

### 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
<b>All Sites - Number of cases</b>	9,402	5,024	5,419	9,814	19,845	29,659
	%	%	%	%	%	%
<b>All Sites</b>	100.0	100.0	100.0	100.0	100.0	100.0
<b>I(total) - Leukemia</b>	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
<b>II(total) - Lymphomas and reticuloendothelial neoplasms</b>	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
<b>III(total) - CNS and miscellaneous intracranial and intraspinal neoplasms</b>	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
<b>IV(total) - Sympathetic nervous system</b>	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
<b>V(total) - Retinoblastoma</b>	6.3	0.5	0.1	0.0	3.1	2.1
<b>VI(total) - Renal tumours</b>	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
<b>All Sites - Number of cases</b>	9,402	5,024	5,419	9,814	19,845	29,659
	%	%	%	%	%	%
<b>VII(total) - Hepatic tumors</b>	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
<b>VIII(total) - Malignant bone tumors</b>	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
<b>IX(total) - Soft-tissue sarcomas</b>	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 specified soft-tissue sarcomas	0.7	1.2	2.2	2.1	1.3	1.5
IXe - Unspecified soft-tissue sarcomas	0.4	0.7	1.0	0.9	0.6	0.7
<b>X(total) - Germ-cell, trophoblastic and other gonadal tumors</b>	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
<b>XI(total) - Carcinomas and other malignant epithelial neoplasms</b>	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
<b>XII(total) - Other and unspecified malignant neoplasms</b>	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*

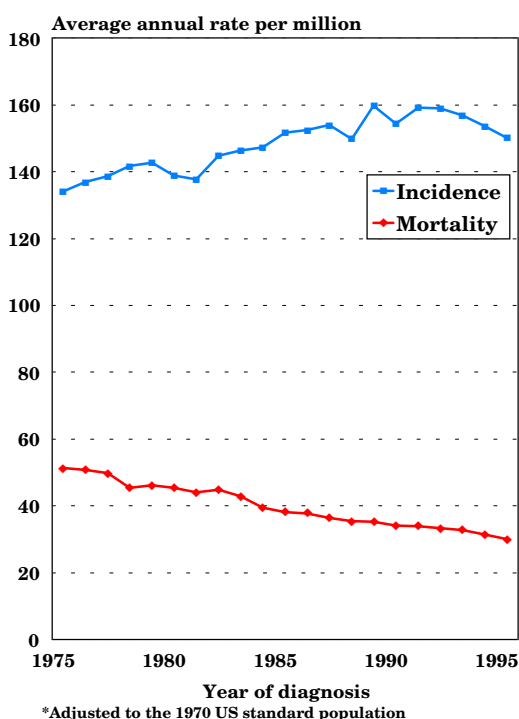
While the incidence rates for some forms of childhood cancer have increased since the mid-1970s, death rates have declined dramatically for most childhood cancers and survival rates have improved markedly since the 1970's. Each year approximately 150 children out of every million children younger than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

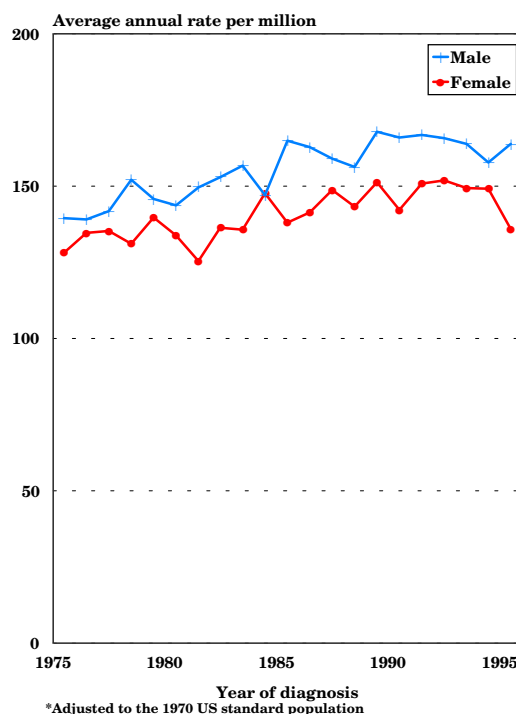
## Sex

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

**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**



younger than 15 years of age, but females have higher rates for adolescents, 15-19 years of age.

