CA CANCER J CLIN 2014;00:00-00

Childhood and Adolescent Cancer Statistics, 2014

Elizabeth Ward, PhD¹; Carol DeSantis, MPH²; Anthony Robbins, MD, PhD³; Betsy Kohler, MPH⁴; Ahmedin Jemal, DVM, PhD⁵

In this article, the American Cancer Society provides estimates of the number of new cancer cases and deaths for children and adolescents in the United States and summarizes the most recent and comprehensive data on cancer incidence, mortality, and survival from the National Cancer Institute, the Centers for Disease Control and Prevention, and the North American Association of Central Cancer Registries (which are reported in detail for the first time here and include high-quality data from 45 states and the District of Columbia, covering 90% of the US population). In 2014, an estimated 15,780 new cases of cancer will be diagnosed and 1960 deaths from cancer will occur among children and adolescents aged birth to 19 years. The annual incidence rate of cancer in children and adolescents is 186.6 per 1 million children aged birth to 19 years. Approximately 1 in 285 children will be diagnosed with cancer before age 20 years, and approximately 1 in 530 young adults between the ages of 20 and 39 years is a childhood cancer survivor. It is therefore likely that most pediatric and primary care practices will be involved in the diagnosis, treatment, and follow-up of young patients and survivors. In addition to cancer statistics, this article will provide an overview of risk factors, symptoms, treatment, and long-term and late effects for common pediatric cancers. CA Cancer J Clin 2014;000:000-000. © 2014 American Cancer Society.

Keywords: childhood cancer, adolescent cancer, pediatric cancer, epidemiology

Introduction

The diagnosis of cancer in children and adolescents is a life-altering event for them as well as their families. Although advances in treatment have increased the overall 5-year survival rate for childhood cancers to approximately 80%, cancer is still the second leading cause of death (following accidents) in children aged 5 to 14 years. Depending on the type of cancer and treatment received, patients who survive 5 years may remain at risk of recurrence or progression of their primary cancer and be at an increased risk of developing subsequent malignant neoplasms, chronic diseases, and functional impairments. It is important that survivors of childhood and adolescent cancer are monitored for long-term and late effects.

In this article, we provide the most recent data on incidence, mortality, and survival rates and trends for cancers in children and adolescents. We also provide an overview of information on risk factors, symptoms, treatment, and important long-term and late effects for the most common cancers that occur in this age group, which includes leukemias and lymphomas, brain and central nervous system (CNS) tumors, embryonal tumors, sarcomas of bone and soft tissue, and gonadal germ cell tumors.

Materials and Methods

Incidence, Mortality, and Survival Data

Two sources were used for cancer incidence data reported in this article. The Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute reports long-term, high-quality, population-based incidence data covering up to 28% of the US population. Data for incidence trends (1975-2010) are from the SEER 9 registries and incidence rates (2001-2010) by single year of age were based on SEER 18 registries. The North American Association of Central Cancer Registries (NAACCR) compiles and reports incidence data for 1995 onward from cancer registries that participate in the SEER program or the Centers for Disease Control and Prevention's National Program of Cancer Registries, covering up to 95% of the US population. Data for incidence rates for the most recent 5 years (2006-2010), including rates by sex, race/ethnicity, and 5-year age group, are from NAACCR and comprise data from 45 states and the District of Columbia,

¹National Vice President, Intramural Research, American Cancer Society, Atlanta, GA; ²Epidemiologist, Surveillance and Health Services Research, American Cancer Society, Atlanta, GA; ³Director, Surveillance and Health Services Research, American Cancer Society, Atlanta, GA; ⁴Executive Director, North American Association of Central Cancer Registries, Springfield, IL; ⁵Vice President, Surveillance and Health Services Research, American Cancer Society, Atlanta, GA

Corresponding author: Carol DeSantis, MPH, Surveillance and Health Services Research, American Cancer Society, 250 Williams St, NW, Atlanta GA 30303; carol.desantis@cancer.org

DISCLOSURES: The authors report no conflicts of interest.

doi: 10.3322/caac.21219. Available online at cacancerjournal.com

covering 90% of the US population.⁶ Further details on exclusions from the SEER and NAACCR incidence data are available elsewhere.^{2,7} Incident cancer cases are classified by histology into 12 major groups using the International Classification of Childhood Cancer.⁸ Mortality data were obtained from the Centers for Disease Control and Prevention's National Center for Health Statistics as reported by the SEER program.⁹

All cancer cases and deaths were analyzed using SEER*-Stat software, which incorporates population data from the US Census Bureau. ¹⁰ Incidence and death rates were age-standardized to the 2000 US standard population and are expressed per million children. Observed (rather than relative) survival statistics are reported as it is not necessary to adjust for lower life expectancy with increasing age for children, as is often done for survival statistics in adults. Changes in observed survival from 1975 through 1979 to 2003 through 2009 and comparisons of 5-year, 10-year, and 15-year survival rates (1991-2000) by cancer type were based on data from the SEER 9 registries, while overall survival (2003-2009) was based on data from the SEER 18 registries. ^{4,11}

Projected Cancer Cases and Deaths in 2013

The precise number of new cancer cases diagnosed each year in the nation and in every state is unknown because cancer registration is incomplete in some states. Furthermore, the most recent year for which incidence and mortality data are available lags 3 to 4 years behind the current year due to the time required for data collection, compilation, and dissemination. Therefore, we projected the numbers of new cancer cases among children and adolescents in the United States in 2014 using a 3-step spatiotemporal model based on 1995 through 2010 high-quality incidence data from 49 states and the District of Columbia. All states did not meet highquality data standards for all years and Minnesota did not submit incidence data to the NAACCR during the 2012 call for data. For the complete details of this methodology, please refer to Zhu et al. 12 We then calculated the estimated number of cases by cancer site by applying the percentage of cases for each site diagnosed during 2006 to 2010 from the NAACCR analytic file to the total number of estimated cases in both children and adolescents.⁶ Estimated numbers of benign and borderline brain tumors in children and adolescents in 2014 were calculated by applying the percentage of all brain tumors that were benign or borderline during 2006 to 2010 in the NAACCR analytic file to our estimates of malignant brain tumors. We estimated the number of cancer deaths expected to occur in children and adolescents in 2014 in the United States overall by applying the percentage of deaths that occurred in the United States in children aged birth to 14 years and 15 to 19 years in 2010 to the

overall estimated number of cancer deaths expected to occur in the United States in 2014 as published previously. 9,13

Other Statistics

The probability of developing cancer before age 15 years and 20 years is estimated by the National Cancer Institute's Dev-Can software based on the average experience of the general population and may overestimate or underestimate individual risk due to differences in exposures or genetic susceptibility.¹⁴

Selected Findings

Cancer Occurrence

An estimated 10,450 new cases and 1350 cancer deaths are expected to occur among children (those aged birth-14 years) in 2014, and an additional 5330 new cases and 610 cancer deaths are expected among adolescents (those aged 15-19 years). These cancers represent 1% of all new cancers diagnosed in the United States. The most common cancers among children and adolescents vary by age (Fig. 1). Cancers that are most common in children are acute lymphoblastic leukemia (ALL) (26%), brain and central nervous system (CNS) tumors (21%), neuroblastoma (7%), and non-Hodgkin lymphoma (NHL) (6%) (Fig. 1). Hodgkin lymphoma (HL) (15%), thyroid carcinoma (11%), brain and CNS tumors (10%), and testicular germ cell tumors (8%) are the 4 most common cancers diagnosed in adolescents (Fig. 1). A child born in the United States has a 0.24% chance of developing cancer before age 15 years and a 0.35% chance of developing cancer before age 20 years; this is equivalent to on average 1 in 408 children being diagnosed with cancer before age 15 years and 1 in 285 children being diagnosed with cancer before age 20 years.

An estimated 379,112 survivors of childhood and adolescent cancer (diagnosed at ages birth-19 years) were alive in the United States as of January 1, 2010. The top 3 cancers among childhood cancer survivors are ALL, brain and CNS tumors, and HL (Table 1). Most (70%) survivors of childhood and adolescent cancer are aged 20 years or older. Approximately 1 in 530 young adults between the ages of 20 years and 39 years is a survivor of childhood cancer.

Table 2 summarizes differences in cancer incidence and mortality by sex and race/ethnicity in 2006 to 2010 for children and adolescents, along with differences in survival for the years 2003 to 2009. In children, incidence and mortality rates are lower in girls than boys, while survival rates are similar. Among adolescents, overall incidence rates are similar between boys and girls, while mortality rates are lower and survival is higher for girls. Some of these differences may reflect the different types of cancers that occur in adolescent boys compared to girls.

Cancer incidence, mortality, and survival rates also vary by race and ethnicity. Non-Hispanic white (white) and

F1

T1

T2

0

 \mathbf{R}

CA CANCER J CLIN 2014;00:00-00

Children (Ages 0-14)

Acute lymphocytic leukemia 2.670 (26%) Brain and CNS 2,240 (21%) Neuroblastoma* 710 (7%) Non-Hodgkin lymphoma 620 (6%) Wilms tumor 510 (5%) Acute myeloid leukemia 500 (5%) Bone tumors[†] 450 (4%) Hodgkin lymphoma 380 (4%) Rhabdomyosarcoma 340 (3%) Retinoblastoma 280 (3%) All sites

10,450

Adolescents (Ages 15-19)



FIGURE 1. Estimated New Cases of Childhood and Adolescent Cancers, United States, 2014.
Estimates are for malignant cancers only and are rounded to the nearest 10. In addition, 730 children and 630 adolescents will be diagnosed with benign and borderline brain tumors in 2014. *Includes ganglioneuroblastoma. †Bone tumors include osteosarcoma and Ewing sarcoma.

Hispanic children have the highest incidence rates for childhood and adolescent cancers. Although incidence rates are substantially lower for non-Hispanic black (black) children and adolescents than for whites and Hispanics, death rates are similar due to lower survival rates in blacks. Incidence and mortality rates for Asian/Pacific Islander children and adolescents are lower than those for whites and generally similar to rates in black children. American Indian/Alaska Native children have the lowest cancer incidence and mortality of all racial/ethnic groups. The 5-year survival rates for American Indian/Alaska Native children and adolescents are in the same range as those for other racial and ethnic minority groups. Reasons for differences in the incidence of childhood cancers by race and ethnicity in the United States are not well understood. Unlike many adult cancers, childhood and adolescent cancer incidence is not consistently higher among populations with lower socioeconomic status. 15-17 In general, the incidence of pediatric cancer is higher in industrialized countries than in developing countries, but international patterns differ by cancer type 18,19 for reasons that are generally unknown.

Racial and ethnic disparities in survival for childhood and adolescent cancers have been noted previously. Factors that could potentially be associated with these disparities include socioeconomic status, parental education, health insurance status, timely diagnosis, enrollment in cooperative group clinical trials, knowledge about the cancer diagnosis, quality of treatment and supportive care, differences in disease biology, genetic polymorphisms in the metabolism of

chemotherapeutic drugs, and variations in adherence to therapy.²⁰⁻²²

Trends in Incidence, Mortality, and Survival

The incidence rate of pediatric cancer in the United States has increased slightly at an annual rate of 0.6% since 1975.² Between 1975 and 2010, incidence rates increased for 4 cancer sites, with annual percent changes ranging from 0.7% to 1.2% per year; they decreased for 1 cancer type and

TABLE 1. US Childhood and Adolescent Cancer Survivors by Cancer Site, as of January 1, 2010

	COMPLETE PREVALENCE COUNTS BY AGE AT PREVALENCE			
SITE	AGES BIRTH TO 19	AGES 20+	ALL AGES	
All sites	113,782	265,330	379,112	
Acute lymphocytic leukemia	30,171	30,318	60,489	
Acute myeloid leukemia	4,045	4,222	8,267	
Hodgkin lymphoma	4,514	30,739	35,253	
Non-Hodgkin lymphoma	6,442	16,301	22,743	
Brain and CNS	20,430	38,653	59,083	
Neuroblastoma	9,704	9,748	19,452	
Wilms tumor	7,831	15,707	23,538	
Bone tumors	3,766	9,366	13,132	
Soft tissue sarcomas	6,849	24,599	31,448	
Testicular germ cell tumors	2,755	17,890	20,645	
Ovarian germ cell tumors	2,464	14,628	17,092	

CNS indicates central nervous system.

Note: Does not include benign and borderline brain tumors.

Source: Howlader et al, 2013.2

TABLE 2. Incidence, Mortality, and Survival Rates for Childhood and Adolescent Cancers by Sex and Race/Ethnicity

	AGES BIRTH TO 14			AGES 15 TO 19		
CHARACTERISTIC	INCIDENCE, 2006-2010*	MORTALITY, 2006-2010*	OBSERVED SURVIVAL (%), 2003-2009	INCIDENCE, 2006-2010*	MORTALITY, 2006-2010*	OBSERVED SURVIVAL (%), 2003-2009
Sex						
Boys	178.0	23.3	81.3	237.7	34.5	80.0
Girls	160.1	21.1	82.0	235.5	24.7	85.4
Race/ethnicity						
Non-Hispanic White	178.2	22.4	84.2	259.4	29.0	85.9
Non-Hispanic Black	134.5	21.9	75.3	171.9	30.6	76.8
Hispanic	167.3	22.6	80.3	220.7	32.4	75.8
Asian/Pacific Islander	131.9	19.1	78.3	167.8	25.6	80.4
American Indian/Alaska Native†	117.1	15.8	78.5	200.1	24.0	77.3

^{*}Rates are per 1,000,000 and age-adjusted to the 2000 US standard population.

