National Cancer Institute

An Analysis of the National Cancer Institute's Investment in Pediatric Cancer Research

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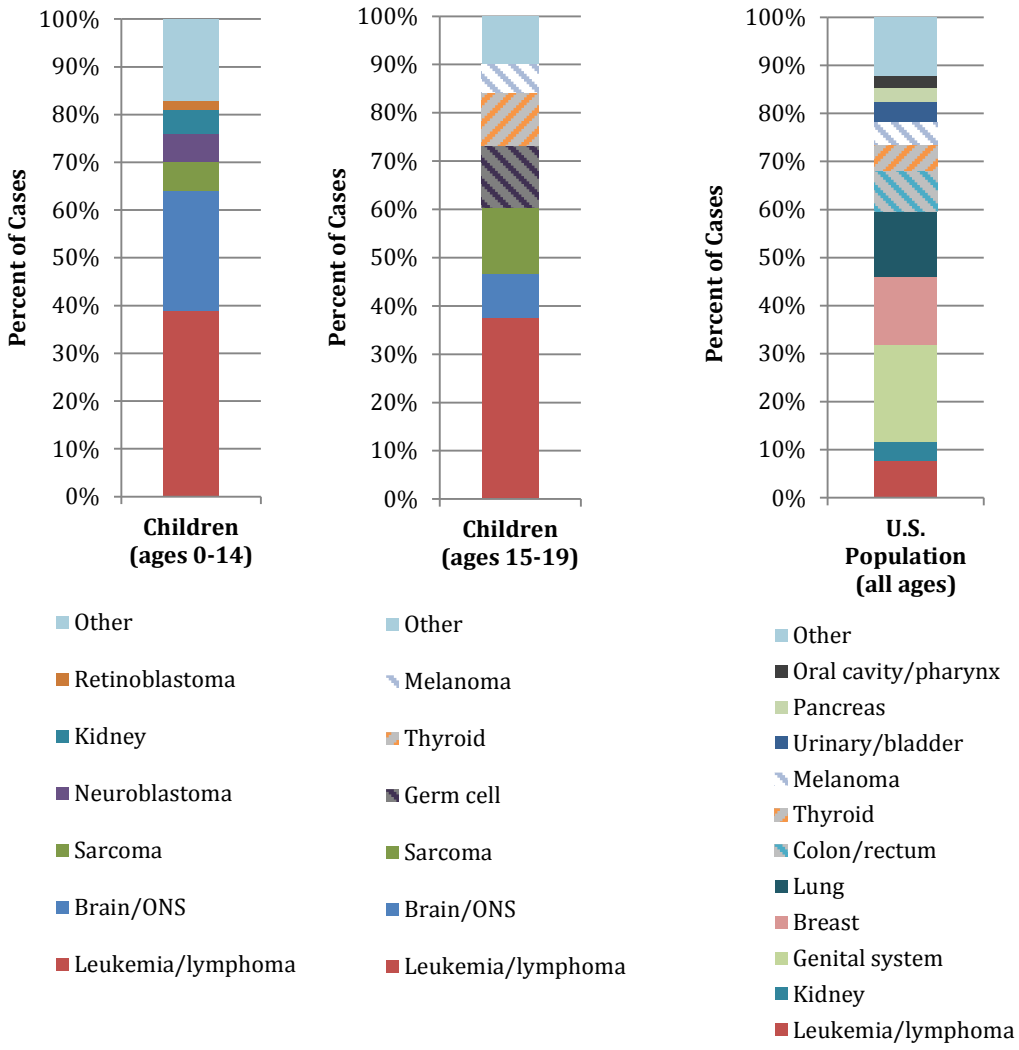
OVERVIEW

Cancer is the leading disease-related cause of death among children in the United States.[1] The types of cancers that most frequently develop in children are different from the most common adult cancers (Figure 1). For example, although leukemia, lymphoma, and brain/other nervous system (brain/other nervous system [ONS]) cancers account for more than half of all childhood cancers, they account for less than 10% of cancer cases in adults (Figure 1). In addition, etiologic differences and genomic variations within even the same cancer type suggest that the childhood and adult cancers may be discrete diseases.[2] These observations warrant a specific focus on pediatric cancers. This report examines the current state of the pediatric cancer burden and highlights the National Cancer Institute's (NCI's) continued investments in research on childhood cancer.

[1] Heron M. Deaths: Leading Causes for 2008. *Natl Vital Stat Rep.* 2012;60(6). Available at: http://www.cdc.gov/nchs/data/nvsr/nvsr60/nvsr60_06.pdf.

[2] Downing JR, Wilson RK, Zhang J, Mardis ER, Pui CH, Ding L, et al. The Pediatric Cancer Genome Project. *Nat Genet.* 2012;44(6):619-22.

Figure 1. Distribution of Leading Cancers by Age in the General U.S. Population*



To aid visually impaired readers, the legend order mirrors the order of data in the stacked column.

Sources: Proportions for "Children (ages 0-14)" and "U.S. Population (all ages)" are based on estimated cases in the U.S. for 2013. American Cancer Society, Cancer Facts & Figures 2013. Proportions for "Children (ages 15-19)" are based on the reported U.S. cases for 2006-2010 from NCI's Surveillance, Epidemiology, and End Results Program.

* The distribution of cancers within the U.S. population is largely representative of the adult population since childhood cancers account for less than 1% of all cancers diagnosed each year.

