Childhood Cancer

Cancer is not a single disease, but includes a variety of malignancies in which abnormal cells divide in an uncontrolled manner. These cancer cells can invade nearby tissues and can migrate by way of the blood or lymph systems to other parts of the body.[1] The most common childhood cancers are leukemias (cancers of the white blood cells) and cancers of the brain or central nervous system, which together account for more than half of new childhood cancer cases.[2]

Cancer in childhood is rare compared with cancer in adults, but still causes more deaths than any factor, other than injuries, among children from infancy to age 15 years.[2] The annual incidence of childhood cancer has increased slightly over the last 30 years; however, mortality has declined significantly for many cancers due largely to improvements in treatment.[2,3] Part of the increase in incidence may be explained by better diagnostic imaging or changing classification of tumors, specifically brain tumors.[4] However, the President's Cancer Panel recently concluded that the causes of the increased incidence of childhood cancers are not fully understood, and cannot be explained solely by the introduction of better diagnostic techniques. The Panel also concluded that genetics cannot account for this rapid change. The proportion of this increase caused by environmental factors has not yet been determined.[5]

The causes of cancer in children are poorly understood, though in general it is thought that different forms of cancer have different causes. According to scientists at the National Cancer Institute, established risk factors for the development of childhood cancer include family history, specific genetic syndromes (such as Down syndrome), high levels of radiation, and certain pharmaceutical agents used in chemotherapy.[4,6] A number of studies suggest that environmental contaminants may play a role in the development of childhood cancers. The majority of these studies have focused on pesticides and solvents, such as benzene. According to the President's Cancer Panel, "the true burden of environmentally induced cancer has been grossly underestimated."[5]

The development of cancer, or carcinogenesis, is a multistep process leading to the uncontrolled growth and division of cells. This process can begin with an inherited genetic mutation or DNA damage initiated by an exogenous agent, such as exposure to a carcinogenic chemical or radiation. Additionally, many external influences, such as environmental exposures or nutrition, can alter gene expression without changing the DNA sequence.[7] These alterations, referred to as epigenetic changes, can promote alterations in the expression of genes important for controlling cell growth and division.[8,9] Because the initiation of carcinogenesis is a multistep process, multiple factors are thought to contribute to the development of cancer.[9] Newer research suggests that childhood cancer may be caused by a combination of genetic predisposition and environmental exposure.[10-16]

Different types of cancer affect children at different ages. This pattern may reflect the different types of exposures and windows of vulnerability experienced by children as they grow older, and the time between the initiation of cancer and its clinical presentation. Children can be

affected by exposures that occur during different developmental stages, such as during infancy and early childhood. Scientific evidence suggests that early childhood cancers may be related to exposure in the womb, or even to parents' exposures prior to conception.[17-21] Furthermore, recent studies suggest that susceptibility to some cancers that arise later in adulthood also may be determined while in the womb.[7]

Leukemia is the most common form of cancer in children. According to the Centers for Disease Control and Prevention, adults and children who undergo chemotherapy and radiation therapy for cancer treatment; take immune suppressing drugs; or have certain genetic conditions, such as Down syndrome; are at a higher risk of developing acute leukemia.[22] Multiple review articles have concluded that ionizing radiation from sources such as x-rays is associated with an increased risk of leukemia.[23-25] CT scans are also an increasing source of ionizing radiation exposure to children,[26] and may be associated with an increased risk of childhood leukemia.[27] Further, studies have consistently shown an approximately 40% increased risk of childhood leukemia after maternal exposure to ionizing radiation during pregnancy.[18,23-25] These confirmed risk factors, however, explain less than 10% of the incidence of childhood leukemia, meaning that the cause is unknown in at least 90% of leukemia cases.[18]

Associations between proximity to extremely low frequency electromagnetic radiation, such as radiation from electrical power lines, and childhood leukemia have been investigated for many years.[5] Some studies suggest an effect on cancer risk, while others do not.[28,29] At this time, a variety of national and international organizations have concluded that the link between exposure to extremely low frequency electromagnetic fields and cancer is controversial or weak.[4,5] Radon is a naturally occurring radioactive element that has been associated with lung cancer; some studies have also found an association between childhood leukemia and radon while other studies have not.[4,30-32] A recent study also reported an association between naturally occurring gamma radiation and childhood leukemia.[33]

