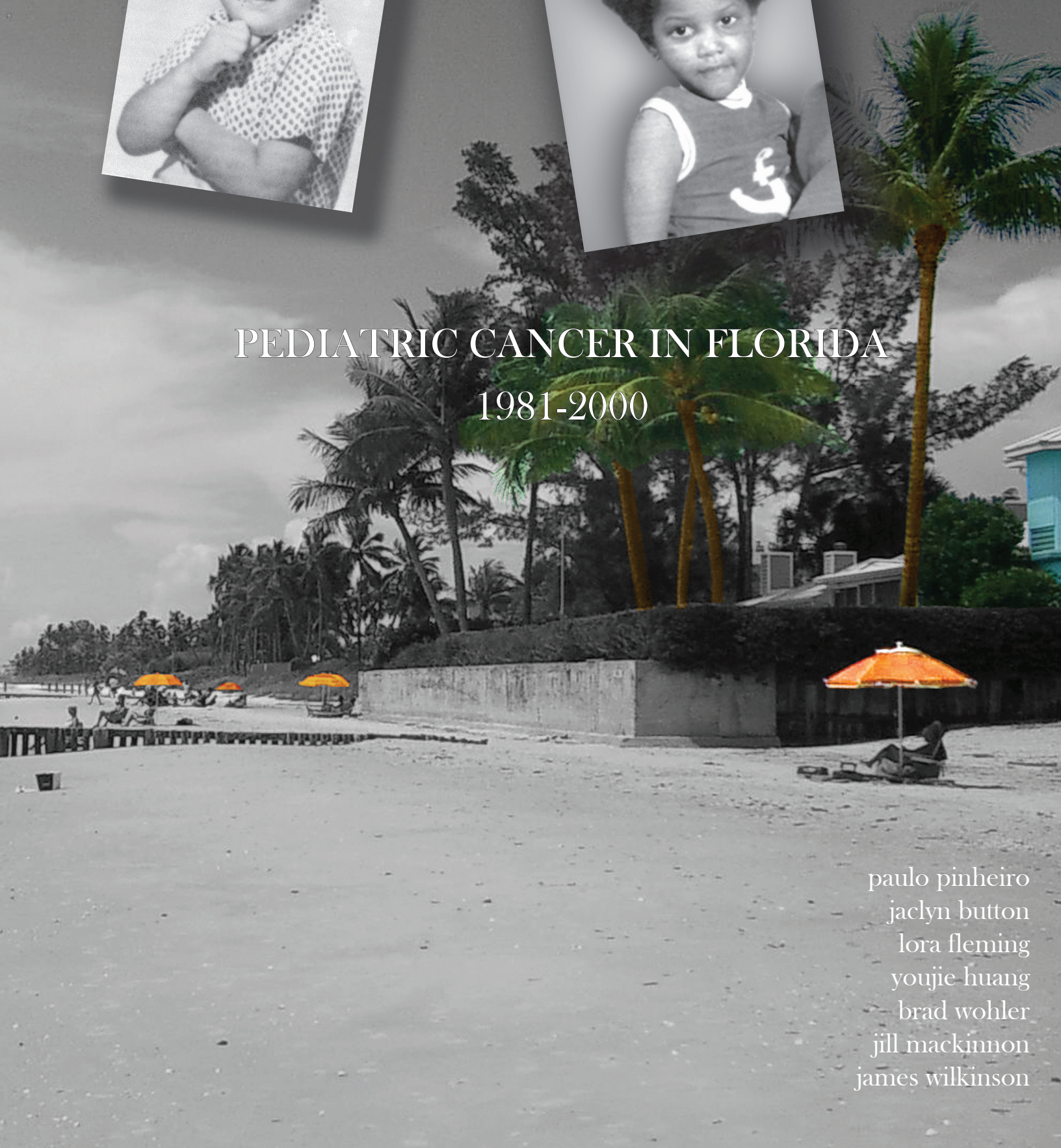




PEDIATRIC CANCER IN FLORIDA  
1981-2000



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2008

**ACKNOWLEDGEMENTS:** The Registry is grateful to the Florida Department of Health, the Centers for Disease Control and Prevention and its National Program of Cancer Registries for funds to enhance registry operations and to conduct special studies. We would also like to recognize the contribution of the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute for the SEER comparative incidence data and risk factor tables reproduced in this volume. We would like to extend our thanks to Gary Levin and Melissa Williams for their support, and the Louisiana Tumor Registry, from whose work on childhood cancer we obtained some ideas for the present report.

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Suggested citation:

Pinheiro PS, Button JH, Fleming LE, Huang Y, Wohler B, MacKinnon JA, Wilkinson JD. Pediatric Cancer in Florida: 1981-2000. Miami: Florida Cancer Data System, 2008.

This work was supported by the Florida Department of Health (Contract COANF) and the Centers for Disease Control and Prevention through the National Program of Cancer Registries (U58/DP000844-01).



ISBN 978-0-615-16949-1

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# EXECUTIVE SUMMARY

## PEDIATRIC CANCER IN FLORIDA

This publication is the first comprehensive description of pediatric cancer in Florida. It is a joint project of the Center for Disease Control and Prevention, National Program of Cancer Registries, and the Florida Cancer Data System. Complete incidence data for children less than 20 years old from Florida diagnosed between 1981 and 2000 were examined. This report systematically reviews incidence, incidence trends, survival, and mortality for all cancers combined and for each specific cancer.

Overall, the occurrence of pediatric cancer in Florida is similar to the rest of the United States. It accounts for 0.7% of all cancers diagnosed in the State, a total of 10,238 cases in 20 years. Although rare, cancer accounts for 10% of the mortality of children aged 2-15 years. In this age group it is the second most frequent cause of death and the first cause of natural death. Acute lymphocytic leukemia and tumors affecting the central nervous system are the most common pediatric cancers.

Progress in fighting childhood cancer has been quite favorable overall. Throughout the 20-year period from 1981 to 2000, the incidence of all pediatric cancers showed a slight increase of 0.9% per year, whereas mortality decreased by 1.9% per year, primarily as a result of improved treatment. Adding to this favorable trend, survival in Florida has increased remarkably for most forms of childhood cancer, having reached 80% after 5 years by 1990-1997.

For acute lymphocytic leukemia, the most common cancer consisting of 20% of cases, survival has now reached 83% after 5 years. For thyroid cancer and retinoblastoma, survival is nearly universal.

Slightly increasing trends in incidence for cancers with less favorable prognoses such as acute myeloid leukemia, brain tumors and non-Hodgkin lymphoma have been observed. However, improvements in survival for each of these cancers offset these unfavorable trends.

Finally, although not unique to Florida, disparities remain. Survival rates for most pediatric cancer are consistently higher in White than in Black children. Among age groups, adolescents tend to have lower survival than their younger counterparts. The challenge remains on one hand to continue improving treatment of childhood cancer, while on the other hand tackling these inequalities among races and age subpopulations.



# INTRODUCTION

In 2000, more than 4 million Floridians, nearly 25% of the population, were younger than 20 years of age. Cancer in this age group is a rare event. From 1981 to 2000, a total of 10,238 new cases of cancer were diagnosed among Florida children and adolescents, representing 0.7 % of all cancer cases diagnosed in the state. This corresponds to an average of 512 new cases per year during the 20-year period. For the same period, there were 2,200 deaths of Floridians under age 20 due to cancer, a yearly average of 110 deaths.

Childhood cancer is a diverse group of rare malignancies, varying widely in histology and anatomical site. In early childhood, ages 0 to 4, many malignancies are embryonal in origin. The genetic component may be very strong and parental exposures may be partly causal<sup>1,2</sup>. In adolescence, however, the effects of post-birth exposures begin to have an impact on cancer occurrence<sup>3</sup>.

Florida is a state with very dynamic demographics. Between 1981 and 2000 the state population increased more than 60%. The race and ethnic composition is unique in the United States. The population, especially in South Florida, has a large established Hispanic community and a constant influx of immigrants mainly from Latin America and the Caribbean.

This report presents detailed cancer incidence on children and adolescents aged 0-19 years old in Florida from 1981 to 2000 and an analysis of pediatric cancer mortality for the same time period. In addition, five-year survival data is analyzed for 8,347 children and adolescents diagnosed between 1981 and 1997, among whom 2,394 deaths were recorded between 1981 and 2002.

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Table 1. Percent of ICCC Category and Subcategory by Age, Florida, 1981-2000

	<b>0-4</b>	<b>5-9</b>	<b>10-14</b>	<b>15-19</b>	<b>&lt;15</b>	<b>&lt;20</b>
All Sites Combined - Number of Cases	3,419	1,908	1,947	2,964	7,274	10,238
All Sites Combined	100.0	100.0	100.0	100.0	100.0	100.0
I Leukemia	35.0	33.3	22.8	14.6	31.3	26.5
I(a) Lymphoid leukemia	29.1	26.7	16.3	7.5	25.1	20.0
Acute lymphocytic leukemia (ALL)	28.8	26.4	16.0	7.3	24.7	19.7
Lymphoid excluding ALL	0.4	0.4	0.3	0.2	0.3	0.3
I(b) Acute non-lymphocytic leukemia	4.1	4.4	4.9	4.9	4.4	4.5
I(c) Chronic myeloid leukemia	0.4	0.8	0.7	1.2	0.6	0.8
I(d) Other specified leukemia	1.4	0.5	0.3	0.3	0.9	0.7
I(e) Unspecified leukemia	1.2	1.3	0.7	0.7	1.1	1.0
II Lymphoma and reticuloendothelial neoplasms	4.7	13.5	19.4	25.1	10.9	15.0
II(a) Hodgkin lymphoma	0.2	3.5	10.1	16.8	3.7	7.5
II(b) Non-Hodgkin lymphoma	2.1	4.9	5.5	6.0	3.7	4.4
II(c) Burkitt lymphoma	1.2	4.3	2.1	0.7	2.3	1.8
II(d) Miscellaneous lymphoreticular neoplasms	1.9	0.4	0.2	0.1	1.1	0.8
II(e) Unspecified lymphoma	0.0	0.0	0.0	0.0	0.0	0.0
III CNS and misc intracranial and intraspinal neoplasms	16.8	27.7	21.5	10.5	20.9	17.9
III(a) Ependymoma	1.8	1.5	1.5	1.0	1.6	1.4
III(b) Astrocytoma	7.9	13.2	12.2	5.7	10.4	9.1
III(c) Primitive neuroectodermal tumors	4.4	7.4	3.6	1.3	5.0	3.9
III(d) Other gliomas	2.0	4.3	3.4	1.6	3.0	2.6
III(e) Misc intracranial and intraspinal neoplasms	0.0	0.2	0.0	0.1	0.1	0.1
III(f) Unspecified intracranial and intraspinal neoplasm	0.8	1.2	0.7	0.7	0.9	0.8
IV Sympathetic nervous system tumors	12.5	3.1	0.9	0.6	6.9	5.1
IV(a) Neuroblastoma and ganglioneuroblastoma	12.3	2.9	0.7	0.4	6.8	4.9
IV(b) Other sympathetic nervous system tumors	0.2	0.2	0.2	0.2	0.2	0.2
V Retinoblastoma	6.6	0.4	0.0	0.0	3.2	2.3
VI Renal tumors	9.9	4.5	1.1	0.8	6.1	4.6
VI(a) Wilms tumor, rhabdoid and clear cell sarcoma	9.7	4.4	0.6	0.3	5.9	4.3
VI(b) Renal carcinoma	0.1	0.1	0.5	0.5	0.2	0.3
VI(c) Unspecified malignant renal tumors	0.1	0.0	0.0	0.0	0.0	0.0
VII Hepatic tumors	2.0	0.5	0.7	0.5	1.2	1.0
VII(a) Hepatoblastoma	1.8	0.2	0.1	0.1	0.9	0.7
VII(b) Hepatic carcinoma	0.1	0.3	0.5	0.4	0.3	0.3
VII(c) Unspecified malignant hepatic tumors	0.0	0.0	0.1	0.0	0.0	0.0
VIII Malignant bone tumors	0.6	5.1	12.1	8.7	4.9	6.0
VIII(a) Osteosarcoma	0.1	2.6	6.5	5.1	2.5	3.2
VIII(b) Chondrosarcoma	0.0	0.0	0.4	0.4	0.1	0.2
VIII(c) Ewing sarcoma	0.4	2.3	4.5	2.7	2.0	2.2
VIII(d) Other specified malignant bone tumors	0.0	0.1	0.5	0.4	0.2	0.2
VIII(e) Unspecified malignant bone tumors	0.1	0.1	0.2	0.2	0.1	0.1
IX Soft-tissue sarcomas	6.1	6.9	7.9	7.2	6.8	6.9
IX(a) Rhabdomyosarcoma and embryonal sarcoma	3.2	3.9	2.7	1.9	3.3	2.9
IX(b) Fibrosarcoma, neurofibrosarc, other fibromatous neoplasms	0.5	1.1	1.0	1.6	0.8	1.0
IX(c) Kaposi sarcoma	1.2	0.1	0.1	0.3	0.6	0.5
IX(d) Other specified soft-tissue sarcomas	0.8	1.1	2.5	2.5	1.3	1.7
IX(e) Unspecified soft-tissue sarcomas	0.4	0.7	1.6	0.9	0.8	0.8
X Germ-cell, trophoblastic and other gonadal neoplasms	2.6	1.6	5.3	12.5	3.1	5.8
X(a) Intracranial and intraspinal germ-cell tumors	0.3	0.8	1.4	0.8	0.7	0.7
X(b) Other and unspecified non-gonadal germ-cell tumors	1.1	0.1	0.4	1.4	0.6	0.9
X(c) Gonadal germ-cell tumors	1.2	0.6	3.1	8.5	1.5	3.5
X(d) Gonadal carcinomas	0.0	0.0	0.2	1.6	0.0	0.5
X(e) Other and unspecified malignant gonadal tumors	0.1	0.1	0.3	0.3	0.1	0.2
XI Carcinomas and other malignant epithelial neoplasms	1.1	1.9	7.7	18.6	3.1	7.5
XI(a) Adrenocortical carcinoma	0.2	0.1	0.1	0.2	0.1	0.1
XI(b) Thyroid carcinoma	0.2	0.7	2.7	6.6	1.0	2.6
XI(c) Nasopharyngeal carcinoma	0.0	0.2	0.8	1.0	0.3	0.5
XI(d) Malignant melanoma	0.2	0.4	2.0	4.9	0.7	1.9
XI(f) Other and unspecified carcinomas	0.5	0.6	2.1	5.9	1.0	2.4
XII Other and unspecified malignant neoplasms	0.7	1.2	0.8	0.7	0.8	0.8
XII(a) Other specified malignant tumors	0.1	0.2	0.2	0.3	0.1	0.2
XII(b) Other unspecified malignant tumors	0.6	1.0	0.6	0.4	0.7	0.6

# MATERIALS AND METHODS

## STRUCTURE OF THE REPORT

This report begins with a chapter on all cancer sites combined as a single group in Floridians under age 20, and comprises a discussion on incidence, a summary of cancer survival and a discussion of cancer mortality in the pediatric age group. The remainder of the report consists of one chapter for each type of pediatric cancer as designated by the International Classification of Childhood Cancers (ICCC) <sup>1</sup>. Group XII, Other and Unspecified Malignant Tumors, which accounts for less than 1% of all pediatric cancers, is not analyzed in a separate chapter. Each chapter discusses incidence and survival, as well as trends in these measures, by selected demographic characteristics. Risk factors are also enumerated. This report is available on the Florida Cancer Data System website [www.fcds.com/downloads](http://www.fcds.com/downloads).

## SOURCES OF DATA

### Incidence

Cancer incidence data are collected, verified, and maintained by the Florida Cancer Data System (FCDS), Florida's statewide cancer incidence registry. The FCDS is administered by the Florida Department of Health and operated by the Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine with funding from the Florida Department of Health and the Centers for Disease Control and Prevention's National Program of Cancer Registries (NPCR). The FCDS began operation with a pilot project for cancer registration in 1979 and commenced statewide collection of cancer incidence data from all Florida hospitals in 1981. The FCDS now collects incidence data from hospitals, freestanding ambulatory surgical centers, radiation therapy facilities, pathology laboratories, and dermatopathologists' offices. More information about cancer incidence and mortality in Florida can be found at [www.fcds.med.miami.edu](http://www.fcds.med.miami.edu) and on the Department of Health's Bureau of Epidemiology website [www.doh.state.fl.us/disease\\_ctrl/epi/cancer/CancerIndex.htm](http://www.doh.state.fl.us/disease_ctrl/epi/cancer/CancerIndex.htm).

### Mortality

Cancer mortality in Florida is based on cancer appearing as the underlying cause of death on death certificates obtained from the Florida Department of Vital Statistics. Cancer mortality is coded according to the International Classification of Diseases - 9th revision <sup>2</sup>. SEER mortality data are obtained from public use files provided by the National Center for Health Statistics (NCHS) and cover all deaths in the United States.

### Data Limitations

Cancer incidence and mortality data are derived from different sources, and employ different coding schemes. Incidence data are obtained from abstracts of patient medical information, collected primarily from hospitals by FCDS. Hospitals code cancer cases according to the International Classification of Diseases for Oncology, Version 3 (ICD-O-3) <sup>3</sup> which includes two distinct components, one for the anatomic site of a tumor and another for tumor morphology. The distribution of cancer in children is different from that in adults, with some cancer types being very specific to young age groups. The International Classification of Childhood Cancer (ICCC) is based on tumor morphology and primary site, with emphasis on morphology rather than on primary site.

Mortality data are coded according to the more general International Classification of Diseases (ICD-9), which is based on anatomic site for some cancers such as kidney tumors, and on morphology for other cancers like leukemia. The use of ICCC to describe the incidence of pediatric cancer and ICD-9 codes for mortality results in categories that in some cases are not strictly comparable, as is the case for neuroblastomas (see below). Therefore, some care must be taken when comparing pediatric incidence and mortality.

For the most commonly occurring tumors, equivalents can be found between incidence and mortality codes. In many cases, an accurate breakdown of mortality data by cancer subcategory is not possible, especially for leukemia, CNS tumors, and bone cancer. The definitions of the following cancers in the death data are not exactly the same as those in the incidence data:

Leukemia – A more detailed and specific coding scheme is used for cancer incidence than that used on death certificates. For pediatric leukemia mortality, the proportion of leukemia cases with unspecified type reaches 20%. Misclassification of the specific subtype of leukemia, especially on death certificates, is common. These two factors make an accurate distinction between ALL and AML impracticable. As a result, the analysis of mortality treats childhood leukemias as a single group.

Brain tumors – Non-invasive tumors of the brain have the potential to be fatal. Mortality data included deaths from both malignant cancers and non-malignant brain tumors. The number of deaths from non-malignant brain tumors in Florida was less than 1 per year.

Sympathetic nervous system tumors (including neuroblastomas) – This group of tumors falls into the ICD category of Endocrine, Other and Thymus cancers. Deaths from cancers in this category other than neuroblastoma are minimal.

### Population

The Florida Consensus Estimating Conference provided population estimates for 1981 to 2000. In 2000, there were 3,049,306 children younger than 15 years of age and 4,072,025 younger than 20 years of age residing in the State of Florida. Nineteen percent of the Florida population is younger than 15 years of age and an additional 6.4% are 15-19 years of age.

### Survival

FCDS computes passive follow-up for all cancer incidence cases through annual linkage of cancer records with deaths registered by the Florida Department of Vital Statistics. For SEER, which performs active follow-up until death, the overall proportion of lost to follow-up for pediatric cases is approximately 14%. Due to FCDS reliance on passive follow-up only, it is probable that survival rates in SEER may be lower than those in Florida. Since survival rates in children and adolescents are relatively high, even active follow-up can be laborious, especially as the child gets older. When children leave their parents' home, they change addresses and females may change last names when they get married, leaving some incident cases unmatched with their respective deaths. In addition to those factors, passive follow-up will be overstated by some fraction due to out-of-state deaths which will not be matched to corresponding incidence records.

	Florida	U.S.*
Number of Children	4,072,025	80,503,018
% of Total Population	25.3	28.5
Age		
0-4	23.4	23.9
5-9	25.4	25.4
10-14	26.1	25.6
15-19	25.1	25.1
Sex		
Female	48.7	48.7
Male	51.3	51.3
Race		
White	74.7	78.1
Black	21.8	16.2
Other	3.5	5.7

\* U.S. population from [www.census.gov](http://www.census.gov)

## **RATE CALCULATIONS**

### **Incidence and Mortality Rates**

Pediatric cancer rates are calculated from the number of new cases of a specific cancer group occurring in a specified population during a year, expressed as the number of cancers per one million children. 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. All incidence and mortality rates in this report are age-adjusted to the 2000 US standard million population, except the age-specific rates shown for five-year age groups, or those specifically stated to be crude rates. Incidence rates are for invasive cancer only.

### **Survival Rates**

The survival rates used in this report are the percentages of patients having survived five years after diagnosis. The duration of survival was calculated as the time elapsed between the date of diagnosis and the date of death, if the patient died, or the closing date of the study. The closing date used in this report was January 1, 2003. The actuarial life-table method was used for survival analysis.

## **CLASSIFICATION OF SITE AND HISTOLOGIC TYPE**

FCDS classified the cases in this report by cancer site and histologic type using the International Classification of Diseases for Oncology, Second Edition (ICD-O-2) <sup>4</sup>. In contrast to that grouping, in which a cancer is categorized primarily by anatomical site, the classification of pediatric cancer is determined primarily by histologic type. The FCDS data used for this report have been grouped according to the SEER modification of the International Classification of Childhood Cancers (ICCC) specifications <sup>5</sup>.

## **HISTOLOGIC CONFIRMATION**

In the FCDS data, 96% of cases are histologically confirmed. This is important because most childhood cancer classifications are based on histologic type. The proportion of histologically confirmed cases varies by ICCC category, ranging from a low of 87% for retinoblastoma (ICCC group V) to a high of 99% for leukemia, lymphoma and soft-tissue sarcoma (ICCC groups I, II and IX).

## **RISK FACTORS**

Throughout this report, 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 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 causality criteria. However, many individuals in the population may have the characteristic or exposure and may 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 learn whether or not previously identified clues are likely to lead us to the causes of a particular cancer. No single study is likely to prove that a particular exposure definitely causes a particular cancer. Not 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 greater understanding of the causes of these cancers within populations of children.

## **ABBREVIATIONS AND CLARIFICATION OF TERMS**

ALL Acute Lymphocytic Leukemia

AML Acute Myeloid Leukemia

HL Hodgkin Lymphoma

NHL non-Hodgkin lymphoma

CNS Central Nervous System

SNS Sympathetic Nervous System

STS Soft Tissue Sarcomas

SEER Surveillance Epidemiology and End Results

FCDS Florida Cancer Data System

AML and ANLL

Acute Myeloid Leukemia (AML), an ICCC-3 term, is used throughout this report instead of, Acute non-Lymphocytic Leukemia (ANLL), the ICCC-2 term for ICCC subcategory I (b). AML is a more easily identified term and a more specific disease than ANLL. ANLL has a slightly broader definition than AML, but over the 20-year period of this study, the difference in numbers between the two entities is negligible.

Brain tumors, neuroblastomas, Wilms tumors

We refer to CNS tumors as brain tumors, SNS tumors as neuroblastomas, and kidney cancers as Wilms tumors, since more than 90% of cases in each of these ICCC categories correspond to these more easily understood terms.

## **ICCC CATEGORIES AND ICCC SUBCATEGORIES**

ICCC categories refer to broad groups of cancers, e.g., leukemia, comprising distinct diseases such as ALL and AML. ICCC subcategories refer to these more specific entities. In some graphs and tables, the data are presented for ICCC subcategories when ICCC categories alone do not describe the findings appropriately.

## **PERCENTAGE POINTS VS. PERCENT RATIO**

Survival rates are proportions. Given that proportions are finite, a percent ratio will depend heavily on the baseline proportion under comparison. Therefore we use the difference in percentage points rather than percent ratios to make comparisons between survival rates in the 1980s and the 1990s, between Blacks and Whites or between different cancers. For example we state that from the 1980s to the 1990s, the 5-year survival rate for osteosarcoma increased 10 percentage points from 64% to 74%, rather than a 16% increase in survival.

## OTHER TECHNICAL DEFINITIONS

**Age-adjusted rates:** Pediatric incidence and mortality rates are expressed as age-adjusted number of cases or deaths per million person years under age 20. For simplicity, these are referred to as “rates per million”. Rates are age-adjusted to the 2000 US standard million population.

**Age groups:** The age group studied and described in this report is ages 0-19, divided into 5-year segments: 0-4, 5-9, 10-14 and 15-19. As in similar reports, the following terms are used throughout the text. Pediatric corresponds to the whole group age 0-19, childhood to 0-14; adolescence is 15-19; early childhood is 0-4; late childhood is 10-14, and infants are less than 1 year old.

**Age-specific rates:** Age-specific rates in this report are presented as cases or deaths per million population per year. The numerator of the rate is the number of cancer cases or deaths 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 and calendar year.

**Average Annual Percentage Change:** Average Annual Percentage Change (AAPC) quantifies changes in incidence and mortality rates from 1981 to 2000 and was computed using Poisson regression models of rate on calendar year, included as a continuous variable, adjusted for age group, a categorical variable, as applicable. This calculation assumes that the rates increased or decreased at a constant rate or with slight variations over the entire interval. In those few instances where any of the yearly rates were equal to zero, the regression coefficients were not calculated. For all trends, the term increase or decrease was used when the coefficient for calendar year was statistically different from 0 at the 0.05 level of significance; otherwise the term stable or level was used.

**ICCC classification:** At the time the World Health Organization’s (WHO) International Agency for Research on Cancer (IARC) published the first monograph on Childhood Cancer <sup>6</sup> in 1988, Dr. R. Marsden published an appendix 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 <sup>7</sup>.

**Mortality rate:** The pediatric 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 2000 US standard million population.

**SEER Program:** Data from the SEER-9 registries were used compute incidence and survival rates to compare with Florida by age group, sex and race. The SEER program began in 1973, as an outgrowth of the NCI’s Third National Cancer Survey. NCI contracts with various medically-oriented non-profit organizations, local city or state Health Departments or Universities for collection of these data. The SEER-9 registries are comprised of the entire states of Connecticut, Iowa, New Mexico, Utah, and Hawaii, and the metropolitan areas of Detroit, Michigan; San Francisco-Oakland, California; Seattle-Puget Sound, Washington; and Atlanta, Georgia. These organizations collect data on all cancers except basal and squamous cell skin cancers. Only residents of the areas designated above are included so that the base populations can be properly determined. The SEER rates in this report were calculated from the SEER public use dataset with SEER\*Stat. The SEER public use dataset is available at [www.seer.cancer.gov/data](http://www.seer.cancer.gov/data) and the SEER\*Stat software at [www.seer.cancer.gov/seerstat](http://www.seer.cancer.gov/seerstat).

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# ALL CANCERS COMBINED

## INCIDENCE

The percent distribution of childhood and adolescent cancer by ICCC group and age group is presented in Table 1. The crude incidence rate for the study period was 154 cancers per million children, equivalent to one cancer in every 6,500 individuals under age 20.

Leukemia (26%), cancer of the central nervous system (18%), and lymphoma (15%) were the three most common cancers in Florida, accounting for 59% of cancers in those aged 0-19. Among ICCC subcategories, the three most common childhood cancers were: acute lymphocytic leukemia (20%), astrocytoma (9%) and Hodgkin lymphoma (7.5%).

### AGE

Table 3 shows that the largest number of cancers occurred in the 0-4 age group, accounting for approximately 33% of all pediatric cases. Cancer in adolescents accounted for 29% of pediatric cases. The 5-9 age group had the lowest proportion of cases of cancer, approximately 19%.

Acute lymphocytic leukemia (ALL) was the most common cancer in all age groups up to age 14. In the age group 0-4, ALL was followed by neuroblastoma, astrocytoma, Wilms tumor and retinoblastoma.

The age group 5-9 had the lowest incidence of cancer of the human lifespan with only 0.1% of the

Figure 1. Number of Pediatric Cancers by ICCC Category and Age, Florida, 1981-2000

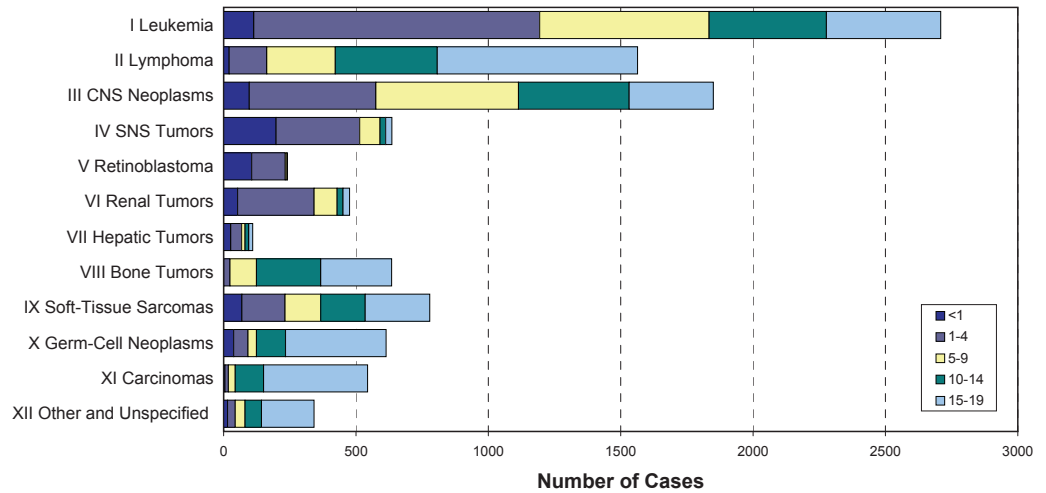
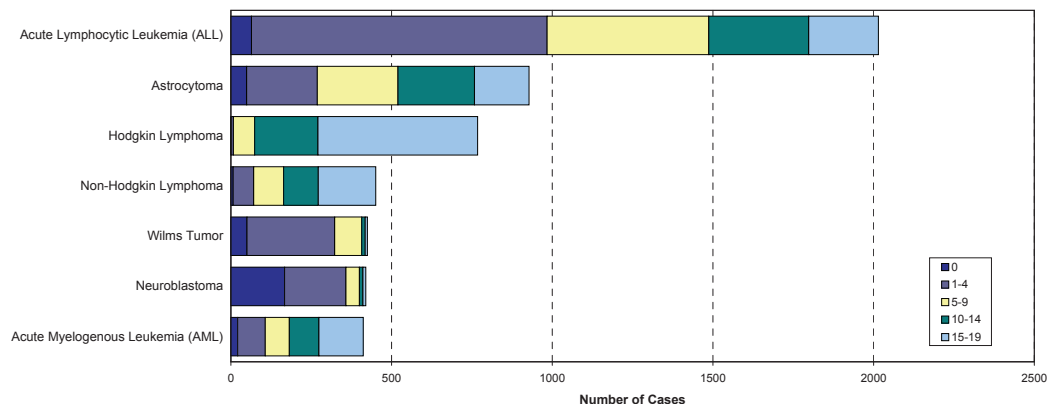


Table 3. Demographic Characteristics of Children with Cancer, Florida, 1981-2000

	Number of Cases	Percent
Number of Children	10,238	100.0
Age		
0-4	3,419	33.4
5-9	1,908	18.6
10-14	1,947	19.0
15-19	2,964	29.0
Sex		
Female	3,419	45.4
Male	5,588	54.6
Race		
White	8,268	80.8
Black	1,791	17.5
Other	110	1.1

Figure 2. Number of Pediatric Cancers by ICCC Subcategory and Age, Florida, 1981-2000





total number of cancer cases in the population. ALL, astrocytoma and non-Hodgkin lymphoma were the most common cancers in this group.

