoma	4.5	4.2	- 7
Epithelial	2.6	3.0	15
Other/Unspecified	1.4	1.0	-29
Bone	0.5	0.5	0

SURVIVAL

The prognosis for infants with cancer is often worse than in children of older ages, even when comparing the same histologic diagnosis. For instance, the 5-year relative survival for children younger than 15 years of age who were diagnosed with acute lymphoid leukemia from 1975-94 was well over 70%, but for infants the survival rate was 35%. Survival was bleak at all ages for acute non-lymphoid leukemia, but it was the poorest for infants, with a relative 5-year survival of 30%. This pattern was also evident for rhabdomyosarcomas and CNS tumors, particularly ependymomas and PNET. For ependymomas, 5-year relative survival for infants was less than 20% and for PNET it was less than 30%. Infant neuroblastoma was an exception. Over 80% of children diagnosed with neuroblastoma during infancy were alive 5 years following diagnosis. In contrast, for children diagnosed with neuroblastoma at age 1 year or older, the 5-year relative survival was about 45%. The 5-year survival from 1975-94 was also very good for children diagnosed with Wilms' tumor (86%) and retinoblastoma (over 90%).

SUMMARY

The age of peak incidence of cancer in children occurs during the first year of life. Neuroblastoma is the most common infant malignancy, followed by the leukemias and the CNS cancers. Female infants and male infants have essentially the same overall cancer incidence rates. White infants have substantially higher cancer rates than black infants for most cancer types. Inci-

dence rates were notably higher for the period 1986-94 compared with 1976-84, although many factors other than a real increase in incidence may be influencing this trend. Relative survival for infants is very good for neuroblastoma, Wilms' tumor and retinoblastoma, but not for most other types of cancer.

The distribution of malignant disease in infants is quite different from that which is found in older children, adolescents, or adults. For instance, embryonal tumors such as neuroblastoma, Wilms' tumor, retinoblastoma, medulloblastoma and hepatoblastoma are more prevalent in infants than in humans of any other age. The descriptive epidemiologic data that is presented here may serve to stimulate ideas for further etiologic research into the multifactorial nature of cancer occurrence. For example, the initial two-hit theory for carcinogenesis was developed primarily from clinical observations of a higher frequency of bilaterality of retinoblastoma in infants than in older children [8,9]. The study of infant cancer can aid in developing new hypotheses related to how aberrant genetic processes, early developmental abnormalities and gene-environment interactions contribute to the carcinogenic process. The study of retinoblastoma, and later of Wilms' tumor, led to the discovery of two important tumor suppressor genes that are related to adult as well as pediatric malignancy [10]. Recent work has shown that hematologic malignancies manifest differently in infants than in older children [11]. All these factors speak to the importance of further research into the epidemiology and biology of cancer in very young children.

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HIGHLIGHTS

Incidence

- The incidence of cancer among adolescents (i.e., 15-19 year-olds) in SEER areas for 1986-95 was 202.2 per million, which was similar to the incidence of cancer among 0-4 year-olds and substantially greater than the incidence for 5-9 and 10-14 year-olds (Table XIII.1).
- The spectrum of cancers that occurred among 15-19 year-olds was distinctive from those that occurred in young children. For SEER areas from 1986-95, the most common tumors among adolescents were Hodgkin's disease (16.1%), germ cell tumors (15.2%), CNS tumors (10.0%), non-Hodgkin's lymphoma (NHL) (7.6%), thyroid cancer (7.2%), malignant melanoma (7.0%), and acute lymphoblastic leukemia (ALL) (6.4%) (Figure XIII.1 and Table XIII.1).
- The embryonal cancers that predominated among young children (e.g., neuroblastoma, Wilms tumor, retinoblastoma, and hepatoblastoma) (Figure XIII.2) were distinctly uncommon among 15-19 year olds (Figure XIII.1 and Table XIII.1).

Trends in Incidence

- The annual incidence of cancer for adolescents increased from 183.0 per million in 1975-79 and to 203.8 per million in 1990-95 (Table XIII.4 and Figure XIII.3).
- The largest contributor to this increase was the germ cell, trophoblastic, and other gonadal tumor category (specifically testicular and ovarian germ cell tumors).
- Smaller increases in incidence were observed for non-Hodgkin's lymphoma (NHL), osteosarcoma, and acute lymphoblastic leukemia (ALL).
- No significant increases in incidence were observed for CNS tumors, melanoma, thyroid cancer, Hodgkin's disease, or soft tissue sarcomas.

Incidence by Gender and Race

- Rates of specific cancer types differed substantially by gender and by race among adolescents.
- For gender, these differences were most remarkable for thyroid cancer (much more common in females) and for the bone tumors, ALL, and NHL (the latter three more common among males) (Table XIII.2).
- Black 15-19 year olds had much lower incidence rates for Ewing's sarcoma, testicular germ cell tumors, and melanoma than did whites. Black adolescents also had modestly lower incidence of ALL and thyroid cancer compared to white 15-19 year olds (Table XIII.3).

Survival

- Overall 5-year survival rates for adolescents with cancer improved from 69% to 77% from 1975-84 to 1985-94 (Table XIII.5).
- For some cancer types (Hodgkin's disease, germ cell tumors, thyroid cancer, and melanoma), 5-year survival rates were 90% or better for the most recent time period (1985-94).
- For other cancer types (e.g., osteosarcoma, Ewing's sarcoma, ALL, and AML) survival rates for adolescents remained less than 60%.

INTRODUCTION

The adolescent population (here defined as age 15-19 years) have variably been included in analyses and reports of childhood cancer. An NIH Policy concerning inclusion of children in clinical research defines children as being younger than 21 years of age, while the Food and Drug Administration considers children to be 15 years and younger. Regardless of the definition of children that is applied for regulatory or reporting purposes, it is instructive to consider the 15-19 year old population separately because the types of tumors that occur in this population differ substantially from those that predominate in younger children and in adults. Additionally, the 15-19 year old age group is one whose participation rate in cancer clinical trials has been noted to be much lower than that for younger children [1].

In this chapter, differences in cancer types and their incidence between the 15-19 year group and younger children will be highlighted. Additional points for emphasis are the changes in cancer incidence for this older age group from 1975 to 1995 and the distinctive sex distribution for individual tumor types. The chapter concludes with a summary of survival rates for the 15-19 year old population, illustrating that survival for many tumor types has improved from 1975-84 to 1985-94.

INCIDENCE

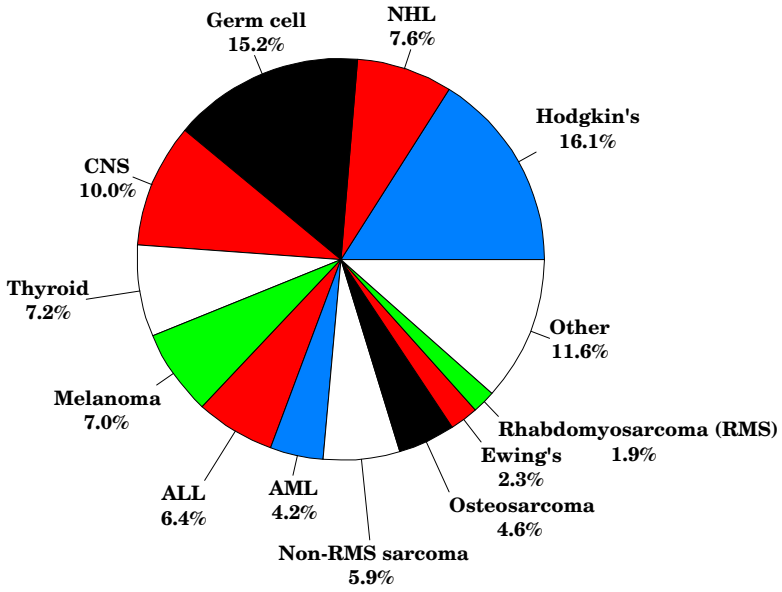
Distribution of tumor types by 5-year age groups