Pesticides, solvents, hazardous air pollutants, motor vehicle exhaust, and environmental tobacco smoke have been studied for a potential role in childhood leukemia. Numerous studies have examined the link between parents' (parental), prenatal, and childhood exposures to pesticides and childhood leukemia, and several meta-analyses of these studies have found associations between pesticide exposure and childhood leukemia in both residential and occupational settings.[20,34-46] Recent literature has also suggested an association between childhood exposures to multiple hazardous air pollutants and leukemia.[47-49] A study exploring the relationship between childhood leukemia and hazardous air pollutants (HAPs) in outdoor air found an increased risk for childhood leukemia in census tracts with the highest concentrations of a group of 25 potentially carcinogenic HAPs, including several solvents.[48] Several other studies have found associations between leukemia and surrogate measures of exposure to motor vehicle exhaust, including residential proximity to traffic and gas stations.[18,50-53] However, other studies conducted in California and Denmark did not find an association between these proxy measures of motor vehicle exhaust and childhood leukemia,[54-57] and review studies have concluded that the overall evidence for a relationship is inconclusive.[18,58]

According to the U.S. Surgeon General, there is also suggestive evidence that prenatal and postnatal exposure to environmental tobacco smoke can lead to leukemia in children.[59]

Cancers of the nervous system, including brain tumors, are the second most common form of cancer in children. Known risk factors for childhood brain tumors include radiation therapy and certain genetic syndromes, although these factors explain only a small portion of cases.[6] Some studies have also reported an association between prenatal exposure to ionizing radiation and brain tumors while a few smaller studies have not.[25,60,61] Other research reports that head CT scans may be associated with an increased risk of brain tumors in children.[27] Research also suggests that parental, prenatal, and childhood exposure to pesticides may lead to brain tumors in children.[43,45,46] There is suggestive evidence linking prenatal and postnatal exposure to environmental tobacco smoke and childhood brain tumors, according to the U.S. Surgeon General.[59] Many studies have examined whether there is an association between cellular phone use and brain cancer. Some of these studies have found an association between cellular phone use and some types of brain cancer, while other studies have found no association.[62-69] Because the use of cellular phones by children has only recently become more common, no long-term epidemiological studies of cancer related to cellular phone use by children are available.[5]

Lymphomas, which affect a child's lymph system, are another common form of childhood cancer. The cause of most cases of childhood lymphoma is unknown, but it is clear that children with compromised immune systems are at a greater risk of developing lymphomas.[6] Extensive review studies have found suggestive associations between parental, prenatal, and childhood exposure to pesticides and childhood lymphomas.[43,46] The U.S. Surgeon General has concluded that there is also suggestive evidence linking prenatal and postnatal exposure to environmental tobacco smoke and childhood lymphomas.[59]

Other childhood cancers that have been associated with environmental exposures include thyroid cancer, Wilms' tumor (a type of kidney cancer), Ewing's sarcoma (a cancer of the bone or soft tissue), and melanoma. Some research has reported an increased risk of thyroid cancer in childhood or early adulthood from exposure to ionizing radiation.[70-72] Much of the evidence for this association comes from studies of individuals in areas with high ionizing radiation exposure due to the Chernobyl accident in eastern Europe. While the only known causal factors for Wilms' tumor and Ewing's sarcoma are certain birth defects and genetic conditions, there is limited research indicating that exposure to pesticides may also be a causal factor in the development of Wilms' tumor and Ewing's sarcoma in children.[36,46,73] Although childhood melanoma is rare, the incidence of melanoma is increasing in children, especially in adolescents. Environmental factors associated with melanoma include sunburns, especially in childhood, and increased exposure to ultraviolet (UV) radiation.[74-76] Depletion of the ozone layer causes more ultraviolet radiation to reach the earth's surface. Even though the use of ozone depleting compounds has been largely phased out and the ozone layer will eventually be restored, higher levels of ultraviolet radiation reaching the earth's surface will persist for many years to come.[77,78] Finally, the increased rates of melanoma in adolescent girls and young

women may reflect increased UV exposure from sunbathing or from the widespread practice of indoor tanning.[79,80]

The two indicators that follow provide the best nationally representative data available on cancer incidence and mortality among U.S. children over time. Indicator H4 presents cancer incidence and mortality for children ages 0 to 19 years for the period 1992–2016. Indicator H5 presents cancer incidence, by cancer type, for children ages 0 to 19 years for the period 1997–2016. Changes in childhood cancer mortality are most likely reflective of changes in treatment options, rather than environmental exposures. However, showing childhood cancer mortality rates in conjunction with childhood cancer incidence rates highlights the magnitude and severity of childhood cancer and indicates the proportion of children that survive.