For the age group 10-14, the three most frequent malignancies were ALL, astrocytoma and bone cancer.

Cancer patterns in adolescents were different than in children, resembling those of young adults. The most common cancers in the age group 15-19 were Hodgkin lymphoma, germ-cell tumors (which include testicular and ovarian cancers), and bone cancer.

**SEX**

Overall, there was an excess of cancer cases in males (55%) in Florida. For all sites combined, pediatric cancer incidence rates were higher in males across all age groups and races, except for Blacks aged 10-14, where rates for females exceeded the rates for males.

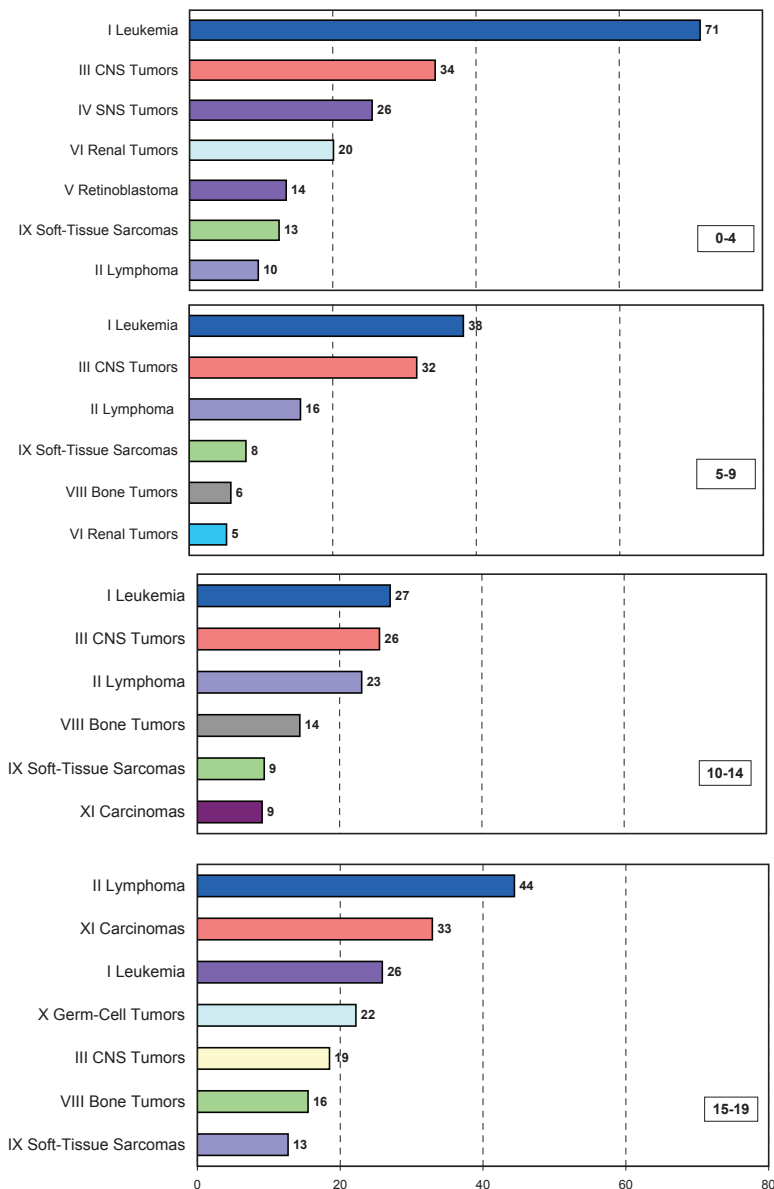
For nearly all ICCC categories, cancer was more common in males than in females with three exceptions. The incidence rate of thyroid carcinoma was nearly 4 times higher in females than in males. Females had approximately 20% higher rates of Wilms tumor and malignant melanoma than males.

**RACE**

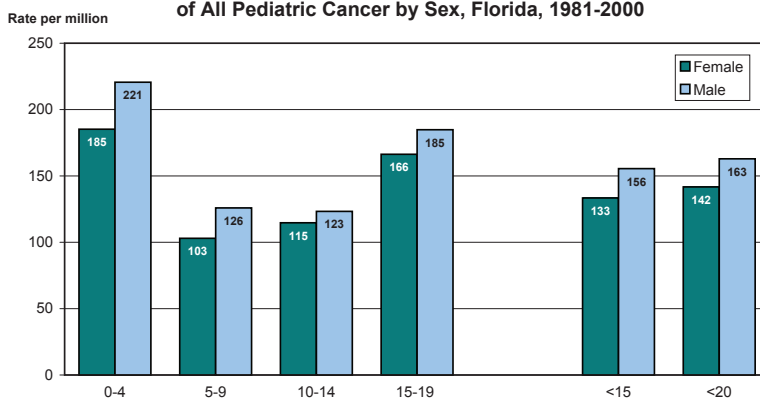
More than four-fifths of the cases (81%) occurred in Whites, and only 18% of cases in Blacks. Children of other races accounted for the remaining 1% of cases. These percentages correspond directly with the proportions of population by race in the state. Incidence rates were 162 per million in Whites and 123 per million in Blacks. As a group, Black females had the lowest incidence rate of pediatric cancer in Florida.

The overall combined rate was 32% higher for Whites. For nearly all categories, incidence rates were higher in Whites than in Blacks. This difference is greater than for cancer in adults, for

**Figure 3. Age-Specific Incidence Rates of Leading Pediatric Cancers, Florida, 1981-2000**



**Figure 4. Age-Specific and Age-Adjusted Incidence Rates of All Pediatric Cancer by Sex, Florida, 1981-2000**



whom the incidence of all cancers is only 6% higher in Whites than in Blacks <sup>1</sup>.

For common cancers, such as leukemia, lymphoma, CNS tumors, germ-cell tumors, and neuroblastomas, rates in Whites were at least 30% higher than in Blacks. For ALL, the most common cancer in childhood, the incidence rate was more than 70% higher in Whites than in Blacks. The incidence rates of Hodgkin lymphoma, bone Ewing sarcoma, gonadal tumors and thyroid carcinoma in Whites were at least double those in Blacks. For malignant melanoma, incidence rates were 7 times higher in Whites than in Blacks.

In contrast, the rates of renal tumors and soft-tissue sarcomas were higher in Blacks than in Whites. Among Blacks, the most common cancers (ICCC subcategory) were ALL, astrocytoma and soft-tissue sarcomas.

**ICCC CATEGORIES**

Incidence rates for each of the twelve ICCC categories are shown in Figure 9. Leukemia had the highest rate (40 per million), followed by malignant tumors of the central nervous system (28 per million), and lymphoma (24 per million). The incidence rates of three most common cancers (ICCC subcategories) were 33 per million for ALL, 14 per million for astrocytoma and 12 per million for Hodgkin lymphoma.

Figure 5. Age-Adjusted Incidence Rates of All Pediatric Cancer by ICCC Category and Sex, Florida, 1981-2000

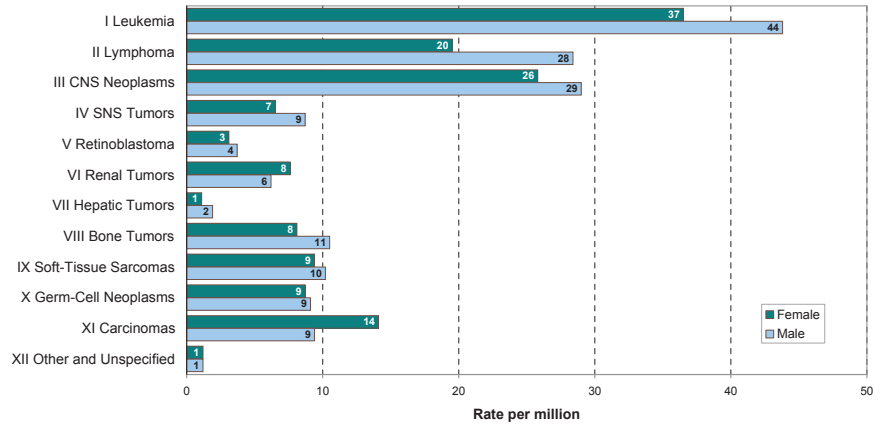


Figure 6. Age-Specific and Age-Adjusted Incidence Rates of All Pediatric Cancer by Race, Florida, 1981-2000

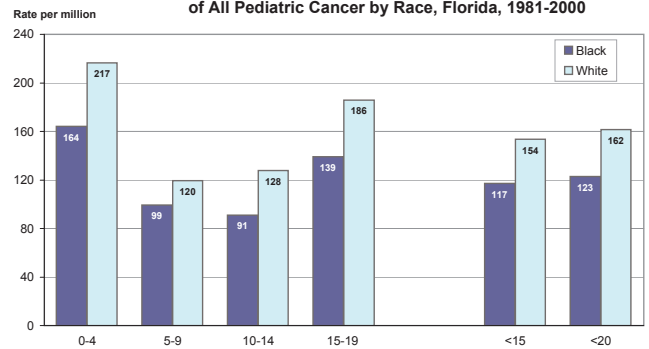
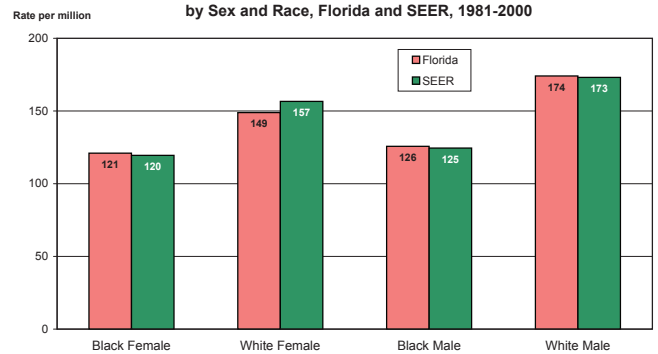


Figure 7. Age-Adjusted Incidence Rates of All Pediatric Cancer by Sex and Race, Florida and SEER, 1981-2000



## FLORIDA AND SEER COMPARISONS

Florida cancer rates were similar to SEER rates for both races. The overall rates for all pediatric cancers in Florida were similar to those observed in the SEER-9 areas (Figure 7). The major differences between Florida and SEER rates are given in Table 4.

Significantly Lower Rates in Florida		Florida Rate (95% CI)	SEER-9 (95% CI)
Soft Tissue Sarcoma	All Races	1.6 (1.3-1.9)	3.1 (2.8-3.4)
Melanoma of the Skin	Whites	3.0 (2.6-3.4)	4.7 (4.4-5.1)
Thyroid Carcinoma	All Races	4.1 (3.6-4.6)	5.4 (5.0-5.8)
Hodgkin Lymphoma	All Races	11.7 (10.8-12.5)	13.4 (12.7-14.0)
Testicular Cancer	All Races	6.6 (5.8-7.5)	8.3 (7.7-9.0)
Significantly Higher Rates in Florida			
Ewing Sarcoma	Blacks	1.1 (0.7-1.8) [n=16]	0.3 (0.1-0.6) [n=5]

Figure 8. Age-Adjusted Incidence Rates of All Pediatric Cancer by ICCC Category, Florida, 1981-2000

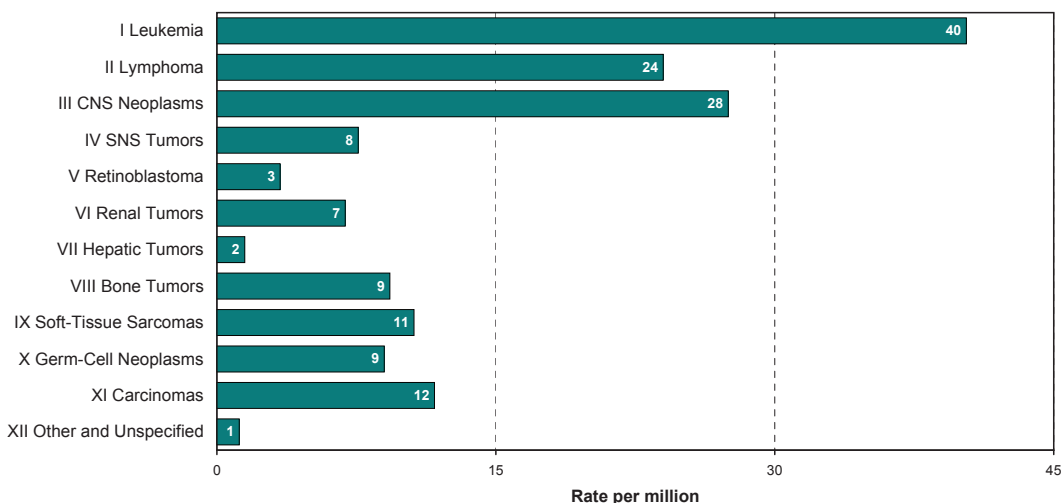
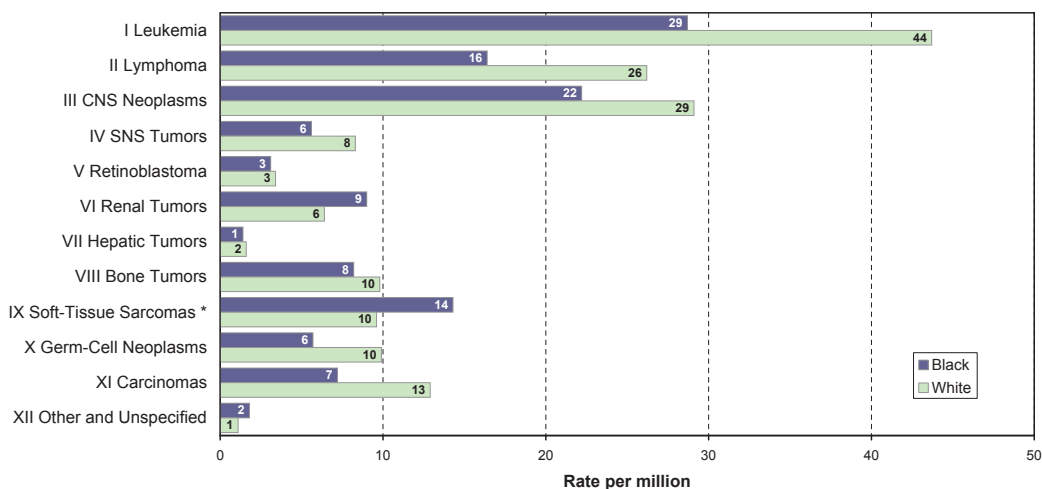


Figure 9. Age-Adjusted Incidence Rates of All Pediatric Cancer by ICCC Category and Race, Florida, 1981-2000



\* Differences in pathologic interpretation of KS may have increased the rate of STS for Blacks.

**TRENDS**

Incidence of all pediatric cancers increased in both sexes in Florida at a rate of 0.9% a year. The incidence increased by 1.1% a year in early childhood, and by 0.9% a year in adolescence. No trends were observed among those aged 5-14.

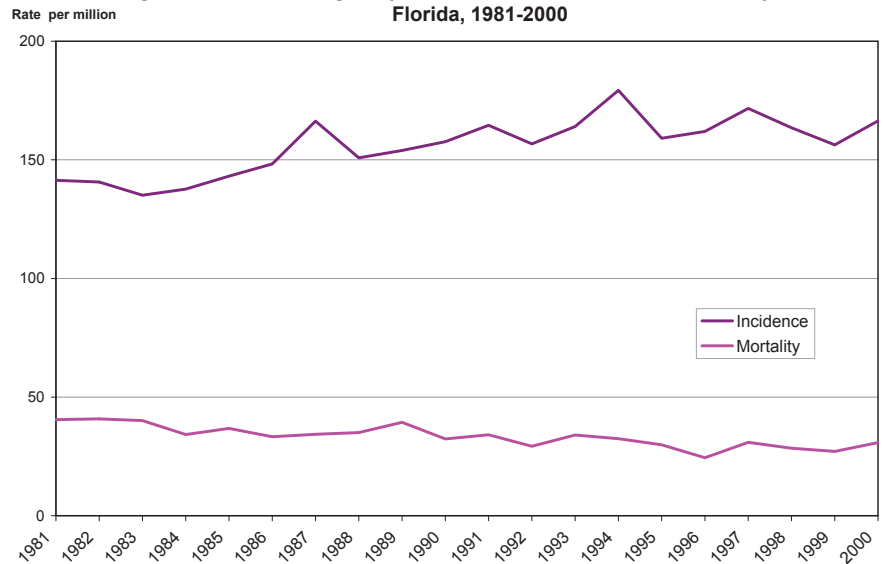
International childhood cancer incidence varies widely by geographical area <sup>2,3</sup>. Therefore, immigration may have some impact on incidence rates in Florida. The U.S. Census Bureau reported a population increase of 58% in the State of Florida between 1981 and 2000. During the same period, the proportion of foreign-born population increased from 9.6% to 17.2% in Florida <sup>4</sup>. As a result, trends in pediatric cancer have to be interpreted against the background of a diverse, mobile population with different patterns of baseline risk factors.

Significant annual increases from 1981 to 2000 were observed for:

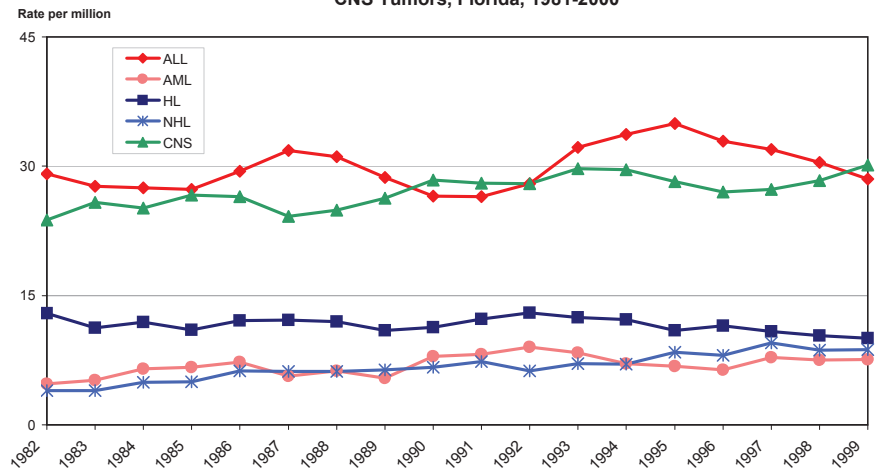
- Thyroid Carcinoma (+3.2 %)
- Malignant Melanoma (+3.2 %)
- Non-Hodgkin Lymphoma (+3.0 %)
- Acute Myeloid Leukemia (+1.9 %)
- Neuroblastoma (+1.9 %)
- Brain Cancer (+1.4 %).

An increasing trend in germ-cell tumors was observed in Whites with an increment of 1.6 % per year. In Blacks, increases were only observed for two cancers: non-Hodgkin lymphoma, which increased by 5.3% a year, and central nervous system cancer with an average increase of 2.2% per year.

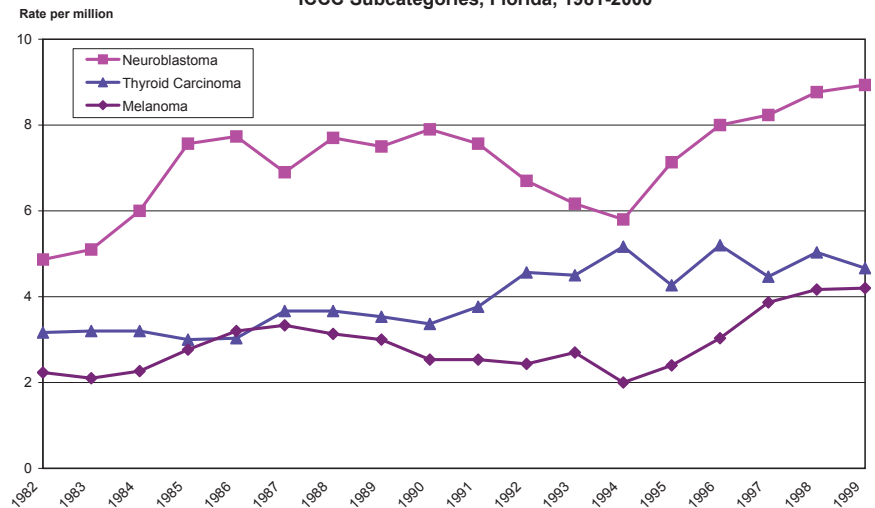
**Figure 10. Trends in Age-Adjusted Pediatric Incidence and Mortality Rates, Florida, 1981-2000**



**Figure 11. Trends in Age-Adjusted Incidence Rates of ALL, AML, HL, NHL, and CNS Tumors, Florida, 1981-2000**



**Figure 12. Trends in Age-Adjusted Incidence Rates of ICC Subcategories, Florida, 1981-2000**



\* Trends are 3-year moving averages.

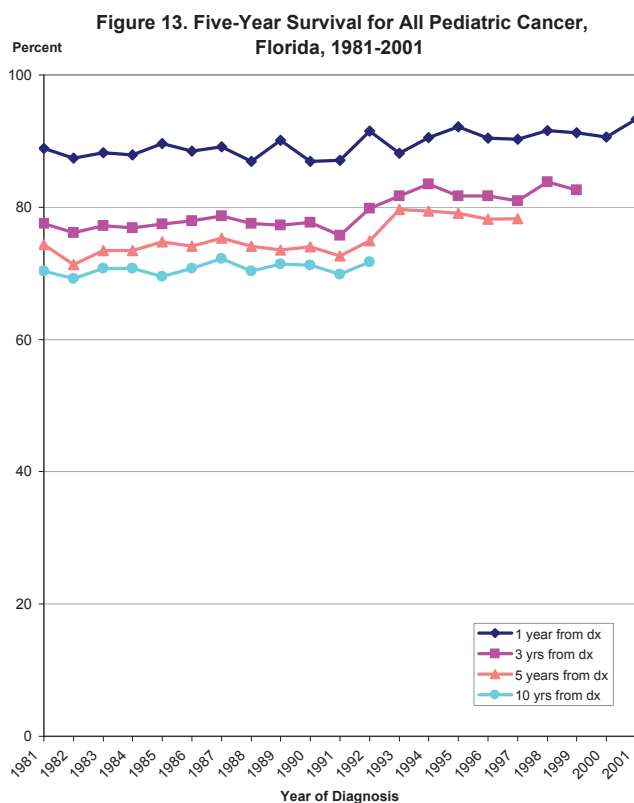
## SURVIVAL

Survival for pediatric cancer in the US and Europe improved remarkably from the 1970s to the 1990s<sup>5,6</sup>. Much of this improvement resulted from the changing prognosis for ALL, as well as other common cancers, due to improved chemotherapy regimens, radiotherapy modalities and other treatments. Multicenter clinical trials and specific study groups for other rarer childhood cancers have also had a major impact on survival<sup>6</sup>.

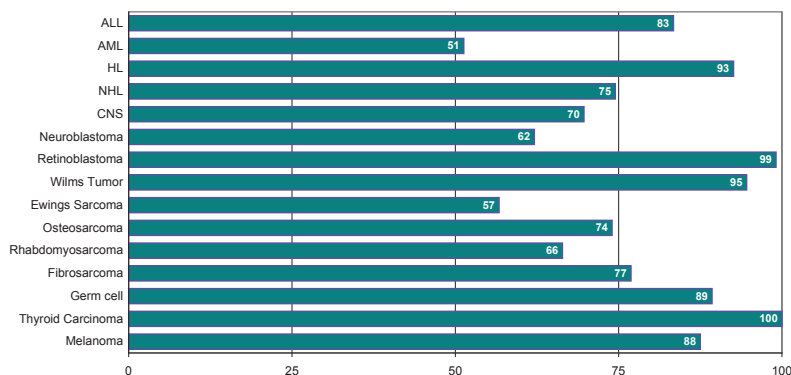
Five-year survival data in Florida was analyzed for 8,347 children and adolescents diagnosed between 1981 and 1997, among whom 2,394 deaths were recorded between 1981 and 2002.

In Florida, the five-year survival rate for all pediatric cancers combined improved substantially from the 1980s to the 1990s. For cancers diagnosed after 1993, nearly 80% of individuals lived longer than 5 years after diagnosis (Figure 13). However, improvements from the 1980s to the 1990s were not uniform. For ALL, retinoblastoma and malignant melanoma, 5-year survival increased more than 5 percentage points. The improvement was remarkable for AML, Wilms tumor, hepatic tumors and osteosarcoma. Survival for all these cancers increased 10 percentage points or more. On the other hand, brain tumors, neuroblastoma, Ewing sarcoma and rhabdomyosarcoma showed no improvement in survival between the 1980s and the 1990s. Germ-cell tumors, Hodgkin lymphoma and thyroid carcinoma did not show an improvement either, but the baseline survival in the 1980s was already very favourable at 87%, 91%, and 100% respectively.

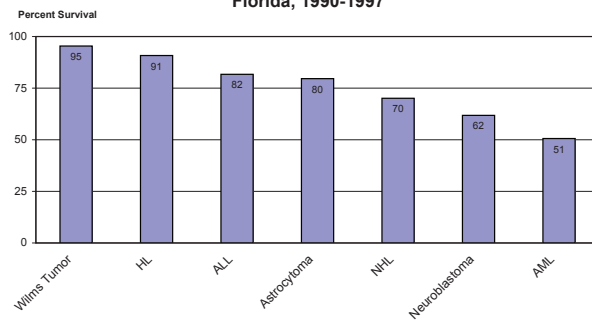
Overall, the 5-year survival rate varied from 43% for hepatocarcinoma to nearly 100% for thyroid cancer and retinoblastoma. AML and Ewing sarcoma were cancers with particularly poor prognoses in the 1990s. The 5-year survival rate was 51% for AML and 57% for Ewing sarcoma. Rhabdomyosarcoma and neuroblastoma also had low 5-year survival rates, 66% and 67%, respectively.



**Figure 14. Pediatric Five-Year Survival by ICCC Subcategories, Florida, 1990-1997**



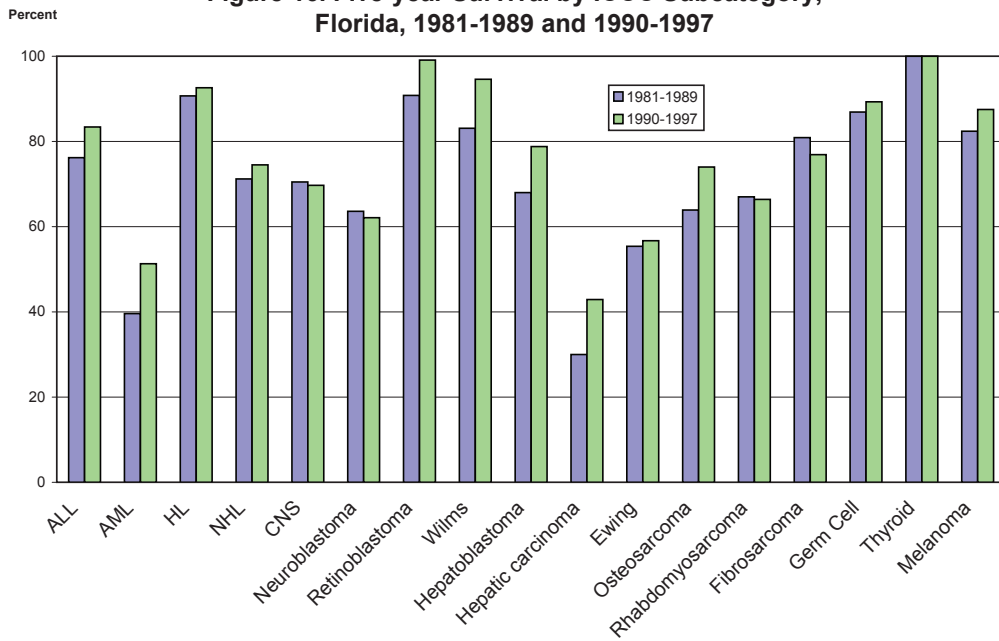
**Figure 15. Five-Year Survival for ICCC Subcategories, Florida, 1990-1997**



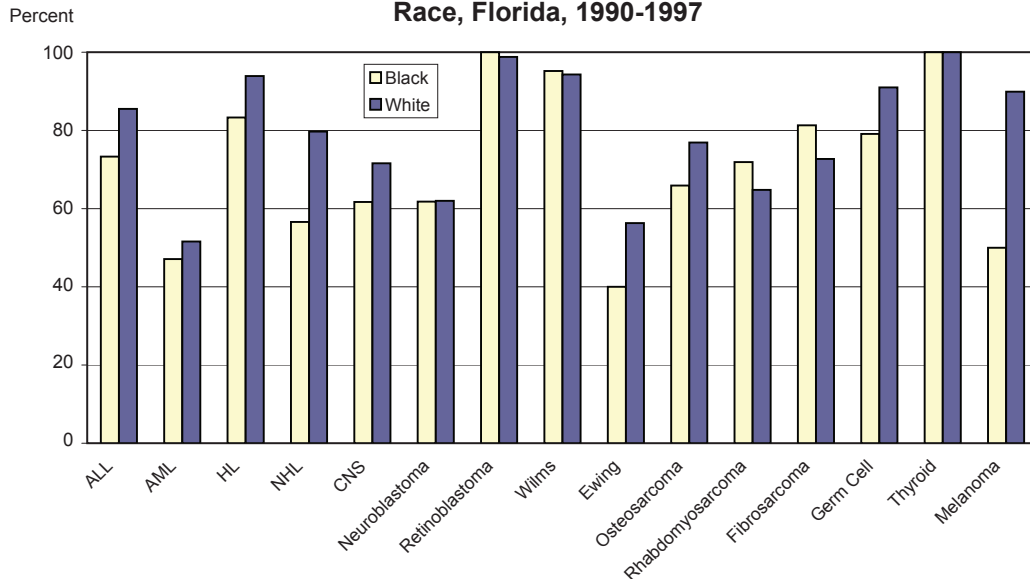
More importantly, racial disparities in survival were common in Florida, as shown by differences between Whites and Blacks in 1990-1997. These differences were quite obvious in the most common pediatric cancers. The 5-year survival rate of ALL was 86% for Whites and 73% for Blacks. For AML the difference was less pronounced, 51% for Whites and 47% for Blacks.

For cancers other than leukemia, the racial difference in survival was more prevalent in cancers that affect children and adolescents aged 10 and older. For cancers which occur mainly in infancy or early childhood - neuroblastomas, retinoblastomas, and Wilms tumor - there were no substantial differences in survival between races. However, for cancers which are relatively common after 10 years of age - brain tumors, Hodgkin lymphoma, non-Hodgkin lymphoma, germ-cell tumors, bone tumors, osteosarcoma and Ewing sarcoma - the differences in survival were always greater than 10 percentage points. This suggests that the determinants of racial disparity have a stronger role in the survival of older children and adolescents than in children aged less than 5.