The incidence of specific cancers by International Classification of Childhood Cancer (ICCC) codes for the period 1986-1995 is shown in Table XIII.1 by 5-year age groups. Figure XIII.1 shows that the most common tumors in the adolescent population were Hodgkin's disease (16.1%), germ cell tumors (15.2%), CNS tumors (10.0%),

Table XIII.1: Age-specific cancer incidence rates per million and percentage of total cases by ICCC category and age group, all races, both sexes, SEER, 1986-95

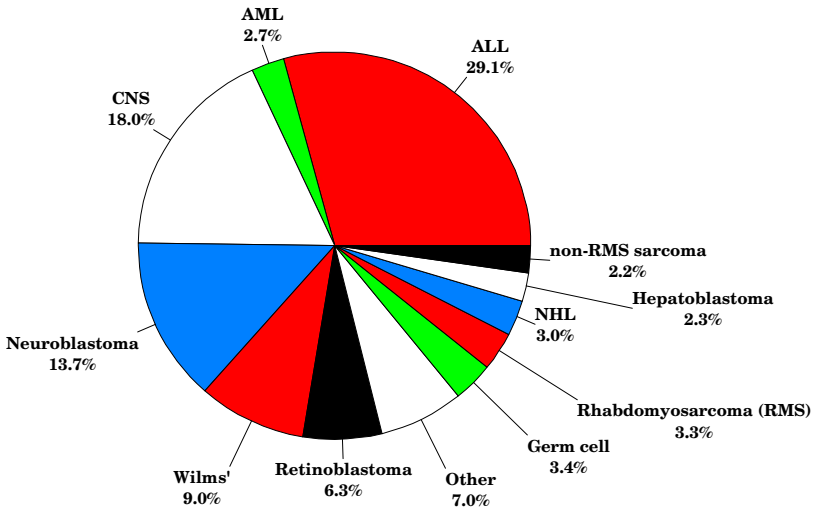
Age (in years) at diagnosis Tumor category	<5 Rate	5-9 Rate	10-14 Rate	15-19 Rate	% of Total for 15-19 Group
All Sites	199.9	110.2	117.3	202.2	100.0%
Acute lymphoblastic leukemia (ALL)	58.2	30.3	17.8	12.9	6.4%
Acute myeloid leukemia (AML) (Ib)	10.1	4.5	5.7	8.5	4.2%
Hodgkin's disease (IIa)	0.8	3.9	11.7	32.5	16.1%
Non-Hodgkins lymphoma (NHL) (IIb,c,e)	5.9	8.9	10.3	15.3	7.6%
CNS tumors (III(total))	36.0	31.9	24.6	20.2	10.0%
Ependymoma (IIIa)	5.6	1.6	1.3	1.1	0.5%
Astrocytoma (IIIb)	15.0	15.9	15.1	12.3	6.1%
Medulloblastoma/PNET (IIIc)	9.6	7.3	4.0	2.5	1.2%
Neuroblastoma & ganglioneuroblastoma (IVa)	27.4	2.6	0.8	0.5	0.2%
Retinoblastoma (V(total))	12.5	0.5	0.0	0.1	0.0%
Wilms', rhabdoid, clear cell sarcoma (VIa)	18.0	5.8	0.6	0.4	0.2%
Hepatic tumors (VII(total))	4.8	0.4	0.4	1.0	0.5%
Hepatoblastoma (VIIa)	4.6	0.2	0.1	0.0	0.0%
Osteosarcoma (VIIIa)	0.3	2.8	8.3	9.4	4.6%
Ewing's sarcoma (VIIIc)	0.3	1.9	4.1	4.6	2.3%
Soft tissue sarcoma (IX(total))	10.9	8.3	10.9	15.9	7.9%
Rhabdomyosarcoma and embryonal sarcoma (IXa)	6.5	4.4	3.5	3.9	1.9%
Non-rhabdo soft tissue sarcoma (IXb-e)	4.4	4.0	7.4	11.9	5.9%
Germ Cell, trophoblastic, & other gonadal tumors (X (total))	6.9	2.4	6.7	30.8	15.2%
Thyroid carcinoma (XIb)	0.1	1.0	4.1	14.6	7.2%
Malignant melanoma (XId)	0.8	0.6	2.8	14.1	7.0%
Other and unspecified carcinomas (XIf)	0.4	0.8	2.8	10.5	5.2%

Figure XIII.1: Distribution of cancer types, age 15-19 all races, both sexes, SEER, 1986-95



non-Hodgkin's lymphoma (NHL) (7.6%), thyroid cancer (7.2%), malignant melanoma (7.0%), and acute lymphoblastic leukemia (ALL) (6.4%). Table XIII.1, as well as comparison of Figures XIII.1 and XIII.2, illustrates that a group of tumors that occurred commonly among children younger than 5 years of age were virtually absent among 15-19 year olds, including: neuroblastoma, Wilms' tumor, retinoblastoma, ependymoma, and hepatoblastoma. These 5 tumor types accounted for approximately 35% of cases among children younger than 5 years of age (Figure XIII.2),

Figure XIII.2: Distribution of cancer types, age <5 all races, both sexes, SEER, 1986-95



but less than 1% of cases among 15-19 year olds.

The distribution of tumor types within several ICCC categories for 15-19 year olds compared with children younger than 15 years of age warrants specific comment. The distribution of soft tissue sarcoma diagnoses differed by age. Rhabdomyosarcoma accounted for 60% of soft tissue sarcoma cases among children younger than 5 years of age. However, the incidence of rhabdomyosarcoma decreased with age, while the incidence of non-rhabdomyosarcoma soft tissue sarcomas increased with age, so that among 15-19 year olds, rhabdomyosarcoma accounted for only 25% of soft tissue sarcoma diagnoses (Table XIII.1). The annual incidence of ALL also decreased with age: among children younger than 5 years of age the rate was 58.2 per million, while for 15-19 year olds the rate was nearly 5-fold less (12.9 per million) (Table XIII.1). Although ALL accounted for nearly 30% of cancer cases among children younger than 5 years of age, it represented only 6.4% of cases among the 15-19 year olds. The incidence of NHL was higher among 15-19 year olds than among younger age groups (Table XIII.1). This increase was largely the result of much higher rates for diffuse large cell lymphoma among 15-19 year olds, while rates for Burkitt's lymphoma and lymphoblastic lymphoma for 15-19 year olds were similar to or less than those observed for children less than 15 years of age (see Lymphoma chapter for details).

Sex-specific incidence

The overall incidence of cancer cases was similar among males and females in the 15-19 year old age group for the years 1986 to 1995 (Table XIII.2). However, the overall similarity masked marked differences in rates for individual tumor types. There was a strong male predominance for ALL, NHL, osteosarcoma, and Ewing's sarcoma, with 60% to over 100% higher rates occurring in males than females. Additionally, rates of CNS tumors and germ cell tumors were 30-40% higher in males than in females. On the other hand, there was a female predominance for Hodgkin's disease, thyroid carcinoma, and melanoma.