Indicator H4 provides an indication of broad trends in childhood cancer over time, while Indicator H5 provides more detailed information about the incidence of specific types of cancer in children.

Both indicators have been revised since the publication of *America's Children and the Environment, Third Edition* (January 2013) to incorporate updates to cancer incidence, mortality, and census data from 1992 to 2016 (H4) and 1997 to 2016 (H5).

Indicator H4: Cancer incidence and mortality for children ages 0 to 19 years, 1992–2016

Indicator H5: Cancer incidence for children ages 0 to 19 years by type, 1997–2016

About the Indicators: Indicators H4 and H5 present information about the number of new childhood cancer cases and the number of deaths caused by childhood cancer. The childhood cancer case data come from a program that collects information from tumor registries located in specific geographic regions around the country each year. The childhood cancer death data come from a national database of vital statistics that collects data on numbers and causes of all deaths each year. Indicator H4 shows how the rates of all new childhood cancers and all childhood cancer deaths have changed over time, and Indicator H5 shows how the rates of specific types of childhood cancers have changed over time.

SEER

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program has provided data on cancer incidence, survival, and prevalence since 1973. SEER obtains its cancer case data from tumor registries in various locations throughout the United States and its cancer mortality data from a national database of vital statistics that collects data on numbers and causes of all deaths each year. Each of the tumor registries collects information for all tumors within a specified geographic region. The sample population covered by the SEER tumor registries is comparable to the general U.S. population in terms of poverty and education. However, the population covered by the SEER tumor registries tends to be more urban and has a higher proportion of foreign-born persons compared with the general U.S. population.[81]

Since its initiation in 1973, the SEER program has expanded to include a greater number of tumor registries. Currently, the SEER program includes data from 18 tumor registries, but complete data from all 18 registries are only available beginning with the year 2000. SEER data are available from 13 different tumor registries that provide data starting in 1992, and represent geographic areas containing 13.8% of the total U.S. population[82] based on the 2000 Census, and 13.4% of the total U.S. population based on the 2010 Census. The registries include the Alaska Native, Atlanta, Connecticut, Detroit, Hawaii, Iowa, Los Angeles, New Mexico, Rural Georgia, San Francisco-Oakland, San Jose-Monterey, Seattle-Puget Sound, and Utah tumor registries.

Data Presented in the Indicators

Childhood cancer incidence refers to the number of new childhood cancer cases reported for a specified period of time. Childhood cancer incidence is shown in Indicator H4 and Indicator H5 as the number of childhood cancer cases reported per million children for one year. The incidence rate is age-adjusted, meaning that each year's incidence calculation uses the age distribution of children from the year 2000. For example, 25.3% of all U.S. children were

between the ages of 5 and 9 years in 2000, and this percentage is assumed to be the same for each year from 1992 to 2016. This age adjustment ensures that differences in cancer rates over time are not simply due to changes in the age composition of the population. Indicator H4 also shows childhood cancer mortality as the number of deaths per million children for each year.

SEER reports the incidence data by single year of age, but reports mortality data in five age groups for children under the age of 20: under 1 year, 1–4, 5–9, 10–14, and 15–19 years. For this reason, both indicators use data for all children 0 to 19 years of age, in contrast to the other indicators in this report that define children as younger than age 18 years.

Trends in the total incidence of childhood cancer, as shown by Indicator H4, are useful for assessing the overall burden of cancer among children. However, broad trends mask changes in the frequency of specific types of cancers that often have patterns that diverge from the overall trend. Moreover, environmental factors may be more likely to contribute to some childhood cancers than to others. Indicator H5 shows trends in incidence for specific types of childhood cancers.