**Figure 16. Five-year Survival by ICCS Subcategory, Florida, 1981-1989 and 1990-1997**



**Figure 17. Five-year Survival by ICCS Subcategory and Race, Florida, 1990-1997**



## MORTALITY

Pediatric cancer mortality rates in Florida have been decreasing for the last two decades. From 1981 to 2000, mortality declined by 31%, while incidence increased by 14%.

### ALL SITES

A total of 2,200 deaths were recorded in the period from 1981 to 2000 in Florida among children and adolescents. The average number of pediatric cancer deaths was 110 per year. The three most common causes of cancer death accounted for 63% of the total cancer deaths. These groups were leukemia (33%), CNS tumors (22%), and lymphomas (8%). The latter were, almost exclusively, deaths from non-Hodgkin lymphoma.

### AGE

Cancer mortality rates were higher in adolescence than in childhood because adolescents had a higher incidence of cancers with less favorable outcomes, such as AML, NHL, STS and bone cancer. In addition, adolescents had lower survival than children for ALL, the most common pediatric cancer.

In children, the mortality rate in 1981-2000 was approximately 30 cases per million, and similar in all three age groups. In adolescence, the rate was 42 cases per million.

For all sites combined, significant declines in mortality occurred for children aged 0-4 and 5-9, but not for children aged 10-14, or for adolescents.

#### Age 0-4

In early childhood, leukemias represented 37% of proportional mortality, whereas brain cancer was the cause of 25% of deaths. Neuroblastoma accounted for 17% of total cancer deaths. From 1981 to 2000, death rates decreased substantially at a rate of -2.6% per year, mainly due to decreases in mortality for leukemia and neuroblastoma.

#### Age 5-9

On average, approximately 20 deaths from cancer occurred in this group per year, the lowest of all age groups. A significant decrease in the number of deaths (-4.1% per year) was observed from 1981 to 2000. The major cause of cancer death in this group was leukemia (34%), followed by brain cancer (31%) and neuroblastoma (11%).

Figure 18. Trends in Age-Adjusted Pediatric Mortality Rates, Florida and U.S., 1981-2000

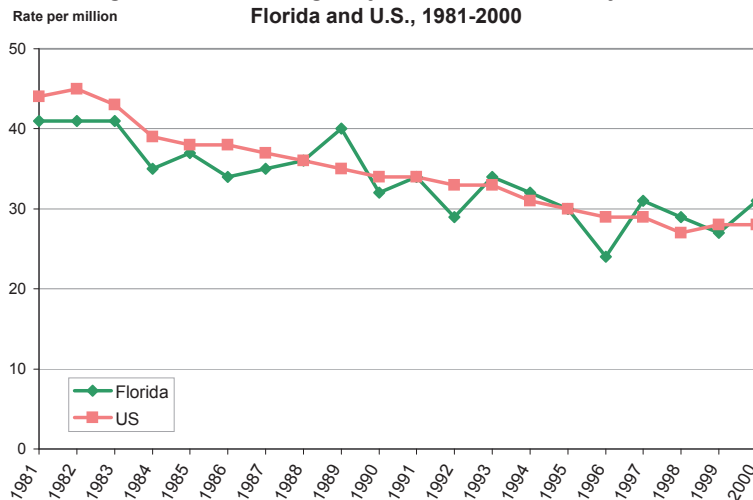
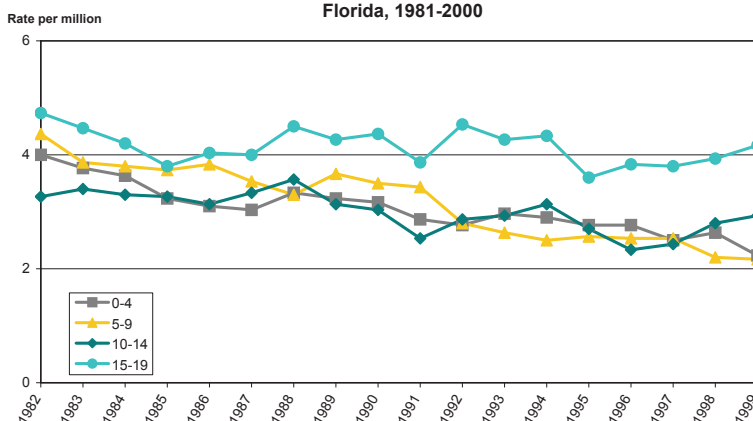


Figure 19. Pediatric Mortality, All Cancers by Age Group, Florida, 1981-2000



\* Trends are 3-year moving averages.

Age 10-14

The leading causes of cancer death in this group were: leukemia (38%), brain cancer (24%), bone cancer (12%), and NHL (8%). Cancer mortality showed a downward trend of -1.3 % per year. The decline was slower than among children younger than 10 years of age. Decreases in leukemia and NHL mortality were partially offset by a slight increase in brain cancer mortality.

Adolescents

In adolescents, leukemia was the leading cause of cancer death with 31% of malignant deaths, followed by bone cancer (15%), brain cancer (13%), NHL (8%) and soft tissue sarcoma (8%). No significant trend in mortality rate was observed for deaths among adolescents in Florida from 1981 to 2000.

RACE

Cancer mortality rates are 35 per million in Blacks and 33 per million in Whites compared to incidence rates of 123 per million in Blacks and 162 per million in Whites. Black children and adolescents are less affected by cancer in general but die more frequently from cancer than White children.

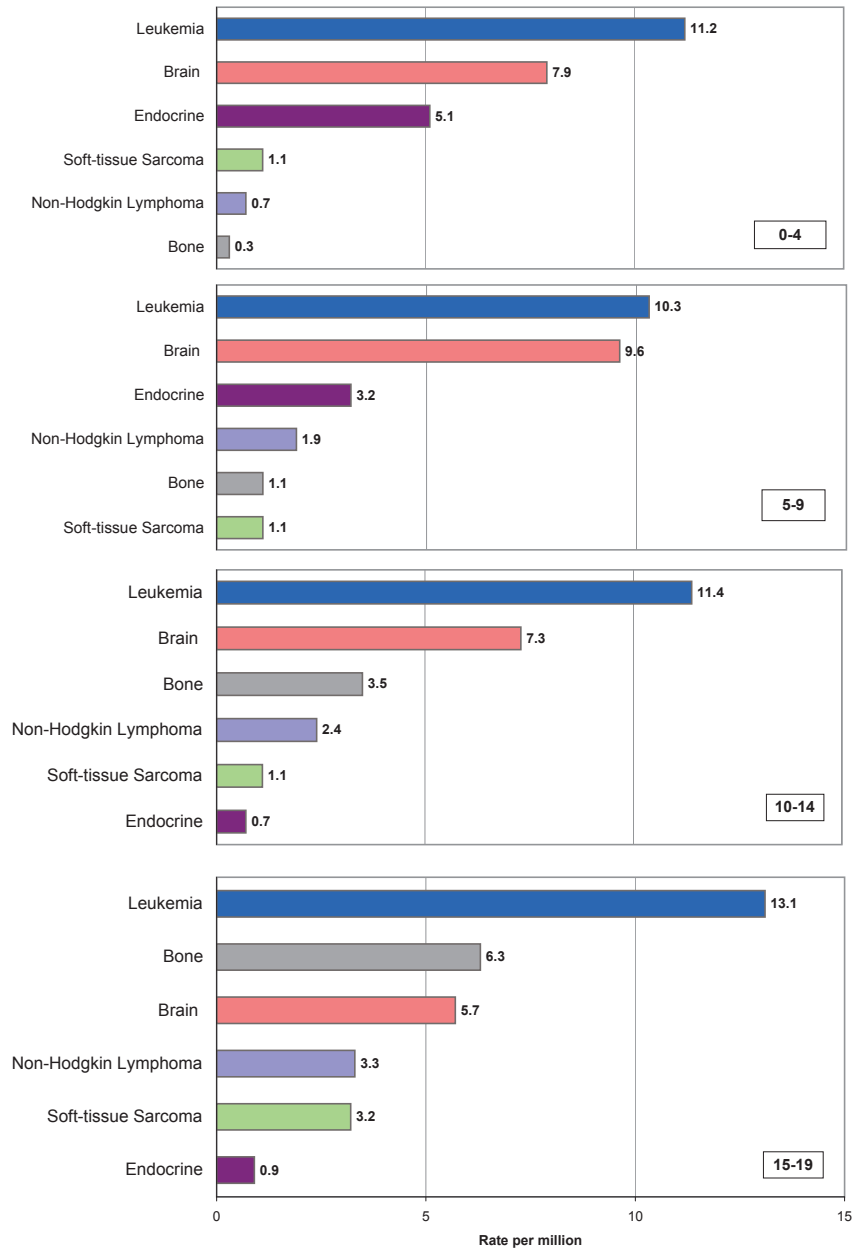
Cancer mortality rates for Whites declined significantly by -2.4% per year. In contrast, the mortality rates for Blacks remained unchanged. Differences in mortality trends are evident in the two most common causes of cancer death. For leukemia, the decrease in mortality was a remarkable -4.0% a year among Whites, whereas a non-significant decrease of -2.5% per year was observed among Blacks. For CNS tumors, the mortality rate was unchanged in Whites, but increased by +3.7% per year in Blacks.

MAIN CAUSES OF CANCER DEATH

Leukemia

One third (33%) of pediatric cancer deaths were caused by leukemia. There were a total of 727 deaths from leukemia in Florida from 1981 to 2000. Throughout this period, leukemia deaths decreased by 45%, with an average decrease of -3.6% per year, even though the incidence of leukemia increased by +0.8% per year in the same time period. The remarkable reduction in mortality occurred in all age groups in children: -5%, -6% and -3.2% per year in the 0-4, 5-9 and 10-14 age groups, respectively. Mortality remained stable in adolescents.

Figure 20. Age-Specific Mortality Rates of Leading Pediatric Cancers, Florida, 1981-2000





## Brain and other CNS

Brain tumors were the cause of 22% of pediatric cancer deaths. Overall, brain tumor mortality remained remarkably stable from 1981 to 2000. However, trends varied among racial groups. In Whites, a non-significant decline of -1% per year in brain cancer mortality was observed, whereas in Blacks, a significant increase of +3.7% per year has occurred. These mortality trends of -1.0 and +3.7 in Whites and Blacks contrasted with significantly increasing incidence trends of +1.2 and +2.2, suggesting remarkably disparate survival trends between races.

## TRENDS

In contrast to incidence, overall cancer mortality declined dramatically by -1.9 % per year from 1981 to 2000. This reduction resulted mainly from decreases in mortality for two diseases: leukemia decreased by -3.6% per year, and non-Hodgkin lymphoma decreased by -4.7 % per year. For NHL, the decrease in mortality occurred simultaneously with an increase in incidence of +3% a year, suggesting large gains in survival. Mortality rates for brain cancer, soft tissue sarcoma, bone cancer and neuroblastoma remained level despite significantly increasing incidence trends for both brain cancer (+1.4% per year) and neuroblastoma (+1.9% per year).

## SUMMARY OF CANCER MORTALITY IN FLORIDA

Mortality due to cancer in childhood and adolescence is relatively rare, accounting for 4.5% of all deaths in ages under 20. For every four cases of pediatric cancer diagnosed in the 1990s, three were alive after 5 years. Of the 2,833 deaths in children in Florida in 2000, the major causes of death were:

- Accidents, Homicides and Suicides (949)
- Conditions from the perinatal period (719)
- Congenital anomalies (331)
- Cancer (128).

Overall, the 1981-2000 Florida data show that age and race have an impact on mortality. Cancer claims more lives in adolescence than in childhood, and proportionately more Black children and adolescents than Whites.

Race is an unavoidable issue. Blacks have lower incidence but also lower survival and higher mortality than Whites. This disparity occurs concurrently with less favourable mortality trends in Blacks for leukemia and brain cancer.

Figure 21. Pediatric Mortality, All Cancers by Race, Florida, 1981-2000

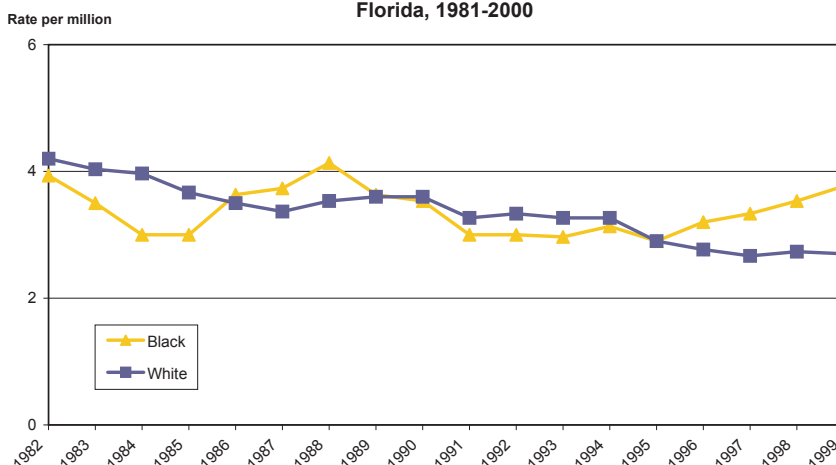
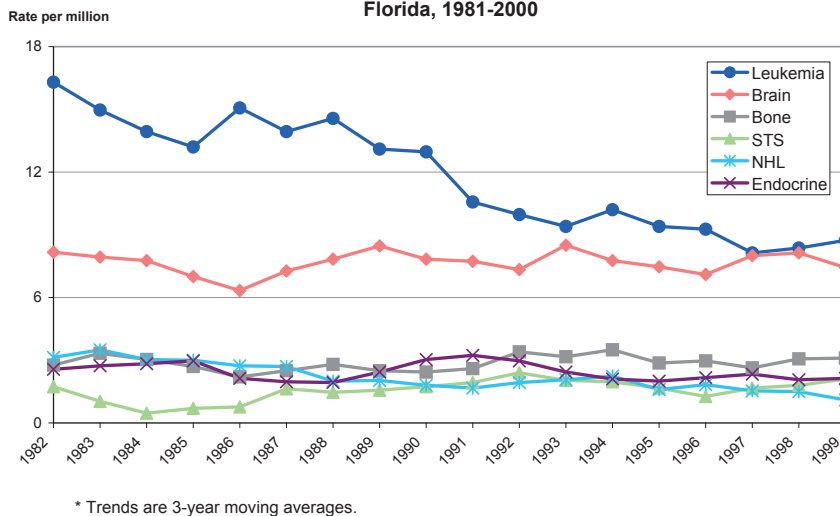


Figure 22. Trends in Age-Adjusted Mortality Rates of Selected Cancers Florida, 1981-2000



Over the years, progress in the fight against cancer has been comparatively more beneficial to young children than to adolescents. Accordingly, the Florida data also show a pattern of higher mortality with an unchanged trend for adolescents, compared to lower mortality and a decreasing trend in children. However, this phenomenon is not unique to Florida. Studies suggest more research and investment into new treatment preferentially targeting younger age groups as the main cause for this gap <sup>8,9</sup>.

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# ICCC I. LEUKEMIA

Leukemia, or better “leukemias”, cancers of the hematopoietic system, involve malignant transformation of either lymphoid or myeloid progenitor cells in the bone marrow. Leukemia is the most common cancer group in children and an important cause of pediatric cancer death. As a result it generates a lot of interest within the medical community, the media, and society at large<sup>1</sup>. Leukemia accounts for 31% of all cancer in children, and 15% in adolescents.

Between 1981 and 2000, an average of 136 new cases of leukemia occurred every year in Florida. Of these, approximately 101 were cases of acute lymphoid leukemia (ALL), 23 were acute myeloid leukemia (AML), and 4 were chronic myeloid leukemia (CML).

## AGE

In those younger than 15, the incidence rate for all types of leukemia in Florida was 45 per million per year. ALL accounted for 79% of the total cases of leukemia in childhood, AML for nearly 14% of cases, and CML for 1.8% of the total incident cases.

In adolescents, the overall rate of leukemia was much lower (26 cases per million), than in children (45 cases per million per year). ALL accounted for 50% of leukemia cases, AML for 34% and CML for 8%.

The incidence rate of ALL peaked in early childhood, and decreased in successive age groups. ALL was the leading form of leukemia in all age groups, although the rate for adolescents is less than half of that in children.

The variation in AML across age groups corresponded to a U-shaped curve, higher for those aged 0-4 and for adolescents, and slightly lower for the intermediate age groups 5-9 and 10-14.

CML is a rare cancer in children. The incidence rate in Florida was uniformly low, except in adolescence where the rate was 300% higher than in childhood.

Table I-1. Age-Adjusted Incidence Rates of Leukemia by ICCC Subgroup, Florida, 1981-2000

	Rate/Million	Count
Leukemia	40.3	2710
Acute lymphoid leukemia	29.9	2015
Acute myeloid leukemia	7.0	465
Chronic myeloid leukemia	1.2	78
Other specified leukemia*	0.8	51
Unspecified leukemia	1.5	101

\* Includes lymphoid leukemias that are not ALL.

Figure I-1. Age-Specific and Age-Adjusted Incidence Rates by ICCC Subcategory and Age, Florida, 1981-2000

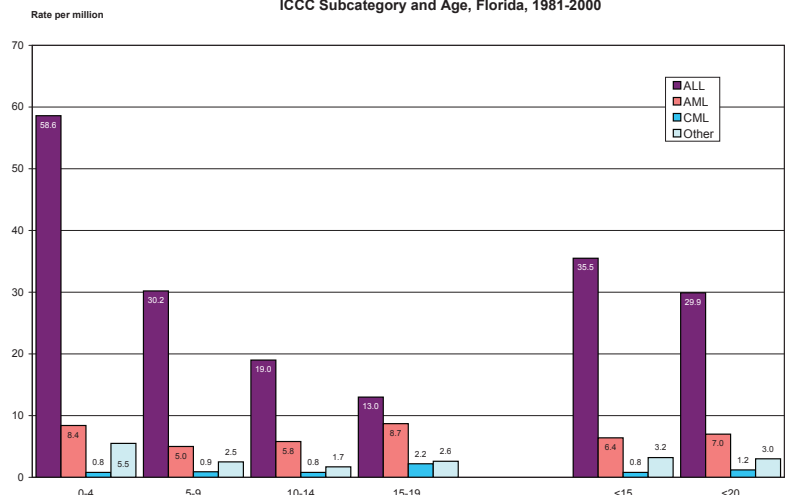
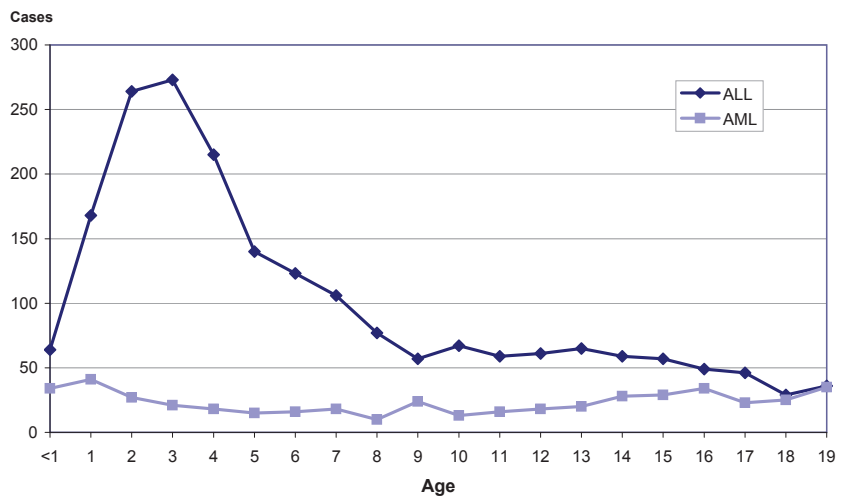


Figure I-2. ALL and AML by Age, Florida, 1981-2000



## SEX

Incidence rates for ALL were 27% higher in males than in females. The preponderance of ALL in males was present in all age groups and increased with age. In adolescents, ALL in males is 60% higher than in females. For AML, a higher rate for males was noted only for those younger than 10 years old. In those aged 10-14 and in adolescents, AML was more common in females. The opposite pattern was observed for CML. In those aged 0-9, CML was more common in females, whereas in those aged 10-19 it was more common in males.

## RACE

The incidence of leukemia was 50% higher in White children (44 per million) than in Black children (29 per million). Differences between White and Black children were more apparent in the youngest age group, 0-4 years old, for both ALL and AML. For ALL, the incidence rate for Whites was more than double that for Blacks in the age group 0-4, 79% higher in those 5-9 years old, and about 30% higher in those older than 10 years of age. For AML, differences of that magnitude were only observed in the age group 0-4, with an 86% excess for White children. CML was more common in Whites only in early childhood; in adolescence, rates were similar in both races.

## SEER

The Florida incidence rate was 40 per million for the period from 1981 to 2000, marginally higher than the rate in the SEER population, 38 per million. Most of that difference was due to the incidence rate for ALL, which was slightly higher in Florida than in the SEER population, 30 per million compared to 29 per million.

Figure I-3. Age-Specific and Age-Adjusted Incidence Rates by Sex, ALL, Florida, 1981-2000

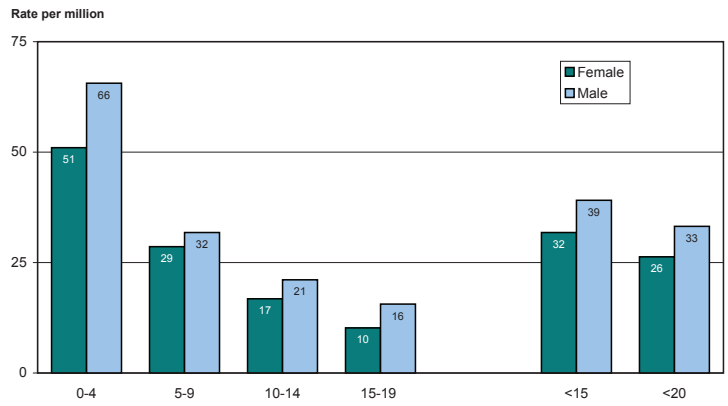


Figure I-4. Age-Specific and Age-Adjusted Rates of AML and CML by Sex, Florida, 1981-2000

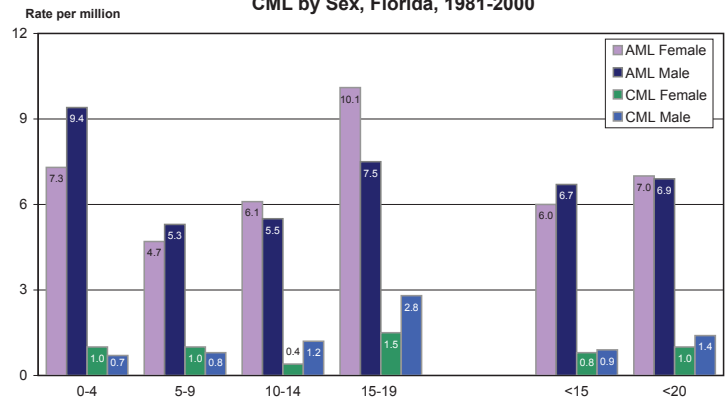


Figure I-5. Age-Specific and Age-Adjusted Incidence Rates of ALL by Race, Florida, 1981-2000

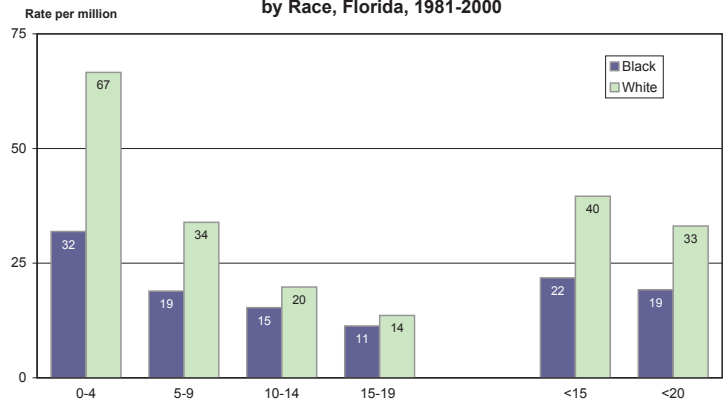
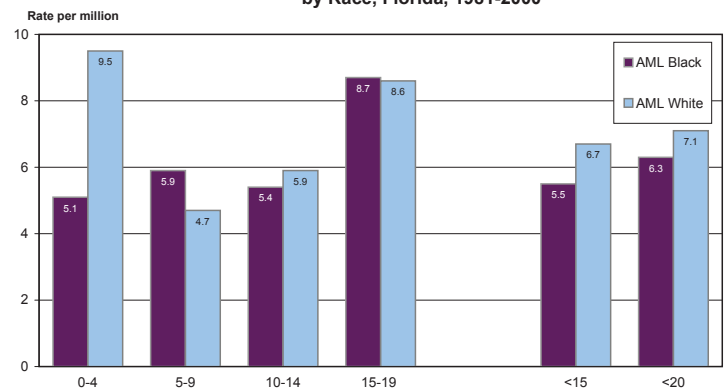


Figure I-6. Age-Specific and Age-Adjusted Incidence Rates of AML by Race, Florida, 1981-2000



The differences in incidence between Blacks and Whites in Florida were less marked than in the SEER population. This resulted from a slightly higher incidence of ALL in Black children in Florida (19 per million) in comparison to Black children in SEER (16 per million). In Whites, rates were 33 per million in Florida and 31 per million in SEER.

**TRENDS**

Unlike the rest of the US and Europe <sup>1</sup>, the incidence of ALL has not increased in Florida between 1981 and 2000; nor are there any clear trends by age group.

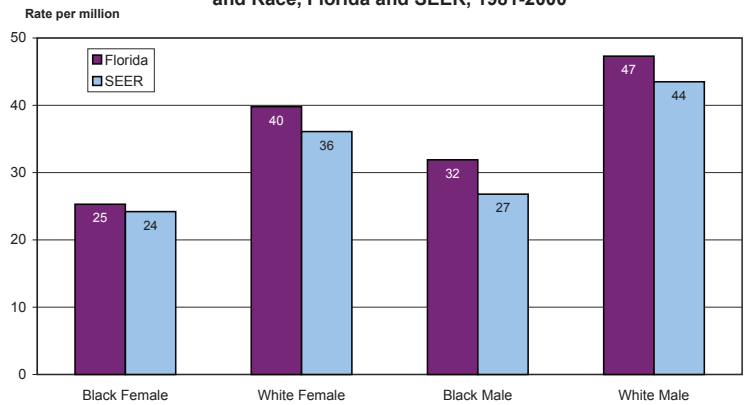
By contrast, the incidence of AML has increased in Florida, although not in a linear fashion. The increase was apparent in all age groups, and amounts to an overall average of +1.9% per year.

**SURVIVAL**

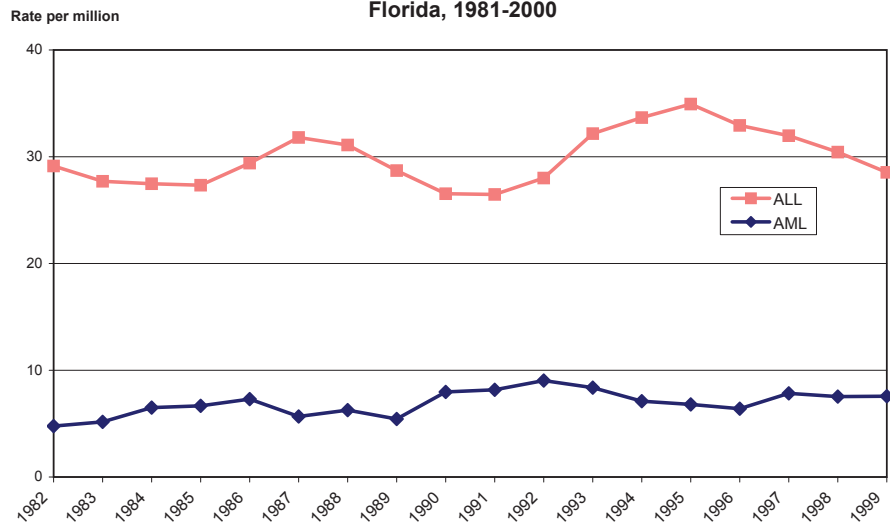
During the 1990s, survival for ALL, at 85% after 5 years, was remarkably higher than survival for AML, only 51%. Survival has shown a positive trend for both ALL and AML and across all age groups in Florida between 1981-1989 and 1990-1997. The increase in survival, also seen elsewhere in the Western world, is likely the result of improved approaches to treatment with the dissemination of randomized controlled trials results<sup>1</sup>. For AML, the increase in survival was exceptional in adolescents, from 28% in the 1980s to 52% in the 1990s. Survival for both diseases was higher in Whites than in Blacks, although more so for ALL (13 percentage points higher in Whites) than for AML (4 percentage points higher in Whites).

In the case of ALL, prognosis is very dependent on age at diagnosis (figure I-9). Survival was particularly low in infants aged 0-1, 55% after 5 years, and highest for those aged 1-4, 91% after 5 years. Above the age of 5, survival rates decreased with age to a low of 61% in adolescents.

**Figure I-7. Age-Adjusted Incidence Rates of Leukemia by Sex and Race, Florida and SEER, 1981-2000**

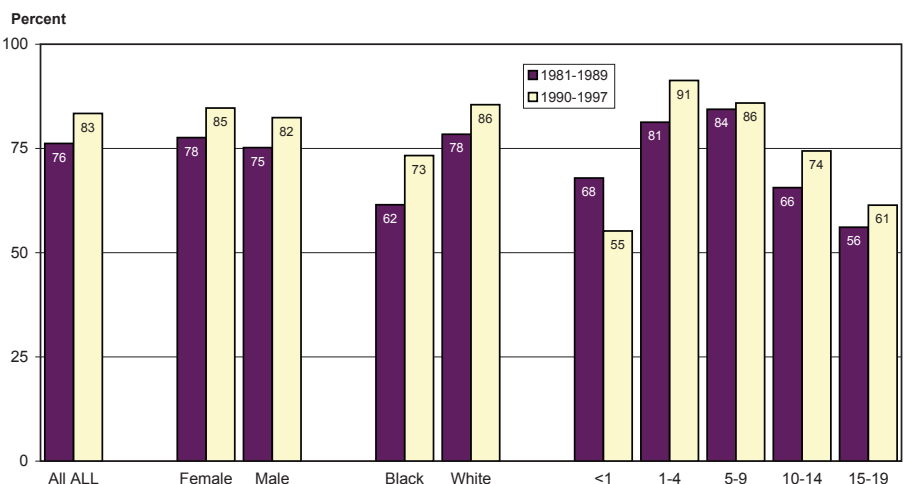


**Figure I-8. Trends in Age-adjusted Incidence Rates of ALL and AML, Florida, 1981-2000**



\* Trends are 3-year moving averages.