The rates by sex for the 15-19 year olds were distinct from those for children younger than 15 years of age. For ALL, there was only a 20% excess of male cases among the children younger than 15 years of age, compared to a nearly 120% excess for the 15-19 year olds. There was a male predominance for Hodgkin's disease in the 0-14 year olds, compared to a female predominance in 15-19 year olds. The situation was reversed for the germ cell, trophoblastic, and other gonadal tumors, which were more common among females

Table XIII.2: Age-adjusted cancer incidence rates per million by ICCC group sex, and age, all races, both sexes, SEER, 1986-95

Age (in years) at diagnosis Tumor category	0-14 Male*	0-14 Female*	0-14 Ratio: M/F	15-19 Male	15-19 Female	15-19 Ratio: M/F
ALL SITES	149.5	128.7	1.2	204.3	199.9	1.0
Acute lymphoblastic leukemia	37.1	30.9	1.2	17.5	8.0	2.2
Acute myeloid leukemia (Ib)	6.6	6.5	1.0	8.4	8.5	1.0
Hodgkin's disease (IIa)	6.5	5.0	1.3	28.8	36.5	0.8
Non-Hodgkin's lymphoma (IIb,c,e)	12.3	4.5	2.7	19.4	11.0	1.8
CNS (III)	33.0	27.9	1.2	23.0	17.3	1.3
Osteosarcoma (VIIIa)	3.8	4.3	0.9	11.5	7.1	1.6
Ewing's sarcoma (VIIIc)	2.3	2.2	1.1	5.8	3.3	1.8
Soft tissue sarcomas (IX)	10.9	9.1	1.2	17.4	14.3	1.2
Germ cell tumors (X)	4.3	6.2	0.7	35.2	26.1	1.4
Thyroid carcinoma (XIb)	0.9	2.9	0.3	3.7	26.2	0.1
Melanoma (XId)	1.3	1.6	0.8	10.5	17.9	0.6

*Adjusted to the 1970 US standard population

in children younger than 15 years of age, but more common among males in the 15-19 year old age group. The male predominance for bone tumors observed in adolescents was absent in the younger than 15 year old age group. For NHL, there was a marked male predominance for both 0-14 year olds and for 15-19 year olds.

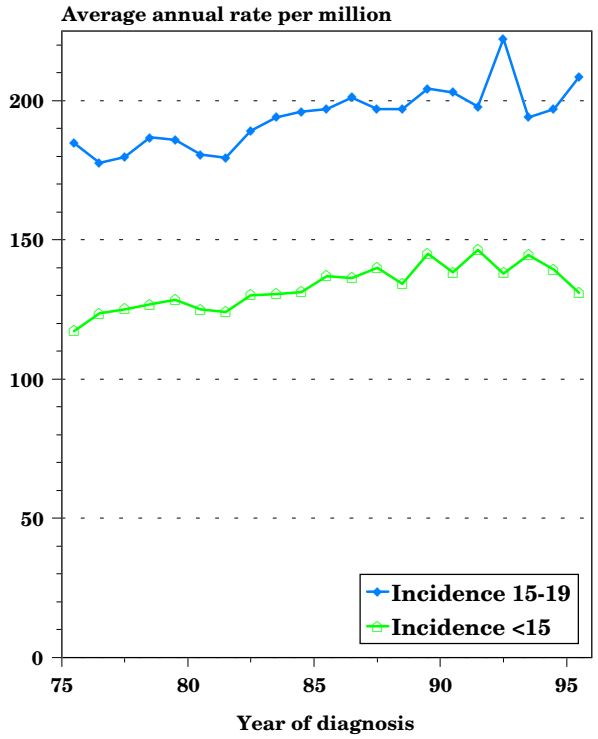
Black-white differences in incidence

The incidence of cancer among whites age 15-19 years for 1986-95 was approximately 1.5-fold higher than that among blacks age 15-19 years (Table XIII.3). In comparing cancer incidence for white and black 15-19 year olds, incidence rates at least 2-fold higher were observed among whites, compared to blacks for ALL, germ cell tumors, thyroid cancer, Ewing's sarcoma, and melanoma. The low incidence for germ cell tumors among blacks was restricted to testicular germ cell tumors in males. White females and black females had similar rates for germ cell tumors (see Germ Cell, Trophoblastic, and Other Gonadal Tumor chapter for additional details). While the very high ratio of white to black cases for melanoma may be explained by the protection afforded from ultraviolet light by melanin, the reasons that blacks have lower rates of Ewing's sarcoma, ALL, testicular germ cell tumors, and thyroid cancer are not apparent.

Table XIII.3: Age-specific cancer incidence rates per million by ICCC group and race age 15-19, SEER, 1986-95

Tumor category	White	Black	W/B Ratio
Total	213.5	144.8	1.5
Acute lymphoblastic leukemia	14.3	6.4	2.2
Acute myeloid leukemia (Ib)	8.3	7.1	1.2
Hodgkin's disease (IIa)	36.5	26.9	1.4
Non-Hodgkin's lymphoma (IIb,c,e)	16.1	9.4	1.7
CNS (III)	21.8	15.8	1.4
Osteosarcoma (VIIIa)	9.2	8.4	1.1
Ewing's sarcoma (VIIIc)	5.4	0.3	18.0
Soft tissue sarcomas (IX)	14.5	20.5	0.7
Germ cell tumors (X)	33.9	13.8	2.5
Thyroid carcinoma (XIb)	15.5	6.7	2.3
Melanoma (XId)	16.1	0.3	53.7

Figure XIII.3: Trends in age-adjusted* cancer incidence rates by age group, all races, both sexes, SEER, 1975-95



*Adjusted to the 1970 US standard population

TRENDS

The average annual age-adjusted cancer incidence among 15-19 year olds increased from 183 per million in 1975-79 to slightly over 203.8 per million in 1990-95 (Figure XIII.3 and Table XIII.4). By comparison, the incidence of cancer for children younger than 15 years of age increased from 124.3 per million in 1975-79 to 139.9 per million in 1990-95. The greatest numeric increase in annual incidence for the 15-19 year group occurred for the germ cell,trophoblastic, and other gonadal (GCTOG) tumors. This increase was primarily the result of an increase in the incidence of testicular germ cell tumors among males (increasing from 22.1 to 28.4 per million) and ovarian germ cell tumors among females (increasing from 7.9 to 13.3

Table XIII.4: Average annual age-specific incidence rates per million adolescents 15-19 years old for selected tumors, all races, both sexes, SEER, 1975-95

Tumor type (ICCC Category)	1975-79 Rate	1980-84 Rate	1985-89 Rate	1990-95 Rate
All Sites	183.0	187.7	199.3	203.8
Acute Lymphoblastic Leukemia (Ia)	10.6	13.2	12.4	13.0
Non-Hodgkin's lymphoma (IIb,c,e)	10.7	14.5	14.4	16.3
Osteosarcoma (VIIIa)	6.6	8.9	9.7	9.3
Germ cell, trophoblastic and other gonadal tumors (X)	23.2	24.0	28.6	32.0
Testicular germ cell tumor (Xc, male)	22.1	26.7	24.9	28.4
Ovarian germ cell tumor (Xc, female)	7.9	8.3	11.8	13.3
Gonadal carcinoma (Xd)	2.7	2.4	4.3	5.3

Rates are per 1,000,000.

per million). As discussed in the chapter for GCTOG tumors, the increase in gonadal carcinomas is likely artifactual and attributable to changes in reporting of ovarian tumors during this time period, specifically inclusion of borderline tumors of the ovary. The incidence of ALL, NHL, and osteosarcoma also increased from 1975-79 to 1990-95 (Table XIII.4). These four tumor types accounted for the majority of the increase in cancer incidence for the 15-19 year old group. No significant increases or decreases in incidence were observed for CNS tumors, melanoma, thyroid cancer, Hodgkin's disease, or soft tissue sarcomas.