Note: Incidence rates include benign and borderline brain tumors.

Data sources: Incidence: North American Association of Central Cancer Registries; Mortality: National Center for Health Statistics and the Centers for Disease Control and Prevention; Survival: Surveillance, Epidemiology, and End Results (SEER) program, 18 SEER Registries, National Cancer Institute.

F2 were stable for 7 cancer sites (Fig. 2). Similar incidence patterns were observed in Europe.²³ The reasons for increasing incidence rates are largely unknown. It is possible that some of this increase may be due to changes in environmental factors. Improved diagnosis and access to medical care over time may also have contributed, as without medical care some children may die of infections or other complications of their cancers without ever being diagnosed.²⁴

The sharp rise in the incidence of CNS tumors that occurred in the 1980s is thought to be largely due to the introduction of magnetic resonance imaging (MRI) and stereotactic biopsy, leading to a more accurate diagnosis (see section on CNS tumors below).²⁵

Death rates for all childhood and adolescent cancers combined declined steadily by an average of 2.1% per year since 1975, resulting in an overall decline of more than 50%.

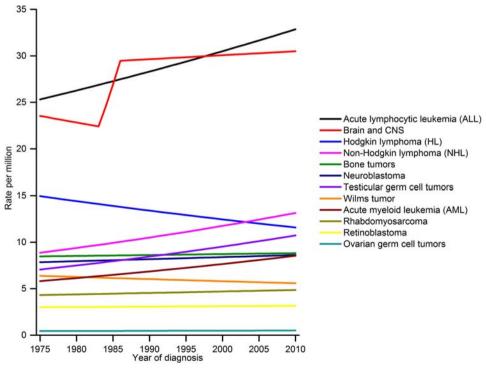


FIGURE 2. Trends in Pediatric Cancer Incidence Rates by Site, Ages Birth to 19 Years, 1975 to 2010.

CNS indicates central nervous system. Note: Lines represent joinpoint fitted trends. Benign and borderline brain tumors are not included. Malignant bone tumors include osteosarcoma and Ewing sarcoma. Average annual percent change for cancers with significant trends during 1975 through 2010: acute lymphocytic leukemia (0.7*), acute myeloid leukemia (1.1*), non-Hodgkin lymphoma (1.1*), testicular germ cell tumors (1.2*), and Hodgkin lymphoma (-0.7*). Source: Surveillance, Epidemiology, and End Results (SEER) program, 9 SEER Registries, National Cancer Institute.

O

R

[†]Based on data from Indian Health Service Contract Health Service Delivery Areas.

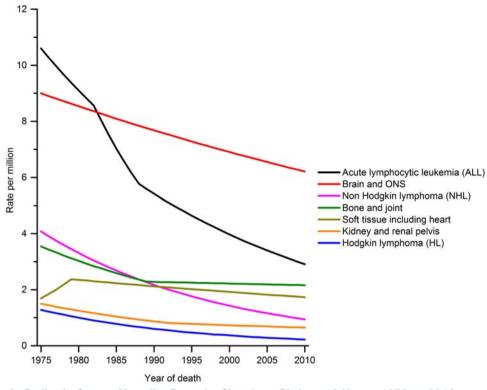


FIGURE 3. Trends in Pediatric Cancer Mortality Rates by Site, Ages Birth to 19 Years, 1975 to 2010.

ONS indicates other nervous system. Note: Lines represent joinpoint fitted trends. The average annual percent change for cancers with significant trends during the most recent period: acute lymphocytic leukemia (-3.1* during 1988-2010), brain (-1.1* during 1975-2010), non-Hodgkin lymphoma (-4.1* during 1975-2010), soft tissue (-1.0* during 1979-2010), kidney (-1.2* during 1992-2010), and Hodgkin lymphoma (-4.9* during 1975-2010). Source: National Center for Health Statistics, Centers for Disease Control and Prevention.

Mortality declines were observed for all major sites shown F3 in Figure 3, with the steepest declines noted in HL, NHL, and ALL. Between 1975 and 2009, there were substantial improvements in 5-year survival rates for many types of childhood cancer due to improved treatment and supportive T3 care (Table 3). Although children who survive 5 years after the diagnosis of their first cancer continue to be at an increased risk of morbidity and mortality related to the cancer and its treatment, an analysis of 5-year 10-year, and 15year survival among childhood and adolescent cancer patients diagnosed between 1991 and 2000 found that for the most part children who survived 5 years after the diagnosis of their primary tumor had a high probability of subsequent survival (Table 4). The cancers with the greatest declines in survival between 5 and 15 years after diagnosis, reflecting continued mortality related to the disease or its treatment, were medulloblastoma (12%), ependymoma (9%), osteosarcoma (7%), and Ewing sarcoma (ES) (7%) (Table 4).

Prevention and Early Detection

In contrast to cancers in adults, only a relatively small percentage of all childhood cancers have known preventable causes. Ionizing radiation exposure is a well-recognized risk factor for cancer in children and adolescents based on studies of medical and environmental radiation exposure. The association between low doses of ionizing radiation received by the fetus in utero from diagnostic radiography and the subsequent risk of leukemia and other childhood cancers was demonstrated in the 1950s. ²⁶ As a result, precautions have been taken to minimize radiation exposure during pregnancy. Radiation exposure from diagnostic computed tomography scans is higher and more variable than exposures from conventional x-rays, and studies suggest that radiation exposure early in life increases the long-term risk of leukemia and brain cancer. ^{27,28} Health care providers are encouraged to limit the use of computed tomography scans in children and pregnant women to those situations in which there is a definite clinical indication and to optimize scans by using the lowest possible radiation dose. ²⁹

In recent years, a number of studies have demonstrated associations between accelerated fetal growth and/or high birth weight and pediatric cancers, including ALL, CNS tumors, Wilms tumor (WT), NHL, and embryonal rhabdomyosarcoma, while low birth weight has been associated with acute myeloid leukemia (AML) and some CNS tumor subtypes. 30-37 Although numerous epidemiologic studies have investigated potential environmental causes of childhood cancers, few strong or consistent associations have been found. The International Agency for Research on

TABLE 3. Pediatric Cancer 5-Year Observed Survival Rates for 2 Time Periods, Ages Birth to 19 Years

	YEAR OF DIAGNOSIS		
	1975-1979, %	2003-2009,* %	
All ICCC sites	63%	83%	
Leukemia	48%	84%	
Acute lymphocytic leukemia	57%	90%	
Acute myeloid leukemia	21%	64%	
Lymphomas and	72%	91%	
reticuloendothelial neoplasms			
Hodgkin lymphoma	87%	97%	
Non-Hodgkin lymphoma	47%	85%	
Brain and CNS	59%	75%	
Ependymoma	37%	81%	
Astrocytoma	69%	85%	
Medulloblastoma	47%	70%	
Neuroblastoma and	54%	79%	
ganglioneuroblastoma			
Retinoblastoma	92%	99%	
Wilms tumor	75%	90%	
Hepatic tumors	25%	74%	
Bone tumors	49%	73%	
Osteosarcoma	45%	71%	
Ewing sarcoma	42%	72%	
Rhabdomyosarcoma	49%	64%	
Testicular germ cell tumors	74%	96%	
Ovarian germ cell tumors	75%	94%	
Thyroid carcinoma	99%	98%	
Melanoma	83%	95%	

CNS indicates central nervous system; ICCC, International Classification of Childhood Cancers.

Note: Does not include benign and borderline brain tumors.

Source: National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program, 9 SEER registries.

Cancer has concluded there is sufficient evidence that parental smoking increases the risk of hepatoblastoma and limited evidence for an association with childhood leukemia (particularly ALL).³⁸ They also found limited evidence that maternal exposure to paint is linked with childhood leukemia.³⁸ It is reasonable to suggest that pediatric tumors reflect, at least in part, an inherent risk associated with the complex process of normal development and chance rather than a response to an external exposure. At the same time, there is substantial evidence that the process of development occurring in immature cells and organisms renders them more vulnerable to toxic exposures than mature, differentiated cells.³⁹ Given the well-documented role of germline and somatic mutations in the development of some childhood cancers, as well as multiple mechanisms through which exogenous exposures can alter development and cause cancer, it is important to minimize population exposures to toxic substances to protect children and other vulnerable populations.³⁹

Early diagnosis of cancer in children is often difficult because of the similarity of some symptoms to those of the more common diseases of childhood. ⁴⁰ Some common symptoms of childhood cancer that should alert parents and health care providers include an unusual mass or swelling; unexplained pallor or loss of energy; a sudden tendency to bruise; a persistent, localized pain or limping; a prolonged, unexplained fever or illness; frequent headaches, often with vomiting; sudden changes in vision; and excessive, rapid weight loss. Further information on symptoms for specific cancer types will be discussed in later sections.

Information for Selected Cancer Sites

Leukemia and Lymphoma

The 2 most common types of leukemia that occur in children and adolescents are ALL and AML. Chronic leukemias are very rare in this age group. ALL accounts for approximately 80% of leukemia cases in children and 56% of leukemia cases in adolescents. AML is less common in children than ALL, comprising approximately 15% of leukemia cases in children and 31% of cases in adolescents. HL accounts for approximately 38% of lymphoma cases in children and approximately 65% of cases in adolescents, while NHL accounts for 62% of lymphoma cases in children and approximately 35% of lymphoma cases in adolescents.

Acute Lymphocytic Leukemia

An estimated 2670 children and 410 adolescents will be diagnosed with ALL in 2014 (Fig. 1). ALL is the most commonly diagnosed cancer in children, accounting for 26% of cancers diagnosed in those aged birth to 14 years. ALL is more common in industrialized countries than in developing countries. In industrialized countries, there is a sharp peak in ALL incidence rates at ages 2 to 4 years; such a peak is not apparent among children in developing countries. ¹⁹ The characteristic age peak for ALL in the United States is striking for white and Hispanic children, but less so for black children (Fig. 4). In the United States, ALL is more common in boys than in girls and Hispanic and white children than in black children (Table 5).

There is evidence that some cases of ALL arise in utero, including the frequent concordance of ALL in monozygotic twins, with an identical leukemic clone identified in some studies. ⁴¹ Inherited risk factors associated with ALL include trisomy 21 (Down syndrome), which confers a 10-fold to 20-fold increased risk; certain genetic syndromes (Bloom syndrome, Fanconi anemia, and Nijmegen breakage syndrome); and congenital immunodeficiency diseases. ⁴¹ Higher birth weight has been associated with a higher risk of ALL in a number of studies. ^{37,42} According to the International Agency for Research on Cancer, there is limited evidence that parental smoking and maternal exposure to paint increase the risk for childhood leukemia (particularly ALL). ³⁸ Recent studies have also suggested

F4

T5

^{*}Cases were followed through 2010.

CA CANCER | CLIN 2014:00:00-00

TABLE 4. Long-Term (5-Year, 10-Year, and 15-Year) Observed and Conditional Survival for Pediatric Cancers by Site, Ages Birth to 19 Years, United States, 1991 to 2000*

	OBSERVED SURVIVAL			ESTIMATED PROBABILITY OF 15-YEAR SURVIVAL	
	5-YEAR	10-YEAR	15-YEAR	AMONG PATIENTS WHO HAVE SURVIVED 5 YEARS	
All ICCC sites	78%	76%	74%	95%	
Leukemia	74%	71%	70%	95%	
Acute lymphocytic leukemia	82%	79%	78%	95%	
Acute myeloid leukemia	46%	43%	43%	94%	
Lymphomas and reticuloendothelial neoplasms	87%	85%	83%	96%	
Hodgkin lymphoma	95%	93%	91%	96%	
Non-Hodgkin lymphoma	78%	77%	76%	97%	
Brain and CNS	72%	69%	66%	92%	
Ependymoma	67%	59%	58%	86%	
Astrocytoma	83%	81%	79%	95%	
MedulÍoblastoma	70%	64%	58%	84%	
Neuroblastoma and ganglioneuroblastoma	69%	66%	65%	94%	
Retinoblastoma	97%	96%	95%	95%	
Wilms tumor	92%	90%	89%	99%	
Hepatic tumors	51%	51%	51%	97%	
Bone tumors	68%	63%	61%	99%	
Osteosarcoma	66%	60%	59%	90%	
Ewing sarcoma	66%	60%	59%	90%	
Rhabdomyosarcoma	65%	62%	61%	90%	
Testicular germ cell tumors	94%	93%	93%	94%	
Ovarian germ cell tumors	96%	96%	96%	100%	
Thyroid carcinoma	98%	98%	97%	99%	
Melanoma	94%	91%	89%	95%	

CNS indicates central nervous system; ICCC, International Classification of Childhood Cancers.