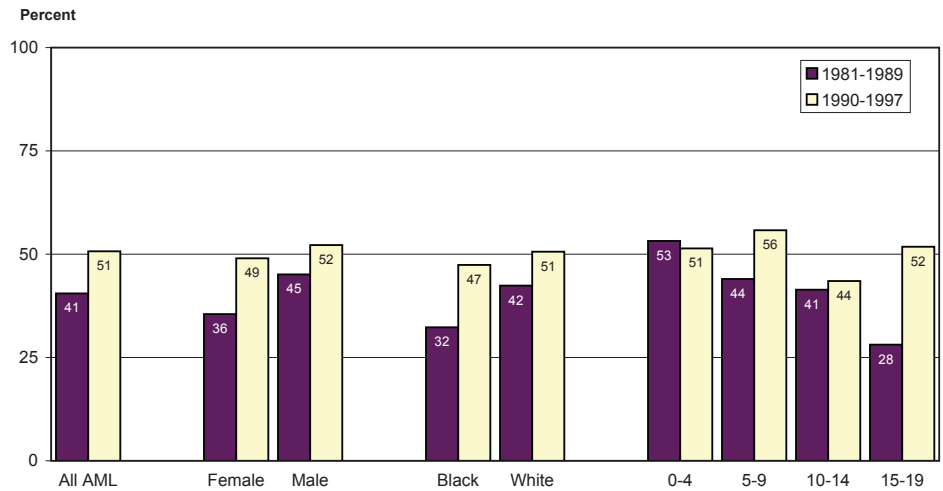
**Figure I-9. Five-year Survival for ALL, by Sex, Race, and Age, Florida, 1981-1989 and 1990-1997**



Lower survival may result from the nature of the malignancy in this age group or from differences in treatment approach. Recently, a benefit of the intensive pediatric protocol for ALL in adolescents has been demonstrated compared to the adult regimen <sup>2</sup>.

Despite the improvement in observed survival from the 1980s to the 1990s, AML remains one of the most fatal cancers in children. It was responsible for only 4.5% of pediatric cancers in 1981-2000 but for 9% of total cancer mortality. In comparison with SEER, survival rates for Florida are slightly higher, especially in the youngest age group of 0-4. Survival rates for AML do not vary substantially with age.

**Figure I-10. Five-year Survival for AML by Sex, Race, and Age, Florida, 1981-1989 and 1990-1997**



## RISK FACTORS

The etiology of childhood and adolescent leukemia remains largely unknown, although some evidence indicates that childhood leukemia may originate in utero. Genetic conditions such as Down syndrome, neurofibromatosis and Shwachman syndrome, among others, have been associated with increased risk of both ALL and AML <sup>3-6</sup>.

For ALL, ionizing irradiation such as in utero exposure to diagnostic X-rays and postnatal exposure to therapeutic doses has been firmly established as a risk factor <sup>7,8</sup>. However, this is likely to explain only a very small percentage of leukemia cases due to the low number of radiation treatments in children and diagnostic X-rays currently used in pregnant women.

Extensive research has taken place into the environmental etiology of childhood leukemia. Exposures such as parental insecticide use, parental medication use and smoking during pregnancy have all been associated with an increased risk of ALL in offspring <sup>9-11</sup>. However, since ALL is a rare disease, most evidence has been obtained from case-control studies in which the possibility of recall bias derived from increased awareness of risk factors among cases and controls may mean that the evidence is not as consistent as would be desired <sup>1</sup>. Electromagnetic fields (EMFs) in the area of residence have been found to increase the risk of pediatric ALL only to a very small degree, if any at all <sup>12</sup>.

More recently, reproductive risk factors have also shown varying degrees of association with ALL. Examples of these are increasing parental age at birth and smaller families <sup>13</sup>, as well as higher birth weights <sup>14</sup> with an increased risk of 1.26 per 1 kilogram at birth. The hypothesis of reduced exposure to infection in the first few months of life leading to reduced immunity has been increasingly studied as a plausible risk factor for ALL. Children in formal day care showed a diminished risk of 0.48 of developing leukemia in comparison with those with no regular activity outside the family <sup>15</sup>. Similarly, better housing is associated with delayed or reduced exposure to infection <sup>15</sup>. In view of these associations, it is not surprising that high socioeconomic status (SES) is thought to be a risk factor for ALL.

Overall, with the exception of in utero radiation exposure, all of the studied risk factors are of very low magnitude. Their attributable risks will be very low and account for very few cases. Nevertheless, trends in reproductive factors and diminished exposure to infections in children of high socio-economic status, may be partly responsible for increasing trends of ALL in populations of rising prosperity <sup>1</sup>.

Risk factors for childhood AML include ionizing irradiation in utero<sup>3,4,6</sup> and exposure to certain chemotherapeutic agents (alkylating and epipodophyllotoxins)<sup>3,4,6,16,17</sup>. Childhood cancer cases are frequently treated with chemotherapy and sometimes with radiotherapy. In Florida, AML is now the most common second cancer in childhood cancer survivors, and the risk of having AML after a first childhood cancer is 36 times higher than in the general pediatric population<sup>18</sup>. Secondary AML accounts for 5-10% of all new AML cases in those below age 20 in Florida<sup>18</sup>.

Other risk factors for AML include alcohol consumption during pregnancy<sup>3,4,6,19</sup>, and parental exposure to pesticides<sup>3,4,6,16,17,20</sup>.

The Philadelphia chromosome, an acquired genetic mutation represented by a translocation of chromosome 22 and chromosome 9, drives the leukemic changes in CML<sup>21,22</sup>. Ionizing radiation has been implicated in some cases, but in most individuals there is no known cause<sup>23,24</sup>. Individuals exposed to benzene or alkylating agents have a higher incidence of CML, probably because of mutagenic effects, just as with radiation<sup>25</sup>.

Table I-2. Current knowledge on causes of acute lymphoblastic leukemia (ALL)

Exposure or Characteristic	Comments	References
<i>Known risk factors</i>		
Sex	Overall, there is about a 30% higher incidence in males compared to females.	3,4,6
Age	There is a peak in the incidence between the ages of about 2 and 5.	3,4,6
Race	There is an approximate 2-fold higher risk in white children compared to black children.	3,4,6
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.	3,4,6,28
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.	3,4,6,28-30
Ionizing radiation postnatal (therapeutic)	Therapeutic radiation for such conditions as tinea capitis and thymus enlargement has been associated with an increased risk.	3,4,6,31
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.	3-6
<i>Factors for which evidence is suggestive but not conclusive</i>		
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.	3,4,6,32
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.	3,4,6,26,32
Maternal age > 35 at pregnancy	A slight increased risk has been somewhat inconsistently associated with older maternal age.	3,4,6



First born or only child	Slight increased risk reported but birth order may be surrogate marker for exposure to infectious agent.	3,4,6
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.	3,4,6,20,34-38
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.	3,4,6
Postnatal infections	Evidence is very inconsistent.	3,4
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.	39,40
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.	3,4,41-44
Vitamin K prophylaxis in newborns	Although an increased risk of ALL was first reported in the early 1990s, several large studies since then have found no association.	3,4, 45-50
Maternal alcohol consumption during pregnancy	Unlikely to be an important risk factor for ALL (but see AML).	3,4
Postnatal use of chloramphenicol	One study reported quite substantial increased risks (approximately 10-fold) with postnatal use of this broad-spectrum antibiotic.	51
<i>Factors unrelated to risk</i>		
Ultrasound		3,4

Table I-3. Current knowledge on causes of acute myeloid leukemia (AML)

Exposure or Characteristic	Comments	References
<i>Known risk factors</i>		
Race (ethnicity)	The highest incidence rates are reported in Hispanic children.	3,4,6
Chemotherapeutic agents	Increased risk is associated with prior exposure to alkylating agents or epipodophyllotoxins.	3,4,6,16,17
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.	3,4,6
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.	3-6
<i>Factors for which evidence is suggestive but not conclusive</i>		
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.	3,4,5,52
<i>Factors for which evidence is inconsistent or limited</i>		
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.	3,4,6,20,27

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.	3,4,6,20
Maternal use of recreational drugs during pregnancy	One report suggested that maternal marijuana use during pregnancy was associated with increased risk.	53
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.	3,4,6
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.	51

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# ICCC II. LYMPHOMA AND RETICULOENDOTHELIAL NEOPLASMS

This group of neoplasms constitutes the third most common group of malignancies in childhood and adolescence. From 1981 to 2000, 1,539 cases of lymphoma were diagnosed in Florida; 768 were cases of Hodgkin lymphoma (HL), 451 of non-Hodgkin lymphoma (NHL), 185 of Burkitt lymphoma and 135 of miscellaneous and unspecified lymphomas. The incidence of lymphoma rose with age starting at 10 cases per million in the 0-4 age group, 16 per million in those aged 5-9, 23 per million in those 10-14, and 44 per million in adolescence. This variation is due to the increase of all types of lymphomas with age, particularly HL.

Unlike the distribution in adults, HL is more common than NHL in childhood and adolescence. Figure II-3 shows lower age-adjusted incidence rates for HL in Florida than in SEER across all sex and race groups. In contrast, Figure II-8 shows that the rates of NHL are slightly higher in Florida.

## HODGKIN LYMPHOMA

HL is a malignancy of the lymphatic system characterized by the presence of Reed-Sternberg cells, a type of malignant B-lymphocyte in the diseased tissues. HL accounted for 10% of all pediatric cancers and 50% of all lymphomas reported in Florida in age groups less than 20 years old.

Epidemiological patterns suggest that HL comprises multiple separate entities. The two main forms are distinguished by the expression of the Epstein-Barr Virus (EBV) genome in the Reed-Sternberg cells. The form showing this expression tends to present histologically as mixed cellularity and predominates in young children, especially males. This form is also more prevalent in developing countries, and is associated with less favorable socioeconomic conditions <sup>1</sup>.

The other form of HL presents as nodular sclerosis, does not seem to be related to the EBV virus, and has been associated with better socioeconomic conditions and a delayed exposure to common infectious agents <sup>2</sup>.

Nodular sclerosis constituted the vast majority of cases in Florida, 79% of those for which a variant for HL was specified. Mixed cellularity constituted 21% of the total of variant-specified cases, and was more common in males (26%) than in females (13%).

Table II-1. Number and Percent of Lymphoma by Sex and ICCC Subcategory, Florida, 1981-2000

	Florida	Female	%	Male	%
All Lymphoma	1539	603	39.2	936	60.8
II(a) Hodgkin	768	361	47.0	407	53.0
II(b,c,e) Non-Hodgkin	743	228	30.7	515	69.3
II(d) Miscellaneous	28	14	50.0	14	50.0

Figure II-1. Age-Specific and Age-Adjusted Incidence Rates of Lymphoma by ICCC Subcategory, Florida, 1981-2000

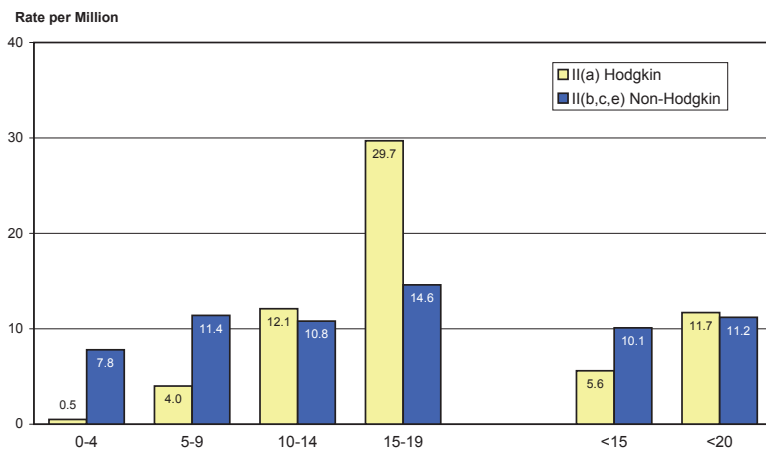
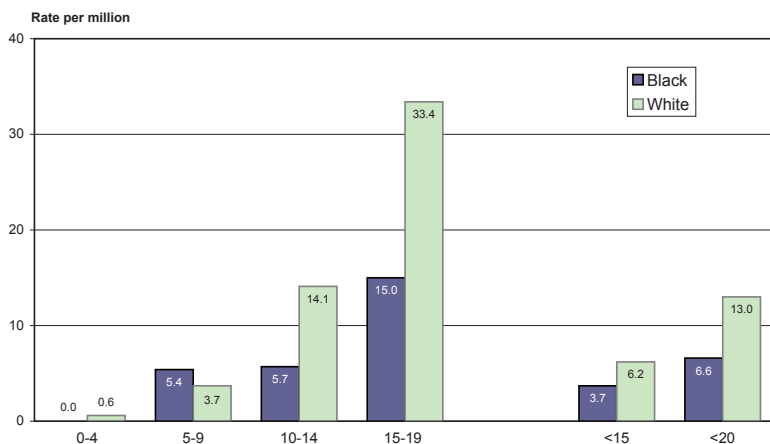


Figure II-2. Age-Specific and Age-Adjusted Incidence Rates of Hodgkin Lymphoma by Race, Florida, 1981-2000



The incidence of nodular sclerosis and mixed cellularity both increased with age, but the relative weight of mixed cellularity cases was much higher in the age groups below 10 years of age.

## AGE

HL is very rare in early childhood. Overall incidence rates increased markedly with age, less than 1 case per million in the 0-4 age group, rising to 4 per million, 12 per million and 30 per million in successive age groups.

## SEX AND RACE

No major difference was observed in the incidence of HL by sex. The incidence rate of HL in Whites, 13 per million, was nearly double that of Blacks, 7 per million.

## SEER

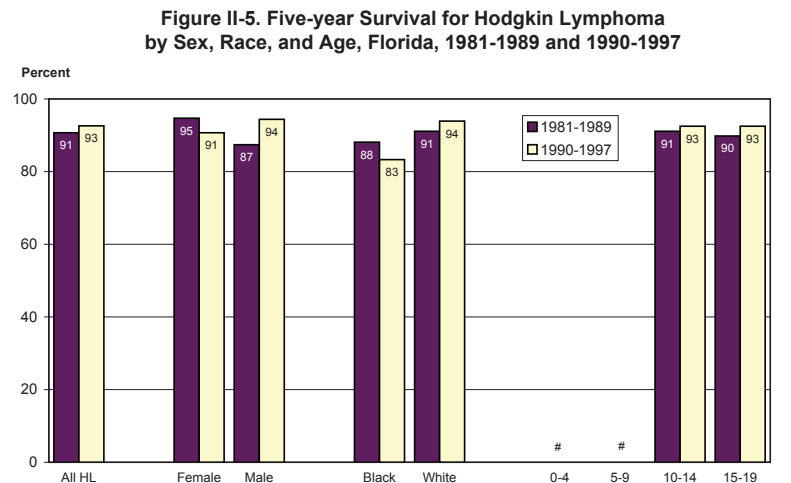
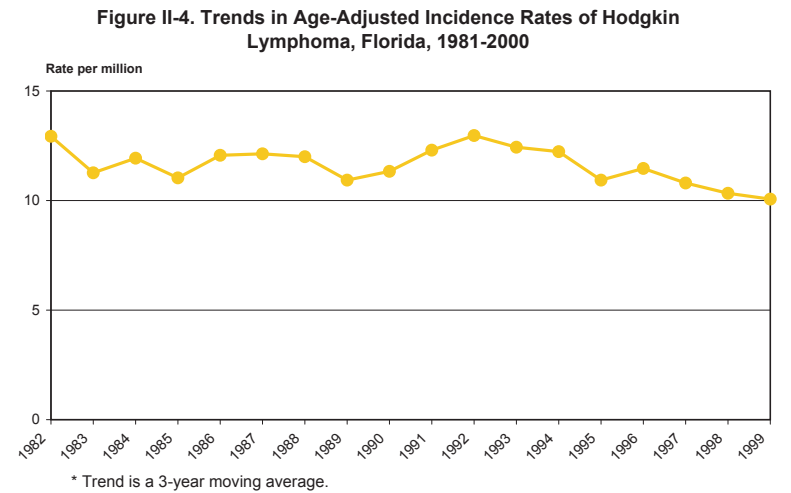
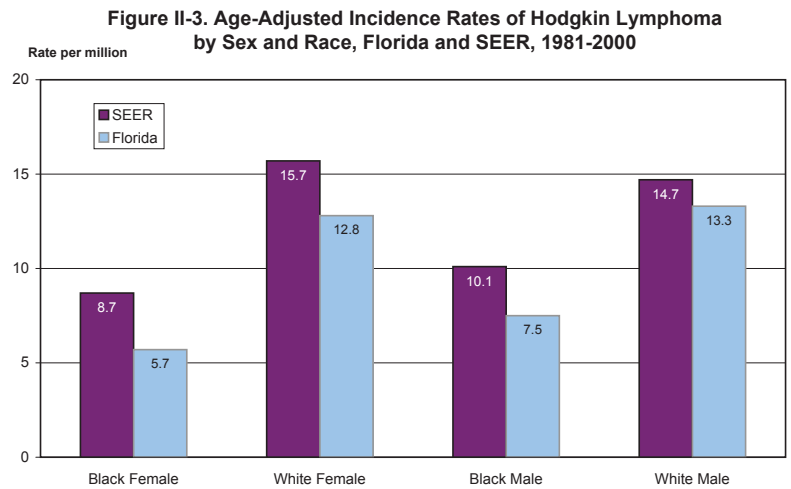
The incidence rate of HL in Florida was significantly lower than in SEER, 11.7 and 13.4 per million respectively. Significantly lower rates were observed in both Blacks, 42% lower, and Whites, 16% lower than in the SEER areas.

## TREND

Although no statistically significant trend in HL was observed throughout the period from 1981 to 2000 in Florida, Figure II-4 shows a clear decrease in incidence rates from 1992 to 2000 in Florida, Figure II-4 shows a clear decrease in incidence rates from 1992 to 2000. In the early 1980s the overall rate was 15 per million whereas in the late 1990s it was 10 per million. SEER reported a decrease from 15 per million in 1975 to 12 per million in 1995<sup>3</sup>.

## SURVIVAL

Currently, HL may be considered a malignancy of very good prognosis, as shown by very high survival rates, 93% after 5 years. There was a 2 percentage point increase in overall survival rate from the period 1981-1989 to 1990-1997 in both sexes. Whites showed a survival advantage over Blacks which increased from the 1980s to the 1990s. The most recent survival rates were 83% for Blacks and 94% for Whites. This disparity is better conveyed by comparing the incidence-mortality ratio, which is 2.8 times higher in Whites than in Blacks.



## RISK FACTORS

Genetic factors appear to be the major causal factors, as evidenced by the strong concordance in occurrence of HL in monozygotic twins <sup>4</sup>, familial aggregations <sup>5</sup>, and inter-ethnic variability of incidence <sup>6</sup>. EBV is thought to be the infectious agent responsible for HL in a proportion of cases. EBV is an ubiquitous virus yet very few people develop this malignancy <sup>7</sup>. So, clearly other factors must play a role in the genesis of HL.

Table II-2. Current knowledge on causes of Hodgkin disease

Exposure or Characteristic	Comments	References
<i>Known to increase risk</i>		
Family history of Hodgkin disease	Monozygotic twins of young adult patients have a 99-fold increased risk. Other siblings have a 7-fold increased risk.	4,28,29
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.	13-19, 29-31
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.	6,32-34
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.	17,27
<i>Factors for which evidence is inconsistent or limited</i>		
Clustering	Young adult cases (age 16-45 years) tend to cluster more than older cases	35

## NON-HODGKIN LYMPHOMA, BURKITT LYMPHOMA AND OTHERS

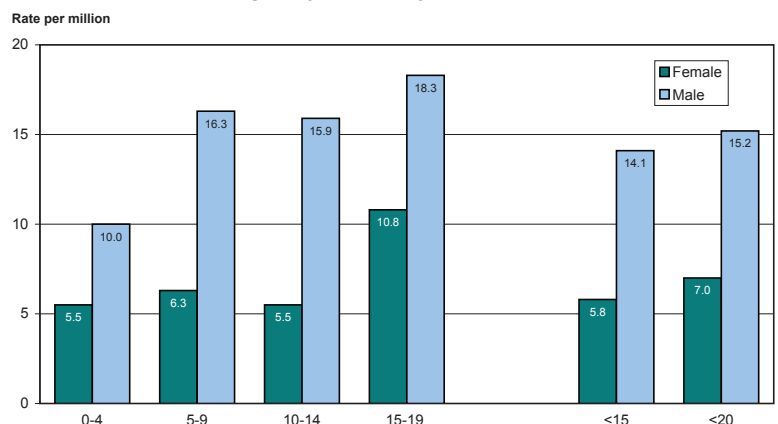
This pooled group of non-Hodgkin lymphomas comprises the following diagnostic subgroups of the International Classification of Childhood Cancer: non-Hodgkin lymphoma (NHL) (IIb), Burkitt lymphoma (BL) (IIc), and unspecified lymphomas (IIe). NHL, BL and unspecified lymphomas are a heterogeneous group of malignant tumors, representing 7.3% of the total of malignancies in Floridians younger than 20 years of age from 1981 to 2000 and corresponding to a total of 743 cases.

This group of malignancies, NHL, is the only numerically important cancer in which a significant increase in incidence has occurred in both adults<sup>8</sup> and children<sup>9</sup> between the 1980s and 1990s worldwide.

### AGE

The incidence of NHL was lowest in young children, 8 cases per million, increased in the groups between 5-14, and was highest in adolescents, with a rate of 15 per million (see Figure II-1).

Figure II-6. Age-Specific and Age-Adjusted Incidence Rates of non-Hodgkin Lymphoma by Sex, Florida, 1981-2000





**SEX**

Unlike HL, this cancer was 2 to 3 times more common in males than in females. This male predominance of NHL was evident across all age groups. Burkitt lymphoma stands out, compared to other forms of NHL, with males showing a much higher incidence than females, and with male-to-female ratios above 5 to 1 for ages 5-14.

**RACE**

NHL was more common in Whites than in Blacks except in adolescents, for whom rates were similar between the races. The difference between races was more apparent for Burkitt lymphoma for which Whites had an incidence 3 times higher than Blacks.

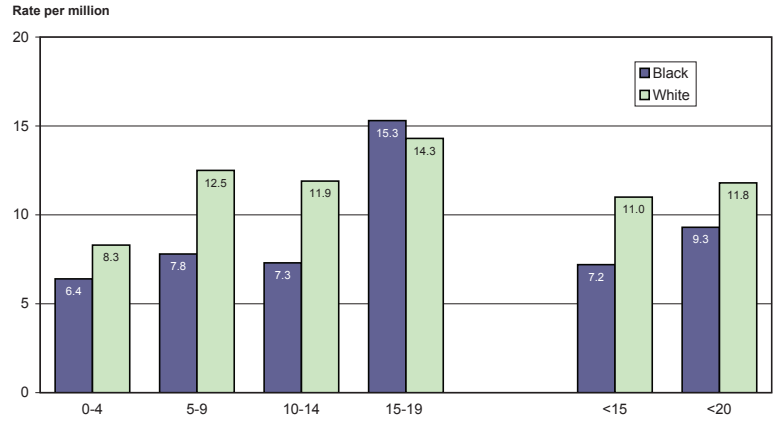
**SEER**

The incidence of NHL was higher for Blacks in Florida than for the SEER population, 9.3 cases per million compared to 7.6 cases per million in SEER. For Whites, the difference in incidence was much smaller: 11.8 cases per million in Florida and 11.0 per million in SEER.

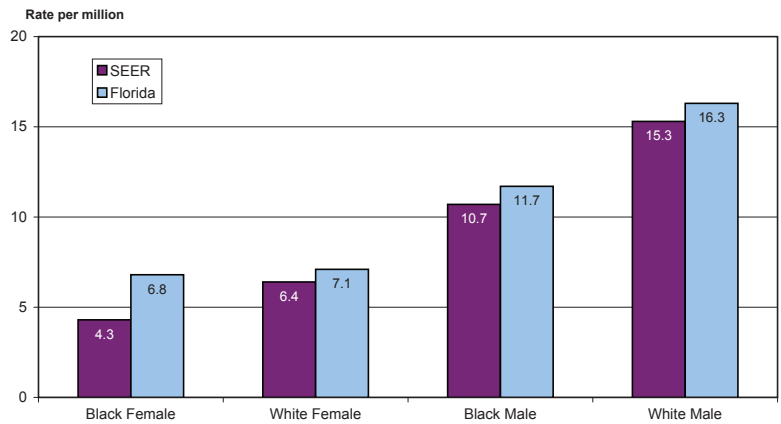
**TREND**

An increasing trend in childhood and adolescent NHL is obvious in the Florida population from 1981 to 2000. The incidence rate increased from 8 per million in 1981 to 14 per million in 2000. The overall trend is +3.1 % a year, with statistically significant increases in those aged 0-4, +4.9% per year, and in adolescents, +3.9% per year. Increases have been reported elsewhere, although less marked than in Florida <sup>9</sup>. The cause of this increase is unknown.

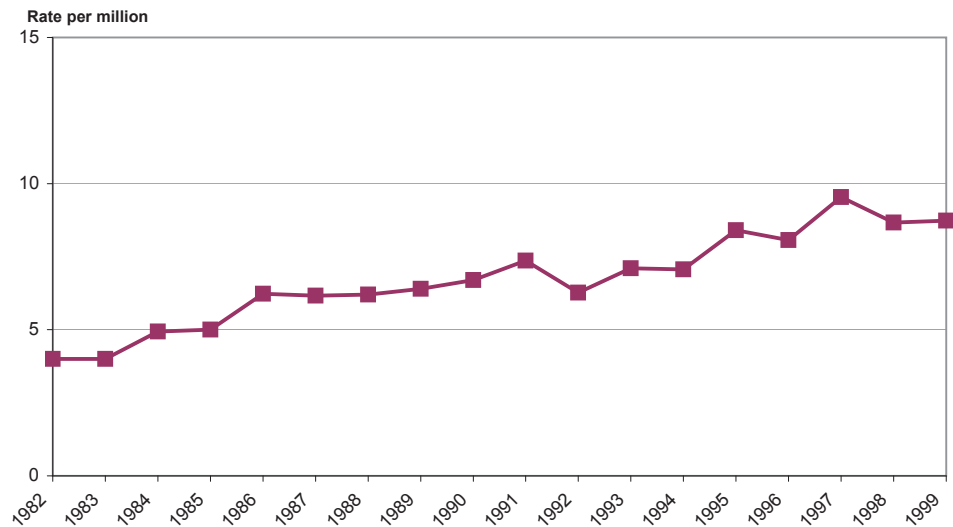
**Figure II-7. Age-Specific and Age-Adjusted Incidence Rates of non-Hodgkin Lymphoma by Race, Florida, 1981-2000**



**Figure II-8. Age-Adjusted Incidence Rates of non-Hodgkin Lymphoma by Sex and Race, Florida and SEER, 1981-2000**



**Figure II-9. Trend in Age-Adjusted Incidence Rate of NHL, Florida, 1981-2000**

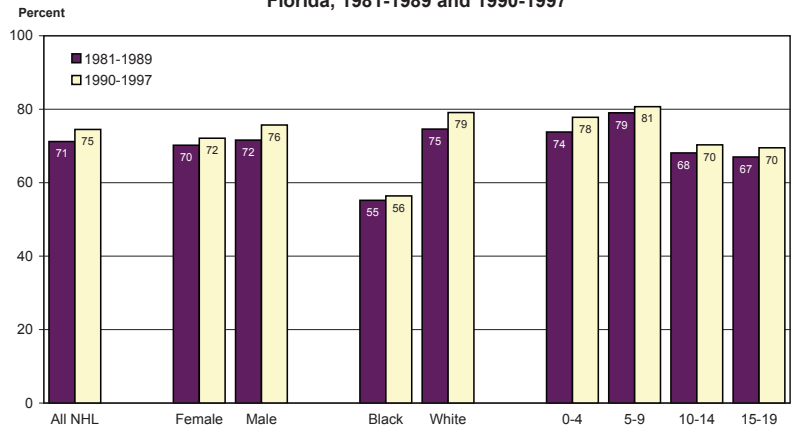


\* Trend is a 3-year moving average.

## SURVIVAL

Overall 5-year survival rates for NHL were slightly higher in males, 76%, than in females, 72%. This may be due to the different case mix of Burkitt lymphoma since this cancer is very responsive to polychemotherapy<sup>10</sup>. A modest improvement in survival rates after 5 years for NHL was observed between the 1980s (71%) and the 1990s (75%) in Florida. This favorable trend also occurred elsewhere, and has been attributed to improved treatment<sup>11</sup>. The ever-present survival disparity for Blacks was very marked for NHL, and widened from the 1980s to the 1990s. Overall survival rates for the more recent period, 1990-1997, were 87% in Whites compared to 68% in Blacks. Adolescents showed lower survival than younger children: 70% after 5 years compared to 80% for children aged 0-9.

Figure II-10. Five-year Survival for NHL by Sex, Race, and Age, Florida, 1981-1989 and 1990-1997



## RISK FACTORS

The major known risk factor for NHL is viral infection of the immune system by either the human immunodeficiency virus (HIV) or the Epstein Barr virus (EBV) (see table II-3). Genetic pathways in the pathogenesis of NHL cannot be discounted, notably the translocation of Myc in the case of Burkitt lymphoma, although this is not entirely specific and occurs in other histologic subtypes of lymphoma<sup>10</sup>. The environmental association most often found for NHL is residential pesticide exposure<sup>12</sup>. Still, none of the major established risk factors seem to have played a role in the increasing incidence of NHL<sup>9</sup>.

Table II-3. Current knowledge on causes of Non-Hodgkin lymphoma (NHL)

Exposure or Characteristic	Comments	References
<i>Known risk factors</i>		
Immunodeficiency	Immunosuppressive therapy, congenital immunodeficiency syndromes (e.g., ataxia telangiectasia), acquired immunodeficiency syndrome (AIDS) all predispose to NHL.	20-23,36-37
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.	23-26,38-39
<i>Factors for which evidence is inconsistent or limited</i>		
Radiation	While a few studies report increased NHL risk in adults or children with ionizing or electromagnetic field (EMF) radiation, others report no association.	40-44

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# ICCC III. CENTRAL NERVOUS SYSTEM AND MISCELLANEOUS INTRACRANIAL AND INTRASPINAL NEOPLASMS

Malignant neoplasms of the central nervous system (CNS) accounted for 18% of pediatric cancers in Florida from 1981 to 2000. They were the largest group of solid tumors in children and the second most common cancer after leukemia, with a rate of 27 cases per million. During the same period, CNS tumors were the second leading cause of death from cancer in children and adolescents, accounting for 22 % of cancer deaths. CNS neoplasms are a heterogeneous group of cancers of different histology and prognosis. According to the ICCC the main diagnostic groups are:

- ependymomas (IIIa)
- astrocytomas (IIIb)
- primitive neuroectodermal tumors (PNET) including medulloblastoma (IIIc)
- other gliomas (IIId)
- miscellaneous (IIIe)
- unspecified cases (IIIf).

Data in this report comprise solely CNS tumors classified as malignant and primary, that is, originating in the CNS. Tumors of benign and uncertain behavior were not collected by FCDS between 1981 and 2000, and are not part of this report. Neuroblastomas and germ-cell intracranial tumors are additional neoplasms which may occur in the CNS, but are classified separately by ICCC and are dealt with in separate chapters of this report.