SURVIVAL

Table XIII.5 shows 5-year relative survival rates for different cancer types for 15-19 year olds , with comparison made between an earlier time period (1975-84)

Table XIII.5: 5-Year Relative Survival Rates by ICCC group and time period, age 15-19, all races, both sexes SEER, 1975-84 and 1985-94

TUMOR CATEGORY	1975-84	1985-94
Total	69%	77%
Acute lymphoblastic leukemia (ALL)	35%	51%
Acute myeloid leukemia (AML) (Ib)	22%	42%
Hodgkin's (IIa)	88%	90%
NHL (IIb,c,e)	56%	69%
Astrocytoma (IIIb)	62%	75%
Medulloblastoma (IIIc)	63%	75%
Osteosarcoma (VIIIa)	49%	59%
Ewing's sarcoma (VIIIc)	36%	56%
Soft tissue sarcoma (IX)	70%	63%
Rhabdomyosarcoma (IXa)	40%	45%
Germ cell tumors (X)	79%	90%
Thyroid carcinoma (XIb)	99%	99%
Melanoma (XId)	84%	92%

and a recent reporting period (1985-94). Important observations concerning survival rates include:

- For all cancer diagnoses in the 15-19 year old age group, the 5-year survival rate for the recent reporting period was 77%, which was higher than that for the other five-year age groups younger than 20 years of age.

- Five-year survival rates of 90% or higher were observed for Hodgkin's disease, germ cell tumors, thyroid carcinoma, and melanoma. For germ cell tumors and melanoma, the survival rates improved between the earlier and recent time period.

- Five-year survival rates for NHL improved between 1975-84 and 1985-94 from approximately 56% to 69%.

- Five-year survival rates for both ALL and AML improved substantially for the 15-19 year old group, with survival rates for 1985-94 of 51% and 42%, respectively, compared to only 35% and 22% for 1975-84.

Five-year survival rates for Ewing's sarcoma improved from 36% to 56% between the earlier and the recent reporting period.

The mortality burden is a function of the survival and the incidence rates. The leukemias are the primary contributor to the cancer mortality burden for cancers developing in the 15-19 year olds. In addition to leukemia, bone cancer, soft tissue sarcoma, CNS cancer, NHL, and Hodgkin's disease are the most common causes of cancer death among this group - see the mortality chapter. Although thyroid carcinoma and melanoma are among the more common cancers in this age group, they contribute little to the overall cancer mortality burden for the 15-19 year old age group.

SUMMARY

The spectrum of malignancies that occur in adolescents is distinctive when compared to those that occur in young children and those that occur in older adults. The embryonal cancers that predominate among young children (e.g., neuroblastoma, Wilms' tumor, retinoblastoma, ependymoma, and hepatoblastoma) are very uncommon among 15-19 year olds. Similarly, the epithelial carcinomas of adults (e.g., lung, breast, colon) rarely occur in 15-19 year olds. While some types of acute leukemias and CNS cancers are shared with both the older adult and the young childhood populations, the 15-19 year old group experiences high rates of a set of tumors (including germ cell tumors, Hodgkin's disease, and the bone cancers) that are relatively characteristic of the adolescent/young adult age group.

The annual incidence of cancer in adolescents increased from 183 per million for 1975-79 to 203.8 per million from 1990-95. The largest contributor to this increase was the germ cell, trophoblastic, and other gonadal tumor category (specifically testicular and ovarian germ cell tumors), with smaller contributions from NHL, osteosarcoma, and ALL.

Rates of specific cancer types differed substantially by sex and by race. For sex, these differences were most remarkable for thyroid cancer (much more common in females) and for the bone tumors, ALL, and NHL (the latter three more common among males). Black 15-19 year olds had much lower incidence rates of Ewing's sarcoma, testicular germ cell tumors, and melanoma than did whites, and modestly lower

incidence rates of ALL and thyroid cancer.

Five-year survival for 15-19 year olds increased from 69% to 77% from 1975-84 to 1985-94, with a 90% survival rate or better for several diagnoses (Hodgkin's disease, germ cell tumors, thyroid cancer, and melanoma). However, for some cancers, the survival rates remained less than 60% (including osteosarcoma, Ewing's sarcoma, ALL, and AML).

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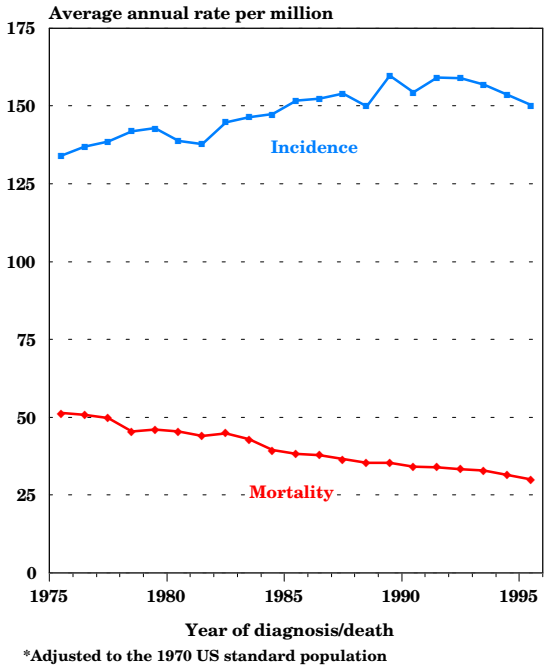
Lynn A. Gloeckler Ries

Introduction

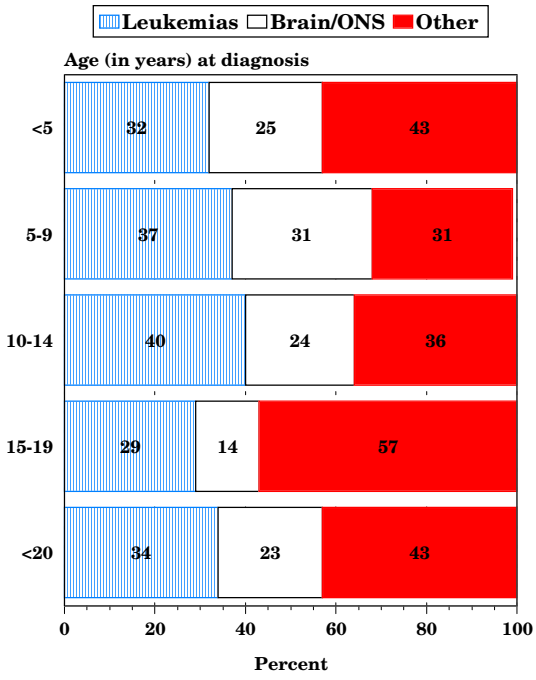
Over the past two decades, childhood cancer mortality in the United States has declined dramatically. To present a comprehensive picture of childhood cancer occurrence and outcome, it would be ideal to include cancer-specific data on incidence, survival, and mortality within each individual chapter of the monograph. The available data on mortality, however, are obtained from death certificates and collected by the National Center for Health Statistics (NCHS) for the entire United States. In addition to the difference in geographic coverage between NCHS and SEER areas, the cancer classification used by NCHS for mortality is less specific than that used by SEER areas. Therefore, we are presenting this separate chapter on cancer mortality and have included incidence [1,2] comparisons based on comparable definitions to the mortality data [3]. A further explanation on differences between the incidence definitions used in the other chapters and mortality is included at the end of this chapter. The mortality data are provided by the National Center for Health Statistics to the National Cancer Institute on public-use tapes.