Note: Does not include benign and borderline brain tumors.

Source: Surveillance, Epidemiology, and End Results (SEER) program, 9 SEER registries, National Cancer Institute.

that early exposure to infections (such as in infant daycare settings) may be protective for childhood ALL. A3,44 Chemical and physical exposures associated with childhood leukemia are more strongly associated with AML than ALL.

Improved treatment for ALL in childhood increased the 5-year survival rate from 57% between 1975 and 1979 to 90% between 2003 and 2009 (Table 3). Treatment generally consists of 4 to 6 weeks of induction chemotherapy initially administered in the hospital, followed by several months of consolidation chemotherapy and 2 to 3 years of maintenance chemotherapy. Allogeneic bone marrow transplantation is recommended for some children whose leukemia has high-risk characteristics at diagnosis and for children who develop recurrence after remission. It may also be used if the leukemia does not go into remission after successive courses of induction chemotherapy.

Disparities in survival between white and black children treated for ALL have been documented in a number of studies. 20,21,46 Notably, the survival disparity has diminished in recent years from a 21% difference in 5-year survival for ALL during 1980 through 1984 (68% vs 47%, respectively, in whites and blacks) to a 6% difference from 2003 through 2009 (90% vs 84%, respectively, in whites

and blacks).¹¹ Survival for infants is lower than that for children aged 1 to 14 years, largely attributable to the high percentage of ALL cases with mixed lineage leukemia gene rearrangements noted among infants.⁴⁷

Long-term adverse health effects among children treated for ALL include neurocognitive defects, growth deficiency, and an increased risk of second cancers such as AML or lymphoma. Early forms of CNS prophylaxis that combined high doses of radiation and intrathecal chemotherapy resulted in a high risk of neurocognitive defects; less-toxic therapies that avoid the use of radiation have reduced, but not eliminated, these risks. In addition, children treated with cranial radiation therapy (CRT) for ALL in the past had an increased risk of developing CNS and head and neck tumors. Radiation therapy is now used in only a small fraction of patients with ALL who are at high risk of CNS recurrence. Patients with ALL who are treated with anthracyclines are at risk for late cardiac effects. 41

Acute Myeloid Leukemia

An estimated 500 children and 230 adolescents will be diagnosed with AML in 2014. The incidence of AML is highest in the first year of life (Fig. 4). Incidence rates for AML are slightly higher in Hispanic children compared

^{*}Cases were diagnosed between 1991 and 2000 and followed through 2010

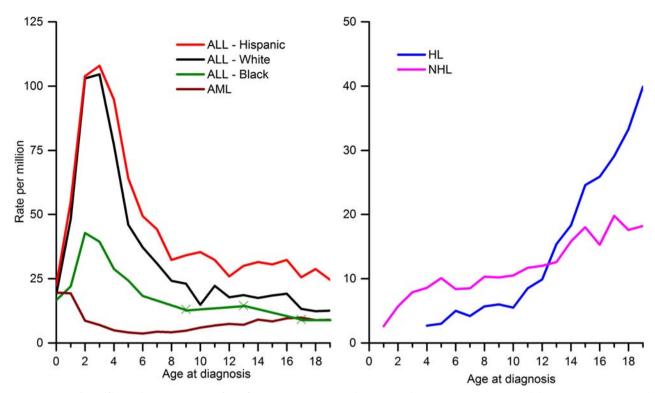


FIGURE 4. Age-Specific Incidence Rates of (*Left*) Acute Lymphocytic Leukemia (ALL) by Race/Ethnicity and Acute Myeloid Leukemia (AML) for All Races Combined and (*Right*) Non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL), 2001 to 2010.

Rates are not shown when based on fewer than 25 cases. Data for whites and blacks exclude Hispanic ethnicity. Due to sparse data for ALL in blacks for some ages, data are shown for combined age groups: 7 to 10 years, 11 to 14 years, and 15 to 19 years as marked by asterisks. Note the differences in scales. Source: Surveillance, Epidemiology, and End Results (SEER) program, 18 SEER Registries, National Cancer Institute.

with other racial/ethnic groups (Table 5). Radiation exposure is an established risk factor for childhood leukemia, and some studies have found associations between childhood leukemia and specific chemicals such as benzene and drugs used to treat cancer such as alkylating agents and topoisomerase II inhibitors; these are more strongly associated with AML than ALL.⁴⁵

Children with AML and high white blood cell counts may develop symptoms due to the impaired transit of blasts through small blood vessels (leukostasis).⁴⁸ Many patients with AML are prone to excessive bleeding or thrombosis due to thrombocytopenia and other blood clotting disorders. Death occurs within the first 2 weeks after diagnosis in 2% to 4% of children with AML due to bleeding or leukostasis.⁴⁸

The treatment of AML consists of induction chemotherapy, CNS prophylaxis, and postremission therapy. Five-year survival rates for AML have improved in past decades but remain lower than for ALL; the 5-year survival rate for AML among children diagnosed between 2003 and 2009 was 64% (Table 3). Allogeneic stem cell transplant may be recommended for children with high-risk disease (unfavorable cytogenetics or residual/refractory disease after induction). Treatment toxicity and long-term effects for patients with AML are similar to those for patients with ALL 48; however, AML less often requires treatment or prophylaxis of the

CNS, and therefore side effects related to radiation of the brain are not as common. Improvements in survival for patients with AML are associated with the use of higher doses of anthracycline chemotherapy than were used in the past. A follow-up study of 5-year survivors of AML treated from 1970 through 1986 found a relatively low prevalence of cardiac disease however, there is concern that the prevalence of anthracycline-related cardiac toxicity may increase in more contemporary patient cohorts treated with higher doses.

Hodgkin Lymphoma

An estimated 380 children and 800 adolescents will be diagnosed with HL in 2014. HL is the most commonly diagnosed cancer among adolescents aged 15 to 19 years and is rare among children aged younger than 5 years (Fig. 4). Incidence rates for HL are approximately 30% higher among white children compared with black and Hispanic children (Table 5). Asian/Pacific Islanders have the lowest incidence rates. Risk factors for HL include Epstein-Barr virus (EBV) infection or having a personal history of mononucleosis, as well as human immunodeficiency virus (HIV) infection.

HL is highly sensitive to radiation and cure can be achieved in some patients using radiation therapy alone, although this is seldom the preferred treatment in children and adolescents. Survival rates for HL have increased from

TABLE 5. Pediatric Cancer Incidence Rates* by Sex and Race/Ethnicity, Ages Birth to 19 Years, United States, 2006 to

	ALL RACES					
	BOYS	GIRLS	NON-HISPANIC WHITE	NON-HISPANIC BLACK	HISPANIC	ASIAN/PACIFIC ISLANDER
All ICCC sites	196.7	182.3	201.7	146.1	184.2	140.8
Leukemia	52.0	43.1	46.9	29.9	59.6	39.4
Acute lymphocytic leukemia	38.4	30.2	34.2	18.3	44.9	28.7
Acute myeloid leukemia	7.9	8.0	7.7	7.1	8.7	8.0
Lymphomas and reticuloendothelial neoplasms	29.8	20.7	27.4	22.2	21.6	18.3
Hodgkin lymphoma	12.9	11.8	13.9	10.3	10.2	7.5
Non-Hodgkin lymphoma	15.1	7.7	11.9	11.4	9.5	10.0
Brain and CNS	45.5	45.9	50.9	36.1	38.7	28.6
Ependymoma	3.2	2.4	3.0	2.1	2.7	2.6
Astrocytoma	16.5	15.5	18.8	12.3	12.0	9.1
Medulĺoblastoma	5.1	3.3	4.8	2.7	3.7	3.3
Neuroblastoma and ganglioneuroblastoma	8.5	7.6	9.7	6.8	5.2	5.9
Retinoblastoma	2.9	3.3	2.7	3.4	3.4	3.1
Wilms tumor	5.3	6.3	6.2	6.7	4.5	2.9
Hepatic tumors	2.8	1.8	2.2	1.7	2.5	3.0
Bone tumors	9.8	7.7	9.2	7.2	8.9	6.7
Osteosarcoma	5.5	4.5	4.6	5.7	5.4	3.9
Ewing sarcoma	3.3	2.4	3.7	0.5	2.5	2.0
Rhabdomyosarcoma	5.4	4.2	4.8	5.5	4.5	2.9
Testicular germ cell tumors	9.9	-	10.9	1.4	13.6	6.1
Ovarian germ cell tumors	-	4.4	3.4	5.3	6.1	4.7
Thyroid carcinoma	3.0	12.6	9.1	2.8	7.2	6.9
Melanoma	3.7	5.8	7.1	0.5	1.4	†

CNS indicates central nervous system; ICCC, International Classification of Childhood Cancers.

Note: Rates include benign and borderline brain tumors.

Source: North American Association of Central Cancer Registries. Data are included from all US states and the District of Columbia except Arkansas, Minnesota, Nevada, Ohio, and Virginia. Rates by Hispanic ethnicity also exclude data from Massachusetts.

87% in 1975 through 1979 to 97% in 2003 through 2009 (Table 3). High doses of radiation used to treat HL in past decades resulted in high rates of pulmonary and cardiac toxicity; current therapies usually combine lower doses of chemotherapy and radiation to achieve high cure rates with less toxicity. 52 Depending on the treatment received, longterm and late effects of treatment can include pulmonary dysfunction, cardiac disease, thyroid abnormalities, infertility, and second malignant neoplasms. Girls aged 10 years and older and young women treated with radiation to the chest for HL have a high relative and absolute risk of breast cancer.⁵³ One study estimated a cumulative risk of breast cancer of 10% by age 45 years for women treated with chest irradiation (greater than 40 grays [Gy]) for HL at age 15 years.⁵⁴ Current guidelines recommend annual MRI as an adjunct to mammographic screening for women who were treated for HL.55

Non-Hodgkin Lymphoma

An estimated 620 children and 420 adolescents will be diagnosed with NHL in 2014. The most common subtypes in children and adolescents are Burkitt lymphoma (BL)

(19%), diffuse large B-cell lymphoma (22%), lymphoblastic lymphoma (20%), and anaplastic large-cell lymphoma (10%).6 The incidence rates of most subtypes of NHL are much higher in boys than in girls (Fig. 5). Both the incidence and subsite distribution of NHL vary throughout the world. For example, in equatorial Africa, lymphomas account for nearly one-half of childhood cancers, reflecting the very high incidence of BL, which is associated with high rates of coinfection with EBV and malaria.¹⁹ BL in Africa, also known as endemic BL, is much more common in boys than in girls and often arises in the jaw or around the eyes. In the United States, the incidence of BL is also much higher in boys than in girls, but occurs most frequently in the abdomen and is more common in white than in black children (Table 5).

EBV infection is also associated with many other types of NHL, although not as strongly as with BL in Africa. Immunosuppression from a variety of causes increases the risk of NHL, including inherited immunodeficiency disorders, HIV infection, and posttransplantation immune suppression.⁵⁶ Multiagent chemotherapy is the main form of treatment for most types of NHL. Clinical trials are currently

F5

^{*}Rates are per 1,000,000 and age-adjusted to the 2000 US standard population.

[†]Statistic not displayed if based on fewer than 25 cases.

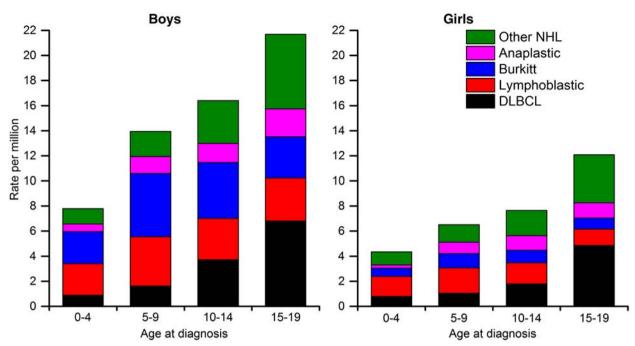


FIGURE 5. Age-Specific Incidence Rates For Major Non-Hodgkin Lymphoma (NHL) Subtypes by Sex, United States, 2006 to 2010.

DLBCL indicates diffuse large B-cell lymphoma. Source: North American Association of Central Cancer Registries. Data are included from all US states and the District of Columbia except Arkansas, Minnesota, Nevada, Ohio, and Virginia.

underway to evaluate the role of monoclonal antibodies in treatment of patients with pediatric B-cell neoplasms.⁵⁶ Survival rates for NHL in children and adolescents have increased dramatically in recent decades, from 47% in 1975 through 1979 to 85% in 2003 through 2009 (Table 3).