Table III-1. Numbers and Percents of CNS Neoplasms by Age and ICCC Subcategory, Florida 1981-2000

	0-4	%	5-9	%	10-14	%	15-19	%	<15	%	<20	%
III CNS	576	100.0	528	100.0	418	100.0	310	100.0	1,522	100	1,832	100.0
IIIa Ependymoma	60	10.4	28	5.3	29	6.9	31	10.0	117	8	148	8.1
IIIb Astrocytoma	269	46.7	251	47.5	238	56.9	170	54.8	758	50	928	50.7
IIIc PNET	151	26.2	141	26.7	71	17.0	38	12.3	363	24	401	21.9
IIId Other gliomas	70	12.2	82	15.5	66	15.8	47	15.2	218	14	265	14.5
IIIe,f Other CNS	26	4.5	26	4.9	14	3.3	24	7.7	66	4	90	4.9

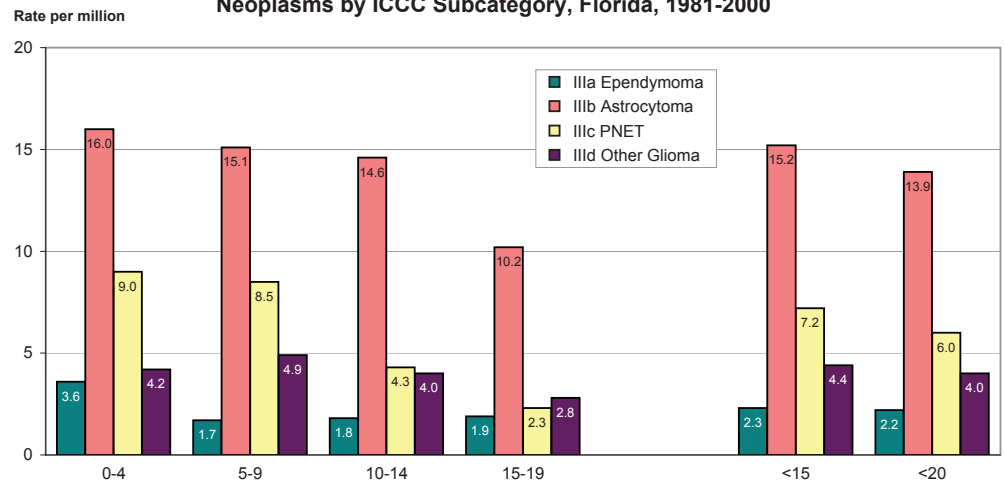
From 1981 to 2000, there were 1,825 malignancies of the CNS registered in Florida. Astrocytomas accounted for 51% of these cases, whereas 20% were primitive neuroectodermal tumors (PNET) including medulloblastoma, 15% other gliomas, and 8% ependymomas. The remaining 6% of cases were miscellaneous and unspecified cases of CNS tumors.

## AGE

Malignancies of the CNS tend to occur at different locations depending on age. Neoplasms of the brain stem and cerebellum were more common in children younger than 10. In children aged 10 and older, cerebral tumors comprised the vast majority of tumors, as is the case in adults.

The incidence of CNS tumors as a group decreased with age from

Figure III-1. Age-Specific and Age-Adjusted Incidence Rates for CNS Neoplasms by ICCC Subcategory, Florida, 1981-2000



34 per million in those aged 0-4, to 32 per million in those 5-9, 26 per million in the 10-14, and 19 per million in adolescents.

Astrocytomas and gliomas showed relatively constant rates throughout childhood, 15 and 4 per million respectively, both decreasing in adolescence. Ependymomas were mostly tumors of early childhood, two times more common in the 0-4 age group, 4 cases per million, than in those aged 5 and above. PNETs were relatively common in those less than age 10, 8 cases per million, decreased in the 10-14 age group, and were very rare in adolescents.

**SEX**

CNS tumors were more common in males than in females across all age groups and histological subtypes. That excess, however, never exceeded 25 percent.

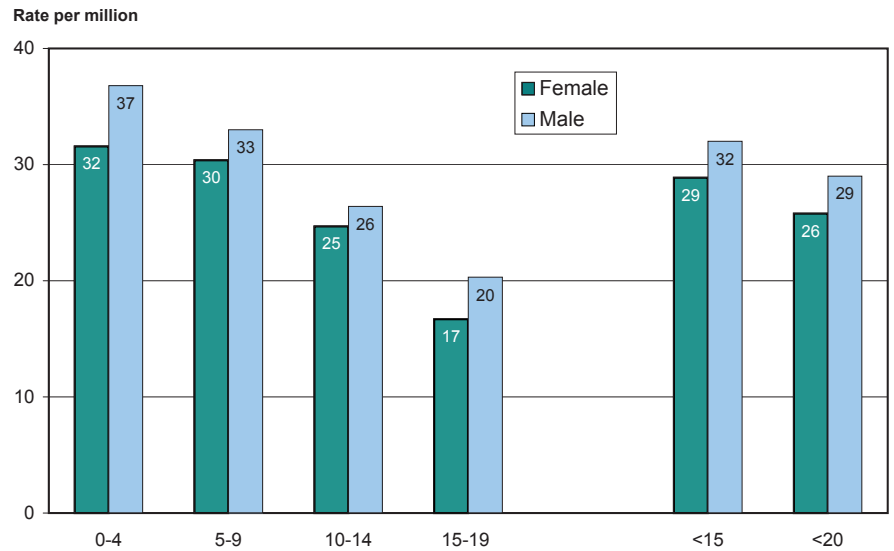
**RACE**

The incidence of CNS tumors was 29 per million for Whites, 32% higher than the rate in Blacks, 22 cases per million. By subgroup, PNETs (65% higher), astrocytomas (38% higher), ependymomas (22% higher) and gliomas (14% higher) were all more common in Whites than in Blacks.

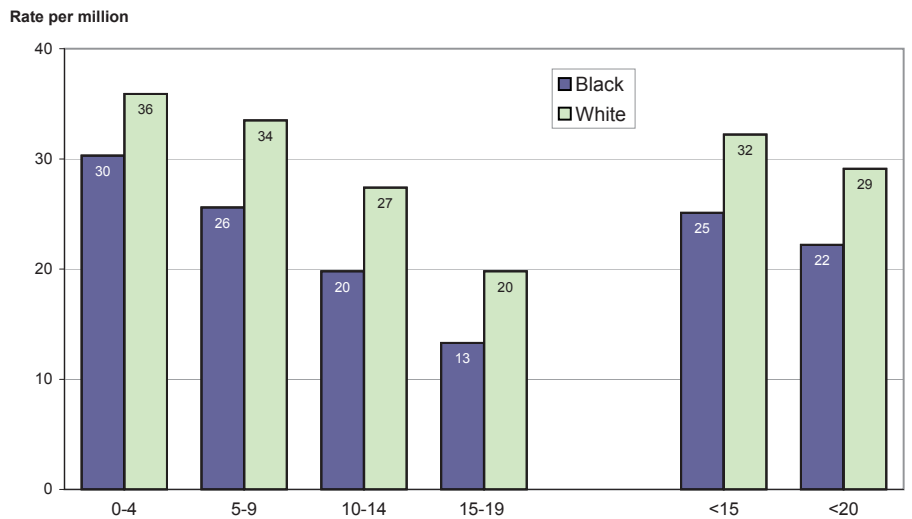
**SEER**

The incidence rates in Florida by race, age group and sex were very similar to those in the SEER areas, as were the proportions by histological subtype. Such similar rates suggest the importance of the genetic component in the genesis of CNS tumors, and/or a uniform distribution of environmental risk factors in the United States.

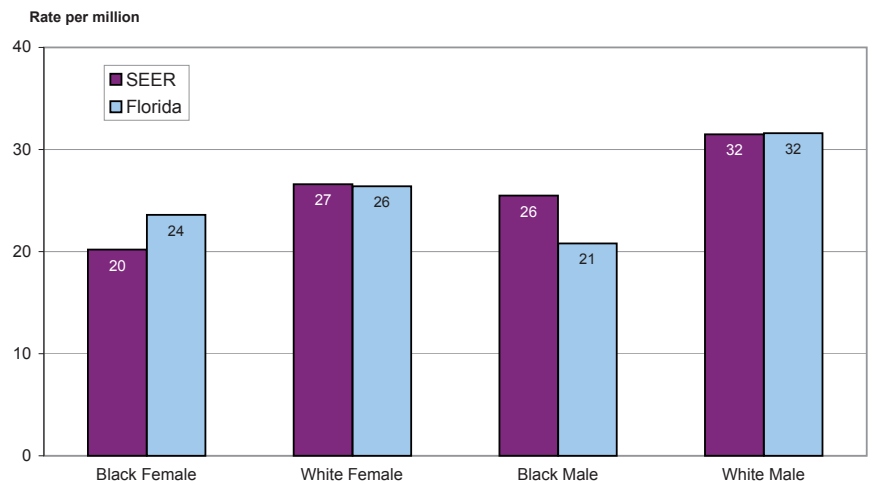
**Figure III-2. Age-Specific and Age-Adjusted Incidence Rates of CNS Neoplasms by Sex, Florida, 1981-2000**



**Figure III-3. Age-Specific and Age-Adjusted Incidence Rates of CNS Neoplasms by Race, Florida, 1981-2000**



**Figure III-4. Age-Adjusted Incidence Rates of CNS Neoplasms by Sex and Race, Florida and SEER, 1981-2000**



## TRENDS

CNS tumor incidence increased significantly from 1981 to 2000, with an average annual percent change of +1.4%. In particular, the gliomas group showed a 3.5% annual increase. Other significant increases occurred for PNETs, +2.1 % per year, and astrocytomas, +1.2 % per year. The increasing trends in these subgroups were partly due to more detailed diagnoses in the latter part of the period analyzed as shown by the trend in the rates of miscellaneous and unspecified cases, which were lower in more recent years. The incidence of ependymomas remained stable.

An increasing trend has also been observed in the SEER population and abroad, and has coincided with the increased availability of magnetic resonance imaging<sup>1</sup>. It has been hypothesized that the increasing incidence rates for CNS tumors may be due to improved detection and reporting during the 1980s. The impact of any simultaneous environmental exposure responsible for an increasing incidence will therefore be difficult to assess<sup>2</sup>.

## SURVIVAL

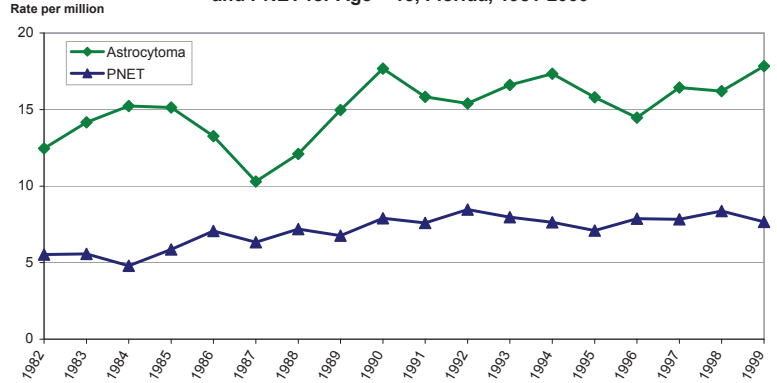
Overall, no improvement in survival rates was observed between the 1980s and the 1990s. Five-year survival for CNS tumors in Florida was 70%, slightly higher than that in SEER areas. The difference in survival rates between sexes was not meaningful. However, by race, as for many other cancers in Florida, the difference was substantial: 10 percentage points higher for Whites than for Blacks from 1990 to 1997. This difference was larger than that observed for cases diagnosed in the 1980s.

Survival was higher for astrocytoma than for the other histologic subgroups. During the study period, this group included some low-grade malignancies such as juvenile pilocytic astrocytoma, which was the most common CNS tumor and accounted for 20% of CNS cases.

Contrary to other childhood cancers, 5-year survival after diagnosis of a CNS tumor was lowest in early childhood (62%), increasing successively in those aged 5-9 (72%) and 10-14 (76%), then decreasing again in adolescence (71%).

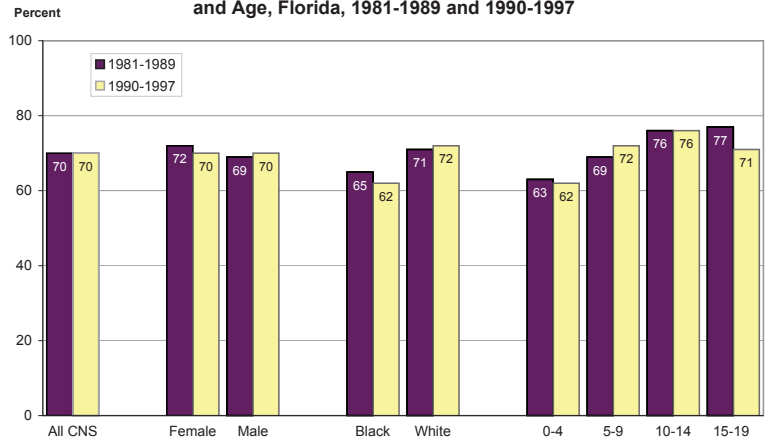
Early childhood poses specific problems in the treatment of CNS tumors. First, this age group shows a higher proportion of ependymomas and PNETs, subtypes which have lower survival rates since they tend to metastasize much earlier than the other types. Second, diagnosis may be delayed in this age group, as CNS tumors may show only non-specific symptoms<sup>3</sup>. Additionally, in terms of treatment, the attempt to preserve vital structures and important brain regions, results in a lower overall rate of complete tumor resection in this group<sup>4</sup>. Finally, neurocognitive sequelae, radiation vasculopathy, and secondary tumors are all known late-effects of radiotherapy in this age group. As a result, in order to minimize serious late effects, treatment protocols tend to avoid or delay radiotherapy in young children which may prevent the use of the most effective therapy<sup>5,6</sup>.

Figure III-5. Trends in Age-Adjusted Incidence Rate of Astrocytoma and PNET for Age < 15, Florida, 1981-2000



\* Trends are 3-year moving averages.

Figure III-6. Five-Year Survival for CNS Neoplasms by Sex, Race, and Age, Florida, 1981-1989 and 1990-1997





## RISK FACTORS

From a population perspective, known inherited genetic factors explain only a small percentage of childhood CNS cancer incidence. Conditions such as neurofibromatosis type 1, nevoid basal cell syndrome and tuberous sclerosis are associated with increased susceptibility to CNS cancer in children <sup>7,8</sup>.

Historically, studies on childhood brain cancers have suffered from the fact that while risk factors may vary for each histologic subtype, brain tumors have been studied as a whole. Given that each subtype is rare, it is difficult to assemble enough cases for epidemiologic research <sup>2</sup>.

The most relevant risk factor is ionizing radiation, exposure to which is largely limited to prevention of CNS relapse in ALL or treatment of a previous brain tumor. Currently, protocols are very cautious and radiotherapy is used more sparingly, so the impact of this exposure is probably much reduced <sup>9</sup>.

Several other possible risk factors have been studied; however none have proven definite. Whereas data on parental occupational exposures have been inconclusive, a meta-analysis of paternal tobacco smoking observed a relative risk of 1.2 <sup>10</sup>. Polyoma virus DNA or protein has been found in all types of brain tumors, but whether or not this viral infection causes these tumors remains unknown <sup>11,12</sup>.

Table III-2. Current knowledge on causes of childhood brain tumors

Exposure or Characteristic	Comments	References
<i>Known risk factors</i>		
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.	13
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.	14,15
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.	7,8,13,16
<i>Factors for which evidence is suggestive but not conclusive</i>		
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.	7,13,17-19
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.	7,13,19,20
Family history of bone cancer, leukemia or lymphoma	The increased risk seen in some studies may be explained by the Li-Fraumeni syndrome.	7,13,24-26
<i>Factors for which evidence is inconsistent or limited</i>		
Electromagnetic fields	A small increase in risk has been observed in some studies, but not most.	7,13,21,30-31
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.	7,13,23

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.	7,13,27
Pesticides	There has been little focused research on this topic. Two small studies suggest an association with use of no-pest strips.	7,13,22,32
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.	7,13,28
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.	7,20,29
Family history of mental retardation	Increased risk observed in one study of adults and one of children.	7

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# ICCC IV. SYMPATHETIC NERVOUS SYSTEM TUMORS

The most common extracranial solid tumors in childhood, sympathetic nervous system (SNS) tumors, accounted for 5% (543) of all pediatric cancers and for 8% of cancer mortality between 1981 and 2000 in Florida. SNS tumors were especially important in early childhood in which they were the third-ranked cause of cancer deaths, responsible for 17% of deaths after CNS tumors and leukemias.

Table IV-1. Number of Cases and Age-Adjusted Incidence Rates of SNS Tumors for Age < 15 by Sex and ICCS Subcategory, Florida, 1981-2000

	Florida		Female		Male	
	Rate	Count	Rate	Count	Rate	Count
All Sympathetic nervous system tumors	9.8	505	8.5	214	11	291
Neuroblastoma and ganglioneuroblastoma	9.5	491	8.2	207	10.7	284
Other sympathetic nervous system tumors	0.3	14	0.3	7	0.3	7

SNS tumors were rare, with an average of 27 new cases diagnosed every year in Florida. They were located in the retroperitoneum and pelvis (72%), the mediastinum (14%), the CNS (10%) and other sites (4%). Neuroblastomas, including also ganglioneuroblastoma, and malignant pheochromocytoma, comprised the most common forms of SNS tumors, accounting for 96% of cases. Most of this chapter focuses on this subcategory.

Neuroblastomas arise from primordial neural crest cells, which migrate during embryogenesis to form the adrenal medulla and sympathetic ganglia. Neuroblastoma is a unique malignancy, the clinical behavior of which may range from spontaneous regression to aggressive metastatic spread<sup>1</sup>. The prognosis depends largely on age and the stage of disease at the time of diagnosis. Infants have the best prognosis, whereas those aged 2 and older have a poorer prognosis<sup>2</sup>.

## AGE

Neuroblastoma is mostly a disease of young children; in Florida 81% of these tumors presented before age 5, and 93% before age 10. Incidence was highest in the first year of life, when it was the most common malignancy, but decreased rapidly, by 50%, for children in the second year of life. As age increased, incidence decreased further. Incidence in those 5-9 years old was only one seventh of that in those younger than age 4. Neuroblastoma was a rare event in children above 10 years old.

Figure IV-1. Age-Specific and Age-Adjusted Incidence Rates of SNS Tumors by Sex, Florida, 1981-2000

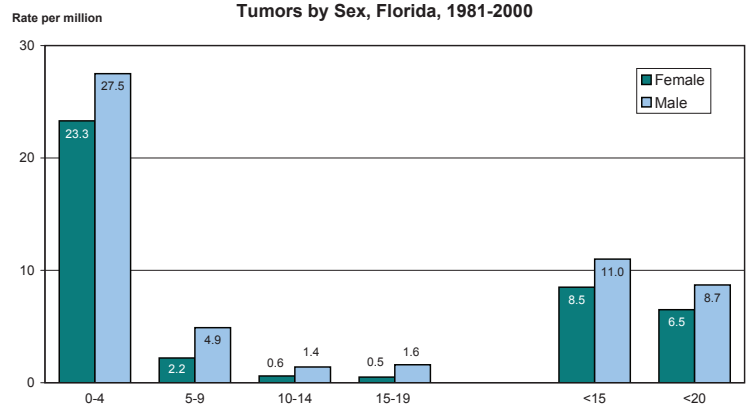
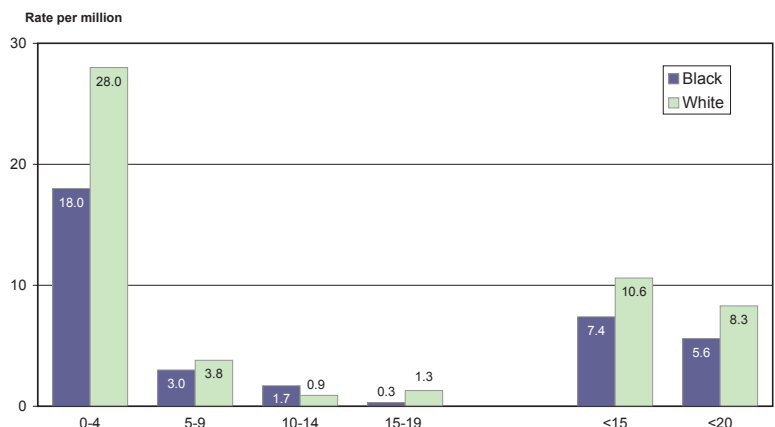


Figure IV-2. Age-Specific and Age-Adjusted Incidence Rates of SNS Tumors by Race, Florida, 1981-2000



## SEX AND RACE

The overall rate for this group of tumors was higher in males, 9 cases per million, than in females, 7 per million. This difference between sexes was present in both Whites and Blacks.

The incidence rate of neuroblastoma was nearly 50% higher in Whites than in Blacks in Florida. The group with the highest rate was White males, whereas Black females showed the lowest rate.

## SEER

The overall Florida rates do not differ from SEER. However, a larger difference in rates between races in Florida was observed. This is a result of the lower rates of neuroblastoma for Blacks in Florida, 5.7 per million compared to 7.1 per million in the SEER areas.

## SCREENING and TRENDS

Most neuroblastomas produce catecholamines, whose metabolites may be measured in the urine as a screen for the disease<sup>3</sup>. However, screening on a population basis has resulted in over-diagnosis of the disease; most of the tumors detected are benign in course, localized in stage, diagnosed at a very young age, and are found to regress spontaneously<sup>4</sup>. As a result, screening programs had no impact on mortality<sup>5</sup>.

Nevertheless, increased awareness of the possibility of early detection, as well as the widespread use of prenatal ultrasound examinations, may have led to an increase in cases<sup>6</sup>. The trend in Florida, where no systematic screening has been implemented, has shown an increase of +1.9% per year from 1981 to 2000.

Figure IV-3. Age-Adjusted Incidence Rates of SNS Tumors by Sex and Race, Florida and SEER, 1981-2000

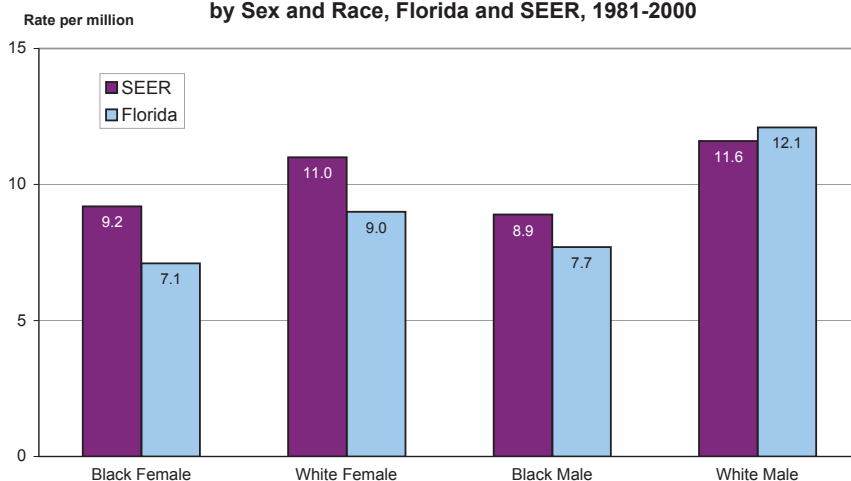
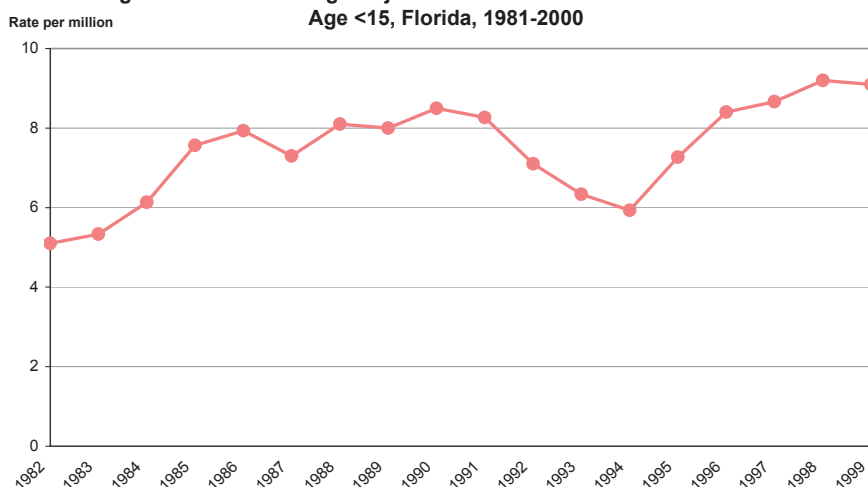
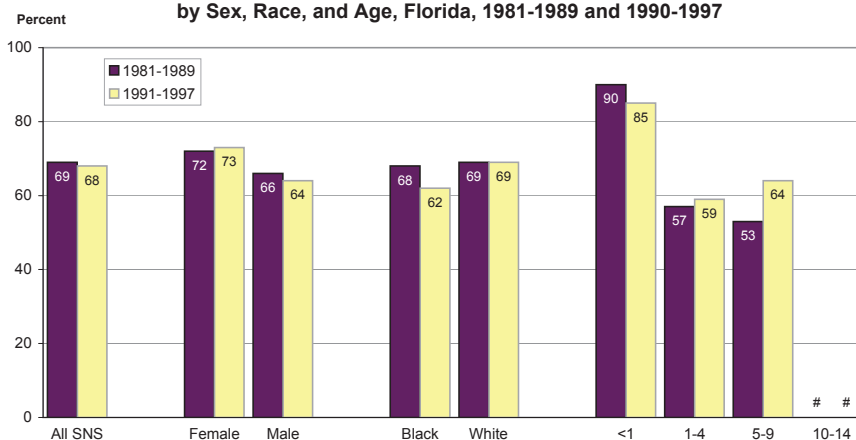


Figure IV-4. Trend of Age-Adjusted Incidence Rate of SNS Tumors for Age <15, Florida, 1981-2000



\* Trend is a 3-year moving average.

Figure IV-5. Five-Year Survival for Neuroblastoma for Age < 15 by Sex, Race, and Age, Florida, 1981-1989 and 1990-1997



## SURVIVAL

In Florida, the overall 5-year survival was 68%, higher for females, 73%, than for males, 62%. In the most recent period of follow-up, 1990-1997, survival was 7 percentage points higher for Whites than for Blacks.

It is known that survival is substantially higher for infants than for those aged 2 and older. Under age 1, survival is largely a function of incidence: the higher the incidence, the more localized disease is found and the higher the survival is <sup>7</sup>. In Florida, both incidence and survival in infants, 85% after 5 years, are similar to those from the SEER populations. Interestingly, it is in the age group of 2-14 years old, that five-year survival rates constitute the best indicator of therapy-related survival since, in this age group, the majority of cases are diagnosed with metastases <sup>8</sup>. In Florida survival in those aged 2-14 was 60% after 5 years, much worse than for infants.

Table IV-2. Current knowledge on causes of neuroblastoma (NB)

Exposure or Characteristic	Comments	References
<i>Factors for which evidence is inconsistent or limited</i>		
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.	10-12
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.	11-13
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.	12,14-15
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.	10
Previous spontaneous abortion/fetal death	Previous spontaneous abortion was associated with increased risk in one study and decreased risk in another.	12,15
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.	11,12,16
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.	11,12
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.	17-19

## RISK FACTORS

The etiology of this embryonal cancer is largely unknown. Several factors have been studied, but provide only inconsistent or limited evidence (see Table IV-2). Half of all advanced stage tumors demonstrate *N-myc* amplification <sup>9</sup>.

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# ICCC V. RETINOBLASTOMA

Retinoblastoma is an uncommon embryonal tumor of the retina. The RB1 gene in chromosome 13, a tumor suppressor gene, is key in the genesis of this malignancy. Loss or mutation of both alleles of this gene is necessary for a tumor to develop <sup>1</sup>. There are two forms of the disease: heritable and non-heritable, comprising 40% and 60% of cases respectively.

The majority of retinoblastomas are non-heritable disease. Two somatic mutations of the RB1 gene are necessary in a single cell some time after conception for a tumor to occur. These non-heritable sporadic tumors tend to occur after the first year of age and are all unilateral.

All bilateral and approximately 15% of unilateral retinoblastomas have one of the variants of the heritable form. The heritable forms tend to occur before the first year of age <sup>2</sup>. In most cases of heritable retinoblastoma, the initial mutation occurs as a new germline mutation; these children, although without a parent with the mutation, will be able to pass the mutation to their offspring. This form is called “sporadic heritable retinoblastoma.” About ten percent of the cases of heritable form are familial retinoblastoma, in which the RB1 gene in chromosome 13 is inherited from a progenitor and then a mutation in the other copy of the RB1 gene occurs in a retinal cell sometime after conception <sup>3</sup>.

Retinoblastoma is a very rare cancer by all accounts, with an average of 12 new cases a year in Florida. It accounted for only 2.3% of cancer cases in Floridians younger than 20 between 1981 and 2000.

## AGE

Retinoblastoma mostly affected infants (43%), and incidence decreased rapidly with age with a cumulative 97% of cases occurring before age 5. The highest age at diagnosis recorded in Florida was 7 years of age.

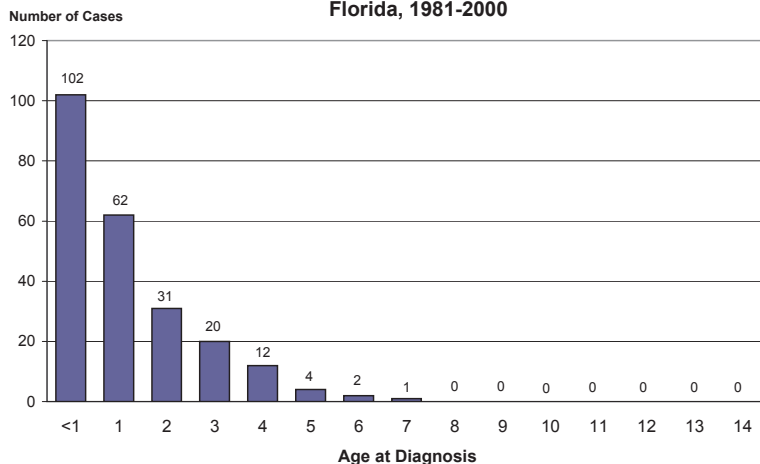
## SEX AND RACE

There is no predisposition for retinoblastoma by race or gender. Right and left eyes are affected equally.

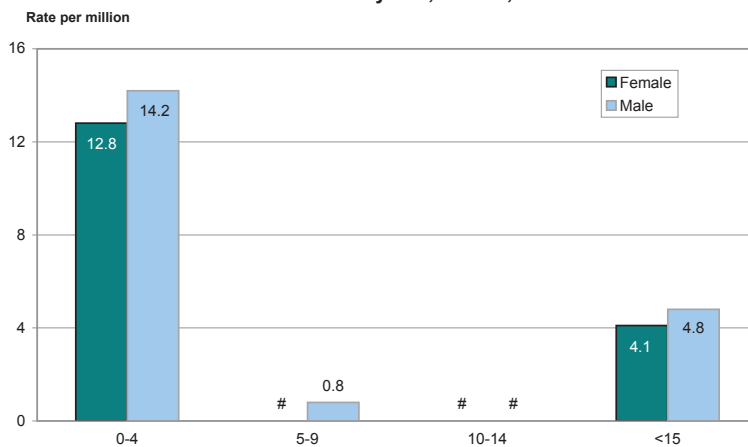
The incidence of retinoblastoma in children less than 15 years of age was slightly higher in males, 4.8 cases per million, than in females, 4.1 cases per million.