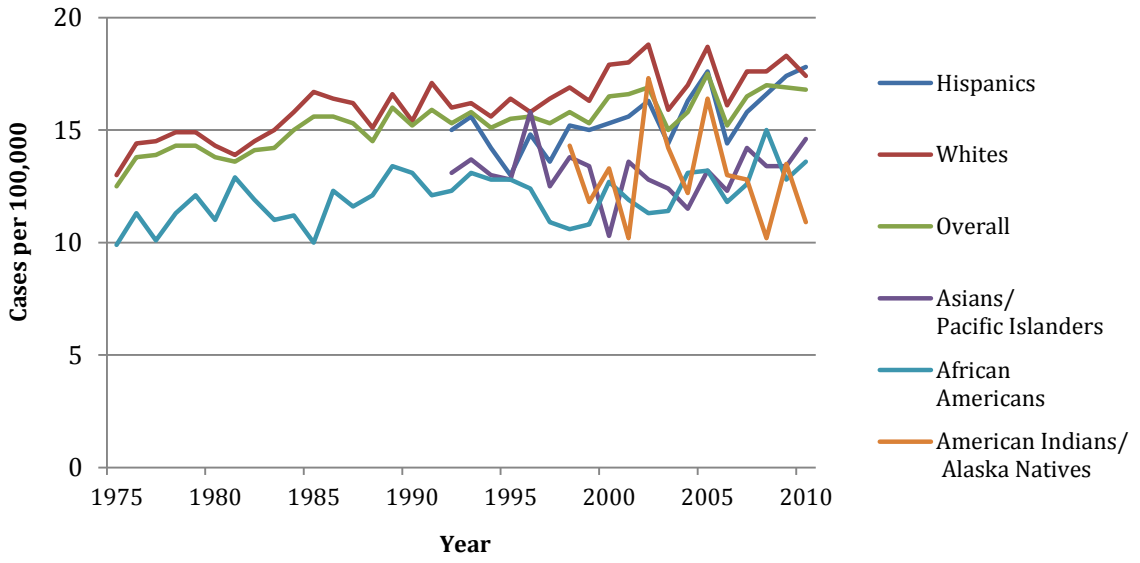
THE BURDEN OF PEDIATRIC CANCER

Incidence Rates

Depending on the data source, ages 0−14, 0−18 or 0−19 years may be used to define pediatric populations. Patients aged 15−19 years, however, are also often included within the adolescent/young adult population. Most of the data described in this report refers to ages 0−18 or 0−19, unless otherwise noted.

The causes of most childhood cancers are unknown, and for the most part these diseases cannot be prevented. The overall incidence of pediatric cancer rose about one-third from 1975 to 2010, from 12.5 to 16.8 cases per 100,000 population (Figure 2). For the period of 1993 to 2010, cancer incidence among children aged 0−19 years increased 0.6% per year.[3] In the individual racial/ethnic groups tracked by NCI's Surveillance, Epidemiology, and End Results (SEER) Program, a rise in incidence over the last two decades is apparent in whites, Asians/Pacific Islanders, and Hispanics (Figure 2). In African American children, incidence rates have risen significantly since 1998 (Figure 2). The incidence of cancer is higher in Hispanic and white children than in children of other ethnicities/races (Figure 2).

Figure 2. U.S. Pediatric Cancer Incidence, Ages 0–18*



To aid visually impaired readers, the legend is arranged in descending order to mirror the order of the data in 2010.

Source: Surveillance, Epidemiology, and End Results Program.

* Incidence data not available prior to 1992 for some races/ethnicities.

[3] SEER Cancer Statistics Review, 1975-2010. Available at: http://seer.cancer.gov/csr/1975_2010.

The most common types of childhood cancer include leukemia (acute lymphoid leukemia [ALL] accounts for 75% of all childhood leukemia cases[3]), brain/ONS cancer, lymphoma (Hodgkin and non-Hodgkin), sarcoma (rhabdomyosarcoma, osteosarcoma, and Ewing sarcoma), neuroblastoma, Wilms tumor, and retinoblastoma. Other childhood cancers include hepatocellular carcinoma, germ cell tumors, pleuropulmonary blastoma, and other less common cancers of children. The cancers with the highest incidence in children are leukemia, lymphoma, and cancers of the brain/ONS, which together constitute 64% of the cancers affecting children under age 15 and 47% of the cancers in children aged 15−19 (Figure 1).

The incidence of leukemia, brain/ONS, soft tissue sarcoma, and germ cell tumors has increased significantly since 1975, and the incidence of lymphoma has increased significantly since 1993 (Table 1). In contrast, the incidence of retinoblastoma has decreased significantly since 1993 (Table 1). The factors leading to increasing incidence are largely unknown. For brain/ONS cancer, whose incidence started to stabilize in the mid-1980s,[3] increased incidence before the mid-1980s may be explained by an increase in the detection of these cancers through the use of new imaging technologies.

Table 1. U.S. Age-Adjusted Cancer Trends, Ages 0–19

	Percent Change	Annual Percent Change (APC) Over the Time Interval				
	Incidence	Incidence Trends			Mortality Trends**	
	1975–2010	1975–2010	1975–1992	1993–2010	1975–1996/98	1996/98–2006
All sites	33.7	0.6*	1.0*	0.6*,#	—	—
Leukemia	39.6	0.7*	1.1*	0.8*	—	—
Lymphoma	7.3	0.1	0.1	0.8*	—	—
Brain/ONS	66	0.9*	2.2*	0.5#	—	—
Neuroblastoma	−11.1	0.3	0.1	−0.3	—	—
Retinoblastoma	−2	0.1	1.2	−1.6*,#	—	—
Renal tumors	30.8	0	0.5	−1.1	—	—
Malignant bone tumors	0.4	0.1	1.2*	−0.2	—	—
Soft tissue sarcomas	46	0.7*	0.8	0.8	—	—
Germ cell tumors	49.2	0.9*	1.5*	0.7	—	—
Other	40.9	1.0*	0.8	1.2*	—	—
Leukemia and lymphoma	—	—	—	—	−3.6*	−2.2*
All other sites	—	—	—	—	−1.9*	−0.3

* The APC is significantly different from zero ($P < .05$).

\# The APC for 1993–2010 is significantly different from the APC for 1975–1992.

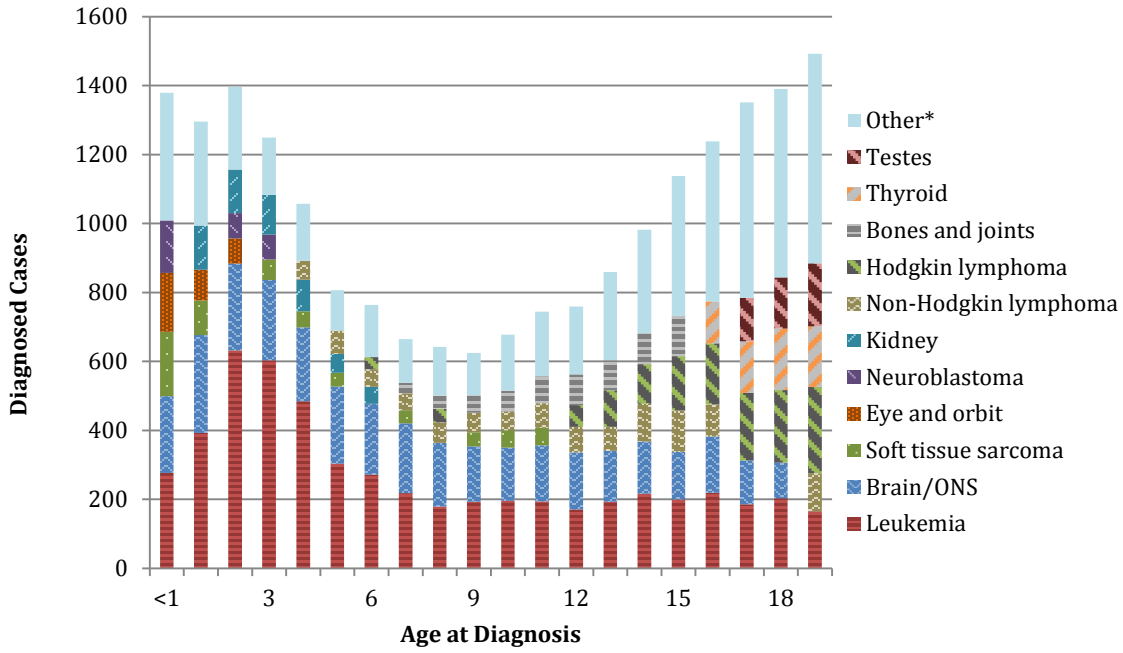
** The mortality trend time intervals for leukemia and lymphoma are for 1975–1998 and 1998–2006. The mortality trend time intervals for all other sites are for 1975–1996 and 1996–2006.