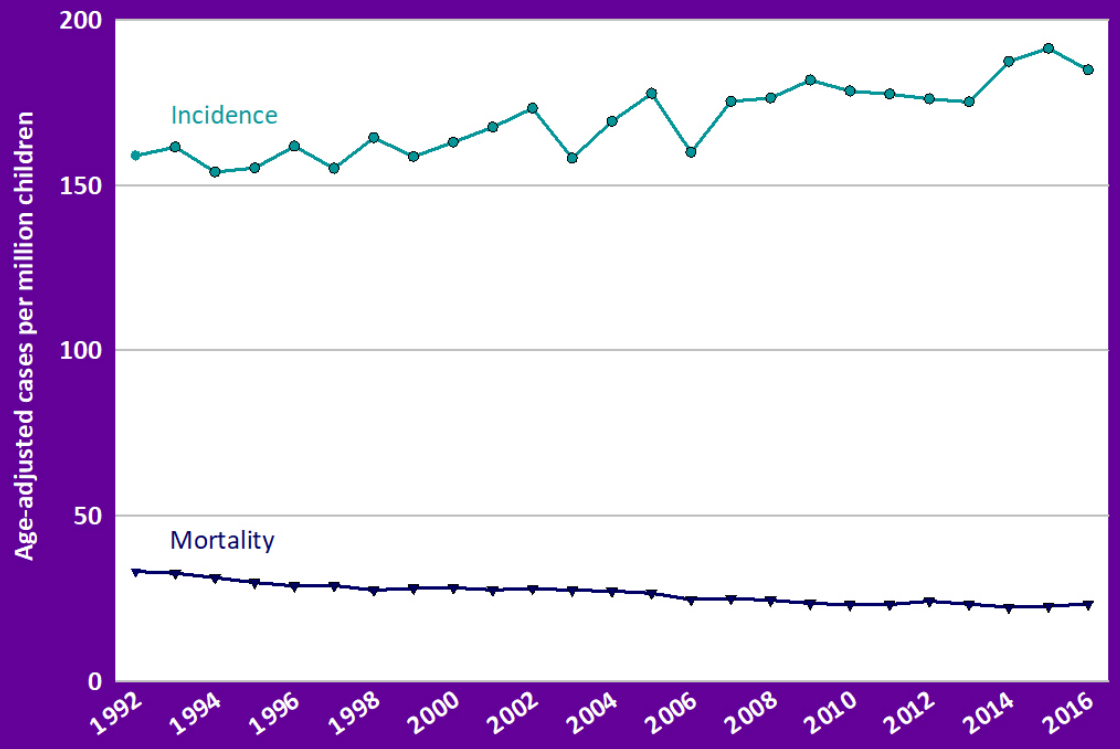
Some types of childhood cancers are very rare, and as such the yearly incidence is particularly low and variable. Due to this fact, Indicator H5 shows the incidence of individual childhood cancers in groupings of four years. Each bar in the graph represents the annual number of cases of that specific cancer diagnosed per million children, calculated as the average number of cases per year divided by the average population of children (in millions) per year for each four-year period.

The SEER cancer incidence data for the 13 longer-established registries, instead of all 18, were used to develop the H4 and H5 indicators because this allowed for more comprehensive trend analysis while still covering a substantial portion of the population. Indicator H4 begins with the earliest available SEER13 incidence data from 1992 and ends with 2016. Childhood cancer mortality data for 1992 to 2016 are also used for indicator H4. Indicator H5 presents data for the series of four-year periods beginning in 1997 and ending in 2016. In addition to the data shown in the Indicator H4 graph, supplemental tables show childhood cancer incidence and mortality by race/ethnicity and sex, as well as childhood cancer incidence by age group. These data tables use data from the three most current years shown in Indicator H4, which are 2014–2016. Combining three years of data allows for more statistically reliable estimates by race/ethnicity, sex, and age group. Five race/ethnicity groups are used in the supplemental tables for Indicator H4: White non-Hispanic, Black non-Hispanic, American Indian/Alaska Native non-Hispanic, Asian or Pacific Islander non-Hispanic, and Hispanic. In addition to the data shown in the Indicator H5 graph, a supplemental table shows childhood cancer incidence by cancer type and age group.

Please see the Introduction to the Health section for discussion of statistical significance testing applied to these indicators.

Indicator H4

Cancer incidence and mortality for children ages 0 to 19 years, 1992-2016



Data: National Cancer Institute, Surveillance, Epidemiology and End Results Program