Blacks and Whites present similar overall rates but showed differences by age group. Whereas in the 0-4

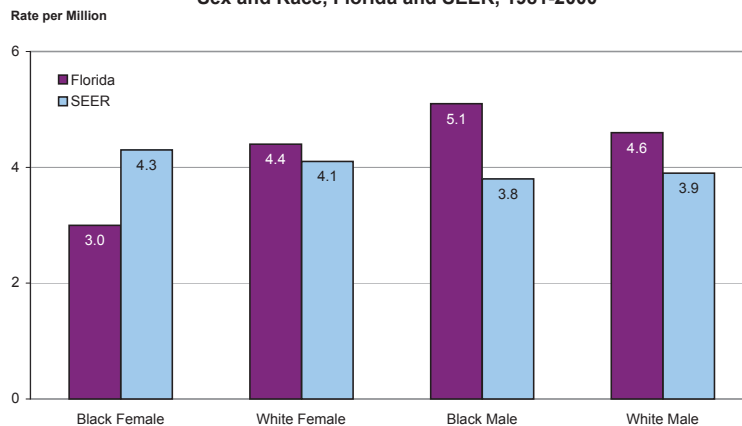
**Figure V-1. Total Childhood Retinoblastoma by Age, Florida, 1981-2000**



**Figure V-2. Age-Specific and Age-Adjusted Incidence Rates of Retinoblastoma by Sex, Florida, 1981-2000**



**Figure V-3. Age-Adjusted Incidence Rates of Retinoblastoma by Sex and Race, Florida and SEER, 1981-2000**



age group retinoblastoma was more common in Whites, in the 5-9 age group this malignancy was more common in Blacks.

## SEER

Overall rates for retinoblastoma were similar between Florida and SEER. By race and sex, the incidence in Black males in Florida is higher than in SEER. Conversely, incidence in Florida's Black females was lower than in SEER.

## TRENDS

Although Figure V-4 does suggest an increasing trend in retinoblastoma, no statistical analysis was performed due to the small number of cases.

## SURVIVAL

Retinoblastoma is an eminently curable cancer and treatment is usually highly successful. Retinoblastoma of the heritable form, which is mostly diagnosed under 1 year of age, did not show a substantial difference in survival compared to retinoblastoma diagnosed in ages 1 to 4. Five-year survival rates in Florida for the period 1991 to 1997 reached 99% with the subgroups of lower survival in the 1980s, males and Whites, catching up with their counterparts in the 1990s.

## RISK FACTORS

In bilateral retinoblastoma, the genetic factors are known. There is a 50% chance that a parent with a germline mutation in the RB1 gene will pass on that mutation to an offspring. If a further mutation or deletion leading to a loss of function of the remaining RB1 allele in one or more retinal cells develops, then the chance that the offspring will develop a tumor is very high <sup>3</sup>.

For non-heritable cases, only limited evidence has been found for paternal occupation as a risk factor, for instance, in the offspring of welders <sup>4</sup>. In vitro fertilization has also been associated with increased risk, whereas multivitamin supplements and barrier contraceptives were associated with decreased risk <sup>5,6</sup>. More interestingly, human papillomavirus (HPV) sequences were detected in about one third of retinoblastomas, suggesting a possible role for HPV infection <sup>7</sup>. However, this evidence calls for caution in its interpretation, as only one observational study was found for each of these exposures.

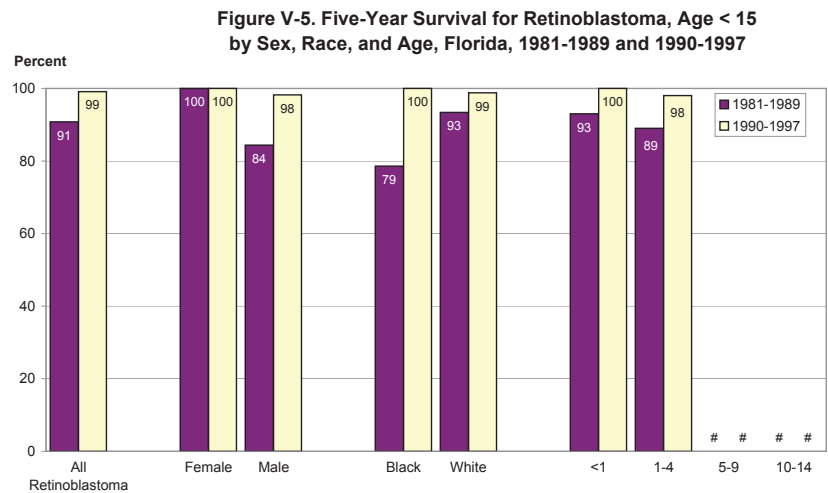
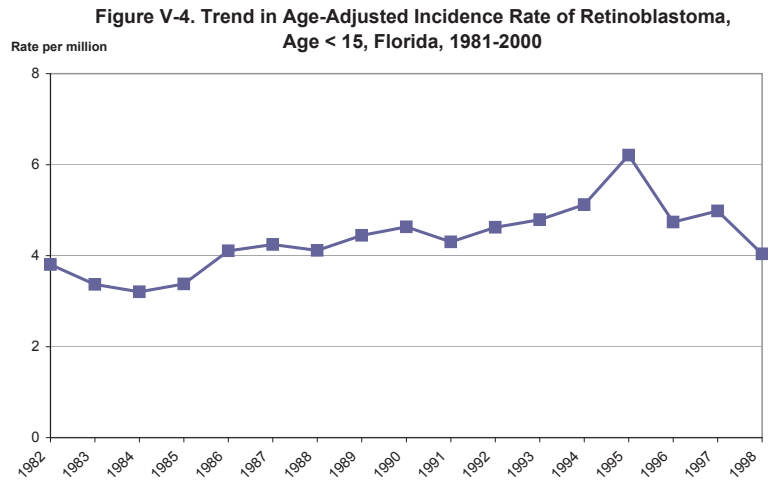


Table V-1. Current knowledge of causes of retinoblastoma

Exposure or Characteristic	Comments	References
<i>Known risk factors</i>		
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.	1,8
13q deletion syndrome	Recognition of this syndrome led to the identification of the retinoblastoma gene.	8
<i>Factors for which evidence is Inconsistent or limited</i>		
Paternal occupation	There is a single report of association with employment in the military, metal manufacturing, and as welder, machinist, or related occupation.	4

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# ICCC VI. RENAL TUMORS

There were 471 renal tumors diagnosed from 1981 to 2000 in Florida, accounting for 4.6% of all cancers in those younger than 20. This equates to a yearly average of 24 new cases of kidney cancer in Florida children.

Although a rare tumor, in early childhood, renal tumors were the fourth leading cancer after leukemia, CNS tumors and neuroblastoma.

Table VI-1. Age-Specific and Age-Adjusted Incidence Rates of Renal Tumors by Histology, Florida, 1981-2000

	0-4		5-9		10-14		15-19		<15		<20	
	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count
8960 Wilms Tumor	19.2	323	5.0	84	0.7	11	0.4	7	8.1	418	6.2	425
8963 Rhabdoid	0.2	4	0.0	0	0.0	0	0.0	0	0.1	4	0.1	4
8964 Clear Cell	0.3	5	0.0	0	0.1	1	0.1	2	0.1	6	0.1	8
8000-8006 Unspecified	0.2	3	0.0	0	0.0	0	0.0	0	0.1	3	0.0	3
Other Renal Carcinoma	0.2	3	0.1	2	0.6	10	1.0	16	0.3	15	0.5	31

Rates are per 1,000,000 and age-adjusted to the 2000 U.S. standard.

Ninety per cent of renal tumors in childhood and adolescence are Wilms tumors, also known as nephroblastomas, 7% of which are bilateral<sup>1</sup>. Together with two other rare types, rhabdoid cell carcinoma and clear-cell sarcoma, Wilms tumors represented 93% of the cases of renal tumors in Florida. The other major tumor type was renal cell carcinoma which accounted for 5% of cases; unspecified renal tumors accounted for the remaining 2%.

## AGE

Wilms tumor is essentially a cancer of young children; 76% of cases occurred before age 5. On rare occasions, Wilms tumor has been described in teenagers and adults. In contrast, renal cell carcinoma increased with age; 86% of these cases occurred at age 10 and above.

## SEX

Unlike most other childhood cancers, renal tumors were more common in females than in males; the rates in females were 23% higher. This difference between sexes was evident in all age groups.

## RACE and SEER

Overall rates for renal tumors in Florida were similar to SEER incidence rates in those aged 0-14, 8.8 cases per million. The known predominance of this cancer in Blacks over Whites was more marked in Florida, 41% higher rates in Blacks compared to only 25% higher in the SEER areas. This difference was mostly observed in males, in

Figure VI-1. Age-Specific and Age-Adjusted Incidence Rates of Renal Tumors by ICCS Subcategory, Florida, 1981-2000

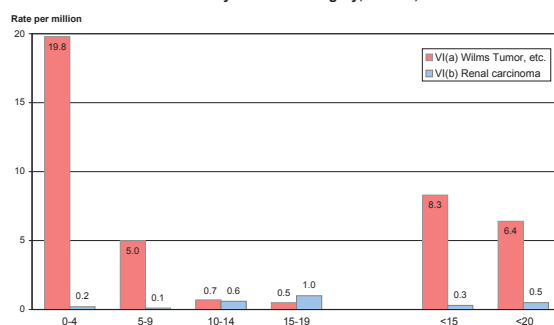


Figure VI-2. Age-Specific and Age-Adjusted Incidence Rates of Wilms' Tumor for Age < 15 by Sex, Florida, 1981-2000

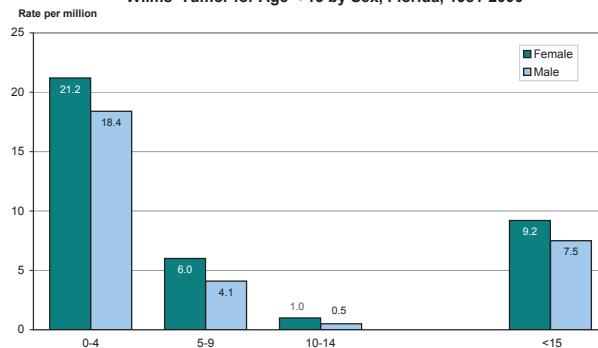
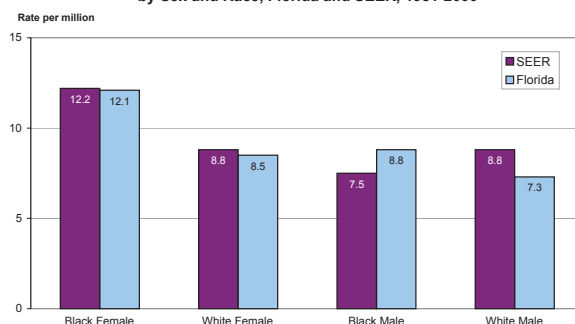


Figure VI-3. Age-Adjusted Rates of Wilms' Tumor for Age < 15 by Sex and Race, Florida and SEER, 1981-2000



whom the incidence for Blacks was higher in Florida than in SEER, whereas for White males, incidence was lower in Florida than in SEER.

## TRENDS

No statistically significant trend was observed for renal tumors from 1981 to 2000.

## SURVIVAL

The prognosis for Wilms tumor is very good, especially in those younger than 5 years old. Five-year survival rates in Florida were highly dependent on age. For those diagnosed from 1990 to 1997, survival rates were 98% in those younger than 5, and 81% in those between 5 and 9 years old.

Remarkable improvements in treatment took place between the 1980s and the 1990s for the age group 0-4. In fact Wilms tumor is one of the most successfully treated pediatric solid malignancies. Advances in therapeutic options have been attributed to the efforts of cooperative study groups and the development of prospective multi-centre randomized trials <sup>2</sup>.

## RISK FACTORS

Wilms tumor may occur as part of several congenital malformation syndromes. Beckwith-Wiedemann syndrome, carries a 5% risk of developing Wilms tumor <sup>3</sup>. Syndromes associated with mutations of the WT1 gene on chromosome 11p13, which encompass aniridia, mental retardation and nephritic syndrome, carry an increased risk of developing Wilms tumor <sup>3</sup>. Children with these congenital abnormalities are at risk of bilateral kidney involvement <sup>4</sup>. A number of other susceptibility genes have been implicated in familial Wilms tumor, but these account for only 2-3% of tumors <sup>5</sup>.

There is some evidence of an association of Wilms tumor with paternal employment as welders or mechanics <sup>6</sup>, high birth weight, and maternal coffee and tea consumption during pregnancy <sup>7</sup>. Ethnicity affects incidence rates more than geographical region of residence <sup>8</sup>, which, together with inconsistent data from case-control studies, suggests that environmental factors play only a marginal role in the etiology of Wilms tumor <sup>2,9</sup>.

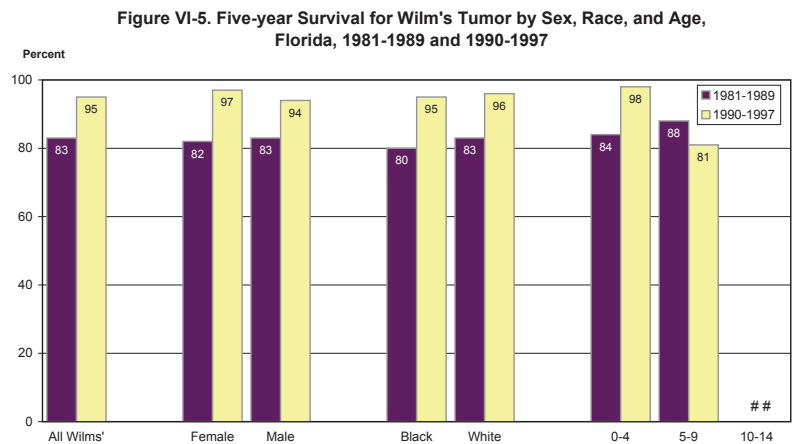
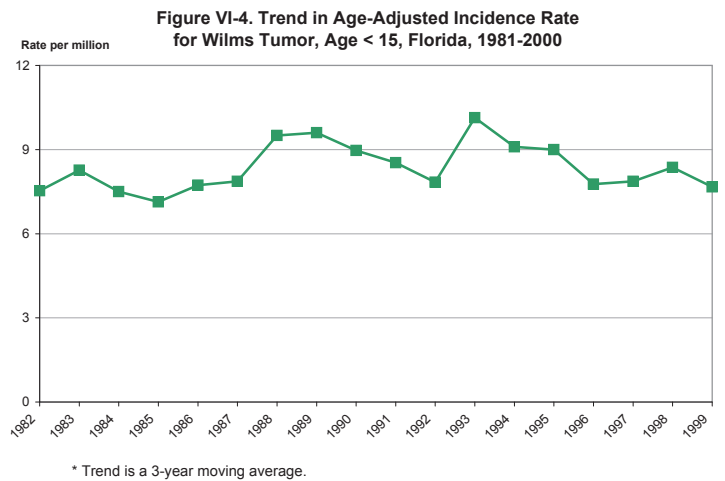


Table VI-2. Current knowledge on causes of Wilms Tumor (WT)

Exposure or Characteristic	Comments	References
<i>Known risk factors</i>		
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
<i>Factors for which evidence is suggestive but not conclusive</i>		
Paternal occupation	An increased risk for fathers employed as a welder or mechanic has been reported in several studies.	13,23,25
<i>Factors for which evidence is inconsistent or limited</i>		
High birth weight	Association with birth weight over 4,000 grams has been reported in some studies.	13,26,27
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.	13,24,28-30
Ionizing radiation (in utero)	Prenatal diagnostic x-ray was associated with increased risk in one study.	31
Maternal consumption of coffee and tea during pregnancy	Three studies reported association with coffee or tea; another did not replicate this finding.	28,32,33
Maternal hair dye use during pregnancy	Use was associated with risk in one study, but not in others.	28,33
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.	13,34,35
Maternal occupation	One study found an association with job groupings that included hairdressers, electronic and clothing manufacturing workers, laboratory workers, dental assistants.	23,36

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# ICCC VII. HEPATIC TUMORS

Although rare in children younger than 20, primary liver cancers are the third most frequent intra-abdominal solid tumor after neuroblastomas and Wilms tumor. In Florida primary liver malignancies accounted for only 1% of all pediatric cancers, but 2% of all pediatric deaths, as a result of their relatively poor prognosis. The ICCC category for liver cancers (VII) comprises hepatoblastomas (VIIa), hepatocellular carcinomas (VIIb), and unspecified tumors (VIIc).

As in adulthood, the liver is commonly affected by secondary malignancies in childhood, mostly from Wilms' tumor, neuroblastoma or leukemia <sup>1</sup>. All of these are more common than primary liver cancers.

In Florida during the period from 1981 to 2000, there were 71 cases of hepatoblastoma, an incidence rate of 1 per million, and 31 cases of hepatocellular carcinoma (HCC), with an incidence rate of 0.5 per million. The incidence rate for hepatic cancer (1.5 per million) was the lowest of any ICCC group in the pediatric population.

## AGE

Hepatoblastoma is mainly a disease of young children typically presenting before age 3. Incidence decreased sharply with age and this tumor was extremely rare after age 10, with only 4 cases diagnosed in the entire state in 20 years. HCC occurred mostly after age 5, with incidence increasing continuously with age; in Florida, from 0.2 per million in young children to 0.7 per million in adolescence.

## SEX

Ratios of males to females in excess of 1.5 were observed in Florida for rates of both hepatoblastoma and HCC which were not evident in the SEER areas.

## RACE

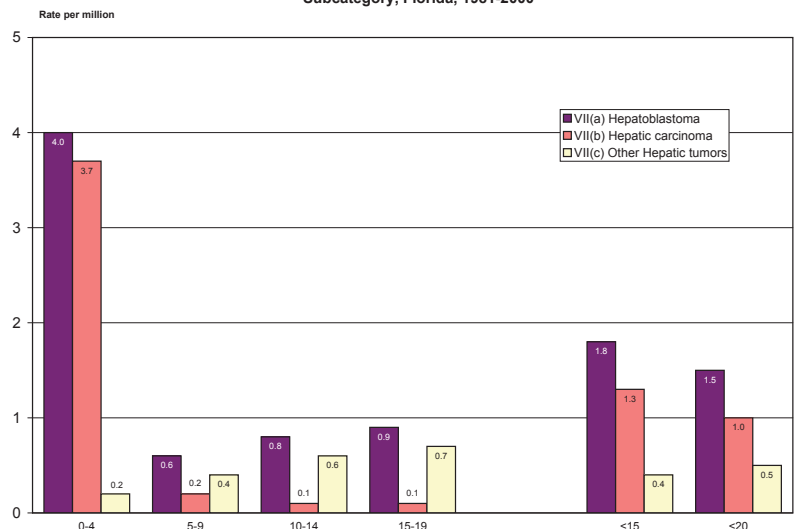
Whereas hepatoblastoma was more common in Whites (1.1 cases per million) than in Blacks (0.8 cases per million), HCC was more common in Blacks (0.6 cases per million) compared to Whites (0.4 cases per million).

Table VII-1. Age-Specific and Age-Adjusted Incidence Rates and Percent of Hepatic Tumors by ICCC Subcategory, Florida, 1981-2000

Age Group	ICCC Subcategory	Rate	Count	Percent
0-4	All Hepatic Cancer	4.0	67	63.8
	VII(a) Hepatoblastoma	3.7	63	60.0
	VII(b) Hepatic carcinoma	0.2	3	2.9
5-9	All Hepatic Cancer	0.6	10	9.5
	VII(a) Hepatoblastoma	0.2	4	3.8
	VII(b) Hepatic carcinoma	0.4	6	5.7
10-14	All Hepatic Cancer	0.8	13	12.4
	VII(a) Hepatoblastoma	0.1	2	1.9
	VII(b) Hepatic carcinoma	0.6	10	9.5
15-19	All Hepatic Cancer	0.9	15	14.3
	VII(a) Hepatoblastoma	0.1	2	1.9
	VII(b) Hepatic carcinoma	0.7	12	11.4
<15	All Hepatic Cancer	1.8	90	85.7
	VII(a) Hepatoblastoma	1.3	69	65.7
	VII(b) Hepatic carcinoma	0.4	19	18.1
<20	All Hepatic Cancer	1.5	105	100.0
	VII(a) Hepatoblastoma	1.0	71	67.6
	VII(b) Hepatic carcinoma	0.5	31	29.5

Rates are per 1,000,000 and age-adjusted to the 2000 U.S. standard.

Figure VII-1. Age-Specific and Age-Adjusted Incidence Rates of Hepatic Tumors by ICCC Subcategory, Florida, 1981-2000



## SEER

Overall liver cancer rates were slightly lower in Florida (1.5 per million) than in the SEER areas (1.8 per million), a result of lower rates of hepatoblastoma in Florida (1.0 per million) compared to SEER (1.3 per million). This lower incidence of hepatoblastoma was apparent across all race groups, and was more pronounced in females. No substantial differences in HCC rates between Florida and SEER were observed.

## TRENDS

Although statistical analysis was not possible due to the small number of cases, an increasing trend is apparent (graph not shown) for hepatoblastoma, as well as a decreasing trend for HCC during the 1980s and 1990s.

The increasing hepatoblastoma trend has been recognized elsewhere<sup>2</sup>. Although this may be related to improved coding of childhood cancer, especially higher accuracy levels for the registration of this tumor, the proportion of surviving infants of very low birth weight has increased (see discussion on risk factors).

The HCC trend may be partly explained by better coding and possibly by widespread hepatitis B vaccination influencing childhood HCC cancer incidence<sup>3</sup>. It is known that the impact of this vaccine on HCC rates is high in developing countries, where HBV is endemic<sup>3</sup> which is not the case of the US.

South Florida does host an increasing number of newly arrived immigrant populations with an unknown degree of vaccination coverage. Nonetheless, the overall impact of vaccination on a very rare disease in the context of Florida will most likely be small.

## SURVIVAL

Five year survival rates improved remarkably between 1981-1989 and 1990-1997 for both types of liver cancer. Survival rates in Florida were very high compared to both SEER and elsewhere<sup>2,4</sup>. Seventy-nine percent of children were alive five years after a diagnosis of hepatoblastoma; 43% survived five years in the case of HCC. The improvement in survival for both types of hepatic cancer observed almost everywhere in the Western world has been the result of multicenter clinical trials and the consequent availability of new therapies, especially in the case of hepatoblastoma<sup>4</sup>. Cure of liver cancer requires complete, gross tumor resection. Hepatoblastoma is most often unifocal, and chemotherapy can often decrease tumor size and extent, allowing complete resection<sup>1</sup>. HCC, on the other hand is, often extensively invasive or multicentric at diagnosis, and does not seem to be sensitive to chemotherapy<sup>1</sup>, hence its lower survival.

Figure VII-2. Age-Adjusted Incidence Rates of Hepatic Tumors by Sex and Race, Florida and SEER, 1981-2000

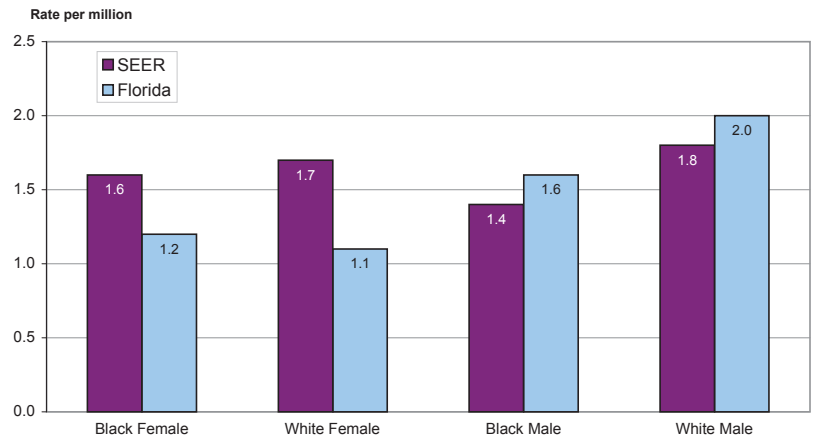
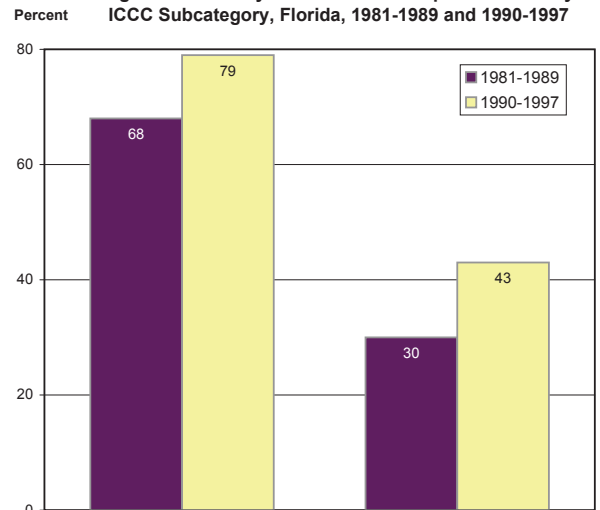


Figure VII-3. Five-year Survival for Hepatic Tumors by ICC Subcategory, Florida, 1981-1989 and 1990-1997



## RISK FACTORS

Predisposing genetic factors for hepatoblastoma include overgrowth syndromes, especially Beckwith-Wiedemann syndrome<sup>5</sup>, and inheritance of a mutated adenomatous polyposis of a colon gene in the dominant disorder familial adenomatous polyposis<sup>6</sup>. An increased risk of hepatoblastoma has also been found in children with very low birth weight<sup>7,8</sup>. Extended oxygenation and furosemide treatment, common in these infants are possibly associated with an increased risk for this rare tumor<sup>9</sup>. Parental occupational exposures to metals, petroleum products, and paints or pigments prior to and during pregnancy have been linked to higher risks of hepatoblastoma in offspring<sup>10</sup>. A potential link between maternal pre-eclampsia and the risk of hepatoblastoma has also been suggested<sup>8</sup>.

Predisposing factors for HCC are those causing diffuse parenchymal liver disease in early life, including tyrosinosis and glycogen storage disease type I<sup>11</sup>, and also early infection with hepatitis B<sup>12,13</sup>. Data on hepatitis C and HCC in children have not been published so far.

Table VII-2. Current knowledge on causes of hepatoblastoma

Exposure or Characteristic	Comments	References
<i>Known risk factors</i>		
Beckwith-Wiedemann syndrome, hemihypertrophy	Hepatoblastoma, Wilms tumor and adrenocortical carcinoma are associated with these syndromes that involve organomegaly.	5,15,16
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.	6,14,17,18
<i>Factors for which evidence is inconsistent or limited</i>		
Parental occupational exposures	Associations with metals, petroleum products, paints and pigments were reported from the only case-control study done to date.	10

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## ICCC VIII. BONE TUMORS

Primary bone cancers accounted for 6% of malignancies in children and adolescents in Florida during the study period. This group of tumors was the sixth most common pediatric cancer. The average number of primary bone tumors was 35 cases per year between 1981 and 2000. The corresponding proportional mortality from 1981 to 2000 was 8.5%.

Malignant bone tumors comprise more than 20 different entities, but the great majority fall within the ICCC subcategories (VIIIa) Osteosarcoma and (VIIIc) Ewing sarcoma. In Florida, these two groups together accounted for 91% of all pediatric bone tumors, 54% osteosarcoma and 37% Ewing Sarcoma. All other groups were rare. Osteosarcomas occurred primarily in the long bones of the lower limbs (73%), and 14% in the long bones of the upper limbs, with only 5% of cases occurring in the central skeletal axis. The locations of Ewing sarcomas included the central skeletal axis in 41% of cases, the long bones of the lower limbs in 29%, and the upper limbs in 14%.

Osteosarcomas derive from primitive bone-forming mesenchymal cells, whereas Ewing sarcomas originate from the neural crest<sup>1</sup>. Osteosarcomas tend to occur in the rapidly growing ends of long bones, especially the distal femur, proximal tibia and proximal humerus. Ewing sarcoma occurs in the axial skeleton (pelvis, scapula and spine) and in the long bones with almost equal frequency. Osteosarcoma occurs in adults also, especially in those older than 65, whereas Ewing sarcoma is primarily a disease of children and adolescents<sup>2</sup>.

### AGE

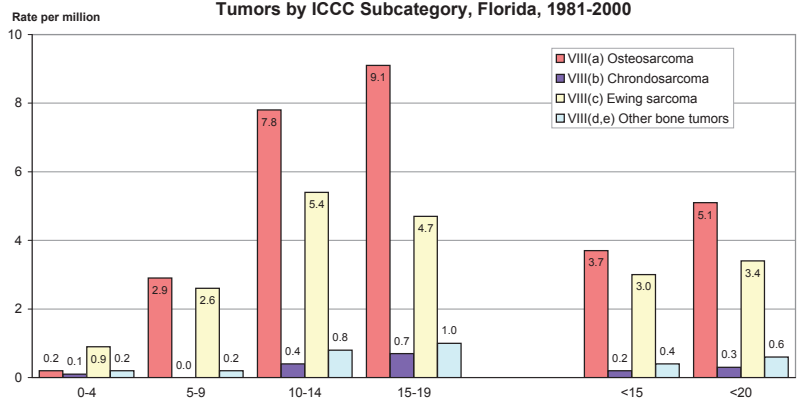
Bone tumors were very rare in early childhood; both types had incidence rates of less than 1 case per million. In the age group 5-9, the incidence rates of both osteosarcoma and Ewing sarcoma were similar, approximately 2.7 cases per million. The highest rate for both tumors occurs in those

Table VIII-1. Age-Specific and Age-Adjusted Incidence Rates and Percent of Bone Tumors by ICCC Subcategory, Florida, 1981-2000

Age		Rate	Count	Percent
0-4	VIII All Malignant Bone	1.3	22	3.6
	VIII(a) Osteosarcoma	0.2	3	0.5
	VIII(b) Chondrosarcoma	0.1	1	0.2
	VIII(c) Ewing sarcoma	0.9	15	2.4
	VIII(d,e) Other bone tumors	0.2	3	0.5
5-9	VIII All Malignant Bone	5.8	97	15.8
	VIII(a) Osteosarcoma	2.9	49	8.0
	VIII(b) Chondrosarcoma	0.0	0	0.0
	VIII(c) Ewing sarcoma	2.6	44	7.2
	VIII(d,e) Other bone tumors	0.2	4	0.7
10-14	VIII All Malignant Bone	14.4	235	38.3
	VIII(a) Osteosarcoma	7.8	127	20.7
	VIII(b) Chondrosarcoma	0.4	7	1.1
	VIII(c) Ewing sarcoma	5.4	88	14.4
	VIII(d,e) Other bone tumors	0.8	13	2.1
15-19	VIII All Malignant Bone	15.5	259	42.3
	VIII(a) Osteosarcoma	9.1	152	24.8
	VIII(b) Chondrosarcoma	0.7	11	1.8
	VIII(c) Ewing sarcoma	4.7	79	12.9
	VIII(d,e) Other bone tumors	1.0	17	2.8
<15	VIII All Malignant Bone	7.3	354	57.7
	VIII(a) Osteosarcoma	3.7	179	29.2
	VIII(b) Chondrosarcoma	0.2	8	1.3
	VIII(c) Ewing sarcoma	3.0	147	24.0
	VIII(d,e) Other bone tumors	0.4	20	3.3
<20	VIII All Malignant Bone	9.3	613	100.0
	VIII(a) Osteosarcoma	5.1	331	54.0
	VIII(b) Chondrosarcoma	0.3	19	3.1
	VIII(c) Ewing sarcoma	3.4	226	36.9
	VIII(d,e) Other bone tumors	0.6	37	6.0

Rates are per 1,000,000 and age-adjusted to the 2000 U.S. (18 age groups) standard.