Incidence source: Surveillance, Epidemiology, and End Results (SEER) Program and the SEER Cancer Statistics Review, 1975–2010.

Mortality source: Smith MA, Seibel NL, Altekruse SF, Ries LA, Melbert DL, O'Leary M, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. *J Clin Oncol.* 2010;28(15):2625-34.

Within the pediatric population, the most frequently diagnosed cancer types vary with age; the top five for each age are shown in Figure 3. Brain/ONS cancers are frequently diagnosed in children of nearly all ages. Eye and kidney cancers are more common in younger children, and lymphomas are more common in older children. Cancers of the testes and thyroid are found more often in older adolescents.

Figure 3. Top Five Diagnosed Cancer Sites for Each Age at Diagnosis



Source: Surveillance, Epidemiology, and End Results (SEER), Cancer Statistics Review 1975–2010.

* Only the top five cancer sites for each age are listed; "other" refers to any cancer not listed for a particular age. The top five cancer sites were determined based on the 2006−2010 age-specific rate.

Mortality Rates

Over the past 30 years, the mortality rate for all pediatric cancers combined has declined by more than 50% (Figure 4). Mortality rates are similar for all racial/ethnic groups (Figure 4) and between boys and girls.[3] The percentage of children who survive 5 years after diagnosis has improved from approximately 62% in the mid-1970s to 83% in recent years (Figure 5). This increase has been due in part to the very high participation of children with cancer in clinical trials, which in turn has facilitated the identification of improved treatment regimens. These statistics, however, do not tell the full story. Pediatric cancer survivors face life-long health issues, including serious chronic conditions and secondary cancers.

In addition, while increases in 5-year survival since 1975 have been observed at for each cancer type (Figure 5), unfortunately, improvements have not been universal across all the cancers within a site or across all age groups of children. For example, children with biologically high-risk neuroblastoma have a 5-year survival rate of less than 50%.[4,5] In addition, outcomes are poor for patients with soft tissue sarcomas and malignant bone tumors (Ewing sarcoma and osteosarcoma) that have spread beyond their primary site and for children with high-grade gliomas (including diffuse intrinsic pontine gliomas). Mortality rates for patients with cancers other than leukemia or lymphoma have not declined since 1996, suggesting that new advances are required to further reduce mortality in these patients (Table 1).[6] These examples illustrate the need for continued research to identify effective treatments for those children who are not likely to be cured with the current therapies.

The cancer types with the highest mortality rates vary with age (Figure 6), although brain/ONS cancers and leukemia are leading causes of cancer-related death in children across all ages. Notably, despite the very low incidence of liver cancer in younger children (only 6−10 cases per 1,000,000 children under 5 years of age[3]), liver cancers are the fourth most common cause of cancer-related mortality in children ages 3 and younger. Neuroblastomas also are relatively common causes of cancer-related mortality in younger children, whereas bone and joint cancers and non-Hodgkin lymphomas are more common causes of cancer-related mortality in older children.

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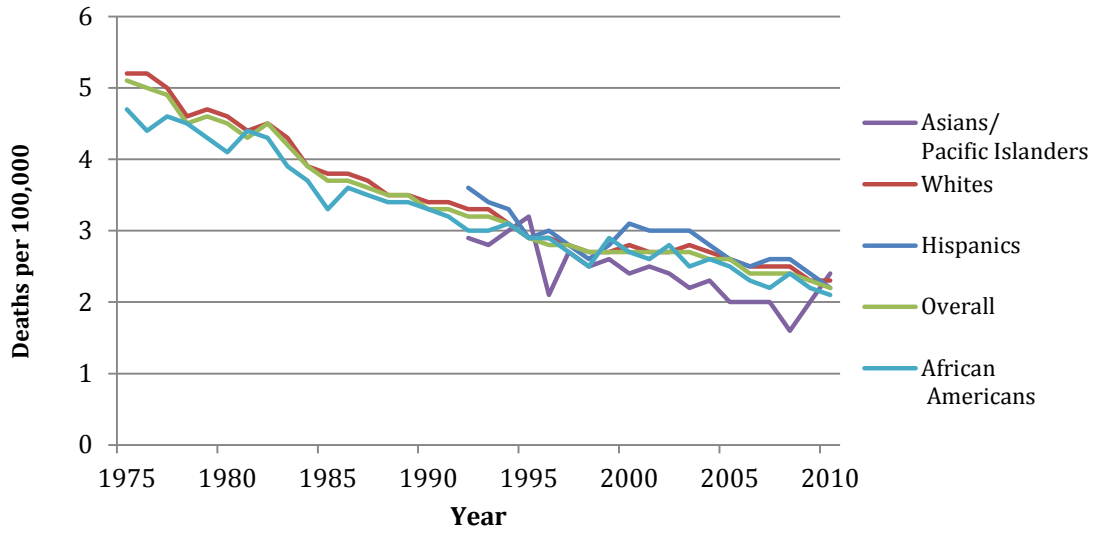
[4] Maris JM. Recent advances in neuroblastoma. *N Engl J Med.* 2010;362(23):2202-11.
[5] Kreissman SG, Seeger RC, Matthay KK, London WB, Sposto R, Grupp SA, et al. Purged versus non-purged peripheral blood stem-cell transplantation for high-risk neuroblastoma (COG A3973): a randomised phase 3 trial. *Lancet Oncol.* 2013;14(10):999-1008.
[6] Smith MA, Seibel NL, Altekruse SF, Ries LA, Melbert DL, O'Leary M, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. *J Clin Oncol.* 2010;28(15):2625-34.