America's Children and the Environment, Third Edition, Updated August 2019

Data characterization

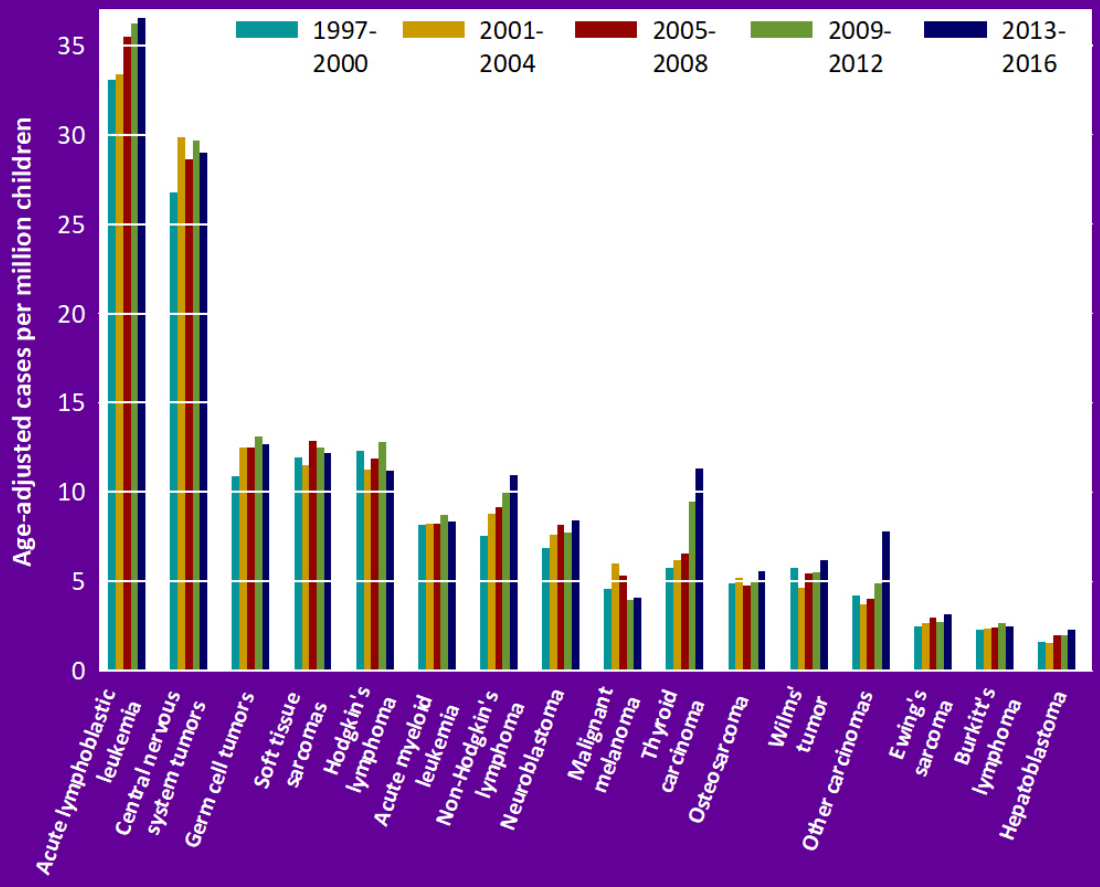
- Cancer incidence data for this indicator are obtained from a database of 13 regional tumor registries located throughout the country, maintained by the National Cancer Institute.
- The population covered by the 13 registries is comparable to the general U.S. population regarding poverty and education, but is more urban and has more foreign-born persons.
- Cancer mortality data for this indicator are obtained from a database of all death certificates in the United States; cause of death is recorded on the death certificates.

- The age-adjusted annual incidence of cancer ranged from 154 to 161 cases per million children between 1992 and 1994 and from 185 to 191 cases per million children between 2014 and 2016. This increasing trend from 1992–2016 was statistically significant.