Figure XIV.1: Trends in childhood cancer age-adjusted* rates, all races, both sexes, age <20 SEER incidence & US mortality, 1975-95



*Adjusted to the 1970 US standard population

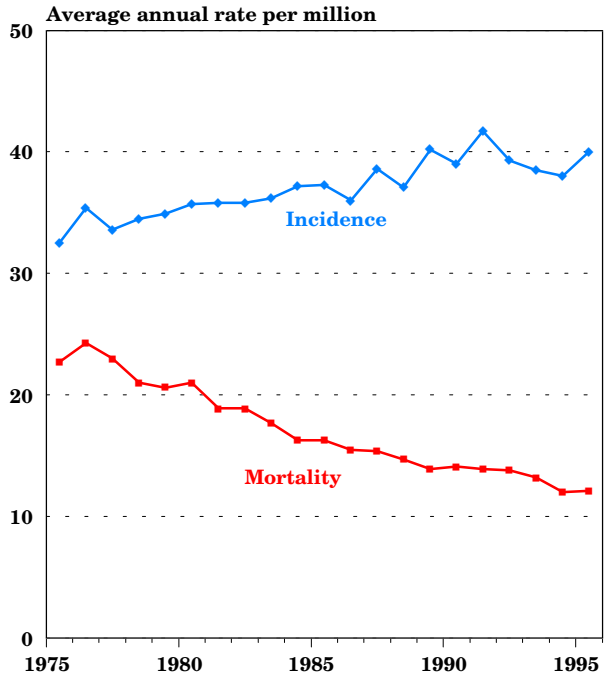
Figure XIV.2: Percent distribution of childhood cancer mortality by type and age group, age <20 all races, both sexes, United States, 1995



All Sites

In contrast to incidence rates, cancer mortality declined substantially between 1975 and 1995 (Figure XIV.1). There were statistically significant declines in mortality for each of the five-year age groups (<5, 5-9, 10-14, and 15-19) for cancers combined. The declines by age group ranged from 2.0 to 3.2 percent per year. The overall decline in mortality was nearly 40 percent between 1975 and 1995, a statistically significant decrease of 2.6 percent per year. The overall incidence increased 0.8 percent per year. There were 2,275 cancer deaths among children in 1995. Except for those 15-19, leukemia and brain/other nervous system comprised more than 50 percent of the deaths due to cancer (Figure XIV.2). The relative difference for

Figure XIV.3: Trends in childhood leukemia age-adjusted* rates, age <20, all races, both sexes SEER incidence, and US mortality, 1975-95



*Adjusted to the 1970 US standard population

the 15-19 year olds was due to deaths from lymphoma (14%), bone (13%), and soft tissue sarcomas (9%). Leukemias and brain cancer, however, accounted for 57% of cancer deaths for all children combined.

Leukemia

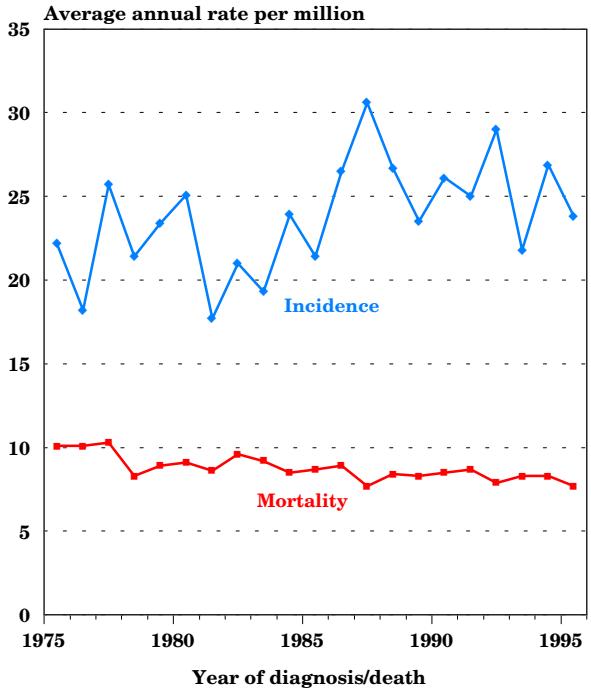
In 1995, thirty-four percent of the childhood cancer deaths were due to leukemia. The death rate from leukemia fell nearly 50 percent between 1975 and 1995 (Figure XIV.3), a statistically significant decline of 3.4 percent per year while the incidence increased between 1975 and 1995. Mortality rates declined significantly for each of the age groups (<5, 5-9,10-14, 15-19, <20) and for both males and females.

Brain / other central nervous system (brain / CNS)

In 1995, nearly one-fourth of childhood cancer deaths were due to invasive malignancies of the central nervous system, primarily the brain. Mortality from brain and other CNS cancer declined an average of 1.1 percent per year. This was an overall decline of 23 percent between 1975 and 1995 (Figure XIV.4). This mortality decline occurred while the incidence rate increased mainly in the mid-1980s [4].

Unlike most benign tumors, noninvasive tumors of the brain/CNS have the potential to be fatal. Figure XIV.5 illustrates mortality rates for brain tumors classified as invasive, unspecified or uncertain, and benign. If the behavior of the

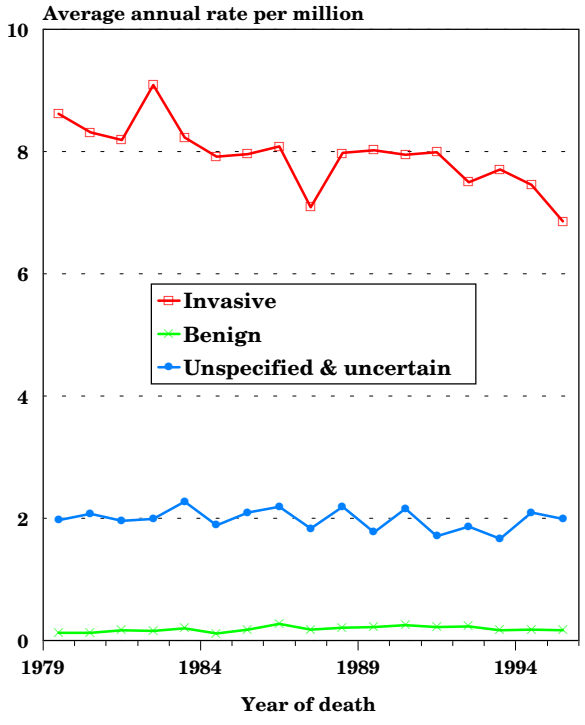
Figure XIV.4: Trends in brain/other nervous system cancer age-adjusted* rates, all races, both sexes age <20, SEER incidence & US mortality, 1975-95



*Adjusted to the 1970 US standard population

tumor is not clear from the death certificate, it is considered "unspecified or uncertain". Some of these tumors will be invasive and some will not. Although mortality from invasive tumors has declined somewhat over the past decade, there appears to be no change over time in the rates of death from brain tumors classified as either "benign" or "unspecified or uncertain". Thus, the reduction in mortality from invasive brain cancer does not appear to be an artifact due to changes in the reporting of the other categories of brain tumors. To avoid changes in death classification between 1978 and 1979, this figure begins in 1979.

Figure XIV.5: Trends in age-adjusted* brain tumor mortality rates by behavior, age <20, United States, 1979-95

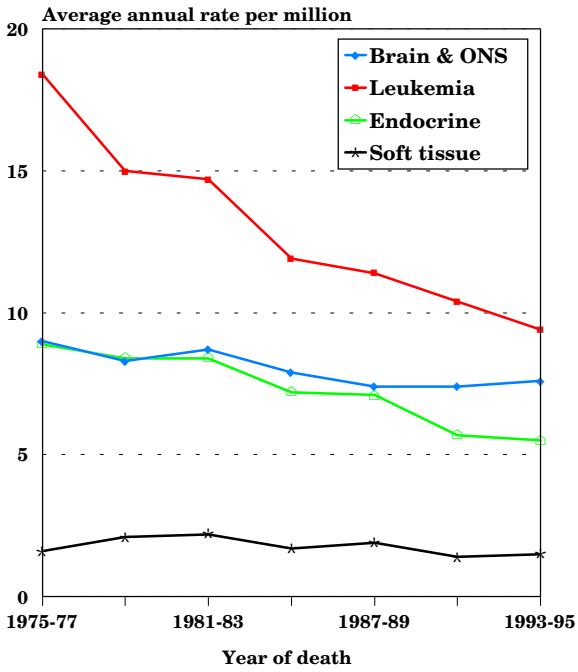


*Adjusted to the 1970 US standard population

Ages 0-4

From 1975 to 1995, death rates from cancer declined 2.9 percent per year among children younger than 5 years of age. The Figure XIV.6 shows the mortality rates for