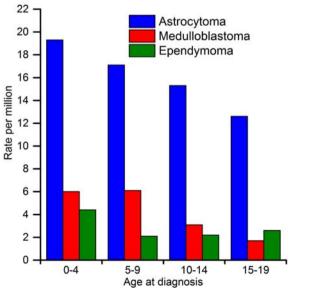
Brain and CNS Tumors

An estimated 2240 children and 540 adolescents will be diagnosed with malignant brain and CNS tumors in 2014 (Fig. 1). In addition, 730 children and 630 adolescents are expected to be diagnosed with benign and borderline malignant brain tumors. Malignant CNS tumors are the second most common cancer in children (accounting for 21% of cases) and the third most common cancer type in adolescents (accounting for 10% of cases). CNS tumors are classified by histologic type and World Health Organization (WHO) grade ranging from I (low) to IV (high). Because the symptoms of benign tumors and the side effects of treatment can be quite severe, since 2004, cancer registries have been collecting data for benign and borderline as well as malignant CNS tumors. We report statistics for both types combined when available. Immunohistochemical analysis, cytogenetic and molecular genetic findings, and measures of mitotic activity are increasingly used in CNS tumor diagnosis and classification. There are several classification systems of CNS tumors and they are F6 still evolving.⁵⁷ Figure 6 provides age-specific incidence

rates for 3 common categories of CNS tumors in children and adolescents.

Astrocytoma

Astrocytomas are the most common type of CNS tumor, accounting for 35% of CNS tumors diagnosed in children between birth and age 19 years (Fig. 6). These tumors arise



O L

O

R

FIGURE 6. Age-Specific Incidence Rates for Common Central Nervous System Tumors, United States, 2006 to 2010.

Source: North American Association of Central Cancer Registries. Data are

included from all US states and the District of Columbia except Arkansas, Minnesota, Nevada, Ohio, and Virginia.

10

from brain cells called astrocytes, which are star-shaped glial cells that normally support the nerve cells in the brain. Astrocytomas range from low grade to high grade. Pilocytic astrocytoma, the most common type of astrocytoma in children, is a low-grade tumor that typically arises in the cerebellum. Fibrillary astrocytoma, another common type of astrocytoma in children, is usually found in the midbrain, has less well-defined borders, and can spread throughout both sides of the brain. ⁵⁷

Medulloblastoma

Medulloblastomas are more common in children aged younger than 10 years compared with older children and adolescents (Fig. 6). They are highly invasive embryonal tumors that arise in the cerebellum and have a tendency to disseminate throughout the CNS early in their course.⁵⁸

Ependymoma

Ependymomas are tumors that begin in the ependymal lining of the ventricular system or the central canal of the spinal cord. Ependymomas range from low grade to high grade.⁵⁷

The symptoms of brain tumors are varied, as is the time course over which they develop and increase in severity. Signs and symptoms of brain tumors depend on where in the brain the tumor is growing, the developmental stage and ability of the child or young person to communicate, and whether intracranial pressure is raised.⁵⁹

Trends in CNS tumors have been of interest because of a sharp increase in overall incidence noted in the mid-1980s (Fig. 2), with significant increases in the incidence rates for pilocytic astrocytoma, primitive neuroectodermal tumors/medulloblastoma, and mixed glioma. ^{25,57,60} Many experts believe that this short-term increase in incidence resulted from the introduction of MRI for evaluating children with neurologic conditions and the increased use of stereotactic biopsies to document histologies in tumors that could not otherwise be biopsied. Furthermore, the increase in the incidence rate for pilocytic astrocytoma corresponds to a similar decrease in incidence for astrocytoma not otherwise specified, likely reflecting improved classification of these tumors. ⁶¹ The overall incidence rate of CNS tumors has been stable since the mid-1980s (Fig. 2).

Children with certain genetic syndromes, including Turcot syndrome, Li-Fraumeni syndrome, neurofibromatosis type 1, and neurofibromatosis type 2, are at an increased risk of developing brain and CNS tumors. Thigh-dose therapeutic radiation is a recognized cause of brain tumors. Children who receive cranial irradiation for ALL or other cancers have an excess risk of brain and CNS tumors. A review of epidemiologic studies on the etiology of brain tumors in child-hood noted that few associations had been consistently replicated in studies by different investigators. A number of recent studies, however, report associations between the

consumption of cured meats during pregnancy and child-hood brain tumors. ⁶³⁻⁶⁶

Treatment of brain and other CNS tumors depends on the histology, grade, location, size, and other prognostic factors. Whenever possible, surgery is performed to remove as much of the tumor as possible while avoiding damage to healthy tissue. Subsequent chemotherapy and/or radiation therapy depends on the type of tumor, and optimal therapy requires coordinated efforts of pediatric specialists in fields such as neurosurgery, neuropathology, radiation oncology, and pediatric oncology who have special expertise in the care of patients with these diseases.

Survival rates vary depending on tumor type, location, and grade. Trends in 5-year survival rates are available for patients with malignant brain tumors only and are presented in Table 3 for several major histologic subtypes. While there has been progress in survival for CNS tumors overall, there has been little progress for some subtypes, such as diffuse intrinsic pontine glioma (DIPG), for which the median survival time after diagnosis remains less than one year.67 Improvements in survival for many types of CNS malignancies have resulted from advances in neurosurgical techniques, delivery of radiation therapy, supportive care, and use of combination chemotherapy.⁶⁸ Nevertheless, children treated for brain tumors have a high risk of long-term morbidity and mortality. Late neurologic complications observed in follow-up studies of 5-year survivors include new onset of seizures, weakness in the arms and legs, blindness, and hearing loss.⁶⁸ Children who receive radiation therapy to the hypothalamic-pituitary axis often experience neuroendocrine effects, including growth hormone deficiency, hypothyroidism, and abnormal timing of menarche.⁶⁸ Cranial radiation therapy, particularly when used in very young children, can also result in neurocognitive deficits. For this reason, treatment protocols for patients with CNS tumors have been modified so that children aged younger than 3 years usually receive chemotherapy first with delayed and/or reduced radiation. Radiation treatment is associated with an increased risk of subsequent neoplasms in survivors of CNS malignancies, including gliomas and meningiomas.⁶⁸ Radiation is not always needed for low-grade tumors.⁵⁷

Embryonal Tumors

Embryonal tumors arise from cells that are normally present in the developing embryo and originate in developing tissues and organ systems. These tumors are usually diagnosed in children before age 5 years. Three common types of embryonal tumors in children are neuroblastoma, Wilms tumor (WT), and retinoblastoma. Other embryonal tumors, including medulloblastoma and rhabdomyosarcoma, are discussed in other sections.

Neuroblastoma

An estimated 710 cases of neuroblastoma will be diagnosed among children aged birth to 14 years in 2014 (Fig. 1). It is the third most common childhood cancer and represents 7% of the total cases diagnosed in this age group. Neuroblastoma is the most common cancer diagnosed during the first year of life; it is very uncommon after age 10 years. Neuroblastoma is an embryonal malignancy of the sympathetic nervous system derived from primitive neural crest cells, which can arise at any site along the sympathetic nervous system chain; nearly one-half arise in the adrenal gland. The incidence rate of neuroblastoma is slightly higher in boys than girls and is substantially higher in whites compared with children of other races/ethnicities (Table 5). Although epidemiologic studies have investigated environmental factors that may be associated with neuroblastoma, no strong or consistent risk factors have been identified. A family history of neuroblastoma is present in 1% to 2% of cases. Children who have siblings with neuroblastoma are nearly 10 times more likely to also be diagnosed with the disease than those without a family history.69

Neuroblastoma can metastasize via the lymphatics and hematogenously; greater than 50% of children have regional or distant-stage disease at diagnosis. 69 A rare form of neuroblastoma (stage 4S) presents in infants with a specific pattern of metastatic disease and is associated with maturation and regression, often spontaneously and without the necessity for cytotoxic therapy. 70 In addition to stage, prognostic factors include age, amplification of the MYCN oncogene, histopathologic features, and DNA ploidy. Depending on the stage and other prognostic factors, children with neuroblastoma are most often treated with surgery and/or chemotherapy and radiation therapy; patients with high-risk disease may receive high-dose chemotherapy followed by stem cell transplantation.⁶⁹ Ongoing clinical trials are investigating treatments for children with high-risk disease for whom 5-year survival remains poor; promising approaches include the development of antibodies directed against GD2, a neuroblastomaspecific surface antigen.⁷¹ Children who are treated for high-risk disease have the greatest risk of treatment-related complications, including severe sensorineural hearing loss, infertility, cardiac toxicity, and second neoplasms related to high-dose chemotherapy.⁶⁹ Overall survival rates for children with neuroblastoma have increased from 54% between 1975 and 1979 to 79% between 2003 and 2009 (Table 3).

Wilms Tumor

An estimated 510 cases of WT will be diagnosed among children in 2014. Also called nephroblastoma, WT is an embryonal tumor of the kidney that usually occurs in children aged younger than 5 years and comprises approximately 92% of kid-

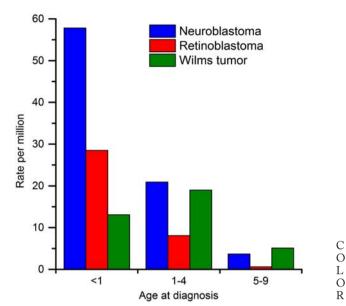


FIGURE 7. Age-Specific Incidence Rates for Embryonal Tumors, United States, 2006 to 2010.

Source: North American Association of Central Cancer Registries. Data are included from all US states and the District of Columbia except Arkansas,

Minnesota, Nevada, Ohio, and Virginia.

ney tumors diagnosed in this age group (Fig. 7). The incidence rate of WT is slightly higher in girls than boys and in black children compared with children of other races/ethnicities (Table 5). WT occurs bilaterally in approximately 5% of cases.⁷² Approximately 6% of children with WT have anomalies associated with germline deletions or mutations in the WT1 region of chromosome 11, including WAGR syndrome (WT, aniridia, genitourinary abnormalities, and mental retardation), sporadic aniridia, hypospadias, undescended testes, and Denys-Drash syndrome. 73,74 Approximately 4% of children with WT have anomalies associated with germline deletions or mutations in the WT2 region of chromosome 11; approximately one-quarter of these children have Beckworth-Wiedemann syndrome, an overgrowth syndrome associated with genetic or epigenetic changes in the WT2 region of chromosome 11, and approximately 3% have constitutional changes at the WT2 locus without any clinical manifestations of overgrowth. Children with genetic alterations at the WT1 and WT2 loci are more likely to present with bilateral or familial WT.73 Additional associations between WT and congenital anomalies, syndromes, and constitutional chromosomal aberrations have been described previously.^{75,76} Screening with ultrasound every 3 months until at least age 8 years is recommended for children with congenital anomalies and syndromes associated with a significantly increased risk of WT.⁷³

The majority of children with WT present with an asymptomatic abdominal mass that is incidentally noted while bathing or dressing the child.⁷⁷ WT may spread by direct extension, via lymphatics, and hematogenously; distant metastases are uncommon at diagnosis.

F7

Treatment involves surgery and may also include radiation and/or chemotherapy. In addition to stage, histology (anaplastic or favorable) and age at diagnosis are important prognostic factors.⁷⁷ Survival rates for WT have increased from 75% in 1975 through 1979 to 90% in 2003 through 2009 (Table 3). Late effects observed among survivors of WT include kyphosis and scoliosis from radiation to the spine, anthracycline-related cardiotoxicity, end-stage renal failure, an increased risk of second malignancies, and infertility and pregnancy complications among girls treated with radiation.^{77,78} The risk of end-stage renal failure is increased among patients treated for bilateral disease⁷⁸ and those receiving radiation to the opposite kidney in unilateral disease, as well as those with congenital syndromes and anomalies associated with the WT1 gene region.^{78,79}

Retinoblastoma

An estimated 280 children will be diagnosed with retinoblastoma in 2014 (Fig. 1). Retinoblastoma usually occurs in children aged younger than 5 years and accounts for approximately 5% of cancers in this age group (Fig. 7). Incidence rates of retinoblastoma appear to be higher in sub-Saharan Africa than in other parts of the world. Within the United States, retinoblastoma incidence is similar in boys and girls, does not vary substantially by race and ethnicity, and has been stable in the US population since 1975 (Table 5) (Fig. 2).

Symptoms of retinoblastoma include leukocoria or "white pupil," in which the pupil of the eye appears white instead of red when light shines into it, eye pain or redness, and vision problems. Retinoblastoma occurs in heritable and nonheritable forms; approximately one-third of retinoblastomas are heritable.80 Hereditary disease is defined as the presence of a positive family history, bilateral or multifocal retinoblastoma, or an identified germline mutation of the retinoblastoma tumor suppressor gene (RB1).81 Among children with a germline mutation, approximately 25% inherit it from a parent while in approximately 75% of cases a new mutation arises in the sperm or egg and is present at the time of conception or shortly thereafter.⁸¹ Children with the heritable form are born with one RB1 mutation and then must acquire another to develop the cancer. They often present at younger ages and are more likely to have bilateral disease. Those with the sporadic form must have 2 acquired mutations in a retinal precursor cell to develop the disease. Patients who are found to carry a germline RB1 mutation have an increased risk of second cancers, especially if they receive radiation therapy. 82 Genetic counseling should be an integral part of therapy for patients with retinoblastoma, whether unilateral or bilateral.80

The type of treatment required for retinoblastoma depends on the extent of the disease within the eye and whether the disease has spread beyond the eye.