Figure 4. U.S. Pediatric Cancer Mortality, Ages 0–18*

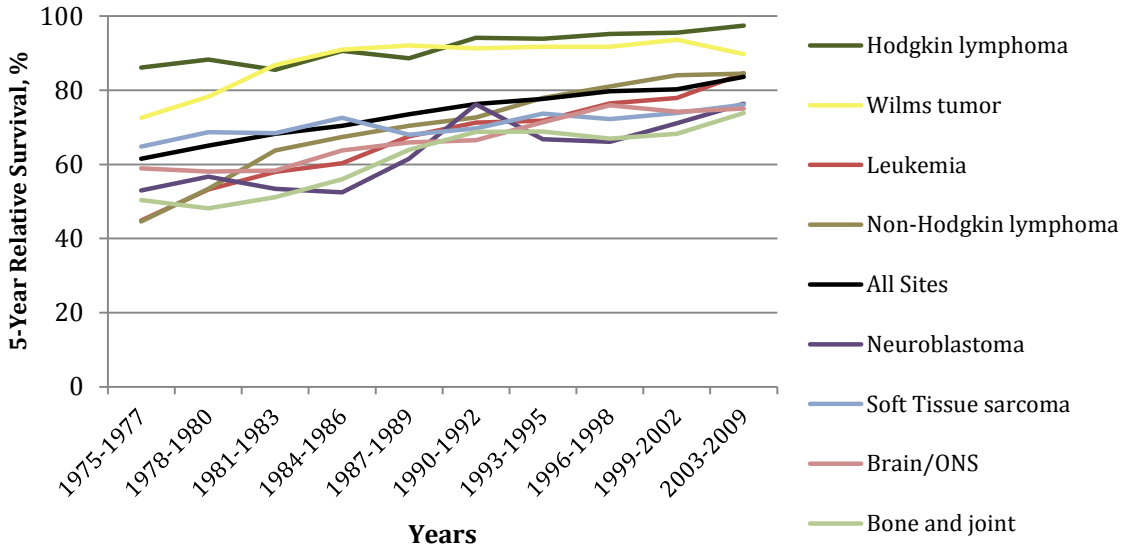


To aid visually impaired readers, the legend is arranged in descending order to mirror the order of the data in 2010.

Source: National Center for Health Statistics.

* Mortality data not available prior to 1992 for some races/ethnicities. Sufficient data for mortality time trend analysis of American Indians and Alaska Natives was not available.

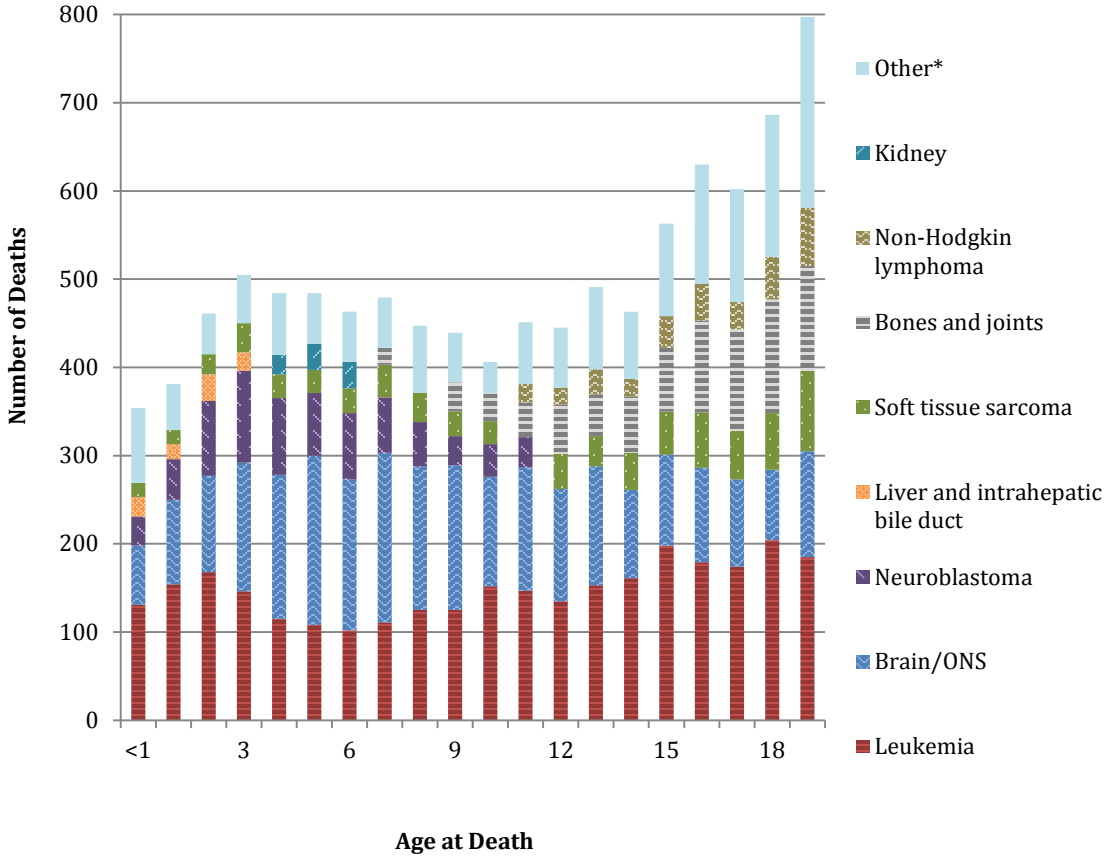
Figure 5. U.S. Pediatric Cancer 5-Year Survival by Site, Ages 0–19



To aid visually impaired readers, the legend is arranged in descending order to mirror the order of the data in 2003-2009.

Source: Surveillance, Epidemiology, and End Results (SEER), Cancer Statistics Review 1975–2010.

Figure 6. Top Five Cancer Sites Associated with Mortality, by Age



Source: Surveillance, Epidemiology, and End Results (SEER), Cancer Statistics Review 1975–2010.

* Only the top five cancer sites for each age are listed; "other" refers to any cancer not listed for a particular age. The top five cancer sites were determined based on the 2006–2010 age-specific rate.

NCI'S INVESTMENT IN PEDIATRIC CANCER RESEARCH

NCI Funding for Pediatric Cancer Research

Special interest categories (SICs) are major scientific disciplines that are of stated or growing interest to the National Institutes of Health (NIH), the Department of Health and Human Services, Congress, and/or the public. At NCI, trained scientific staff analyze the research proposals within grant applications, contracts, and intramural proposals to estimate their percent relevance to specific SICs for each project. This information is publicly available through the NCI Funded Research Portfolio (NFRP).[7]

The "childhood cancers" SIC was developed to identify projects with obvious relevance to pediatric cancer research. It is important to note that the "percent relevance" statistic captures projects that have a relevance to "childhood cancers" described in their research proposal. Although research projects in basic biology often give researchers valuable insight into specific cancer types, including pediatric cancers, these projects are not captured by the "childhood cancers" SIC estimates.