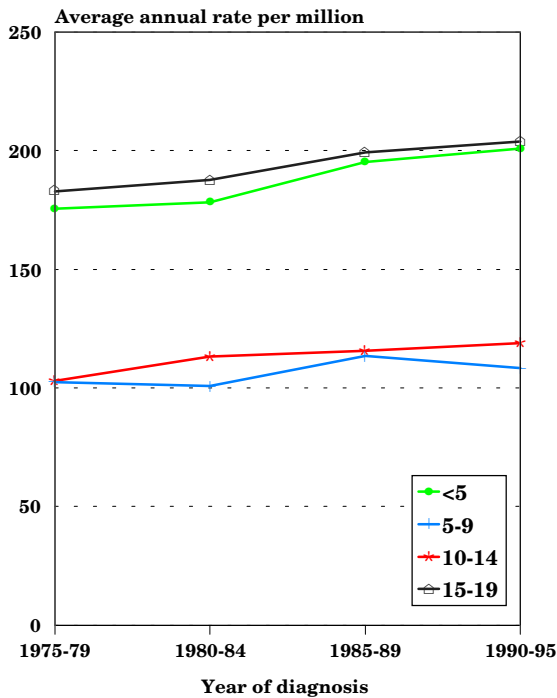
## Age (5-year age groups)

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 ICCG 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).

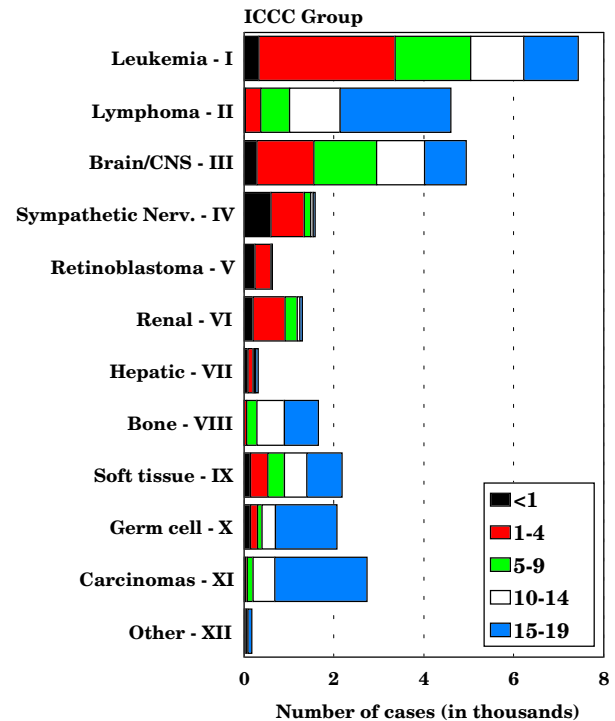
Figure 4 shows the numbers of cases used in this study by ICCC group and age. Leukemia (group I) had the largest number of cases. Note that these numbers are over the period 1975 to 1995 for the SEER areas

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**



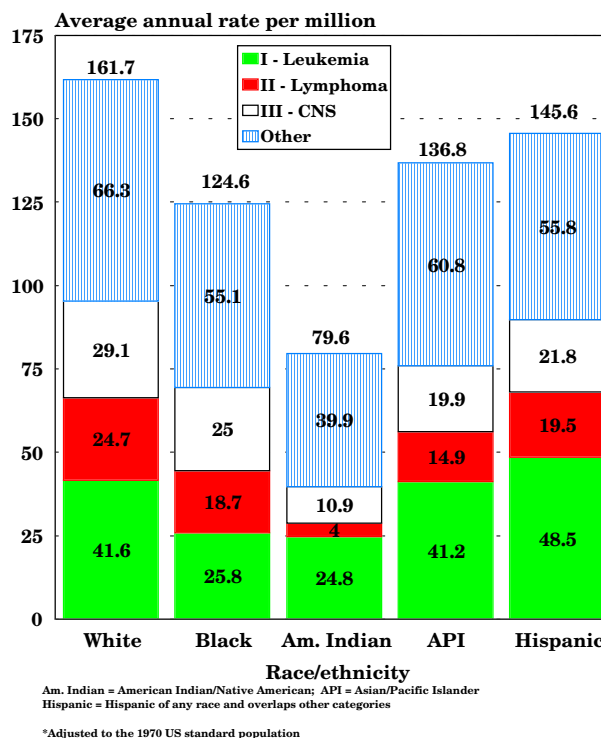


While the ICCC major groupings indicate which broad groups of sites/histologies are important, the sub-groups under each are necessary to really delineate which histologies are driving these rates. More detailed information on the ICCC groups and sub-groups are contained in other chapters.