Treatment options consider both cure and preservation of sight. Small tumors may sometimes be treated with cryotherapy, laser therapy, or thermotherapy. Patients with advanced unilateral intraocular disease often receive enucleation; this results in a cure rate of greater than 95%.80 Children with bilateral disease and some children with unilateral disease may be treated with systemic and intraocular chemotherapy to shrink tumors to a size at which local modalities such as cryotherapy and laser are effective. Patients with more advanced regional or distant disease are treated with chemotherapy and sometimes surgery and/or radiation.⁸² Recent studies have investigated the efficacy of intraarterial chemotherapy, with promising results.⁸³ Overall survival rates for retinoblastoma have increased from 92% between 1975 and 1979 to 99% between 2003 and 2009 (Table 3). Late effects of retinoblastoma include visual impairment and an increased risk of secondary neoplasms, including bone and soft tissue sarcomas and melanoma.84

Bone Tumors and Soft Tissue Sarcomas

An estimated 450 children and 370 adolescents will be diagnosed with bone tumors in 2014 (Fig. 1). The 2 most common types of pediatric bone tumors are osteosarcoma (56%) and Ewing sarcoma (ES) (33%). The most common type of pediatric soft tissue sarcoma is rhabdomyosarcoma, which will be diagnosed in an estimated 340 children in 2014 (Fig. 1). Another type of soft tissue sarcoma, Kaposi sarcoma, although extremely rare among children in the United States, is very common in children in Africa due to the high prevalence of HIV infection. ^{18,19}

Osteosarcoma

Osteosarcoma (OS) is the most common type of bone cancer diagnosed in children and adolescents. The incidence of OS increases with age throughout childhood and adolescence, but then decreases; it is very rare among children aged younger than 5 years (Fig. 8). The incidence of OS is slightly higher in boys compared with girls and rates are also higher in black and Hispanic children compared with white and Asian/Pacific Islander children (Table 5). OS arises from primitive bone-forming stem cells and usually develops in areas in which the bone is growing rapidly, such as the distal femur and proximal tibia. OS commonly appears as sporadic pain in the affected bone that may worsen at night or with activity, with progression to local swelling. 85

Risk factors for OS include prior radiation treatment for another tumor. Radiation-associated OS usually occurs 7 to 15 years after successful treatment of the primary tumor. Some studies have found that taller children are at a greater risk of developing OS, while others have not. 86 The incidence of OS is increased among individuals with the

F8

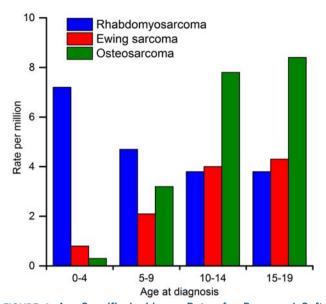


FIGURE 8. Age-Specific Incidence Rates for Bone and Soft Tissue Sarcomas, United States, 2006 to 2010. Source: North American Association of Central Cancer Registries. Data are included from all US states and the District of Columbia except Arkansas, Minnesota, Nevada, Ohio, and Virginia.

hereditary form of retinoblastoma and Li-Fraumeni syndrome, as well as several other genetic syndromes.⁸⁵

Approximately 20% of patients with OS have detectable metastases at diagnosis, most commonly in the lung.87 Nearly all patients receive systemic therapy because the majority of patients treated with local therapy alone develop distant metastases within several years. Current standard therapy consists of neoadjuvant chemotherapy followed by limb-sparing (or equivalent) surgery and adjuvant chemotherapy. 85 Amputation is rarely needed. The 5-year survival rate for OS was 71% in 2003 through 2009, up from 45% in 1975 through 1979 (Table 3). Therapy-related late effects can include anthracycline-induced cardiomyopathy, cisplatin-related hearing loss, kidney dysfunction, second malignancies, and infertility, especially in patients receiving alkylating agents. Patients treated for OS may have physical limitations resulting from surgical resection.⁸⁵

Ewing Sarcoma

ES is the second most common malignant bone tumor in children and adolescents. It is more common among older children and adolescents than young children (Fig. 8). Notably, incidence rates of ES are nearly 7.5 times higher in whites than blacks, with smaller differences compared with Hispanics and Asians/Pacific Islanders (Table 5). Similar differences in incidence are observed globally. 19 ES tumors are characterized by genetic translocations involving a specific genetic breakpoint region (EWSR1).88

ES tumors arise about equally in bones of the extremities and those in other parts of the body, but may also arise in soft tissues. They typically present as pain at the tumor site,

sometimes along with a mass or swelling. Metastases are present in approximately 25% of patients at diagnosis; the most common metastatic sites are the lungs, bone, and bone marrow.⁸⁹ Treatment of ES typically involves induction chemotherapy followed by local therapy (surgery and/or radiation) and adjuvant chemotherapy. There is continuing uncertainty about whether surgery or radiation therapy is preferred for local control, and in some cases both preoperative and postoperative radiation therapy is used. 90 Survival rates for ES have increased from 42% between 1975 and 1979 to 72% between 2003 and 2009 (Table 3). ES survivors are at increased risk of developing second cancers, cardiac and pulmonary conditions, infertility, and musculoskeletal problems. 90

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is a cancer made up of cells that normally develop into skeletal muscles. This cancer accounts for 3% of childhood cancers and 2% of adolescent cancers. There are 2 major subtypes of RMS: embryonal RMS (approximately 75% of cases), whose incidence is highest in children aged younger than 5 years, and alveolar RMS (approximately 16% of cases), whose incidence does not vary by age in children and adolescents.⁹¹ Embryonal RMS is morphologically similar to fetal muscle while alveolar RMS typically contains spaces reminiscent of pulmonary alveoli. 92 Although classic alveolar RMS is readily distinguishable from embryonal RMS, histologic patterns may overlap and it is sometimes difficult to distinguish between focal dense or sclerosing patterns of RMS and small foci of alveolar RMS.93 This distinction is clinically important because the embryonal form typically shows less aggressive clinical behavior and has a better prognosis than the alveolar form. 92,94 The PAX-FOX01 fusion gene (or in a small percentage of cases the PAX7-FOX01 fusion gene) is almost always present in the alveolar form but never in the embryonal form of RMS. 93,95 The most common anatomic sites for embryonal RMS are the head and neck area (including the extraocular muscles of the eye), the genitourinary tract, and the retroperitoneum, whereas alveolar RMS occurs most often in the trunk and extremities.⁹⁶ RMS often presents with pain and/or a mass or swelling at the tumor site. 94 RMS is associated with a number of genetic syndromes, including Li-Fraumeni syndrome and neurofibromatosis type 1.97 All patients with RMS receive systemic chemotherapy in conjunction with either surgery and/or radiation for local tumor control.⁹⁸ Survival has improved for RMS (from 49% in 1975-1979 to 64% in 2003-2009), yet remains lower than that for many other pediatric cancers (Table 3). Late effects of treatment for RMS vary depending on whether radiation therapy was given and the specific chemotherapy agents received, which have differed over time. Treatments for patients with intermediate-risk and

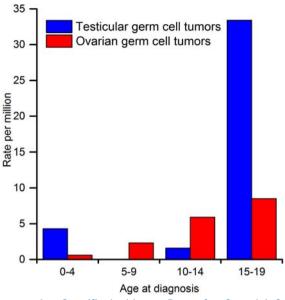


FIGURE 9. Age-Specific Incidence Rates for Gonadal Germ Cell Tumors, United States, 2006 to 2010. Rates are not shown when based on fewer than 25 cases. Source: North

American Association of Central Cancer Registries. Data are included from all US states and the District of Columbia except Arkansas, Minnesota, Nevada, Ohio, and Virginia.

high-risk disease continue to be studied in clinical trials in the hopes of achieving better outcomes. 99

Ovarian Germ Cell Tumors

An estimated 110 adolescent girls will be diagnosed with malignant ovarian germ cell (OGC) tumors in 2014 (Fig. 1). OGC tumors are more common in older girls (those aged 10-F9 14 years) and adolescents than in younger girls (Fig. 9). The risk of OGC tumors is increased among individuals with several genetic syndromes involving sex chromosomes, including Turner syndrome and Swyer syndrome. 100 OGC tumors often cause abdominal pain, distension, and weight gain. 101 Surgery is the primary treatment; unilateral salpingooophorectomy is an option for most patients to preserve fertility. Patients with early-stage disease may be monitored after surgery, while those with nonlocalized disease receive chemotherapy. The 5-year survival rate for patients with OGC tumors is 94% (Table 3). The chemotherapy regimens most commonly used for OGC tumors may cause hearing loss and kidney toxicity. 102

Testicular Germ Cell Tumors

An estimated 430 malignant testicular germ cell tumors (TGCT) will be diagnosed in boys aged 15 to 19 years in 2014, making it the fourth most common cancer in this age group. Some TGCT also occur in boys aged younger than 4 years (Fig. 9). The incidence of TGCT is higher among whites and Hispanics than among blacks (Table 5). Nonseminomas are more common than seminomas among adolescent boys; nonseminoma germ cell tumors are divided into 4 subtypes (choriocarcinoma, yolk sac, embryonal carcinoma, and

teratoma), and approximately 60% contain more than one of these histologic patterns. 103,104 A lump on the testicle is usually the first sign and often leads to diagnosis at an early stage.

Risk factors for TGCT include a history of cryptorchidism and a family history of the disease. 102 Orchiectomy is the primary treatment for all TGCT; subsequent treatment varies by stage. Patients with early-stage cancers (American Joint Committee on Cancer stages I and II) may be observed closely after surgery; those with continued elevation of serum markers should undergo radiation therapy. Later-stage cancer requires chemotherapy. Survival rates for testicular cancer have improved substantially since the mid-1970s (from 74% to 96% in 2003-2009), and most patients have a good prognosis (Table 3).

Role of the Primary Care Physician and **Specialized Care Providers**

Children and adolescents with cancer should be treated at medical centers that specialize in childhood cancer by multidisciplinary teams including pediatric oncologists, surgeons, radiation oncologists, and other specialists with experience in treating cancer in children and adolescents such as nurses, psychologists, and social workers. At pediatric cancer centers, treatment protocols are available for most types of cancer that occur in children and adolescents, and the opportunity to participate in clinical trials is offered to the majority of patients and their families. Member institutions of the Children's Oncology Group (COG), a National Cancer Institute-supported clinical trials group, care for greater than 90% of children and adolescents diagnosed with cancer each year in the United States (childrensoncologygroup.org). The COG has nearly 100 active clinical trials open at any given time, which include studies to test treatments for many types of childhood cancer at diagnosis and after recurrence, improve understanding of pediatric cancer biology, and improve supportive care and long-term survivorship. Children and adolescents diagnosed with types of cancer more commonly noted in adults can also benefit from treatment in pediatric cancer centers. Since pediatric cancers are most often treated with chemotherapy and sometimes radiation, and both modalities can result in long-term and late effects as children age, it is important that survivors receive appropriate follow-up care after treatment has ended.

While undergoing active treatment, children may experience pain and other symptoms due to the cancer itself, pain and anxiety related to medical procedures and hospitalizations, physical side effects of treatment, separation anxiety, and psychological distress. 105,106 Psychosocial support for parents and other family members is an important component of care for children and adolescents with cancer. 107 Oncology social workers, psychologists, and other staff at pediatric cancer centers provide psychosocial support to families as well as help to address practical issues such as insurance and opportunities for children to continue with their education while undergoing treatment.

Despite advances in treatment and survival, some children with cancer will not survive the disease. Although patients, families, and health care providers often find it difficult to discuss issues concerning prognosis, goals of care, and transitions to end-of-life care, it is important that health care providers are available, attentive, and sensitive to these concerns. 108,109 Pediatric oncology centers often partner with the family's pediatrician and hospice professionals to provide care to terminally ill children to manage pain and other symptoms, help families to make informed decisions about the child's care, and support them through bereavement. 110,111 Even in a high-quality palliative care setting, the loss of a child to cancer is an incredibly difficult experience for parents, siblings, and other family members. Health care providers may play an important role in helping families through the grieving process and providing referrals for counseling and community-based support services.

Transition From Active Treatment to Survivorship Care

Children treated for cancer often maintain their relationship with their primary care pediatrician for preventive care, health maintenance, and acute care. After cancer treatment, children and adolescents may be monitored by their pediatric oncologist for 3 years or more, depending on the disease, age of the patient, and other factors. Follow-up care by pediatric oncologists focuses on checking for recurrence; more extensive follow-up may be offered by the treating oncologist or by referral to a comprehensive clinic. When the time comes for discontinuing visits to the pediatric oncologist for initial follow-up care, long-term follow-up care is still needed. Such follow-up care includes assessment of short-term and long-term complications and late effects of cancer therapies; detection of recurrent and secondary cancers; counseling about behaviors such as smoking, diet, and physical activity; assessment of psychosocial adjustment and quality of life; and treatment for any identified late effects.