- Childhood cancer mortality decreased from 33 deaths per million children in 1992 to 23 deaths per million children in 2016, a statistically significant decreasing trend.
- Childhood cancer incidence and mortality rates were generally higher for boys than for girls. In 2014–2016, rates of cancer incidence and mortality for boys were 196 cases per million and 25 deaths per million, compared with 179 cases per million and 20 deaths per million for girls. These differences by sex were statistically significant for cancer incidence (after adjustment for age and race/ethnicity) and cancer mortality. (See Tables H4a and H4b.)
- In 2014–2016, cancer incidence was consistently greater for boys than girls in each race/ethnicity group. The difference was statistically significant for American Indian and Alaska Native (AIAN) non-Hispanic children and Hispanic children (after adjustment for age). The differences were not statistically significant for other race/ethnicity groups. (See Table H4a.)
- In 2014–2016, cancer mortality was consistently greater for boys than girls in each race/ethnicity group. The difference was statistically significant for White non-Hispanic children, AIAN non-Hispanic children, and Hispanic children. (See Table H4b).
- In 2014–2016, childhood cancer incidence was highest among White non-Hispanic children at 202 cases per million. AIAN non-Hispanic children had an incidence rate of 176 cases per million, Asian and Pacific Islander (API) non-Hispanic children had an incidence rate of 177 cases per million, Hispanic children had an incidence rate of 182 cases per million, and Black non-Hispanic children had an incidence rate of 142 cases per million. (See Table H4a.)
    - The cancer incidence rate for White non-Hispanic children was statistically significantly higher than the rates of Black non-Hispanic, API non-Hispanic, and Hispanic children after accounting for differences by age and sex. The cancer incidence rate for Black non-Hispanic children was statistically significantly lower than the rates of API non-Hispanic and Hispanic children after accounting for differences by age and sex. The remaining differences between race/ethnicity groups were not statistically significant.
- Childhood cancer incidence rates vary by age. In 2014–2016, children under 5 and those of ages 15 to 19 years experienced the highest incidence rates of cancer at approximately 227 and 252 cases per million, respectively. Children ages 5 to 9 years and 10 to 14 years had lower incidence rates at 124 and 151 cases per million, respectively. These differences among age groups were statistically significant. (See Table H4c.)

Indicator H5

Cancer incidence for children ages 0 to 19 years, by type, 1997-2016



Data: National Cancer Institute, Surveilliance, Epidemiology, and End Results Program

America's Children and the Environment, Third Edition, Updated August 2019

Data characterization

- Data for this indicator are obtained from a database of 13 regional tumor registries located throughout the country, maintained by the National Cancer Institute.
- The population covered by the 13 registries is comparable to the general U.S. population regarding poverty and education, but is more urban and has more foreign-born persons.

- Leukemia, which includes acute lymphoblastic leukemia and acute myeloid leukemia, was the most common cancer diagnosis for children from 2013–2016, representing 26% of total cancer cases. Incidence of acute lymphoblastic (lymphocytic) leukemia was 33 cases per million in 1997–2000 and 37 cases per million in 2013–2016. The rate of acute myeloid

(myelogenous) leukemia was 8.2 cases per million in 1997–2000 and 8.3 cases per million in 2013–2016.
    - The increasing trend for incidence of acute lymphoblastic leukemia was statistically significant after accounting for differences by age, sex, and race/ethnicity. The trend for acute myeloid leukemia was not statistically significant.
- Central nervous system tumors represented 17% of childhood cancers in 2013–2016. The incidence of central nervous system tumors was 27 cases per million in 1997–2000 and 29 cases per million in 2013–2016.
    - The trend for incidence of central nervous system tumors was not statistically significant.
- Lymphomas, which include Hodgkin's lymphoma, non-Hodgkin's lymphoma, and Burkitt's lymphoma, represented 14% of childhood cancers in 2013–2016. Incidence of Hodgkin's lymphoma was 12.3 cases per million in 1997–2000 and 11.2 cases per million in 2013–2016. There were approximately 8 cases of non-Hodgkin's lymphoma per million children in 1997–2000 and 11 cases per million in 2013–2016. Incidence of Burkitt's lymphoma was 2.3 cases per million children in 1997–2000 and 2.5 cases per million in 2013–2016.
    - The increasing trend in the incidence rate of non-Hodgkin's lymphoma was statistically significant. There was no statistically significant trend in the incidence rates of Hodgkin's lymphoma and Burkitt's lymphoma.
- Between the years 1997 and 2016, increasing trends in the incidence of thyroid carcinoma, other and unspecified carcinomas, Ewing's sarcoma, and hepatoblastoma were statistically significant. The increasing trend in neuroblastomas was statistically significant after accounting for differences by age, sex, and race/ethnicity. There was no statistically significant trend in the incidence rate of germ cell tumors, soft tissue sarcomas, malignant melanomas, osteosarcomas, or Wilms' tumor (tumors of the kidney).
- Different types of cancer affect children at different ages. The incidence of neuroblastomas and Wilms' tumor was highest for young children (ages 0 to 4 years). Leukemias occur in all age groups, but the incidence is highest among 0- to 4-year-olds. The incidence of Hodgkin's and non-Hodgkin's lymphomas, thyroid carcinomas, malignant melanomas, other and unspecified carcinomas, germ cell tumors, and osteosarcomas was higher in those 15 to 19 years old. Differences among age groups were statistically significant for each of these cancer types. (See Table H5a.)

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