Using the "childhood cancers" SIC, an estimate of NCI's investment in pediatric cancer research projects is made by multiplying each such project's total annual funding by its percent relevance to "childhood cancers" and summing across all projects. By this measure, NCI's estimated investment in research on pediatric cancers increased from $172.7 million in fiscal year (FY) 2007 to $208.1 million in FY 2012 (Figure 7). In addition, NCI supported an estimated $60.4 million in pediatric cancer research in FY 2009 and 2010, using funds from the American Recovery and Reinvestment Act (ARRA).[8] Funding in pediatric cancer research is spread across the Divisions, Offices, and Centers (DOCs) that fund and conduct research at NCI (Figure 7). In 2012, the bulk (84%) of the funding for pediatric cancer research was through NCI's Division of Cancer Treatment and Diagnosis, Division of Cancer Biology, Office of the Director, and Center for Cancer Research.

Progress in cancer research has changed experts' understanding of cancer. It is now widely recognized that cancer is a collection of many diseases that no longer fit neatly into categories. The degree of heterogeneity is such that it may not be an exaggeration to state that each cancer is unique at the molecular level. However, different types of cancer often share important molecular characteristics, explaining the long-standing observations that studies of one type of cancer often provide unanticipated insights into another type and that studies of the basic features of cancer can illuminate features of a variety of cancers. For example, crizotinib, a drug developed for non-small cell lung cancer in adults, is remarkably active in children with anaplastic large cell lymphoma. In addition, vesmodegib, a drug developed for basal cell carcinoma in adults, is active in children with a particular subtype of medulloblastoma.

Unfortunately, the coding and accounting system used by the NIH described above is not able to capture the important overlaps illustrated by these examples, so the reported funding level for pediatric cancers, for example, cannot be taken as a definitive report of all research relevant to pediatric cancer at the NCI. It should also be noted that the annually reported funding levels are retrospective views of the work NCI has supported, and do not represent prospective funding targets.

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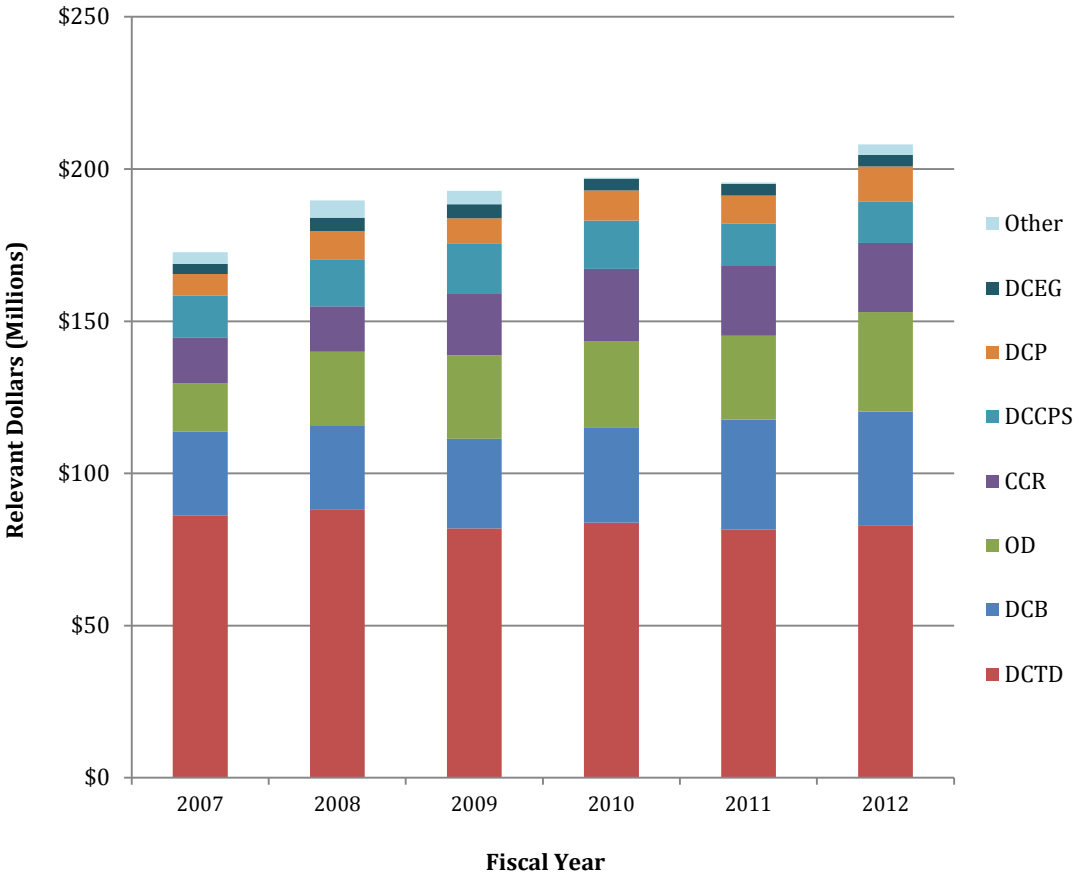
[7] NFRP. See http://fundedresearch.cancer.gov/nciportfolio.

[8] For more information regarding ARRA funding at NCI, see Recovery Act Funding at NCI (http://www.cancer.gov/aboutnci/recovery/recoveryfunding).

Figure 7. Childhood Cancer Funding Across NCI Divisions, Offices, and Centers



To aid visually impaired readers, the legend order mirrors the order of data in the stacked column.

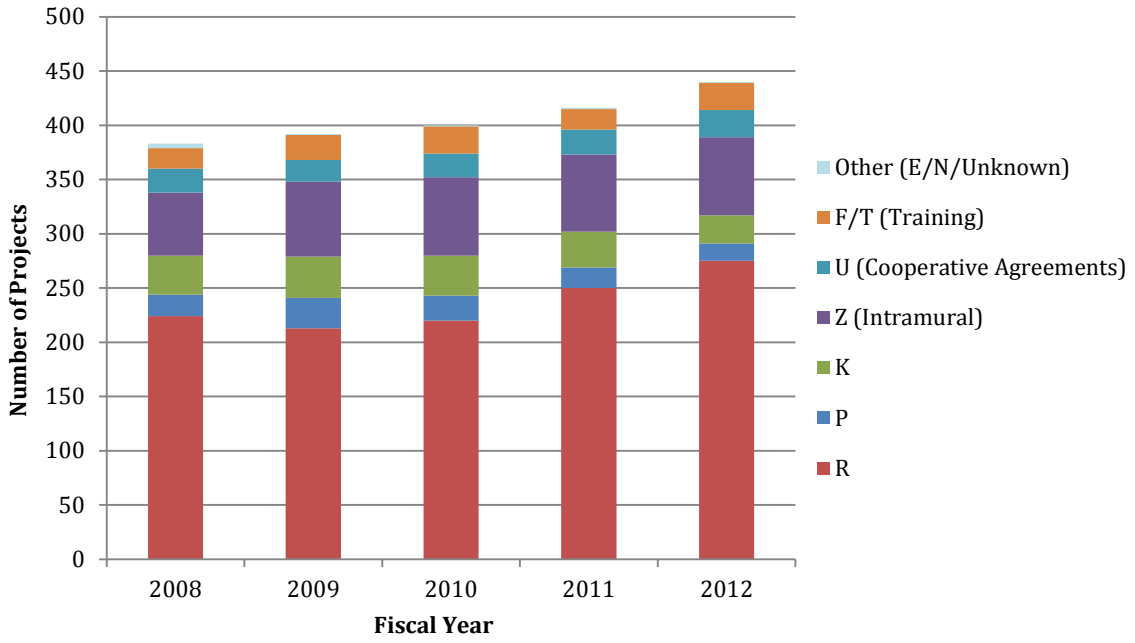
Source: NCI Funded Research Portfolio: http://fundedresearch.cancer.gov/nciportfolio