At the completion of treatment, it is important that a primary care clinician receives information from the cancer care team concerning cancer treatments and dosages, possible late effects, and guidance on appropriate follow-up care, and coordinates with providers or centers that are providing long-term survivorship care. The availability and duration of follow-up and specialized survivorship care by the pediatric oncologist and/or survivorship center will influence the roles and responsibilities of the primary care clinician. Research is currently underway to define optimal models for survivorship care. 113

Specific areas of concern for cancer survivors during childhood and adolescence include neurocognitive and neurosensory impairment, disordered growth and development, and gonadal and reproductive function. 114 Neurocognitive difficulties are associated with CRT and certain chemotherapy exposures; CRT and focal irradiation for facial malignancies and certain chemotherapy drugs are associated with vision or hearing impairment. It is recommended that children at high risk receive serial testing for neurocognitive and vision/hearing deficits as some of these may worsen with time and may require therapeutic and educational interventions. 115 Survivors who received CRT and facial radiation therapy are also at risk for injury to the hypothalamic-pituitary axis, resulting in growth impairment, hypothyroidism, delayed or accelerated puberty, infertility, and obesity and metabolic syndrome. Survivors of childhood cancer sometimes develop dental problems as a result of chemotherapy and radiation therapy administered during the development of permanent teeth. Patients receiving anthracyclines or thoracic irradiation are at an increased risk of cardiac-related health problems, generally manifesting as left ventricular dysfunction. A baseline electrocardiogram and test of cardiac function (such as an echocardiogram or multiple-gated acquisition scan) is recommended at the first follow-up/long-term care visit and then at regular intervals as specified by the COG or the clinician's follow-up plan. 115,116 Although uncommon, primary care physicians should remain alert for late recurrences and secondary neoplasms. 117,118 Many of the late effects of childhood and adolescent cancer may not become apparent until adulthood. Therefore, it is important that young adults who are transitioning from pediatric to adult primary care receive information regarding their cancer experience, including diagnosis and treatment, as well as subsequent follow-up recommendations, especially if they are not participating in specialized survivorship care programs. 119 The COG has developed long-term follow-up guidelines for survivors of childhood cancers. 115 These guidelines help health care providers and patients know what to watch for and what type of surveillance is appropriate for problems that can be reduced or prevented. More information on these guidelines is available at the COG Web site (survivorshipguidelines.org).

Epidemiologic and Clinical Studies of Long-Term and Late Effects Among Survivors

The Childhood Cancer Survivor Study (CCSS), a study of the mortality experience of 20,483 patients who were 5-year survivors of childhood and adolescent cancer and who were diagnosed between 1970 and 1986, found an increased risk of all-cause mortality up to 30 years after diagnosis.³ Among the 2534 deaths identified in the study, greater

than one-half (58.0%) were due to recurrence/progressive disease and 470 (18.5%) were due to subsequent neoplasms (standardized mortality ratio [SMR], 15.2; 95% confidence interval [95% CI], 13.9-16.6). Increased risks for mortality were from cardiac causes (142 deaths; SMR, 7.0 [95% CI, 5.9-8.2]), pulmonary causes (67 deaths; SMR, 8.8 [95% CI, 6.8-11.2]), and other medical causes (200 deaths; SMR, 2.6 [95% CI, 2.3-3.0]).

The CCSS also reported on the incidence of late recurrences and subsequent neoplasms distinct from the primary diagnosis among 14,359 patients from the larger cohort who could be contacted and agreed to participate in active follow-up. 117,120 The cumulative incidence of late recurrences (first recurrences occurring greater than 5 years after diagnosis) in the cohort overall was 4.4%, 5.6%, and 6.2%, respectively, at 10 years, 15 years, and 20 years. 117 Survivors of astrocytoma, ES, medulloblastoma, and "other leukemias" had the highest incidence of late recurrences, with a cumulative incidence at 20 years of 14.4, 13.0, 9.3, and 9.4%, respectively. The cumulative incidence of diagnosis with one subsequent (benign or malignant) neoplasm after a median follow-up of 23 years was 9.6%; among patients who developed at least one subsequent neoplasm, 27.9% developed a second neoplasm, and 39.6% developed a third neoplasm. There were 802 subsequent malignant neoplasms (standardized incidence ratio, 6.0; 95% CI, 5.5-6.4), 159 nonmalignant meningiomas (plus 11 malignant meningiomas), and 168 other benign and in situ neoplasms. Breast cancer was the most common subsequent malignant neoplasm (188 incident tumors), followed by thyroid cancers (128 incident tumors). The median latency between the primary cancer diagnosis and subsequent malignancy ranged from 9 years for a leukemia diagnosis to 23 years for small intestine and colorectal cancer diagnoses. A case-control study estimated the relationship between radiation dose to the breast and ovaries and the risk of breast cancer among women in the CCSS who were diagnosed between 1970 and 1986. A linear relationship was found between radiation dose to the breast and relative risks for breast cancer, with an estimated relative risk of 6.4 at a dose of 20 Gy and 11.8 at a dose of 40 Gy. 121 Breast cancer risk was attenuated among women who also received radiation doses of 5 Gy or greater to the ovaries, reflecting the important role of hormonal stimulation on radiation-induced breast cancer. 121 The elevated risk of breast cancer noted among survivors of childhood and adolescent cancers supports the importance of evidencebased screening guidelines for this high-risk group. 122,123

It is hoped that the risk of second and subsequent neoplasms will decline in more contemporary cohorts due to reductions in the use of radiation therapy as well as reductions in radiation doses and field sizes.¹²¹ Although much of the increased incidence of cancer in survivors of pediatric cancer is associated with the late effects of cancer treatment, survivors of some cancers may have an increased risk related to genetic factors and syndromes associated with their primary cancer. 119

The prevalence of chronic health conditions was evaluated among 1713 adult cancer survivors enrolled in the St. Jude Lifetime Cohort Study using physical examinations and laboratory tests. ¹²⁴ Among survivors who had been treated with cardiotoxic therapies, 56% had cardiac abnormalities, 46% of which were newly discovered as a result of the St. Jude Lifetime Cohort Study evaluation. The American Heart Association recently published a scientific statement on long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy; this extensive review covers pathophysiology, course, monitoring, management, prevention, and research directions. ¹²⁵

Global Burden of Childhood Cancer

An estimated 175,000 cases of cancer are diagnosed annually in children aged younger than 15 years worldwide, and fewer than 40% of patients (mostly those in high-income countries) are thought to be adequately diagnosed and treated. 126 A child's probability of surviving cancer is poor in less-developed countries, and extreme discomfort is likely in the absence of palliative care. Many childhood cancers are highly curable if diagnosed at an early stage, and some treatment regimens are relatively simple, inexpensive, and well established. 127 For example, approximately 50% of African patients with BL can be cured with a 28-day course of low-dose cyclophosphamide and prednisone and 4 intrathecal injections costing less than \$50.128,129 A number of organizations have drawn attention to the survival disparity for retinoblastoma, which is highly treatable when detected early, between high-income and low-income countries. 130 Approaches for improving outcomes for children and adolescents in low-income countries, including public awareness campaigns, community health worker and physician education, hospital twinning, and equipment donation, could improve early detection and treatment. 131 Hospital twinning, which involves the pairing of hospitals in high-income countries with those in low- and middle-income countries to share knowledge, skills, and resources, has proven to be a viable model for improving outcomes for childhood and adolescent cancer in these countries. 131 As in high-income countries, palliative care is an essential component of care in low- and middle-income countries, and it is important that health care providers be trained in palliative care and that drugs such as morphine be available worldwide. 131

Challenges and Future Directions

Childhood cancer is a success story of modern medicine in which effective treatments have been identified for previously untreatable diseases. For many pediatric cancers, much progress has been made using chemotherapeutic agents and treatment modalities introduced decades ago with refinement to improve disease-free survival while minimizing treatment-related morbidity. 132 Better understanding of treatment-related toxicity has not only guided the design of less-toxic therapies, but also the development of treatment summaries, survivorship plans, and efforts to harmonize survivorship guidelines worldwide that serve as a model for the survivorship care of adult patients with cancer. 133 It is important that more recent cohorts of childhood and adolescent patients with cancer continue to be followed to determine how therapy modifications impact the prevalence and spectrum of late effects. For example, the increased use of dexamethasone in contemporary ALL therapy has resulted in a higher prevalence of osteonecrosis and spurred research to identify clinical and genetic factors predisposing patients to this complication and its long-term functional limitations. Likewise, longer followup is needed to determine whether restricting the anthracycline dose actually reduces the risk of cardiomyopathy or simply delays the time to the onset of clinically symptomatic left ventricular systolic dysfunction.⁴⁹ It is important to apply known interventions that can reduce the impact of cancer and treatment-related late effects on quality of life, morbidity, and mortality as well as to develop and test new interventions. For example, survivors of HL who are treated with chest irradiation have an increased risk of developing lung cancer, and tobacco use increases this risk 20-fold. 134 Successful smoking prevention and cessation strategies among survivors can decrease the risk of this prevalent and highly morbid cancer of adulthood, while also decreasing the development and progression of atherosclerosis and other second cancers. Screening of young women at an increased risk of breast cancer due to chest irradiation has already been mentioned. Survivors of childhood cancer, particularly those who received radiation to the hypothalamic-pituitary axis, are also at risk of obesity. 135 Obesity can, in turn, exacerbate the increased risks of cardiovascular disease associated with anthracycline therapy and radiation therapy to the chest. Modifiable cardiovascular risk factors, such as hypertension, can potentiate the risk of major cardiac events and both behavioral and medical interventions

can potentially reduce these risks. 136 Research to define optimal intervention strategies and well-integrated survivorship care models are both needed.

Five-year survival rates for some cancers, primarily leukemias and lymphomas, have continued to improve over the past decade, while improvements in survival for a number of solid tumors have plateaued within the past 10 to 20 years. For progress to be sustained and renewed, it is important that research be conducted to identify novel and innovative therapies that build on an increased understanding of cellular pathways promoting tumor cell growth and survival. Research to achieve this aim will likely involve the full spectrum of basic to applied research, with "bench-to-bedside" application requiring clinical trials with biologically defined patient subsets, thereby requiring even greater cooperation by national and international childhood cancer clinical trial groups. Figure 1.

Although advances in the treatment of childhood cancer have saved many lives over recent decades, there has been less progress made in understanding the causes and prevention of childhood and adolescent cancers. Numerous studies have investigated the causes of childhood cancers; however, few strong or consistent associations leading to preventive strategies have been identified. Most childhood cancer studies have been case-control in design, and depend on parental recall to identify environmental exposures that occurred in their past and their child's life. This method is subject to recall bias (parents of a child who is ill may recall exposures that parents of healthy children do not) and measurement error (for the most part, estimates of exposure based on recall are less accurate than those based on records or actual measurements). In addition, most prior epidemiologic studies did not examine histologic or molecular subtypes of tumors, although it is quite likely that such subtypes may differ in etiology. Some of these limitations are being addressed in more recent studies. 137 Of particular note, an International Childhood Cancer Cohort Consortium has been established to facilitate collaboration in the analyses of cancer risk factors among investigators conducting prospective cohort studies. ¹³⁸

References

- Murphy SL, Xu J, Kochanek KD. Deaths: Final Data for 2010. National Vital Statistics Reports. Vol 61. No. 4. Hyattsville, MD: National Center for Health Statistics; 2013.
- Howlader N, Noone AM, Krapcho M, et al, eds. SEER Cancer Statistics Review, 1975-2010. Bethesda, MD: National Cancer Institute; 2013.
- Armstrong GT, Liu Q, Yasui Y, et al. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. J Clin Oncol. 2009;27:2328-2338.
- 4. Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence-SEER 9 Regs Research Data, Nov. 2012 Sub (1973-2010) <Katrina/Rita Population Adjustment>--Linked To County Attributes-Total US, 1969-2011 Counties. Bethesda, MD: National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Surveillance Systems Branch; 2013.
- 5. Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence-SEER 18 Regs Research Data+Hurricane Katrina Impacted Louisiana Cases, Nov. 2012 Sub (2000-2010)
- <Katrina/Rita Population Adjustment>-Linked To County Attributes-Total US, 1969-2011 Counties. Bethesda, MD: National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Surveillance Systems Branch; 2013.
- Surveillance, Epidemiology and End Results (SEER) Program. SEER*Stat Database: North American Association of Central Cancer Registries (NAACCR) Incidence-CiNA Analytic File, 1995-2010, for NHIAv2 Origin, Custom File With County, ACS Facts and Figures Projection Project, North American Association of Central Cancer Registries. Bethesda,