Figure VIII-1. Age-Specific and Age-Adjusted Incidence Rates of Malignant Bone Tumors by ICCC Subcategory, Florida, 1981-2000





over 10 years old. Osteosarcoma was clearly the most common bone cancer in those aged 10-14 and 15-19. Incidence was highest in adolescence, 9.1 cases per million. The incidence of Ewing sarcoma was highest in those 10-14, 5.4 cases per million, decreasing to 4.7 per million in adolescents.

**SEX**

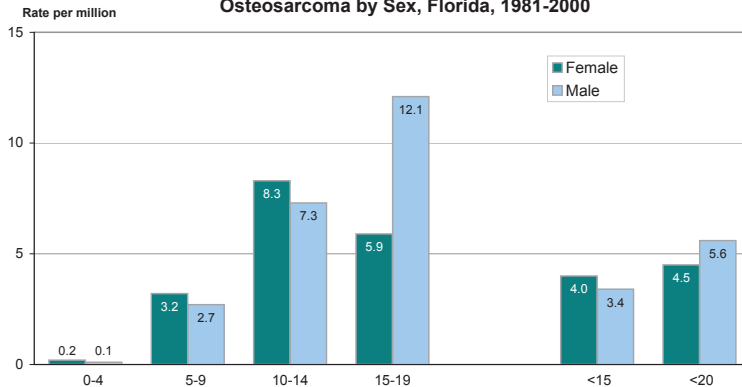
Bone cancer was 30% more common in males than in females. Higher rates occurred in males for both osteosarcoma and Ewing sarcoma. However, this varied depending on age group. Both tumors peaked in the age group 10-14 in females and in the 15-19 age group in males. The peak at an earlier age in females is presumably related to the occurrence of maximum skeletal growth at an earlier age<sup>3</sup>. In childhood, osteosarcoma was more common in females. Conversely, in adolescence, males have nearly double the rates of females. For Ewing sarcoma, males had higher rates in all age groups, especially in adolescents.

**RACE**

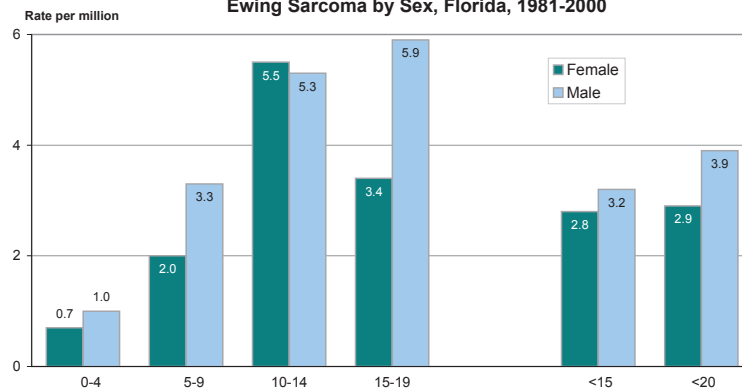
The incidence rate for osteosarcoma was higher in Blacks (5.9 per million) than in Whites (4.9 per million). The highest rates for this tumor were found in Black adolescents (11 per million). In Whites, the rates increased with age, from 0.2 per million in those aged 0-4, to slightly more than 8 cases per million after age 10, whereas in Blacks the incidence increased substantially with each age group and did not stabilize after age 10 (see Figure VIII-4).

The overall incidence of Ewing sarcoma was much higher in Whites (4.1 per million) than in Blacks (1.1 per million). Ewing sarcoma in Whites was most common in the age group 10-14 (6.7 per million), decreasing slightly in adolescence to 5.3 per million. In Blacks, Ewing sarcoma was extremely rare. Only sixteen cases were observed from 1981 to 2000 in this group in the state of Florida.

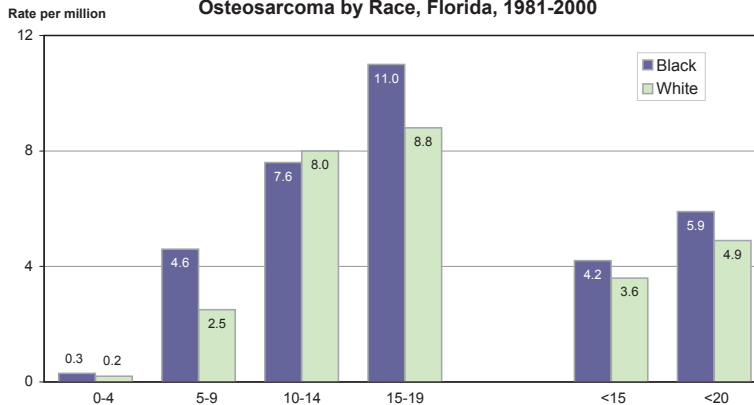
**Figure VIII-2. Age-Specific and Age-Adjusted Incidence Rates of Osteosarcoma by Sex, Florida, 1981-2000**



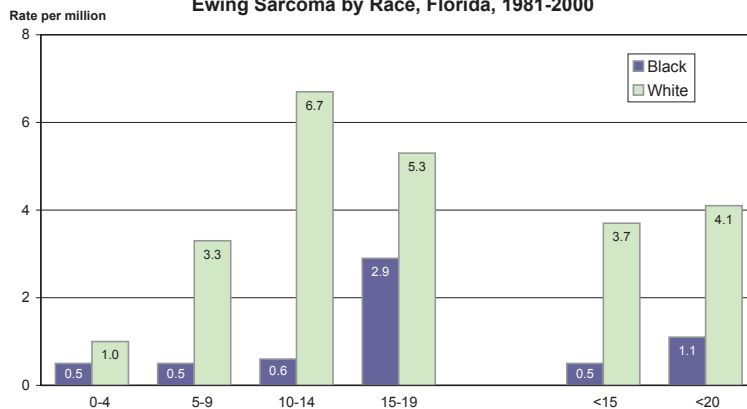
**Figure VIII-3. Age-Specific and Age-Adjusted Incidence Rates of Ewing Sarcoma by Sex, Florida, 1981-2000**



**Figure VIII-4. Age-Specific and Age-Adjusted Incidence Rates of Osteosarcoma by Race, Florida, 1981-2000**



**Figure VIII-5 Age-Specific and Age-Adjusted Incidence Rates of Ewing Sarcoma by Race, Florida, 1981-2000**



**SEER**

The overall annual incidence rate for bone tumors in Florida was 9.3 per million, slightly higher than in the SEER areas where it was 8.8 per million.

Incidence in Blacks was higher in Florida than in SEER for both tumors, only slightly higher for osteosarcoma, but substantially higher for Ewing sarcoma, 1.1 per million in Florida compared to 0.3 per million in SEER. As a result, the White-to-Black ratio for Ewing sarcoma for the years 1981 to 2000 was less than 4 to 1 in Florida compared with 10 to 1 for SEER.

**TRENDS**

The incidence of osteosarcoma rose from 3.7 per million in 1981 to 5.6 per million in 2000, but the trend of +1.8% increase per year was not statistically significant ( $p=0.059$ ). No obvious trend was observed for Ewing sarcoma throughout the period 1981 to 2000. This analysis was made difficult by the small numbers of cases per year.

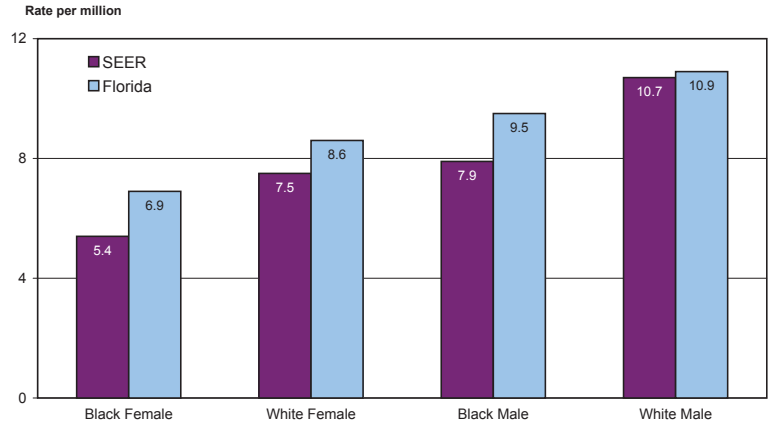
**SURVIVAL**

Hematogeneous spread may occur early in bone tumors, and nearly 25% have metastatic disease at presentation<sup>4</sup>. This may account for the relatively low survival for bone cancer, 65% after 5 years in Florida.

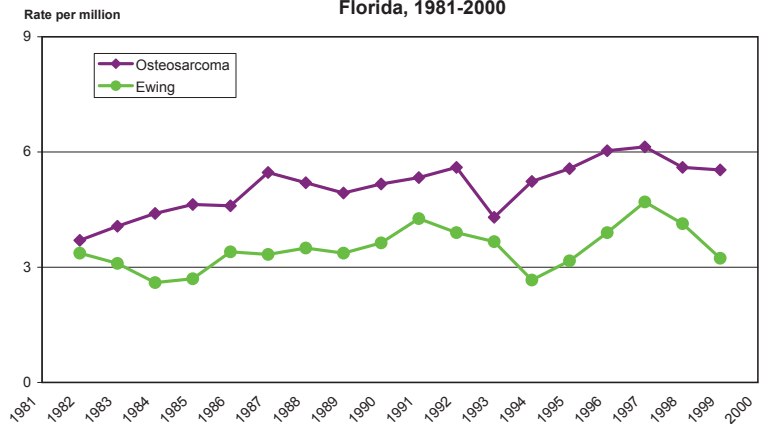
Survival rates for Florida were high in the case of osteosarcoma, 74% after 5 years for cases diagnosed during the period 1990 to 1997. An improvement over time is noticeable when compared to 64% 5-year survival in the 1980s. By race, a persistent survival difference was evident in both periods. In the 1990s, survival rates were lower in Blacks (67%) than in Whites (77%). Nevertheless, survival rates in both sexes, both races, and all age groups, increased substantially from the 1980s to the 1990s, except for those aged 10-14.

For Ewing sarcoma, 5-year survival rates increased only marginally from 55% during the 1980s to 57% during the 1990s. Survival for Blacks in the 1990s was 16 percentage points lower than for Whites. By sex, the five year survival rate in

**Figure VIII-6. Age-Adjusted Incidence Rates of Malignant Bone Tumors by Sex and Race, Florida and SEER, 1981-2000**

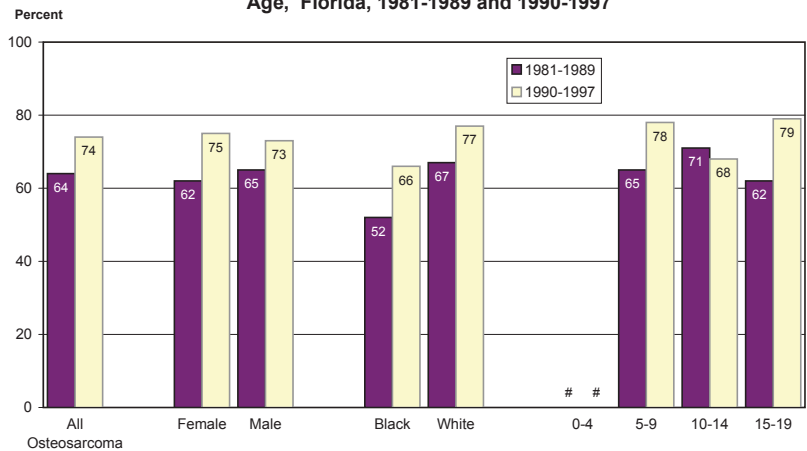


**Figure VIII-7. Trends in Age-Adjusted Incidence Rates of Malignant Bone Tumors by ICC Subcategory, Florida, 1981-2000**



\* Trends are 3-year moving averages.

**Figure VIII-8. Five-year Survival for Osteosarcoma by Sex, Race, and Age, Florida, 1981-1989 and 1990-1997**



females (67%) was substantially higher than in males (50%). Survival was also remarkably lower for adolescents (44%) than for children (64%) in Florida.

Reports have attributed the improvement in bone cancer survival to the introduction of chemotherapy along with surgery for osteosarcoma, and of surgery or radiotherapy for Ewing sarcoma in the late 1970s and early 1980s. In addition, early detection and inclusion of patients in collaborative trials with centralized quality assurance systems may have boosted survival for bone cancer through improved treatment<sup>5</sup>. Nonetheless, it is unclear why survival in Florida has improved for osteosarcoma, but not for Ewing sarcoma.

## RISK FACTORS

Ionizing radiation, in particular, radiotherapy for a previous cancer, alkylating agents, and certain genetic conditions like hereditary retinoblastoma and the Li-Fraumeni syndrome (suppressor genes RB and p53 respectively), and Rothmund syndrome have all been shown to increase the risk of osteosarcoma (see Table VIII-2).

For Ewing sarcoma, the lower incidence among Black and East Asian populations, as well as the cytogenetic differences between Ewing sarcoma in European and Japanese patients, indicate that genetic factors are important in its etiology<sup>6</sup>. In fact, 95% of cases present translocations, with fusion of the EWS gene on chromosome 22 with other genes<sup>7</sup>. Personal histories of umbilical hernia and paternal occupation in farming have also been identified as possible risk factors in Ewing sarcoma (Table VIII-3).

Figure VIII-9. Five-year Survival for Ewings Sarcoma by Sex, Race, and Age, Florida, 1981-2000

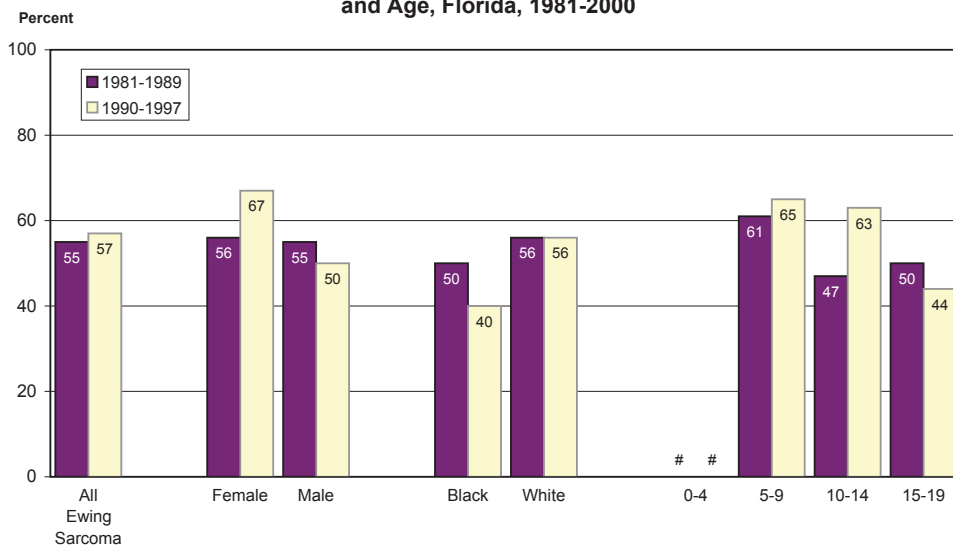


Table VIII-2. Current knowledge on causes of osteosarcoma

Exposure or Characteristic	Comments	References
<i>Known risk factors</i>		
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.	8-10
Hereditary retinoblastoma, Li-Fraumeni syndrome, and Rothmund-Thomson Syndrome	Increased risk is well documented for these genetic conditions.	11-14
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.	1,18
<i>Factors for which evidence is limited or inconsistent</i>		
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.	19-23
Prior trauma to tumor site	One study found a small positive association between damage to the tumor site and increased risk of osteosarcoma.	20
Prenatal exposure and development	Short birth length and fetal x-rays were associated with an increased risk in a single study.	20
Parental exposures	An association with chicken farming and another with gardening with fertilizer, herbicides or pesticides have been reported in single studies.	24,25
Fluoride in drinking water	The few epidemiologic studies as well as ecologic and time trend analyses suggest that fluoride is unlikely to cause osteosarcoma.	26-29

Table VIII-3. Current knowledge on causes of Ewing Sarcoma (ES)

Exposure or Characteristic	Comments	References
<i>Known risk factors</i>		
Race	ES is almost exclusively a disease of White children. Rates in Whites are approximately 9 times those in Blacks.	2,22,30
<i>Risk factors for which evidence is limited or inconsistent</i>		
Growth	As for osteosarcoma, recent studies have not found a consistent association with increased height or weight, or age at pubertal growth spurt.	16,17,19,22,30,31
Hernia	An association was found between hernias and increased risk in one study.	16
Paternal occupation	Paternal occupation in agriculture has been associated with increased risk in two studies, although only in one were the results statistically significant.	16,17
Ingestion of poison or overdose of medication	A prior poisoning episode was more common among cases than controls in a single study.	17
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.	13,32,33

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## ICCC IX. SOFT TISSUE SARCOMAS

Soft tissue sarcomas (STS) are a heterogeneous group of malignancies of mesenchymal origin arising from fibrous, adipose, muscle and other connective tissue. In Florida, the three main histological types were rhabdomyosarcoma (42%), fibrosarcoma (15%), and Kaposi sarcoma (8%). These three groups accounted for 64% of the tumors in the group. Together, all STS constituted the fifth most common childhood cancer in Florida, nearly 7% of all malignancies in childhood and adolescence, corresponding to an average of 35 new cases every year. The proportional mortality for this group of tumors was 5%.

Table IX-1. Counts and Age-Specific and Age-Adjusted Incidence Rates of Soft Tissue Sarcoma by Subcategory, Florida, 1981-2000

	0-4		5-9		10-14		15-19		<15		<20	
	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate
All Soft Tissue Sarcoma	210	12.5	132	7.9	153	9.4	212	12.7	495	9.9	707	10.6
IX(a) Rhabdomyosarcoma	111	6.6	75	4.5	52	3.2	55	3.3	238	4.7	293	4.4
IX(b) Fibrosarcoma	17	1	21	1.3	19	1.2	48	2.9	57	1.1	105	1.6
IX(c) Kaposi sarcoma	42	2.5	2	0.1	2	0.1	8	0.5	46	0.9	54	0.8
IX(d) Other Specified STS	23	1.4	18	1.1	46	2.8	71	4.2	87	1.8	158	2.4
IX(d) PNET	3	0.2	3	0.2	3	0.2	3	0.2	9	0.2	12	0.2
IX(e) Unspecified soft-tissue sarcomas	14	0.8	13	0.8	31	1.9	27	1.6	58	1.2	85	1.3

\* Differences in pathologic interpretation may have increased the incidence of KS.

Rhabdomyosarcomas are derived from mesenchymal cells which would normally differentiate into striated muscle. Rhabdomyosarcoma is the fourth most common solid tumor in children, and the most common STS. It occurs mostly in younger children and more frequently affects the head and neck, and the genitourinary system. Fibrosarcomas derive from fibrous tissue mesenchymal cells, and are more common in adolescence<sup>1</sup>.

The overall annual incidence rate of STS in Florida from 1981 to 2000 was 10.4 cases per million. The rate for rhabdomyosarcoma was 4.4 per million, and for fibrosarcoma 1.6 per million. Rhabdomyosarcomas occurred at sites throughout the body: 19% in the head and neck, 19% in the genitourinary system, 18% in the pelvis, 16% in the limbs and 9% in the orbit. The most common locations for fibrosarcoma were the limbs (38%) and head and neck (15%).

Figure IX-1. Age-Specific Incidence Rates of Soft Tissue Sarcoma by ICCS Subcategory, Florida, 1981-2000

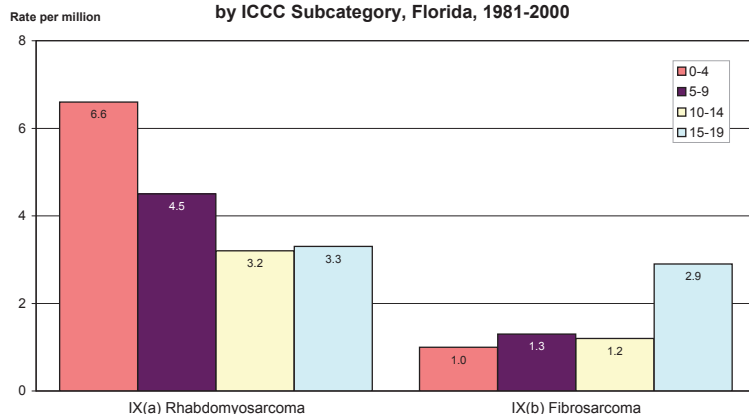
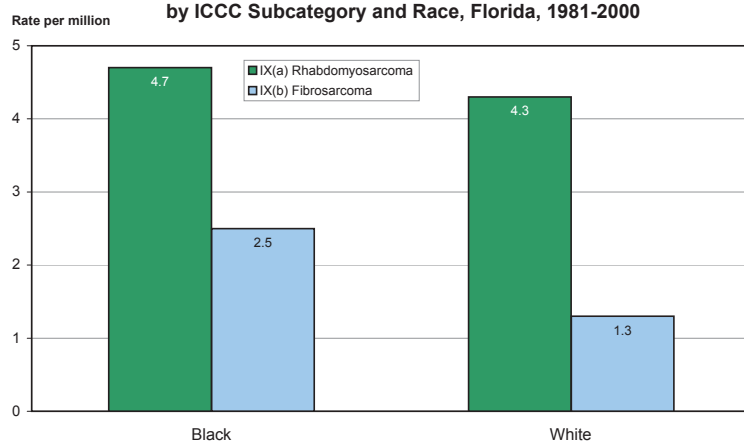


Figure IX-2. Age-Adjusted Incidence Rates of Soft Tissue Sarcoma by ICCS Subcategory and Race, Florida, 1981-2000





## AGE

Rhabdomyosarcoma is the most common type in all age groups. The rate of rhabdomyosarcoma was higher in young children (6.6 per million), decreased to 4.5 per million in those aged 5-9, and decreased to 3.3 per million for the age groups 10-14 and 15-19.

For fibrosarcoma, a nearly opposite age distribution was observed. Rates were fairly stable around 1.2 per million in childhood, but more than doubled in adolescence to 2.9 per million.

## SEX AND RACE

Rates of rhabdomyosarcoma in Florida were similar between races and sexes. For fibrosarcomas, rates were only slightly higher in males than in females. Between races, differences were more marked, with twice the incidence in Blacks as in Whites. That predominance was found also in the SEER registries, although the difference was smaller, only 50% higher in Blacks than in Whites.

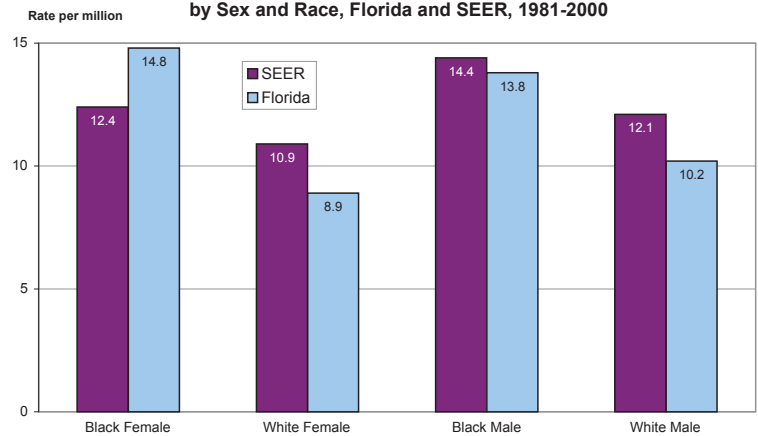
## SEER

The overall rate for STS was lower in Florida (10.4 per million) than in the SEER areas (11.4 per million). For rhabdomyosarcoma, rates were very similar between Florida and SEER. For fibrosarcoma, however, the rate in Florida was half of that in SEER. For Whites, this difference was significant: Florida (1.3 per million) and SEER (2.8 per million).

## TRENDS

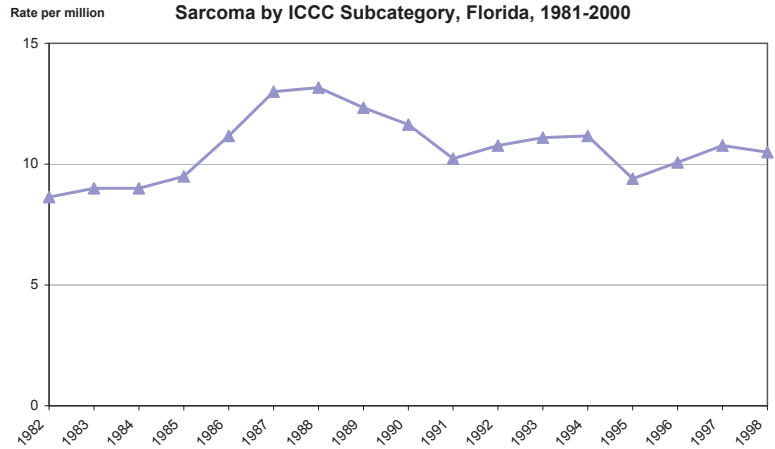
Unlike trends reported elsewhere <sup>2</sup>, no significant trend in STS as a whole, or for rhabdomyosarcoma in particular, was observed in Florida. Nevertheless, the incidence rate for rhabdomyosarcoma in Black children in 2000 was three times higher than in 1981. Trends for STS, however, have to be interpreted with caution. Modern diagnostic laboratory techniques for the classification of STS have shown varying degrees of misclassification in the group of childhood tumors comprising fibrosarcoma, rhabdomyosarcoma, undifferentiated neuroblastoma, and others <sup>3,4</sup>.

Figure IX-3. Age-Adjusted Incidence Rates of Soft Tissue Sarcoma by Sex and Race, Florida and SEER, 1981-2000



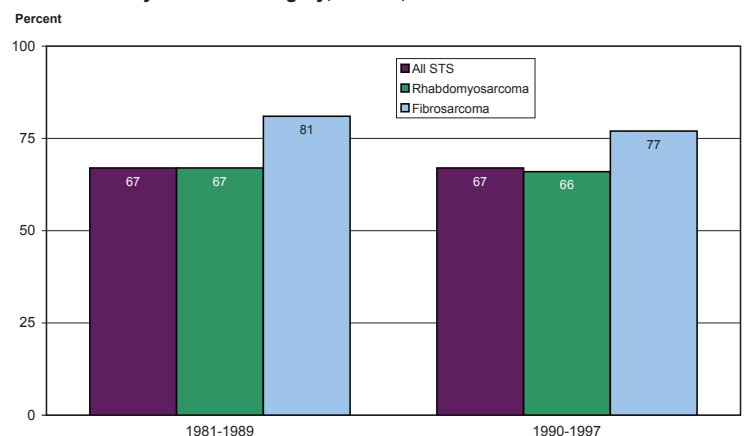
\* Differences in pathologic interpretation may have increased the incidence of KS in Blacks.

Figure IX-4. Trends in Age-Adjusted Incidence Rates of Soft Tissue Sarcoma by ICC Subcategory, Florida, 1981-2000



\* Trend is a 3-year moving average.

Figure IX-5. Five-year Survival for Soft Tissue Sarcoma by ICC Subcategory, Florida, 1981-1989 and 1990-1997



## SURVIVAL

Survival for rhabdomyosarcoma was not high, 66% after 5 years. It is known that approximately 15% of the cases of this tumor have metastatic disease at presentation<sup>5</sup>. In comparison, survival for fibrosarcoma was higher, 77% after five years. Unlike other reports<sup>2,6</sup> survival for rhabdomyosarcoma in Florida has not improved from the 1980s to the 1990s. Survival for this cancer was similar in both sexes, higher in those aged 0-9 and lowest in the 10-14 age group.

## RISK FACTORS

STS occasionally presents as part of congenital malformation syndromes: Li-Fraumeni-Syndrome and neurofibromatosis Type 1<sup>7,8</sup>. However, these account for only a small proportion of STS cases. Chemotherapy with procarbazine independently or in conjunction with radiation therapy is the only known risk factor for STS<sup>9,10</sup>. HIV-infected patients are at high risk of developing Kaposi sarcoma. However, this risk is low among HIV-infected children in Europe and North America; Kaposi sarcoma has been an extremely rare event in these age groups<sup>11,12</sup>.

Table IX-2. Risk factors for soft tissue sarcomas in children

Exposure or Characteristic	Comments	References
<i>Known risk factors</i>		
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.	13,14
Genetic conditions	Li-Fraumeni syndrome (associated with p53 mutations), and neurofibromatosis (associated with NF1 mutations)	7, 8
<i>Factors for which evidence is inconsistent or limited</i>		
Socioeconomic status	Low socioeconomic status is associated with increased risk.	15
Ionizing radiation (in utero)	Diagnostic x-rays during pregnancy were associated with 2-fold increase in risk in one study.	16
Parental use of recreational drugs	Parents use of marijuana and cocaine during the pregnancy was associated with increased risk in one study.	14,17

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# ICCC X. GERM-CELL, TROPHOBLASTIC AND OTHER GONADAL TUMORS

This ICCC classification groups germ cell tumors, trophoblastic and other gonadal (GCTOG) neoplasms into the following subcategories:

- intracranial and intraspinal germ-cell tumors (Xa)
- non-CNS, non-gonadal germ-cell tumors (Xb)
- gonadal germ-cell (Xc)
- gonadal carcinomas (Xd)
- unspecified malignant gonadal tumors (Xe).

Table X-1. Counts and Age-Specific and Age-Adjusted Incidence Rates of Germ Cell Neoplasms by ICCC Subcategory, Florida 1981-2000

	0-4		5-9		10-14		15-19		<15		<20	
	n	Rate	n	Rate	n	Rate	n	Rate	n	Rate	n	Rate
X All GCTOG	89	5.3	30	1.8	104	6.4	371	22.2	594	4.5	594	8.9
X(a) Intracranial and intraspinal germ-cell tumors	9	0.5	16	1	27	1.7	24	1.4	76	1.1	76	1.2
X(b) Other and unspecified non-gonadal germ-cell tumors	38	2.3	1	0.1	8	0.5	41	2.4	88	0.9	88	1.3
X(c) Gonadal germ-cell tumors	40	2.4	12	0.7	60	3.7	251	15	363	2.3	363	5.5
X(d) Gonadal carcinomas	0	0	0	0	3	0.2	47	2.8	50	0.1	50	0.8
X(e) Other/unspecified gonadal tumors	2	0.1	1	0.1	6	0.4	8	0.5	17	0.2	17	0.3

Rates are per 1,000,000 and age-adjusted to the 2000 U.S. (18 age groups) standard.

GCTOG tumors constitute another group of biologically diverse neoplasms with heterogeneous histological types, which accounted for 6% of all childhood cancers in Florida from 1981-2000.

Germ cell tumors originate in toti-potent primordial germ cells which undergo either embryonic (embryonal carcinomas, germinomatous tumors and teratomas) or extra-embryonic differentiation<sup>1</sup>. Embryonal carcinomas represent tumors of immature totipotent cells<sup>2</sup>. Germinomatous tumors display morphological features of undifferentiated germ epithelium: seminomas in the testis, dysgerminoma in the ovary and germinoma in the brain<sup>3</sup>. Teratomas display features that mimic the organ structures of all germ layers<sup>2</sup>. Yolk-sac tumors and choriocarcinoma follow an extra-embryonic differentiation<sup>1</sup>.