Abbreviations for NCI Divisions, Offices, and Centers: Center for Cancer Research (CCR); Division of Cancer Biology (DCB); Division of Cancer Control and Population Sciences (DCCPS); Division of Cancer Epidemiology and Genetics (DCEG); Division of Cancer Prevention (DCP); Division of Cancer Treatment and Diagnosis (DCTD); Office of the Director (OD).

Total relevant dollars per fiscal year: $172.7M, 2007; $189.7M, 2008; $192.8M, 2009; $197.1M, 2010; $195.5M, 2011; $208.1M, 2012.

NCI uses a variety of mechanisms to fund research in pediatric cancer (Figure 8). The majority of funds are allocated to the cancer research community in the form of extramural research and center grants (using R, P, and U mechanisms); in FY 2012, $170 million of the estimated relevant investment in childhood cancers was funded through these three mechanisms. In FY 2012, NCI distributions to pediatric cancer research included nearly $4.3 million through career development (K) awards and $3.7 million through training (F and T) awards, thereby bolstering the future biomedical workforce. Also in FY 2012, nearly $26.5 million was invested in research on pediatric cancer through NCI intramural research programs (the Z mechanism), which conduct research across the cancer continuum.

Figure 8. NCI's Childhood Cancer Projects* by Mechanism



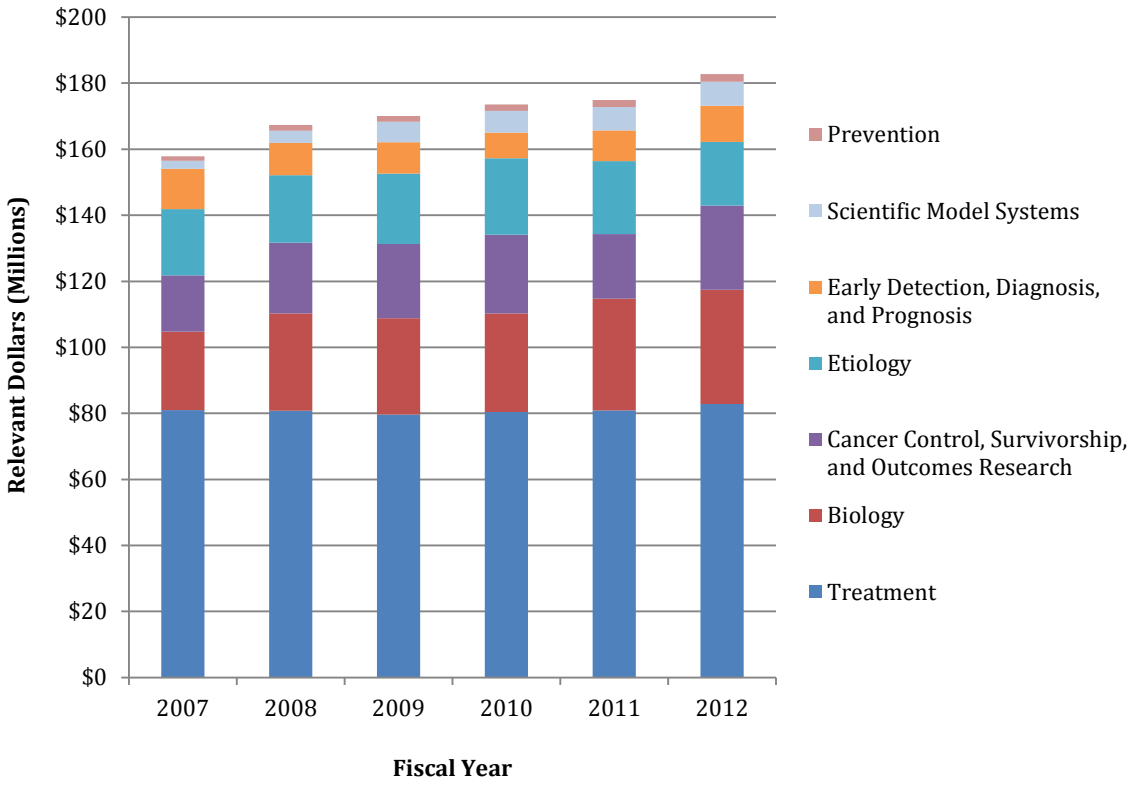
To aid visually impaired readers, the legend order mirrors the order of data in the stacked column.

Source: NCI Funded Research Portfolio: http://fundedresearch.cancer.gov/nciportfolio.

* Project list is limited to projects with at least 25% relevance to the "childhood cancers" SIC.

In addition to being classified by their relevance to specific SICs, NCI projects are classified according to the Common Scientific Outline (CSO),[9] a system organized around seven broad areas of scientific interest in cancer research. In recent years, the single largest amount by percentage (approximately 45%) of NCI's estimated funding for research in pediatric cancer has supported projects in the area of treatment (Figure 9). Basic scientific research can provide clues into the underlying biology and causes, or etiology, of pediatric cancers; 30% of the FY 2012 dollars relevant to childhood cancers were invested in such projects. Research investments in cancer control, survivorship, and outcomes research comprised 14% of the funding relevant to childhood cancers.

Figure 9. Relevant Dollars by CSO Code for NCI's Childhood Cancer Projects*



To aid visually impaired readers, the legend order mirrors the order of data in the stacked column.