Figure XIV.6: Trends in age-specific cancer mortality rates by type, age <5, all races, both sexes United States, 1975-95

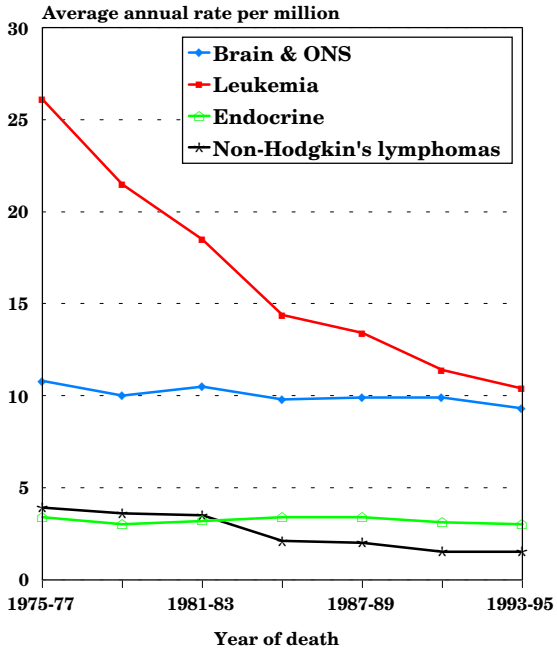


the four leading causes of cancer death among young children. The death rates have declined for each. For leukemias, the death rates declined by an average of 3.5 percent each year or more than 50 percent between 1975 and 1995. After leukemia and brain/CNS cancer, endocrine malignancies were responsible for the most cancer deaths. Most of the cancers classified as "endocrine" in this age group were neuroblastomas. In 1995,there were 558 deaths due to cancer among children younger than 5 years of age in the entire United States.

Ages 5-9

There were 523 deaths due to cancer among children 5-9 years of age in the entire United States in 1995. The age group 5-9 years of age had the largest decline in cancer mortality. The top four mortality sites were leukemia, brain/CNS, endocrine and non-Hodgkin's lymphoma.

Figure XIV.7: Trends in age-specific cancer mortality rates by type, age 5-9, all races, both sexes United States, 1975-95



The decline in leukemia deaths was 5 percent per year (Figure XIV.7).

Ages 10-14

There were 503 deaths due to cancer among children 10-14 years of age in the entire United States in 1995. The death rate declined 2.5 percent per year. The decline for leukemias was 3 percent per year. The top four mortality sites were leukemia, brain/CNS, bone/joints, and non-Hodgkin's lymphoma (Figure XIV.8).

Ages 15-19

There were 691 deaths due to cancer among children 15-19 in the entire United States in 1995. The overall cancer death rate declined 2 percent per year. The top five cancer mortality sites are shown for this age group since the death rates for soft tissue and non-Hodgkin's lymphoma were similar for the most recent time period (Figure XIV.9).

Recent cancer mortality (1990-1995) by race / ethnicity

The cancer mortality rates for all races combined and for white children declined 2.4 and 3.0 percent per year, respectively. The mortality rates for black and for Hispanic children declined 0.5 percent per year between 1990 and 1995. For American Indian children and Asian Pacific Islander children, the death rates increased slightly at 0.5 percent per year. The cancer death rates for American Indian children (23.8 per million) and for Asian Pacific Islander children (29.2 per million) were less than those for white children (32.9), black children (32.5) or Hispanic children (33.5 per million children). The mortality data are for the whole United States except for Hispanics for which four states (New Hampshire, Oklahoma, Connecticut and Louisiana) are excluded. Hispanics can be of any race and are therefore, not mutually exclusive from the other categories.

Figure XIV.8: Trends in age-specific cancer mortality rates by type, age 10-14, all races both sexes, United States, 1975-95

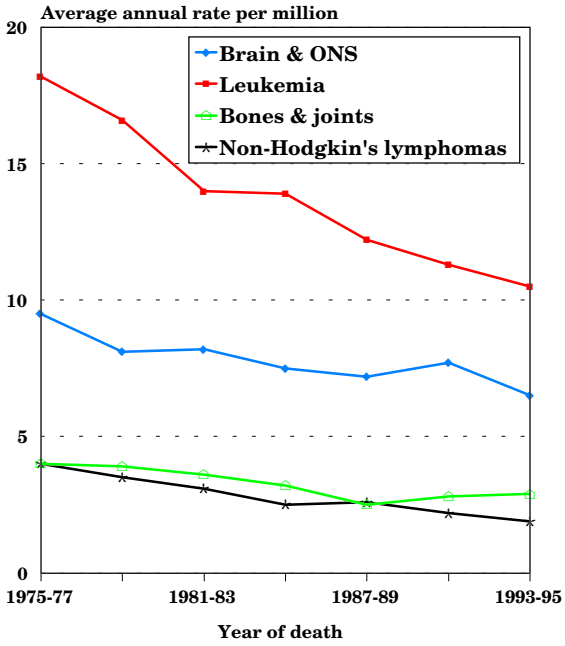
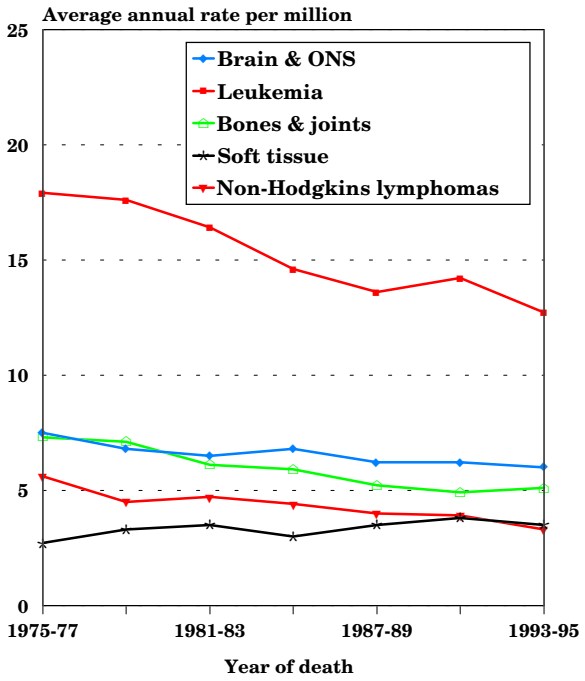


Figure XIV.9: Trends in age-specific cancer mortality rates by type, age 15-19, all races both sexes, United States, 1975-95



Problems comparing incidence to mortality

The histology site groupings presented in other chapters of this monograph are based on the International Childhood Cancer Classification (ICCC) [5]. While they are useful groupings for incidence, there are problems when comparing incidence to mortality. The ICCC uses histology as its main criteria and secondarily primary site. The underlying cause of death, on the other hand, is coded by the International Classification of Diseases, which is based primarily on site of origin rather than histology especially for solid tumors [3]. For example, mortality data would use kidney cancer but the ICCC grouping would be Wilms' tumor. Therefore, all of the incidence rates presented in this chapter are based primarily on site rather than histology. Note, that this does not effect non-solid tumors such as leukemia which would have comparable groups in each. More incidence and mortality rates using comparable categories can be found in the SEER Cancer Statistics Review: 1973-1996 [6].

Summary

Cancer mortality has declined dramatically for children. In the United States today few children die from cancer in comparison to other causes of death. In 1995, for children younger than 20 years of age, the major causes of death were:

- conditions from the perinatal period (13,449);
- accidents (13,234);
- congenital anomalies (7,949);
- homicides (4,617);
- SIDS (3,397);
- cancer (2,275);
- suicides (2,227 deaths).

Of the nearly 60,000 deaths among children younger than 20 years of age, less than 4% were due to neoplasms (cancer). If infants are excluded, the number one cause of death was accidents followed by homicides, suicides and then cancer.