The clinical behavior and biologic characteristics of GCTOG, especially testicular cancer, are different depending on whether the age group affected is early childhood or adolescence.

Figure X-1. Age-Specific and Age-Adjusted Incidence Rates of Germ Cell Neoplasms by ICCC Subcategory, Florida, 1981-2000

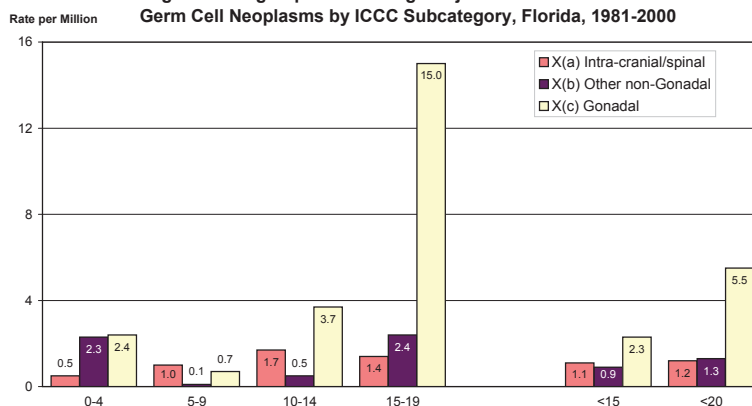
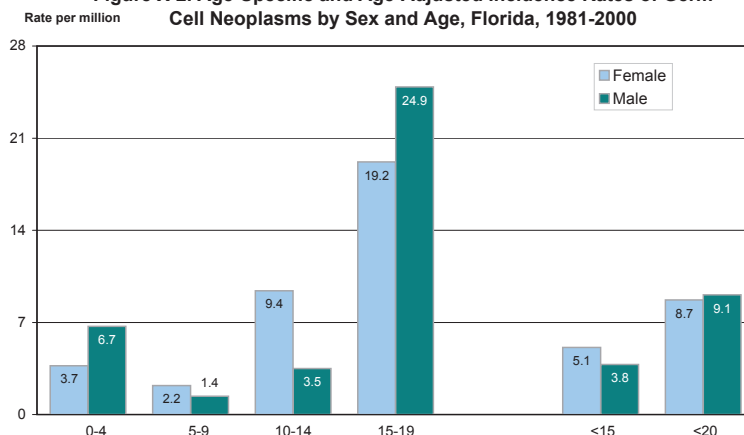


Figure X-2. Age-Specific and Age-Adjusted Incidence Rates of Germ Cell Neoplasms by Sex and Age, Florida, 1981-2000



In Florida, an average of 30 new cases of GCTOG occurred every year, corresponding to a total of 594 cases observed between 1981 and 2000. The majority, 70%, were located in the gonads (testes and ovaries), 13% were intracranial or intraspinal, and the remaining 17%, the so-called non-CNS non-gonadal tumors, occurred mostly in the mediastinum and retroperitoneum.

## AGE

The largest group of GCTOG tumors, gonadal tumors, showed a J-shaped distribution with age, with low incidence in the age group 5-9 and a peak incidence in adolescence with rates more than 5 times higher than in early childhood. The gonadal germ cell tumors and carcinomas made up 50% of all GCTOG diagnosed in those aged 0-19. Mediastinal and retroperitoneal tumors were more common in early childhood and adolescence with low incidence in ages 5-14. Intracranial tumors showed a low incidence in those younger than 5 years of age and a higher incidence in those 10-14.

## SEX

By sex, two J-shaped curves were observed, with higher rates in early childhood and adolescence. The curve in males was more pronounced than in females, and showed higher rates in early childhood and adolescence. In early puberty, ages 10-14, the rate was much higher for females than males.

In males, gonadal tumors of testicular tissue, including embryonal carcinomas, malignant teratomas or yolk-sac tumors, represented 73% of GCTOG tumors, followed by intracranial (germinomas in the brain) and intraspinal tumors (mostly sacrococcygeal teratomas) which made up 19%. Extra-gonadal tumors (8%) were relatively rare.

In females, 52% of GCTOG were gonadal germ cell tumors, (teratomas, dysgerminomas and yolk-sac tumors); 23% were extragonadal, mostly choriocarcinomas; 18% were gonadal carcinomas (ovarian cystadenocarcinomas); and only 6% were intracranial or intraspinal, mostly brain germinomas.

Figure X-3. Age-Adjusted Incidence Rates of Germ Cell Neoplasms by ICCS Subcategory and Sex, Florida, 1981-2000

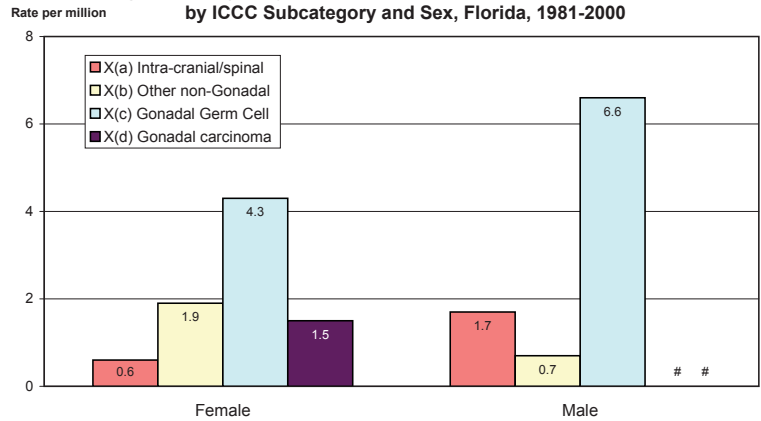


Figure X-4. Age-Specific and Age-Adjusted Incidence Rates of Germ Cell Neoplasms by Race and Age, Florida, 1981-2000

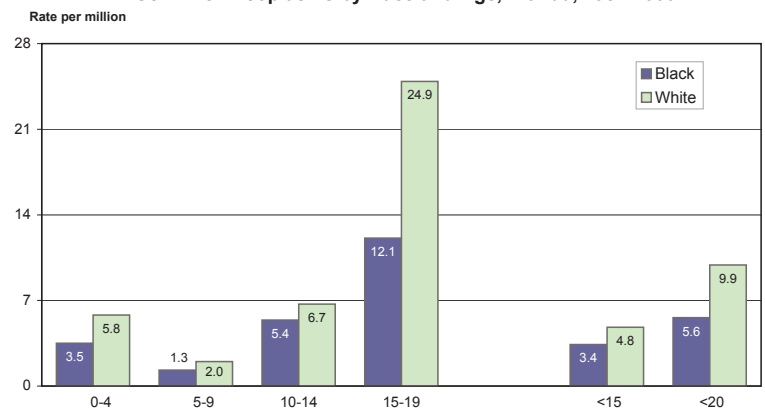
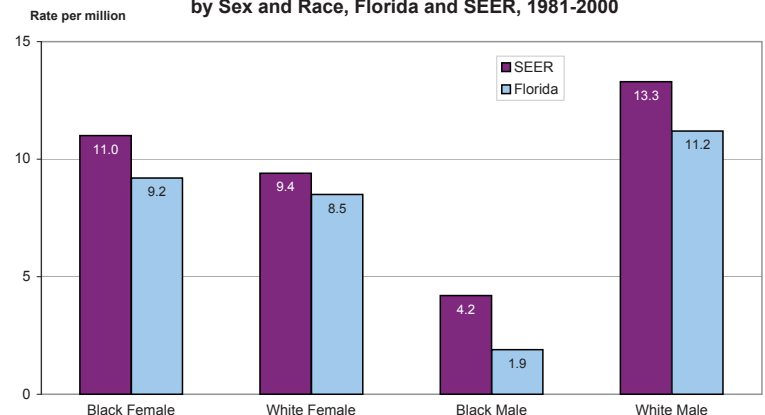


Figure X-5. Age-Adjusted Rates of Germ Cell Neoplasms by Sex and Race, Florida and SEER, 1981-2000



## RACE

GCTOG tumors were more common in Whites than in Blacks in every age group, especially in adolescence. Black males were the group least affected by GCTOG. Black females showed a rate four times higher than Black males. Conversely, in Whites, males presented a 30% higher rate than females. The distribution of GCTOG tumors by sex and race was unique, with White males and Black females more affected, closely followed by White females. Black males presented significantly lower rates than all other groups due to their lower incidence of testicular cancer, 0.4 per million compared to 8.4 per million in White males.

## SEER

Overall, testicular cancer rates in those aged 0-19 were significantly lower in Florida (6.6 per million) than in SEER (8.3 per million). The extremely low incidence of gonadal tumors in Black adolescent males in Florida, 0.4 per million compared to 1.6 per million in SEER, made a large contribution to this difference. The incidence of testicular cancer in Black Floridians aged 20 and older was also very low compared to SEER. For females younger than 20 in Florida, the incidence rate of ovarian carcinoma, 1.5 per million, was substantially higher than in SEER, 1.0 per million.

## TRENDS

There were no significant trends in the incidence of GCTOG tumors from 1981 to 2000.

## SURVIVAL

Survival for GCTOG tumors was generally high, 89% after 5 years for those diagnosed from 1990 to 1997. A slight improvement in survival rates was observed from the 1980s to the 1990s, more evident in adolescents than in those aged 10-14. In those less than 10 years of age, a decrease in survival rates was observed. Overall survival was substantially higher for Whites than for Blacks, 91% and 79% respectively. Gonadal tumors showed a higher survival rate than non-gonadal tumors.

## RISK FACTORS

The high degree of heterogeneity and the relative rarity of these tumors make the epidemiologic study of GCTOG difficult. The knowledge of risk factors for germ cell tumors is scarce and limited to testicular cancer in adolescents. Cryptorchidism and a family history of testicular germ cell tumor, long recognized as risk factors for cancer of the testis, indicate that exposures in early life may be critical to determining risk<sup>4,5</sup>.

Figure X-6. Trends in Age-Adjusted Incidence Rates of Germ Cell Neoplasms by ICCC Subcategory, Florida, 1981-2000

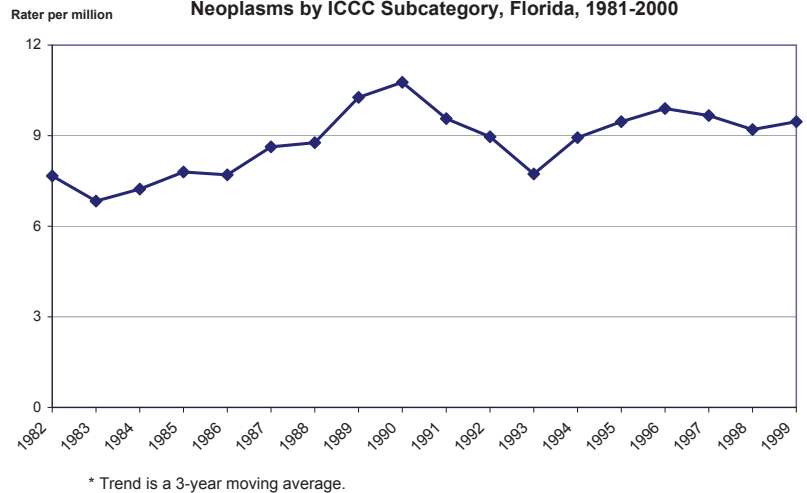


Figure X-7. Five-year Survival for Germ Cell Neoplasms by Sex, Race, and Age, Florida, 1981-2000

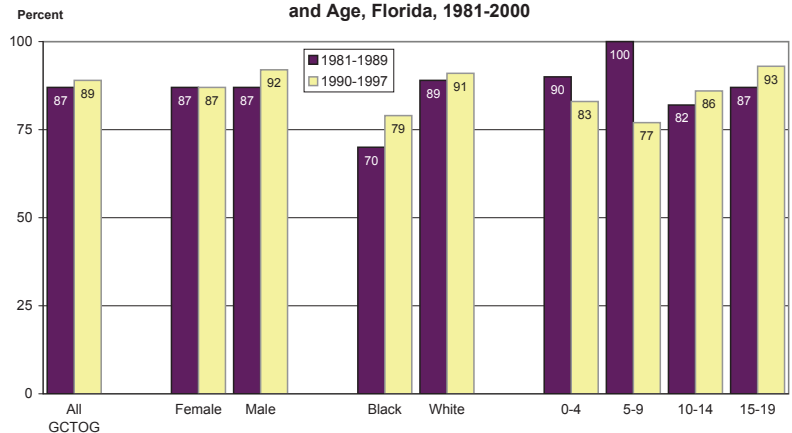


Table X-2. Current knowledge on causes of childhood malignant germ cell tumors

Exposure or Characteristic	Comments	References
<i>Known risk factors</i>		
Cryptorchidism	Risk is increased 2.5 - 11-fold. The contralateral as well as ipsilateral testis is at increased risk	4,6,7
<i>Factors for which evidence is suggestive but not conclusive</i>		
High maternal hormone levels during pregnancy	Use of oral contraceptives during pregnancy, high pre-pregnancy weight, bleeding, hyperemesis and spotting indicate high hormone levels.	4,6,8-10
Family history of germ cell tumor	When malignant germ cell tumors occur in the same family, they are usually of the same histologic type.	11,12
Hernia	Central nervous system and genitourinary anomalies have also been observed in germ cell tumor patients.	4,6,13
Pre-term birth	Excess risk was not explained by cryptorchidism.	14,15
Trauma	The causality of this association is not clear. Trauma may result in closer scrutiny and earlier detection of an existing tumor.	16-18
<i>Factors for which evidence is inconsistent or limited</i>		
Virus infection	E.g., mumps, cytomegalovirus, Epstein-B virus, and parvovirus B19	19-23
High birth weight		4,14,15
Prenatal X-ray exposure		14,24
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.	15,25,26
Constitutional chromosome abnormalities, particularly sex chromosome abnormalities	E.g., Klinefelter syndrome (47,XXY), inverted Y	27-31

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# ICCC XI. CARCINOMAS AND OTHER MALIGNANT NEOPLASMS

Carcinomas are malignancies which arise in epithelial tissues. In adults, they account for the majority of cancers, whereas in children they are relatively rare. Nevertheless, a variety of carcinomas occur in the 0-19 age group, especially in adolescents. Carcinomas as a group were the fourth-ranked pediatric cancer, after leukemia, brain tumors and lymphoma.

Carcinomas in these age groups varied widely in their anatomic location. Of 772 cases reported in Florida in the 20-year period under analysis, 268 (35%) were thyroid carcinoma and 196 (25%) were malignant melanoma. These two groups, the most important in numerical terms, correspond to subgroups (XIb) and (XIc) of the ICCC classification, respectively. The three other subgroups are (XIa) adrenocortical carcinomas, (XIc) nasopharyngeal carcinomas, and (XIe) other and unspecified carcinomas. Their relative weight in the group of carcinomas was 2%, 7%, and 31% respectively. The majority of Class XIe of the ICCC classification corresponds to skin cancers, squamous-cell and basal-cell carcinomas, which are not part of the list of cancers reportable to the Florida Cancer Data System.

## AGE

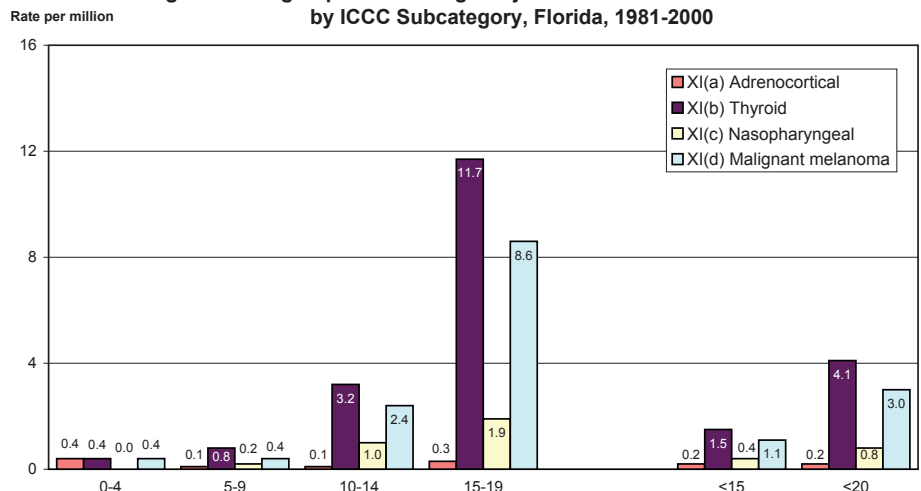
All cancers in this group showed an increasing trend with age. Overall, 71% of carcinomas occurred in adolescents; thyroid carcinoma was the most common subcategory of carcinoma in both childhood and adolescence.

Table XI-1. Age-Specific Incidence Rates of Carcinoma by ICCC Subcategory and Sex, Florida, 1981-2000

	Age Group	Total	Female	Male
XI All Carcinoma	0-4	2.1	1.5	2.8
	5-9	2.2	1.8	2.6
	10-14	9.1	11.2	7.2
	15-19	32.9	41.4	24.7
XI(a) Adrenocortical carcinoma	0-4	0.4	0.2	0.5
	5-9	0.1	0.1	0.1
	10-14	0.1	0.1	0
	15-19	0.3	0.4	0.2
XI(b) Thyroid carcinoma	0-4	0.4	0.4	0.3
	5-9	0.8	1	0.7
	10-14	3.2	5	1.4
	15-19	11.7	19.6	4.2
XI(c) Nasopharyngeal carcinoma	0-4	0	0	0
	5-9	0.2	0	0.4
	10-14	1	1	1
	15-19	1.9	1.6	2.1
XI(d) Malignant melanoma	0-4	0.4	0.2	0.5
	5-9	0.4	0.5	0.4
	10-14	2.4	2	2.7
	15-19	8.6	10.1	7.2
XI(f) Other and unspecified carcinomas	0-4	1.1	0.6	1.5
	5-9	0.7	0.2	1.1
	10-14	2.5	3	2
	15-19	10.4	9.8	11

Rates are per 1,000,000 and age-adjusted to the 2000 U.S. (18 age groups) standard.

Figure XI-1. Age-Specific and Age-Adjusted Incidence Rates of Carcinoma by ICCC Subcategory, Florida, 1981-2000



## SEX AND RACE

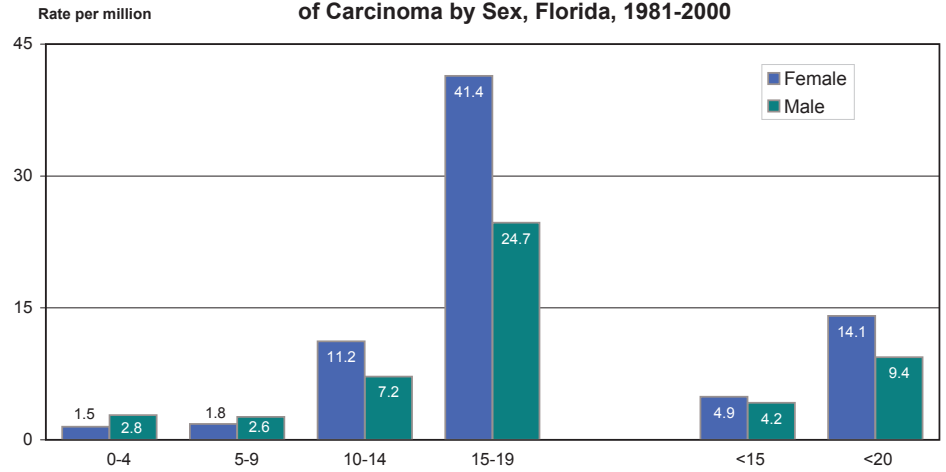
Whites were more affected than Blacks by carcinomas, with a ratio of 1.8. This difference in incidence results from thyroid cancer, which was 4 times more common in Whites than in Blacks. Malignant melanoma was virtually non-existent in Black children. On the other hand, carcinoma of the nasopharynx was 5 times more common in Blacks than in Whites, but far less common overall than either thyroid cancer or melanoma.

When sex is combined with race, White females had the highest incidence of all types of carcinoma, because thyroid carcinoma was more common in Whites and nearly 4 times more frequent in females than in males. This predominance of thyroid carcinoma in females also explains why the overall incidence of carcinoma in Black females was higher than in Black males. The incidence for malignant melanoma was 18% higher in White females than in White males.

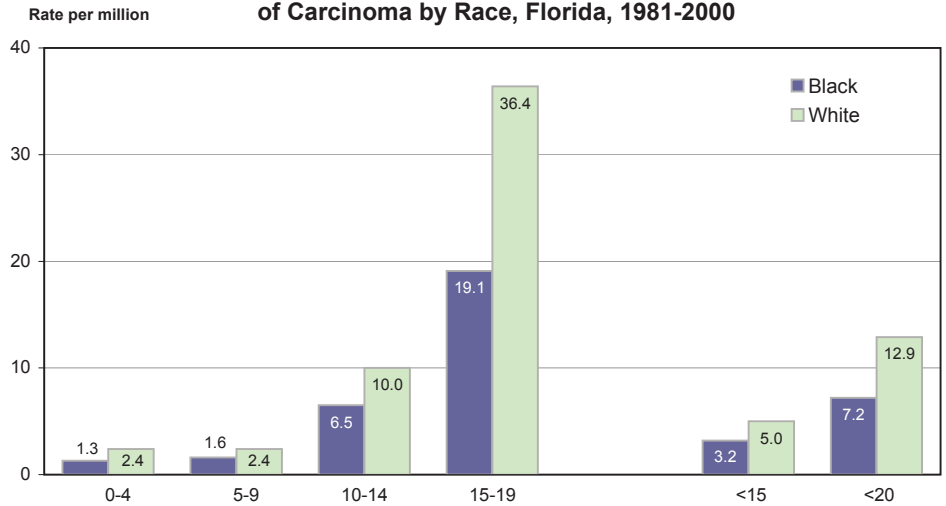
## SEER

The rates for both thyroid carcinoma and melanoma are higher in the SEER areas than in Florida. The lower rates of melanoma in Florida may be due to a higher percentage of White Hispanic children in Florida than in the SEER areas, since this ethnic group reportedly has a substantially lower incidence rate of melanoma than non-Hispanic Whites in the US<sup>1</sup>.

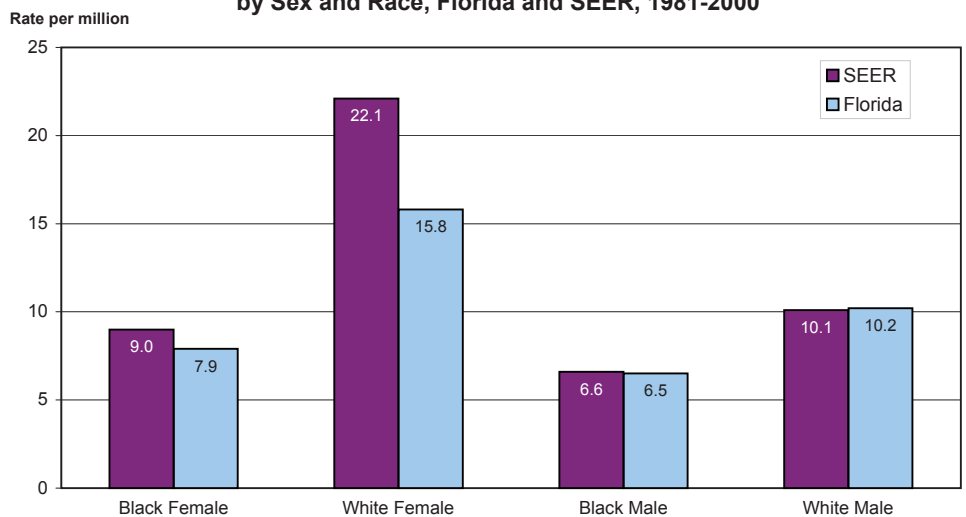
**Figure XI-2. Age-Specific and Age-Adjusted Incidence Rates of Carcinoma by Sex, Florida, 1981-2000**



**Figure XI-3. Age-Specific and Age-Adjusted Incidence Rates of Carcinoma by Race, Florida, 1981-2000**



**Figure XI-4. Age-Adjusted Incidence Rates of Carcinoma by Sex and Race, Florida and SEER, 1981-2000**



## TRENDS

Changing trends for both thyroid cancer and melanoma are apparent. The trend for thyroid cancer increases continuously from the beginning to the end of the period; an increasing trend for melanoma was only observed beginning in the mid-1990s.

The increase in thyroid cancer was +3.2 % per year for all ages combined. An even steeper increase was observed in adolescents, +4.2 % per year. Increasing thyroid cancer is attributed primarily to intensive diagnostic activity <sup>2,3</sup>.

Melanoma trends elsewhere have been apparent for adolescents, but not for children, and have been attributed to a complex picture of increasing exposure to risk factors such as ultraviolet radiation, as well as improved surveillance, the development of the “cult of body image”, and changes in diagnostic practices <sup>4</sup>. In Florida, the incidence rate of melanoma for all ages combined increased at +3.2 % per year from 1981 to 2000. In adolescents, this increase was also statistically significant, +2.9% per year.

## SURVIVAL

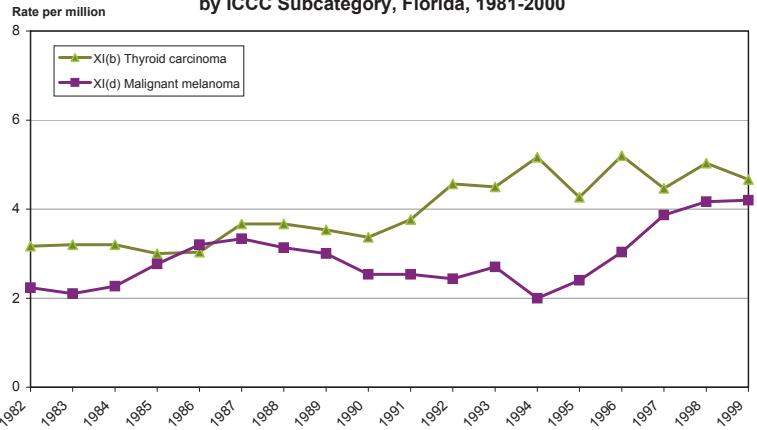
### Thyroid cancer

The prognosis for thyroid cancer is very good for both adults and children. In Florida, there have been no deaths registered in patients diagnosed with thyroid cancer before age 20. Survival for thyroid carcinoma in these age groups has been excellent since the 1970s. Despite being more advanced at the time of presentation and showing higher rates of recurrence than in adults, the prognosis of thyroid cancer in children and adolescents was better than in adults <sup>5</sup>.

### Malignant Melanoma

Five-year survival for pediatric melanoma has improved from 82% to 88% between the 1980s and the 1990s. Females aged less than age 20 presented better survival rates (94%) than males (81%). More awareness of exposure, together with a greater emphasis on body image may contribute to earlier detection, resulting in improvements in survival <sup>4</sup>.

Figure XI-5. Trends in Age-Adjusted Incidence Rates of Carcinoma by ICCS Subcategory, Florida, 1981-2000



\* Trends are 3-year moving averages.

Figure XI-6. Five-year Survival for Thyroid Carcinoma by Sex, Race, and Age, Florida, 1981-1989 and 1990-1997

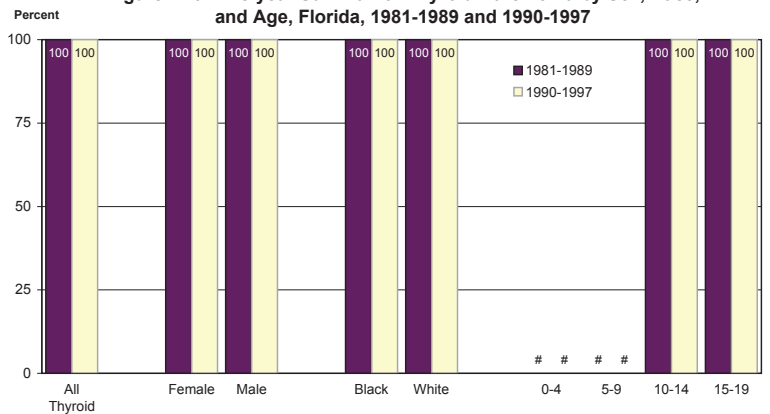
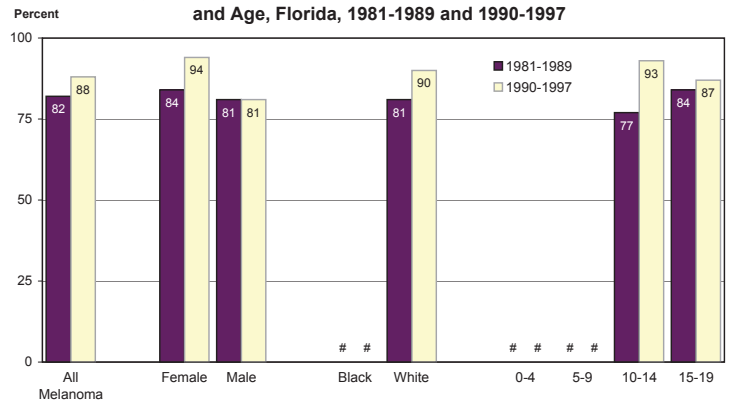


Figure XI-7. Five-year Survival for Melanoma by Sex, Race, and Age, Florida, 1981-1989 and 1990-1997



## RISK FACTORS

### Thyroid cancer

The best known cause of thyroid carcinoma is ionizing radiation, recently demonstrated again by the increase in the vicinity of the Chernobyl nuclear accident of 1986, especially in the childhood population <sup>6,7</sup>. Some thyroid carcinomas are linked to hereditary factors, as is the case with multiple endocrine neoplasia (MEN) syndromes type I, IIA and IIB. To a lesser extent, iodine deficiency, and conversely, high iodine intake, may be related to different types of thyroid carcinoma <sup>8,9</sup>.

### Malignant Melanoma

The most important risk factor for the development of adolescent and adult skin melanoma is believed to be intermittent sun exposure (ultraviolet radiation) during childhood, for which a minimum latency time for development of the cancer of 10 years seems likely <sup>10</sup>. In contrast, the risk of developing melanoma in childhood is more dependent on a family history of melanoma, the genetic disease Xeroderma Pigmentosum, or immunosuppression <sup>11,12</sup>.

Table XI-2. Current knowledge on causes of Thyroid Carcinoma

Exposure or Characteristic	Comments	References
<i>Known risk factors</i>		
Ionizing radiation exposure	Irradiation treatment for cancer, acne tinea capitis, enlarged thymus; environmental, atomic bomb in Japan, and nuclear power plant accident in Chernobyl	16-22
<i>Factors for which evidence is suggestive but not conclusive</i>		
Hormonal factors		13,17-22
<i>Factors for which evidence is suggestive but not conclusive</i>		
Benign thyroid disease		17-20
Inherited cancer susceptibility syndromes	Familial adenomatous polyposis and multiple endocrine neoplasia, types I, IIA, and IIB	17-20

Table XI-3. Current knowledge on causes of Melanoma


Exposure or Characteristic	Comments	References
<i>Known risk factors</i>		
Sun exposure	One or more episodes of severe sunburn associated with increased risk of subsequent melanoma	14,15
Melanocytic and dysplastic nevi		14,15

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ISBN: 978-0-615-16949-1