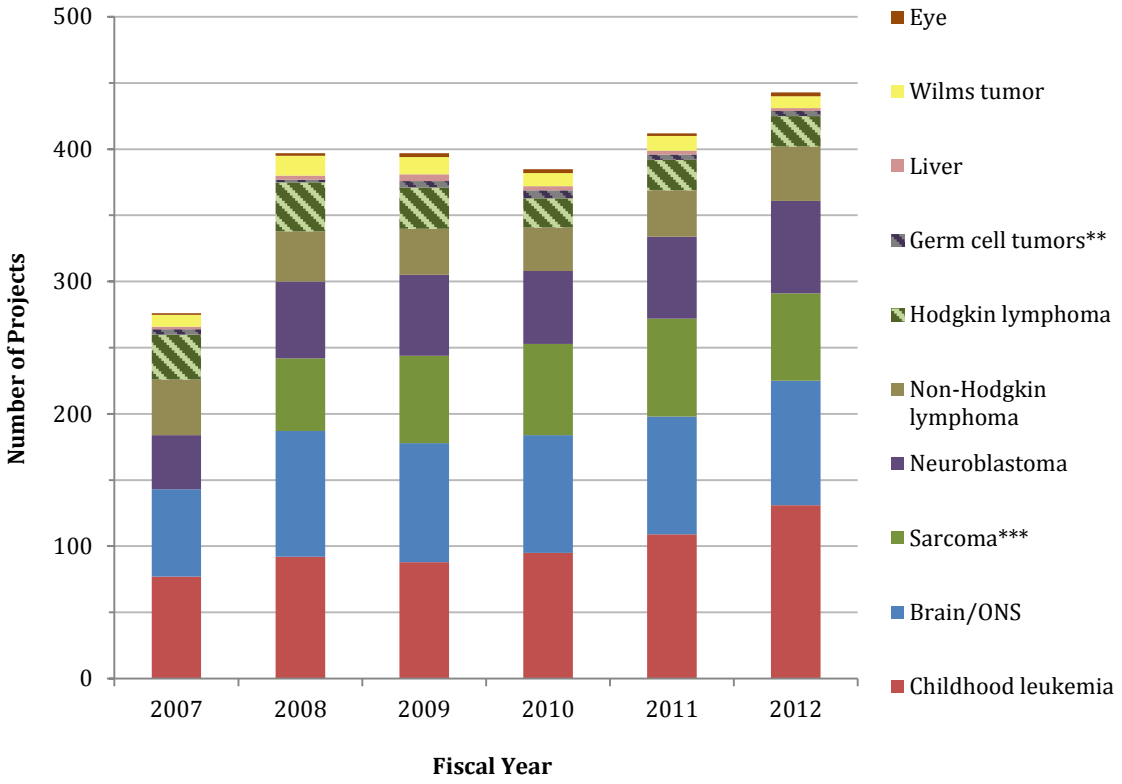
Source: NCI-Funded Research Portfolio: http://fundedresearch.cancer.gov/nciportfolio

* Project list is limited to projects coded to the CSO with at least 25% relevance to the "childhood cancers" SIC. CSO codes and subcodes are not mutually exclusive. Relevant dollars per CSO code are calculated by multiplying the relevant funding for a project by each CSO code weight.

[9] https://www.icrpartnership.org/CSO.cfm.

Even as NCI's funding for research on pediatric cancer has increased in recent years, the proportion of projects relevant to specific cancer sites has remained constant (Figure 10). In 2012, of the 440 projects with at least 25% relevance to the "childhood cancers" SIC, 30% (n = 131) involved childhood leukemia; nearly 21% (n = 94), brain cancer; 16% (n = 70), neuroblastoma; 15% (n = 66), sarcoma; and nearly 15% (n = 64), lymphoma. It is important to note, however, that these organ-specific estimates cannot be taken as a definitive report of all pediatric research relevant to each cancer site, as cancers often share important molecular characteristics and studies of one type of cancer may provide unanticipated insights into another type. In addition, basic cancer research often has general applicability to cancer and thus would not be represented in organ-specific estimates.

Figure 10. NCI's Childhood Cancer Projects* by Cancer Site



To aid visually impaired readers, the legend order mirrors the order of data in the stacked column.

Source: NCI-Funded Research Portfolio: http://fundedresearch.cancer.gov/nciportfolio

* Project list is limited to projects with at least 25% relevance to the "childhood cancers" SIC and at least 10% relevance to the specified cancer site. Cancer sites are not mutually exclusive, and some projects are associated with multiple cancer sites.

** Includes testicular and ovarian cancer projects.

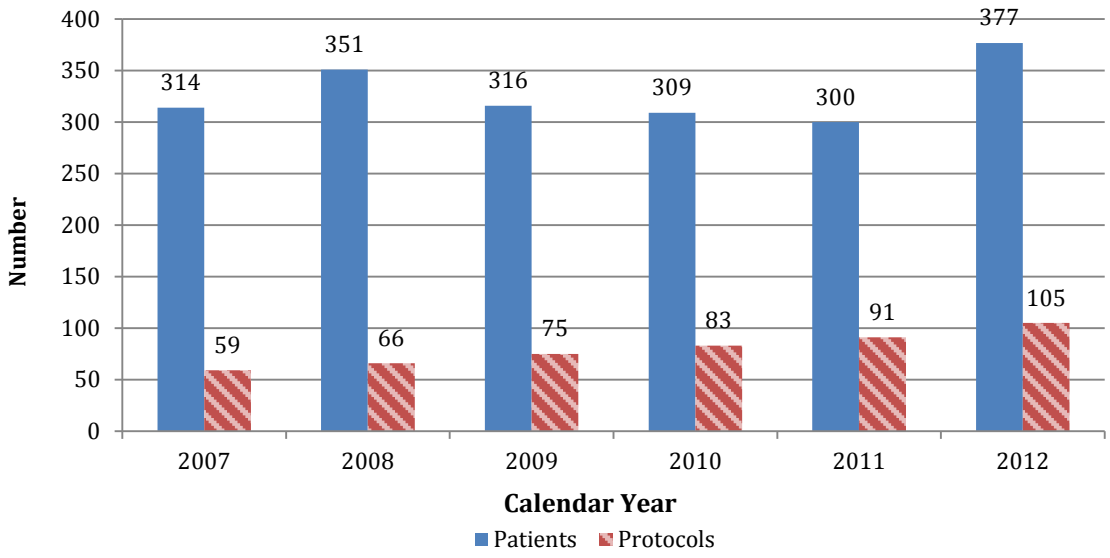
*** Sarcoma data is not available for FY 2007.

Pediatric Clinical Trials

The accrual rate for clinical trials is much greater for children than for adults. Each year, approximately 4000 children are enrolled in NCI-sponsored clinical trials conducted by the Children's Oncology Group. Other children enroll in the clinical trials of consortia supported by NCI (e.g., the Pediatric Brain Tumor Consortium and the New Approaches to Neuroblastoma Therapy Consortium) or enroll in clinical trials at NCI-supported cancer centers.[10] Enrollment in available clinical trials at first diagnosis has become a standard of care for children in the United States[11], and successes in identifying more effective treatments for childhood cancer can be attributed in part to the high rates of participation in such trials.[12]

The NCI Pediatric Oncology Branch (POB) and several other intramural laboratories and branches in the Center for Cancer Research (CCR) enroll pediatric patients in their clinical trials. Since 2007, the number of CCR clinical trial protocols enrolling pediatric patients has risen from 59 to 105 (Figure 11), an increase of 78%. Total pediatric patient enrollment has increased 20% during the same period, from 314 to 377 patients.