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Cancer Information Service (CIS) – 1-800-4-CANCER or
http://cis.nci.nih.gov/contact/faqform.html

- The Cancer Information Service is the National Cancer Institute's link to the public, providing current scientific information in understandable language to patients, their families, the general public and health professionals. Through a network of 19 regional offices located throughout the country, the CIS serves the entire United States and Puerto Rico. CIS staff are available Monday through Friday from 9:00 a.m. to 4:30 p.m. local time. Callers with TTY equipment may call 1–800–332–8615. Recorded information on cancer topics is available 24 hours a day.

NCI publications on childhood cancer: Available by calling 1-800-4-CANCER (1-800-422-6237).
Also, these publications may be viewed on the Cancer Net's Kids Home page at
http://cancernet.nci.nih.gov/occdocs/KidsHome.html

- *Managing Your Child's Eating Problems: During Cancer Treatment* This booklet includes information about the importance of nutrition, the side effects of cancer and its treatment, ways to encourage your child to eat, and special diets.

- *Talking With Your Child About Cancer:* This booklet is for a parent whose child has been diagnosed with cancer. It addresses the health-related concerns of young people of different ages; it suggests ways to discuss disease-related issues with a child.

- *When Someone In Your Family Has Cancer:* This booklet is for young people whose parent or sibling has cancer. It includes sections on the disease, its treatment, and emotional concerns.

- *Young People With Cancer: A Handbook For Parents:* This booklet discusses the most common types of childhood cancer, treatments, side effects, and issues that may arise when a child is diagnosed with cancer. It offers medical information and practical tips gathered from parents.

National Cancer Institute Information (http://cis.nci.nih.gov/resources/resources.html)

- The National Cancer Institute is the Federal Government's principal agency for cancer research and training. The Web site contains information about the latest news on cancer research and treatment, upcoming events at NCI, job opportunities, and links to cancer information resources. A publication index, containing some full-text NCI publications, is also available.

PDQ® (http://cancernet.nci.nih.gov/pdq.htm):
- NCI's comprehensive cancer database, including summaries on cancer treatment, screening, prevention, and supportive care, and information on ongoing clinical trials.
- PDQ® is a dynamic database that is updated regularly to ensure that the information it contains is consistent with the results of the latest cancer research. PDQ® contains:

cancer information summaries describing the latest advances in cancer treatment, supportive care, screening, and prevention; an extensive register of over 1,500 ongoing clinical trials, with information about studies around the world; and directories of over 23,000 physicians and over 11,000 organizations active in cancer treatment and care. Most cancer information summaries appear in two versions: a technical version for the health professional and a non-technical version for patients, their families, and the public. Both are available in English and Spanish. The information in the database is peer reviewed by editorial boards of oncology experts and updated monthly.

cancerTrials™ Web site (http://cancertrials.nci.nih.gov/):

- NCI's comprehensive clinical trials information center for patients, health professionals, and the public. Includes information on understanding trials, deciding whether to participate in trials, finding specific trials, plus research news and other resources.

CancerNet™ (http://cancernet.nci.nih.gov/index.html):

- The NCI International Cancer Information Center's World Wide Web site, CancerNet™, provides both health professionals and the public access to a variety of information on cancer.

MEDLINEplus (http://www.nlm.nih.gov/medlineplus/)

- The National Library of Medicine's MEDLINEplus Web site includes links to information about a number of health topics, medical dictionaries, databases (including MEDLINE), clearing houses, directories, organizations, publications and health news, and consumer health libraries.

NCI Office of Liaison Activities:

- Throughout the Nation, hundreds of cancer advocacy and outreach organizations provide education and support to their communities. The Office of Liaison Activities is NCI's central point of contact to the national advocacy organizations and, through them, to the community-based groups. This office maintains ongoing communications and information exchange between the cancer advocacy organizations and NCI, encouraging input and feedback from them, and cooperates and collaborates with these groups in areas of mutual interest. The Office of Liaison Activities serves as a catalyst and resource to link advocates with NCI programs, working groups and advisory committees, and helps to integrate consumer advocate representatives throughout the NCI. The Office of Liaison Activities also builds relationships with professional societies and federal agencies, and provides input and perspective to NCI on complex issues relevant to cancer patients and the public. Telephone number 301-594-3194 and FAX 301-480-7558.

On the SEER Web page, http://www-seer.ims.nci.nih.gov/, the Cancer Statistics Branch (CSB) provides additional information on cancer statistics. This monograph can be viewed at this Web address under Publications. Other SEER publications/monographs (SEER Cancer Statistics Review (CSR); SEER Prostate Cancer Trends, 1973-1995; Racial/Ethnic Patterns of Cancer in the United States; and Cancer Rates and Risks) are also included in this area of the Web page. The CSR is an annual compendium of the most recent cancer statistcis available. The current version, 1973-1996, includes two chapters on childhood cancer: one by primary cancer site and a second by the International Classification of Childhood Cancer.

The CSB provides additional SEER data on the SEER Web page under Scientific Systems:

- CANQUES is an interactive system on the Web that allows the user to access over 10 million pre-calculated cancer statistics.
- A SEER public-use file with SEER*Stat provides an easy to use PC desktop system for the production of a myriad of cancer statistics such as incidence rates, survival rates by various demographic and tumor variables. This CD-ROM can be ordered from the Web page.

The Applied Research Branch (ARB) Web site, http://www-dccps.ims.nci.nih.gov/ARB/index.html, provides information on the following topics: Risk Factor Monitoring & Methods, SEER-Medicare, Cancer Statistics Methods & Models, Dietary Assessment, Breast Cancer Surveillance Consortium, Health Services & Economics, HMO Cancer Research Network, Outcomes Research. Under Cancer Statistics Methods & Models, there is information about the methodology and estimation for cancer prevalence and the probability of developing cancer.

ICCC GROUP	MORPHOLOGY	TOPOGRAPHY
I Leukemia		
(a) Lymphoid Leukemia		
Excluding ALL	9820, 9822-9827, 9850	C00.0-C80.9
ALL	9821	C00.0-C80.9
(b) Acute Leukemia		
Excluding AML	9840, 9841, 9864, 9866, 9867, 9891, 9894, 9910	C00.0-C80.9
AML	9861	C00.0-C80.9
(c) Chronic Myeloid Leukemia	9863, 9868	C00.0-C80.9
(d) Other Specified Leukemias	9830, 9842, 9860, 9862, 9870-9890, 9892, 9893, 9900, 9930-9941	C00.0-C80.9
(e) Unspecified Leukemias	9800-9804	C00.0-C80.9
II Lymphomas and Reticuloendothelial Neoplasms		
(a) Hodgkin's disease	9650-9667	C00.0-C80.9
(b) Non-Hodgkin's lymphomas	9591-9595, 9670-9686, 9690-9717, 9723, 9688	C00.0-C80.9
(c) Burkitt's lymphoma	9687	C00.0-C80.9
(d) Miscellaneous lymphoreticular neoplasms	9720, 9731-9764	C00.0-C80.9
(e) Unspecified lymphomas	9590	C00.0-C80.9
III CNS and Miscellaneous Intracranial and Intraspinal Neoplasms		
(a) Ependymoma	9383, 9390-9394	C00.0-C80.9
(b) Astrocytoma	9380	C72.3
	9381, 9400-9441	C00.0-C80.9
(c) Primitive neuroectodermal tumors	9470-9473	C00.0-C80.9*
(d) Other gliomas	9380	C70.0-C72.2, C72.4-C72.9
	9382, 9384, 9442-9460, 9481	C00.0-C80.9
(e) Miscellaneous intracranial and intraspinal neoplasms	8270-8281, 8300, 9350-9362, 9480, 9505, 9530-9539	C00.0-C80.9
(f) Unspecified intracranial and intraspinal neoplasms	8000-8004	C70.0-C72.9, C75.1-C75.3

*For this monograph, any cases with site codes C00.0-C69.9, C73.9-C75.0, C75.4-C77.9 were removed from this group.