- MD: National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Surveillance Systems Branch; 2013.
- 7. Copeland G, Lake A, Firth R, et al. Cancer in North America: 2006-2010. Vol 1: Combined Cancer Incidence for the United States, Canada and North America. Springfield, IL: North American Association of Central Cancer Registries Inc; 2013.
- 8. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. *Cancer*. 2005;103:1457-1467.
- Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Mortality-All COD, Aggregated With County, Total US (1990-2010) «Katrina/ Rita Population Adjustment»-Linked To County Attributes-Total US, 1969-2011 Counties. Bethesda, MD: National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Surveillance Systems Branch; 2013. Released April 2013; underlying mortality data provided by National Center for Health Statistics.
- 10. Surveillance Research Program, National Cancer Institute SEER*Stat Software. Version 8.1.2. seer.cancer.gov/seerstat.
- 11. Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence- SEER 18 Regs Research Data+Hurricane Katrina Impacted Louisiana Cases, Nov. 2012 Sub (1973-2010 varying)-Linked To County Attributes-Total US, 1969-2011 Counties. Bethesda, MD: National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Surveillance Systems Branch; 2013.
- Zhu L, Pickle LW, Ghosh K, et al. Predicting US-and state-level cancer counts for the current calendar year: Part II: evaluation of spatiotemporal projection methods for incidence. *Cancer*. 2012;118:1100-1109.
- 13. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014;64:9-29.
- 14. DevCan. Probability of Developing or Dying of Cancer Software. Version 6.7.0. Bethesda, MD: Statistical Research and Applications Branch, National Cancer Institute; 2013. srab.cancer.gov/devcan.
- Pan IJ, Daniels JL, Zhu K. Poverty and childhood cancer incidence in the United States. Cancer Causes Control. 2010;21:1139-1145.
- Barry MS, Auger N, Burrows S. Portrait of socio-economic inequality in childhood morbidity and mortality over time, Quebec, 1990-2005. J Paediatr Child Health. 2012;48:496-505.
- Kroll ME, Stiller CA, Murphy MF, Carpenter LM. Childhood leukaemia and socioeconomic status in England and Wales 1976-2005: evidence of higher incidence in relatively affluent communities persists over time. *Br J Cancer*. 2011;105:1783-1787.
- Bunin GR. Nongenetic causes of childhood cancers: evidence from international variation, time trends, and risk factor studies. *Toxicol Appl Pharmacol*. 2004;199:91-103.
- Stiller CA, Parkin DM. Geographic and ethnic variations in the incidence of childhood cancer. *Br Med Bull*. 1996;52:682-703.
- 20. Bhatia S. Disparities in cancer outcomes: lessons learned from children with

- cancer. *Pediatr Blood Cancer*. 2011;56: 994-1002.
- 21. Pui CH, Pei D, Pappo AS, et al. Treatment outcomes in black and white children with cancer: results from the SEER database and St Jude Children's Research Hospital, 1992 through 2007. J Clin Oncol. 2012;30:2005-2012.
- Linabery AM, Ross JA. Childhood and adolescent cancer survival in the US by race and ethnicity for the diagnostic period 1975-1999. Cancer. 2008;113:2575-2596.
- Steliarova-Foucher E, Stiller C, Kaatsch P, et al. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCISproject): an epidemiological study. *Lancet*. 2004;364: 2097-2105.
- 24. Kroll ME, Stiller CA, Richards S, Mitchell C, Carpenter LM. Evidence for under-diagnosis of childhood acute lymphoblastic leukaemia in poorer communities within Great Britain. Br J Cancer. 2012; 106:1556-1559.
- Smith MA, Freidlin B, Ries LA, Simon R. Trends in reported incidence of primary malignant brain tumors in children in the United States. J Natl Cancer Inst. 1998;90: 1269-1277
- Doll R, Wakeford R. Risk of childhood cancer from fetal irradiation. Br J Radiol. 1997;70:130-139.
- Mathews JD, Forsythe AV, Brady Z, et al. Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. BMJ. 2013;346:f2360.
- Pearce MS, Salotti JA, Little MP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet*. 2012;380:499-505.
- National Cancer Institute. Radiation Risks and Pediatric Computed Tomography (CT): A Guide for Health Care Providers. cancer.gov/cancertopics/causes/radiation/ radiation-risks-pediatric-CT. Accessed November 20, 2013.
- 30. Bjorge T, Sorensen HT, Grotmol T, et al. Fetal growth and childhood cancer: a population-based study. *Pediatrics*. 2013; 132:e1265-e1275.
- Milne E, Greenop KR, Metayer C, et al. Fetal growth and childhood acute lymphoblastic leukemia: findings from the childhood leukemia international consortium. *Int J Cancer*. 2013;133:2968-2979.
- 32. O'Neill KA, Bunch KJ, Murphy MF. Intrauterine growth and childhood leukemia and lymphoma risk. *Expert Rev Hematol*. 2012;5:559-576.
- Chokkalingam AP, Metayer C, Scelo G, et al. Fetal growth and body size genes and risk of childhood acute lymphoblastic leukemia. Cancer Causes Control. 2012;23: 1577-1585.
- 34. MacLean J, Partap S, Reynolds P, Von Behren J, Fisher PG. Birth weight and order as risk factors for childhood central nervous system tumors. *J Pediatr.* 2010; 157:450-455.
- Rangel M, Cypriano M, de Martino Lee ML, et al. Leukemia, non-Hodgkin's lymphoma, and Wilms tumor in childhood:

- the role of birth weight. Eur J Pediatr. 2010:169:875-881
- Ognjanovic S, Carozza SE, Chow EJ, et al. Birth characteristics and the risk of childhood rhabdomyosarcoma based on histological subtype. *Br J Cancer*. 2010;102: 227-231.
- 37. Roman E, Lightfoot T, Smith AG, et al. Childhood acute lymphoblastic leukaemia and birthweight: insights from a pooled analysis of case-control data from Germany, the United Kingdom and the United States. Eur J Cancer. 2013;49: 1437-1447.
- 38. Cogliano VJ, Baan R, Straif K, et al. Preventable exposures associated with human cancers. *J Natl Cancer Inst.* 2011; 103:1827-1839.
- Landrigan PJ, Goldman LR. Children's vulnerability to toxic chemicals: a challenge and opportunity to strengthen health and environmental policy. *Health Aff* (Millwood). 2011;30:842-850.
- 40. Dang-Tan T, Franco EL. Diagnosis delays in childhood cancer: a review. *Cancer*. 2007;110:703-713.
- 41. Margolin J, Rabin KR, Steuber CP, Poplack, DG. Acute lymphoblastic leukemia. In: Pizzo PA, Poplack DG, eds. Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia, PA: Wolters Kluwer Health/ Lippincott Williams & Wilkins; 2010:518-565.
- 42. Caughey RW, Michels KB. Birth weight and childhood leukemia: a meta-analysis and review of the current evidence. *Int J Cancer*. 2009;124:2658-2670.
- 43. Urayama KY, Buffler PA, Gallagher ER, Ayoob JM, Ma X. A meta-analysis of the association between day-care attendance and childhood acute lymphoblastic leukaemia. *Int J Epidemiol*. 2010;39:718-732.
- 44. Urayama KY, Ma X, Selvin S, et al. Early life exposure to infections and risk of childhood acute lymphoblastic leukemia. *Int J Cancer*. 2011;128:1632-1643.
- 45. Eden T. Aetiology of childhood leukaemia. *Cancer Treat Rev.* 2010;36:286-297.
- 46. Kadan-Lottick NS, Ness KK, Bhatia S, Gurney JG. Survival variability by race and ethnicity in childhood acute lymphoblastic leukemia. *JAMA*. 2003;290:2008-2014.
- Smith MA, Seibel NL, Altekruse SF, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. J Clin Oncol. 2010;28:2625-2634.
- 48. Cooper TM, Hasle H, Smith FO. Acute myeloid leukemia, myeloproliferative and myelodysplastic disorders. In: Pizzo PA, Poplack DG, eds. Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010:566-610.
- Hudson MM, Neglia JP, Woods WG, et al. Lessons from the past: opportunities to improve childhood cancer survivor care through outcomes investigations of historical therapeutic approaches for pediatric hematological malignancies. *Pediatr Blood Cancer*. 2012;58:334-343.
- Orgel E, Zung L, Ji L, Finklestein J, Feusner J, Freyer DR. Early cardiac outcomes following contemporary treatment for childhood acute myeloid leukemia: a

- North American perspective. *Pediatr Blood Cancer*, 2013:60:1528-1533.
- 51. Mulrooney DA, Dover DC, Li S, et al; Childhood Cancer Survivor Study. Twenty years of follow-up among survivors of childhood and young adult acute myeloid leukemia: a report from the Childhood Cancer Survivor Study. *Cancer*. 2008;112: 2071-2079.
- 52. Metzger M, Krasin MJ, Hudson MM, Onciu M. Hodgkin lymphoma. In: Pizzo PA, Poplack DG, eds. Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010:638-662.
- 53. Swerdlow AJ, Cooke R, Bates A, et al. Breast cancer risk after supradiaphragmatic radiotherapy for Hodgkin's lymphoma in England and Wales: a National Cohort Study. J Clin Oncol. 2012;30:2745-2752.
- 54. Travis LB, Hill D, Dores GM, et al. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. *J Natl Cancer Inst.* 2005;97:1428-1437.
- 55. Saslow D, Boetes C, Burke W, et al; American Cancer Society Breast Cancer Advisory Group. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin. 2007;57:75-89.
- 56. Gross TG, Perkins SL. Malignant non-Hodgkin lymphomas in children. In: Pizzo PA, Poplack DG, eds. Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia, PA: Wolters Kluwer Health/ Lippincott Williams & Wilkins; 2010:663-682
- 57. Blaney SM, Haas-Kogan D, Poussaint Y, et al. Gliomas, ependymomas, and other nonembryonal tumors. In: Pizzo PA, Poplack DG, eds. Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010:717-771.
- 58. Packer RJ, Rorke-Adams LB, Lau CC, Taylor MD, Vezina G, Kun LE. Embryonal and pineal tumors. In: Pizzo PA, Poplack DG, eds. Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010:772-808.
- Wilne SH, Dineen RA, Dommett RM, Chu TP, Walker DA. Identifying brain tumours in children and young adults. *BMJ*. 2013; 347:f5844.
- Black WC. Increasing incidence of childhood primary malignant brain tumorsenigma or no-brainer? *J Natl Cancer Inst*. 1998;90:1249-1251.
- 61. McKean-Cowdin R, Razavi P, Barrington-Trimis J, et al. Trends in childhood brain tumor incidence, 1973-2009. *J Neurooncol*. 2013;115:153-160.
- 62. Baldwin RT, Preston-Martin S. Epidemiology of brain tumors in childhood–a review. *Toxicol Appl Pharmacol*. 2004;199:118-131.
- Huncharek M, Kupelnick B. A metaanalysis of maternal cured meat consumption during pregnancy and the risk of childhood brain tumors. *Neuroepidemiol*ogy. 2004;23:78-84.
- 64. Bunin GR, Gallagher PR, Rorke-Adams LB, Robison LL, Cnaan A. Maternal supplement, micronutrient, and cured meat intake during pregnancy and risk of medulloblastoma during childhood: a children's oncology

- group study. Cancer Epidemiol Biomarkers Prev. 2006;15:1660-1667.
- 65. Pogoda JM, Preston-Martin S, Howe G, et al. An international case-control study of maternal diet during pregnancy and childhood brain tumor risk: a histology-specific analysis by food group. *Ann Epidemiol*. 2009;19:148-160.
- 66. Searles Nielsen S, Mueller BA, Preston-Martin S, Farin FM, Holly EA, McKean-Cowdin R. Childhood brain tumors and maternal cured meat consumption in pregnancy: differential effect by glutathione Stransferases. Cancer Epidemiol Biomarkers Prev. 2011;20:2413-2419.
- Warren KE. Diffuse intrinsic pontine glioma: poised for progress. Front Oncol. 2012;2:205.
- Armstrong GT. Long-term survivors of childhood central nervous system malignancies: the experience of the Childhood Cancer Survivor Study. Eur J Paediatr Neurol. 2010;14:298-303.
- Brodeur GM, Hogarty MD, Mosse YP, Maris JM. Neuroblastoma. In: Pizzo PA, Poplack DG, eds. Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010:886-922.
- Nickerson HJ, Matthay KK, Seeger RC, et al. Favorable biology and outcome of stage IV-S neuroblastoma with supportive care or minimal therapy: a Children's Cancer Group study. J Clin Oncol. 2000;18: 477-486.
- Matthay KK, George RE, Yu AL. Promising therapeutic targets in neuroblastoma. *Clin Cancer Res.* 2012;18:2740-2753.
- 72. Montgomery BT, Kelalis PP, Blute ML, et al. Extended followup of bilateral Wilms tumor: results of the National Wilms Tumor Study. *J Urol.* 1991;146(2 pt 2):514-518.
- National Cancer Institute. Wilms Tumor and Other Childhood Kidney Tumors Treatment (PDQ®). cancer.gov/cancertopics/pdq/treatment/wilms/HealthProfessional. Accessed December 3, 2013.
- 74. Breslow NE, Norris R, Norkool PA, et al. Characteristics and outcomes of children with the Wilms tumor-Aniridia syndrome: a report from the National Wilms Tumor Study Group. J Clin Oncol. 2003;21:4579-4585.
- Scott RH, Stiller CA, Walker L, Rahman N. Syndromes and constitutional chromosomal abnormalities associated with Wilms tumour. *J Med Genet*. 2006;43:705-715
- Dumoucel S, Gauthier-Villars M, Stoppa-Lyonnet D, et al. Malformations, genetic abnormalities, and wilms tumor. *Pediatr Blood Cancer*. 2014;61:140-144.
- Fernandez C, Geller JI, Ehrlich PF, et al. Renal tumors. In: Pizzo PA, Poplack DG, eds. Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010:861-885.
- Wright KD, Green DM, Daw NC. Late effects of treatment for wilms tumor. Pediatr Hematol Oncol. 2009;26:407-413.
- 79. Breslow NE, Collins AJ, Ritchey ML, Grigoriev YA, Peterson SM, Green DM. End stage renal disease in patients with Wilms tumor: results from the National