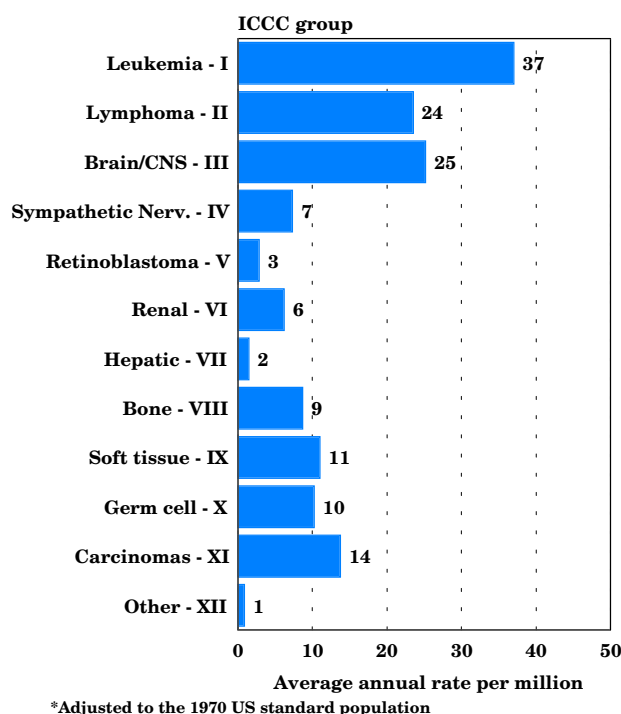
## Race/ethnicity

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



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



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 ICCG group, all races, both sexes, SEER 1986-94