Source: Kramárová E, Stiller CA, Ferlay J, Parkin DM, Draper GJ, Michaelis J, Neglia J, Qureshi S (1996) International Classification of Childhood Cancer1996. IARC Technical Report No.29, International Agency for Research of Cancer, Lyon.

ICCC GROUP	MORPHOLOGY	TOPOGRAPHY
IV Sympathetic Nervous System Tumors		
(a) Neuroblastoma and ganglioneuroblastoma	9490, 9500	C00.0-C80.9
(b) Other sympathetic nervous system tumors	8680, 8693-8710, 9501-9504, 9520-9523	C00.0-C80.9
V Retinoblastoma	9510-9512	C00.0-C80.9
VI Renal Tumors		
(a) Wilms' tumor, rhabdoid and clear cell sarcoma	8963	C64.9, C80.9
	8960, 8964	C00.0-C80.9
(b) Renal carcinoma	8010-8041, 8050-8075, 8082, 8120-8122, 8130-8141, 8143, 8155, 8190-8201, 8210, 8211, 8221-8231,8240, 8241, 8244-8246, 8260-8263, 8290, 8310, 8320, 8323, 8401, 8430, 8440, 8480-8490, 8504, 8510, 8550, 8560-8573	C64.9
	8312	C00.0-C80.9
(c) Unspecified malignant renal tumors	8000-8004	C64.9
VII Hepatic Tumors		
(a) Hepatoblastoma	8970	C00.0-C80.9
(b) Hepatic carcinoma	8010-8041, 8050-8075, 8082, 8120-8122, 8140, 8141, 8143, 8155, 8190-8201, 8210, 8211, 8230, 8231,8240, 8241, 8244-8246, 8260-8263, 8310, 8320, 8323, 8401, 8430, 8440, 8480-8490, 8504, 8510, 8550, 8560-8573	C22.0, C22.1
	8160-8180	C00.0-C80.9
(c) Unspecified malignant hepatic tumors	8000-8004	C22.0, C22.1
VIII Malignant Bone Tumors		
(a) Osteosarcoma	9180-9200	C00.0-C80.9
(b) Chrondosarcoma	9220-9230	C00.0-C80.9
	9231, 9240	C40.0-C41.9
(c) Ewing's sarcoma	9260	C40.0-C41.9, C80.9
	9363, 9364	C40.0-C41.9
(d) Other specified malignant bone tumors	8812, 9250, 9261-9330, 9370	C00.0-C80.9
(e) Unspecified malignant bone tumors	8000-8004, 8800, 8801, 8803, 8804	C40.0-C41.9

Source: Kramárová E, Stiller CA, Ferlay J, Parkin DM, Draper GJ, Michaelis J, Neglia J, Qureshi S (1996) International Classification of Childhood Cancer1996. IARC Technical Report No.29, International Agency for Research of Cancer, Lyon.

ICCC GROUP	MORPHOLOGY	TOPOGRAPHY
IX Soft-Tissue Sarcomas		
(a) Rhabdomyosarcoma and embryonal sarcoma	8900-8920, 8991	C00.0-C80.9
(b) Fibrosarcoma, neurofibrosarcoma and other fibromatous neoplasms	8810, 8811, 8813-8833, 9540-9561	C00.0-C80.9
(c) Kaposi's sarcoma	9140	C00.0-C80.9
(d) Other specified soft-tissue sarcomas	8840-8896, 8982, 8990, 9040-9044, 9120-9134, 9150-9170, 9251, 9581	C00.0-C80.9
	8963	C00.0-C63.9, C65.9-C76.8
	9231, 9240, 9363, 9364	C00.0-C39.9, C44.0-C80.9
	9260	C00.0-C39.9, C47.0-C76.8
(e) Unspecified soft-tissue sarcomas	8800-8804	C00.0-C39.9, C44.0-C80.9
X Germ-Cell, Trophoblastic and other Gonadal Neoplasms		
(a) Intracranial and intraspinal germ-cell tumors	9060-9102	C70.0-C72.9, C75.1-C75.3
(b) Other and unspecified non-gonadal germ-cell tumors	9060-9102	C00.0-C55.9, C57.0-C61.9, C63.0-C69.9, C73.9-C75.0, C75.4-C80.9
(c) Gonadal germ-cell tumors	9060-9102	C56.9, C62.0-C62.9
(d) Gonadal carcinomas	8010-8041, 8050-8075, 8082, 8120-8122, 8130-8141, 8143, 8155, 8190-8201, 8210, 8211, 8221-8241, 8244-8246, 8260-8263, 8290, 8310, 8320, 8323, 8430, 8440, 8480-8490, 8504, 8510, 8550, 8560-8573	C56.9, C62.0-C62.9
	8380, 8381, 8441-8473	C00.0-C80.9
(e) Other and unspecified malignant gonadal tumors	8590-8670, 9000	C00.0-C80.9
	8000-8004	C56.9, C62.0-C62.9

Source: Kramárová E, Stiller CA, Ferlay J, Parkin DM, Draper GJ, Michaelis J, Neglia J, Qureshi S (1996) International Classification of Childhood Cancer1996. IARC Technical Report No.29, International Agency for Research of Cancer, Lyon.

ICCC GROUP	MORPHOLOGY	TOPOGRAPHY
XI Carcinomas and other Malignant Epithelial Neoplasms		
(a) Adrenocortical carcinoma	8370-8375	C00.0-C80.9
(b) Thyroid carcinoma	8010- 8041, 8050-8075, 8082, 8120-8122, 8130-8141, 8155, 8190, 8200, 8201, 8211, 8230, 8231, 8244-8246, 8260-8263, 8290, 8310, 8320, 8323, 8430, 8440, 8480, 8481, 8500-8573	C73.9
	8330-8350	C00.0-C80.9
(c) Nasopharyngeal carcinoma	8010- 8041, 8050-8075, 8082, 8120-8122, 8130-8141, 8155, 8190, 8200, 8201, 8211, 8230, 8231, 8244-8246, 8260-8263, 8290, 8310, 8320, 8323, 8430, 8440, 8480, 8481, 8504, 8510, 8550, 8560-8573	C11.0-C11.9
(d) Malignant melanoma	8720-8780	C00.0-C80.9
(e) Skin carcinoma	8010- 8041, 8050-8075, 8082, 8090-8110, 8140, 8143, 8147, 8190, 8200, 8240, 8246, 8247, 8260, 8310, 8320, 8323, 8390-8420, 8430, 8480, 8542, 8560, 8570-8573, 8940	C44.0-C44.9
(f) Other and unspecified carcinomas	8010-8082, 8120-8155, 8190-8263, 8290, 8310, 8314-8323, 8430-8440, 8480-8580, 8940, 8941	C00.0-C10.9, C12.9-C21.8, C23.9-C39.9, C48.0-C48.8, C50.0-C55.9, C57.0-C61.9, C63.0-C63.9, C65.9-C72.9, C75.0-C80.9
XII Other and Unspecified Malignant Neoplasms		
(a) Other specified malignant tumors	8930, 8933, 8950, 8951, 8971-8981, 9020, 9050-9053, 9110, 9580	C00.0-C80.9
(b) Other unspecified malignant tumors	8000-8004	C00.0-C21.8, C23.9-C39.9, C42.0-C55.9, C57.0-C61.9, C63.0-C63.9, C65.9-C69.9, C73.9-C75.0, C75.4-C80.9

Source: Kramárová E, Stiller CA, Ferlay J, Parkin DM, Draper GJ, Michaelis J, Neglia J, Qureshi S (1996) International Classification of Childhood Cancer1996. IARC Technical Report No.29, International Agency for Research of Cancer, Lyon.

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