- Wilms Tumor Study Group and the United States Renal Data System. *J Urol.* 2005; 174:1972-1975.
- Hurwitz RL, Shields CL, Shields JA, et al. Retinoblastoma. In: Pizzo PA, Poplack DG, eds. Principles and Practice of Pediatric Oncology. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010: 809-837.
- 81. National Cancer Institute. Retinoblastoma Treatment (PDQ®). cancer.gov/cancertopics/pdq/treatment/retinoblastoma/Health Professional. Accessed December 3, 2013.
- 82. Chintagumpala M, Chevez-Barrios P, Paysse EA, Plon SE, Hurwitz R. Retinoblastoma: review of current management. *Oncologist*. 2007;12:1237-1246.
- 83. Houston SK, Murray TG, Wolfe SQ, Fernandes CE. Current update on retinoblastoma. *Int Ophthalmol Clin*. 2011;51:77-91.
- Kleinerman RA, Yu CL, Little MP, et al. Variation of second cancer risk by family history of retinoblastoma among longterm survivors. *J Clin Oncol*. 2012;30:950-957.
- 85. Gorlick R, Bielack S, Teot L, Meyer J, Randall RL, Neyssa M. Osteosarcoma: biology, diagnosis, treatment, and remaining challenges. In: Pizzo PA, Poplack DG, eds. Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010:1015-1044.
- 86. Mirabello L, Pfeiffer R, Murphy G, et al. Height at diagnosis and birth-weight as risk factors for osteosarcoma. *Cancer Causes Control*. 2011;22:899-908.
- Kaste SC, Pratt CB, Cain AM, Jones-Wallace DJ, Rao BN. Metastases detected at the time of diagnosis of primary pediatric extremity osteosarcoma at diagnosis: imaging features. Cancer. 1999:86:1602-1608.
- Delatte O, Zucman J, Melot T, et al. The Ewing family of tumors—a subgroup of small-round-cell tumors defined by specific chimeric transcripts. N Engl J Med. 1994;331:294-299.
- 89. Esiashvili N, Goodman M, Marcus RB Jr. Changes in incidence and survival of Ewing sarcoma patients over the past 3 decades: Surveillance Epidemiology and End Results data. J Pediatr Hematol Oncol. 2008;30:425-430.
- Ginsberg JP, Goodman P, Leisenring W, et al. Long-term survivors of childhood Ewing sarcoma: report from the childhood cancer survivor study. J Natl Cancer Inst. 2010;102:1272-1283.
- 91. Gurney JG, Young JL, Roffers SF, Smith MA, Bunin GR. Soft tissue sarcomas. In: Ries LAG, Smith MA, Gurney JG, et al, eds. Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975-1995. Bethesda, MD: National Cancer Institute, SEER Program; 1999.
- Davicioni E, Anderson MJ, Finckenstein FG, et al. Molecular classification of rhabdomyosarcoma-genotypic and phenotypic determinants of diagnosis: a report from the Children's Oncology Group. *Am J Pathol*. 2009;174:550-564.
- 93. Rudzinski ER. Histology and fusion status in rhabdomyosarcoma. *Am Soc Clin Oncol Educ Book.* 2013:425-428.

- McDowell HP. Update on childhood rhabdomyosarcoma. Arch Dis Child. 2003;88: 354-357.
- 95. Linardic CM. PAX3-FOXO1 fusion gene in rhabdomyosarcoma. *Cancer Lett.* 2008; 270:10-18.
- 96. Marshall AD, Grosveld GC. Alveolar rhabdomyosarcoma-the molecular drivers of PAX3/7-FOX01-induced tumorigenesis. *Skelet Muscle*. 2012:2:25.
- 97. Xia SJ, Pressey JG, Barr FG. Molecular pathogenesis of rhabdomyosarcoma. *Cancer Biol Ther.* 2002;1:97-104.
- Wexler LH, Meyer WH, Helman LJ. Rhabdomyosarcoma. In: Pizzo PA, Poplack DG, eds. Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010:923-953.
- Arndt CA, Rose PS, Folpe AL, Laack NN. Common musculoskeletal tumors of childhood and adolescence. *Mayo Clin Proc.* 2012;87:475-487.
- 100. Olson TA, Schneider DT, Perlman EJ. Germ cell tumors. In: Pizzo PA, Poplack DG, eds. Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010:1045-1067.
- 101. De Backer A, Madern GC, Oosterhuis JW, Hakvoort-Cammel FG, Hazebroek FW. Ovarian germ cell tumors in children: a clinical study of 66 patients. *Pediatr Blood Cancer*. 2006;46:459-464.
- 102. Hastings CA, Torkildson JC, Agrawal AK. Germ cell tumors. In: Handbook of Pediatric Hematology and Oncology: Children's Hospital and Research Center Oakland. 2nd ed. Chichester, UK: John Wiley and Sons, Ltd; 2012:193-199.
- 103. Milose JC, Filson CP, Weizer AZ, Hafez KS, Montgomery JS. Role of biochemical markers in testicular cancer: diagnosis, staging, and surveillance. *Open Access J Urol*. 2011;4:1-8.
- 104. Cost NG, Lubahn JD, Adibi M, et al. A comparison of pediatric, adolescent, and adult testicular germ cell malignancy [published online ahead of print September 17, 2013]. Pediatr Blood Cancer. doi: 10.1002/pbc.24773.
- 105. Krane EJ, Casillas J, Zeltzer L. Pain and symptom management. In: Pizzo PA, Poplack DG, eds. Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010:1256-1287.
- 106. Oppenheim D. The child's subjective experience of cancer and the relationship with parents and caregivers. In: Kreitler S, Ben Arush MW, eds. Psychosocial Aspects of Pediatric Oncology. Chichester, UK: John Wiley and Sons, Ltd; 2004:109-138.
- 107. Wiener LS, Hersh SP, Alderfer MA. Psychiatric and psychosocial support for the child and family. In: Pizzo PA, Poplack DG, eds. Principles and Practice of Pediatric Oncology. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010:1322-1346.
- 108. Bryant R. Managing side effects of childhood cancer treatment. J Pediatr Nurs. 2003;18:113-125.
- 109. Skeen JE, Wesbter ML. Speaking to children about serious matters. In: Kreitler S,

- Ben Arush MW, eds. Psychosocial Aspects of Pediatric Oncology. Chichester, UK: John Wiley and Sons, Ltd; 2004:281-312.
- 110. Wolfe J, Tournay A, Zeltzer L. Palliative care for children with advanced cancer. In: Kreitler S, Ben Arush MW, eds. Psychosocial Aspects of Pediatric Oncology. Chichester, UK: John Wiley and Sons, Ltd; 2004:45-70.
- 111. Postovsky S, Ben Arush MW. Care of a child dying of cancer. In: Kreitler S, Ben Arush MW, eds. Psychosocial Aspects of Pediatric Oncology. Chichester, UK: John Wiley and Sons, Ltd; 2004:93-108.
- 112. National Cancer Policy Board, Institute of Medicine, National Research Council of the National Academies; Hewitt M, Weiner SL, Simone JV, eds. Childhood Cancer Survivorship: Improving Care and Quality of Life. Washington, DC: National Academies Press: 2003.
- 113. Singer S, Gianinazzi ME, Hohn A, Kuehni CE, Michel G. General practitioner involvement in follow-up of childhood cancer survivors: a systematic review. *Pediatr Blood Cancer*. 2013;60:1565-1573.
- 114. Kurt BA, Armstrong GT, Cash DK, et al. Primary care management of the childhood cancer survivor. *J Pediatr*. 2008;152:458-466.
- 115. Children's Oncology Group. Long-term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers. Version 3.0. survivorshipguide lines.org Accessed November 18, 2013.
- 116. Shankar SM, Marina N, Hudson MM, et al; Cardiovascular Disease Task Force of the Children's Oncology Group. Monitoring for cardiovascular disease in survivors of childhood cancer: report from the Cardiovascular Disease Task Force of the Children's Oncology Group. *Pediatrics*. 2008;121:e387-e396.
- 117. Wasilewski-Masker K, Liu Q, Yasui Y, et al. Late recurrence in pediatric cancer: a report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2009;101:1709-1720.
- 118. Meadows AT, Friedman DL, Neglia JP, et al. Second neoplasms in survivors of childhood cancer: findings from the Childhood Cancer Survivor Study cohort. *J Clin Oncol.* 2009;27:2356-2362.
- 119. Henderson TO, Friedman DL, Meadows AT. Childhood cancer survivors: transition to adult-focused risk-based care. *Pediatrics*. 2010;126:129-136.
- 120. Friedman DL, Whitton J, Leisenring W, et al. Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2010;102:1083-1095.
- 121. Inskip PD, Robison LL, Stovall M, et al. Radiation dose and breast cancer risk in the childhood cancer survivor study. *J Clin Oncol.* 2009;27:3901-3907.
- 122. Henderson TO, Amsterdam A, Bhatia S, et al. Systematic review: surveillance for breast cancer in women treated with chest radiation for childhood, adolescent, or young adult cancer. *Ann Intern Med*. 2010;152:444-455; W144-W154.
- 123. Yahalom J. Evidence-based breast cancer screening guidelines for women who received chest irradiation at a young age. *J Clin Oncol*. 2013;31:2240-2242.
- 124. Hudson MM, Ness KK, Gurney JG, et al. Clinical ascertainment of health outcomes

- among adults treated for childhood cancer. JAMA. 2013;309:2371-2381.
- 125. Lipshultz SE, Adams MJ, Colan SD, et al. Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: pathophysiology, course, monitoring, management, prevention, and research directions: a scientific statement from the American Heart Association. *Circulation*. 2013;128:1927-1995.
- 126. American Cancer Society. Global Cancer Facts & Figures. 2nd ed. Atlanta, GA: American Cancer Society; 2011.
- Ribeiro R, Pui CH. Treatment of acute lymphoblastic leukemia in low- and middleincome countries: challenges and opportunities. Leuk Lymphoma. 2008;49:373-376.
- 128. Hesseling P, Molyneux E, Kamiza S, Israels T, Broadhead R. Endemic Burkitt lymphoma: a 28-day treatment schedule with cyclophosphamide and intrathecal methotrexate. *Ann Trop Paediatr*. 2009;29:29-34.
- 129. Bhakta N, Martiniuk AL, Gupta S, Howard SC. The cost effectiveness of treating paediatric cancer in low-income and middle-income countries: a case-study approach using acute lymphocytic leukaemia in Brazil and Burkitt lymphoma in Malawi. Arch Dis Child. 2013;98:155-160.
- 130. Dimaras H, Dimba EA, Gallie BL. Challenging the global retinoblastoma survival disparity through a collaborative research effort. *Br J Ophthalmol*. 2010;94:1415-1416.
- Hopkins A, Burns E, Eden T. International twinning partnerships: an effective method of improving diagnosis, treatment and care for children with cancer in low-middle income countries. J Cancer Policy. 2013;1:e8-e19.
- 132. Green DM, Kun LE, Matthay KK, et al. Relevance of historical therapeutic approaches to the contemporary treatment of pediatric solid tumors. *Pediatr Blood Cancer*. 2013;60:1083-1094.
- 133. Kremer LC, Mulder RL, Oeffinger KC, et al; International Late Effects of Childhood Cancer Guideline Harmonization Group. A worldwide collaboration to harmonize guidelines for the long-term follow-up of childhood and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Pediatr Blood Cancer*. 2013;60:543-549.
- 134. Nathan PC, Ford JS, Henderson TO, et al. Health behaviors, medical care, and interventions to promote healthy living in the Childhood Cancer Survivor Study cohort. *J Clin Oncol.* 2009;27:2363-2373.
- 135. Green DM, Cox CL, Zhu L, et al. Risk factors for obesity in adult survivors of child-hood cancer: a report from the Childhood Cancer Survivor Study. J Clin Oncol. 2012; 30:246-255.
- 136. Armstrong GT, Oeffinger KC, Chen Y, et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. *J Clin Oncol.* 2013;31:3673-3680.
- 137. Anderson LM. Environmental genotoxicants/carcinogens and childhood cancer: bridgeable gaps in scientific knowledge. *Mutat Res.* 2006;608:136-156.
- 138. Miller JW, Beresford SA, Neuhouser ML, et al. Homocysteine, cysteine, and risk of incident colorectal cancer in the Women's Health Initiative observational cohort. Am J Clin Nutr. 2013;97:827-834.