Figure 7

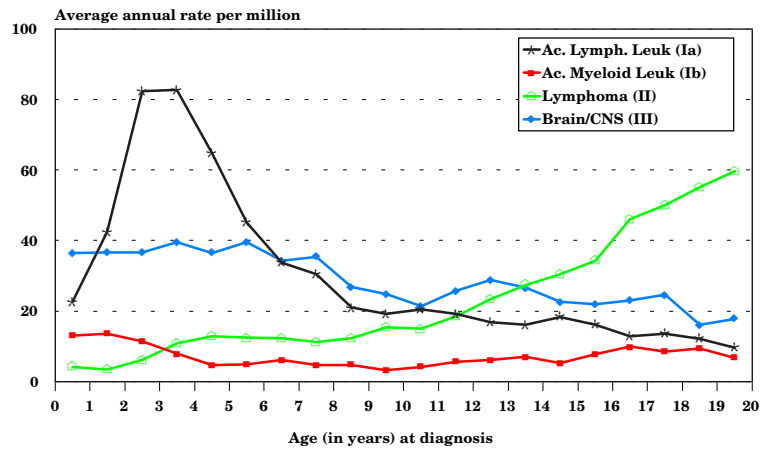


Figure 8

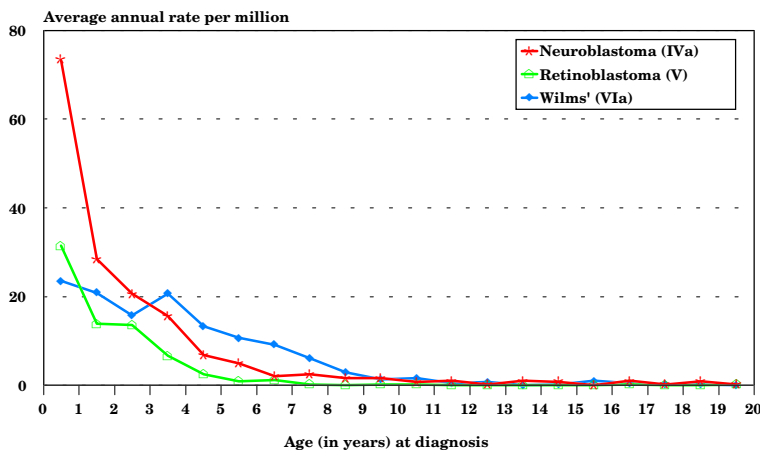
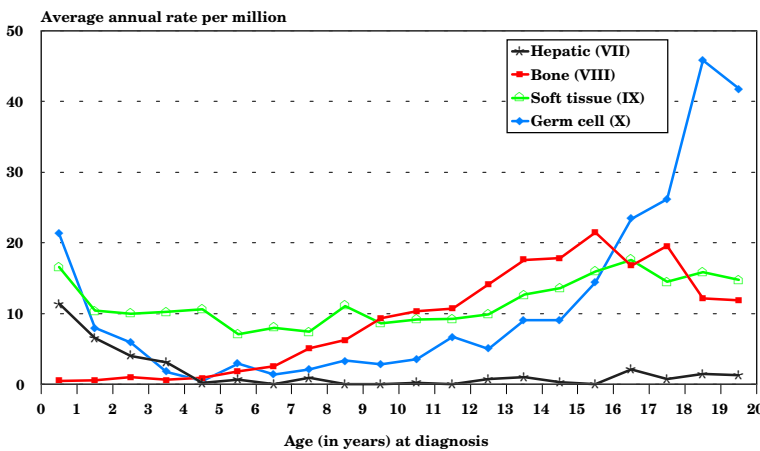


Figure 9





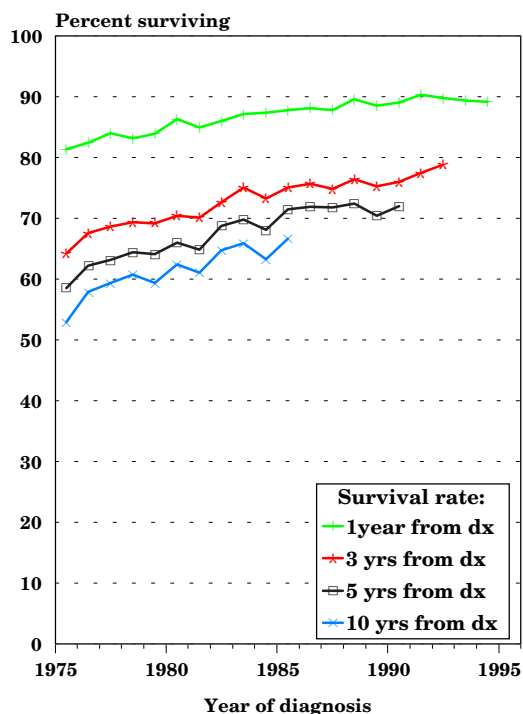
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(ICCC group II) and germ cell (ICCC group X) for 1986-94 (Figures 7-9). Among those older than 9 years of age, there were very low incidence rates for neuroblastoma (ICCC group IVa), retinoblastoma (ICCC group V), Wilms' tumor (ICCC group VIa), and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

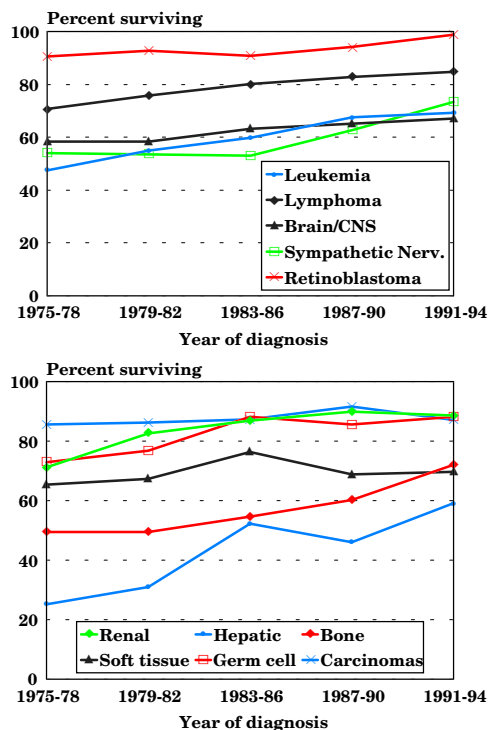
## SURVIVAL

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 ICCG 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 ge-

netic 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  $y = \ln r$  and  $x = \text{calendar year}$ . The  $EAPC = 100 \cdot (e^m - 1)$ . 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 - 8<sup>th</sup> revision* and for 1979 to 1995 to the *ICD 9<sup>th</sup> 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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