Figure 11. Center for Cancer Research Protocols with Pediatric Patients*



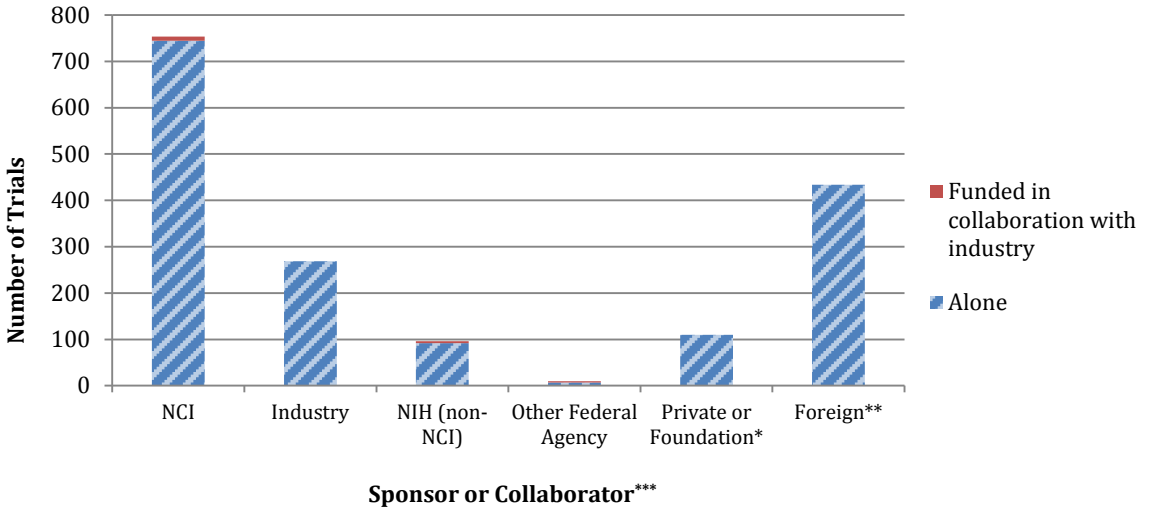
Source: NCI's Center for Cancer Research

* Total number of new patients less than 18 years of age enrolled in clinical trials.

[10] Accrual data from the Cancer Therapy Evaluation Program, NCI.
[11] Sullivan R, Kowalczyk JR, Agarwal B, Ladenstein R, Fitzgerald E, Barr R, et al. New policies to address the global burden of childhood cancers. *Lancet Oncol.* 2013;14(3):e125-35.
[12] Reaman GH. Pediatric cancer research from past successes through collaboration to future transdisciplinary research. *J Pediatr Oncol Nurs.* 2004;21(3):123-7.

ClinicalTrials.gov is an online registry of publicly and privately supported clinical studies. Registration of clinical trials is required for "applicable clinical trials" as outlined in the Food and Drug Administration Amendments Act.[13] Although not all trials must be registered, the number of studies registered has increased each year as additional policies have been enacted and as more sponsors and investigators have voluntarily registered their studies.[14] Each clinical trial is self-reported by the sponsor or investigator, and the record should be updated or corrected throughout the life cycle of the trial. In addition, there are numerous quality control measures in place to ensure the completeness of the data, but ultimately the accuracy of the data depends on the diligence of the person creating the trial record. In short, those using the registry for research should be aware of its limitations. Regardless, as the single best source for extramural clinical trial data, ClinicalTrials.gov was used to examine NCI's role in pediatric cancer trials beyond those carried out by intramural researchers. As of April 2013, 1673 clinical trials relevant to pediatric cancer were open for enrollment.[15] Of these, 46% had NCI involvement—that is, NCI, an NCI-designated cancer center, or a university with an NCI-designated cancer center was listed as a sponsor or collaborator for the trial (Figure 12).

Figure 12. Open Pediatric Clinical Trials Relevant to Cancer



Source: http://ClinicalTrials.gov

* The sponsors/collaborators for these trials are hospitals, foundations, or academic institutions that do not have an NCI-designated cancer center.

** Only foreign trials reported in ClinicalTrials.gov are represented.

*** A sponsor is the organization that oversees the clinical study; a collaborator is an organization that provides support for a clinical study.

[13] For more information, see http://clinicaltrials.gov/ct2/manage-recs/fdaaa.
[14] ClinicalTrials.gov. Available at: http://clinicaltrials.gov/.
[15] Search term = cancer; recruitment = open/exclude unknown status; age group = child (ages 0–17); http://clinicaltrials.gov/.

The Landscape of Pediatric Literature

As noted above, NCI projects are coded for their percentage relevance to SICs, including "childhood cancers," but this coding is based on the research proposal. A project's relevance, however, may not be exhaustively described in the proposal, or new discoveries may lead to additional applications of the findings. Moreover, although research projects in basic biology may give researchers valuable insights into pediatric cancers, these projects will not be reflected in the "childhood cancers" SIC unless a clear statement of relevance to childhood cancer is apparent in the proposal. These caveats underscore the reality that SIC relevance is simply an estimation that may under- or overestimate the actual funding that is relevant to childhood cancers.

In an approach that contrasts sharply with the prospective nature of the coding-based SIC estimate, a literature survey was used to identify any project that produced outputs relevant to research on pediatric cancer, regardless of the project's associated SIC codes. This approach yields additional insight into the pediatric cancer research field and provides a context for NCI's estimated investments in this area.

A search of the National Library of Medicine's PubMed database for journal articles relevant to pediatric cancer that were published in 2012 and that acknowledged NCI support identified 583 articles citing 498 unique NCI project numbers (Table 2).[16] These unique project numbers were then mapped to a list of projects coded as "childhood cancers" from FY 2007−2012 obtained through the NFRP. Projects funded prior to FY 2007 are not publicly available in the NFRP and are not coded to the "childhood cancers" SIC. To capture these earlier projects, project numbers were also mapped to a list of FY 2000−2006 NCI projects that were relevant to pediatric cancer (Table 2) that had been obtained from IMPAC II, a private database of NIH awards.[17] Of the 498 NCI projects that were found to have published results that were relevant to pediatric cancer, 216 (43%) were coded as "childhood cancers" in NFRP and 100 (20%) were identified in IMPAC II as relevant to pediatric cancer.

[16] Search criteria: ("NCI" OR "CA"[Grant Number]) AND (pediatric OR childhood) AND (cancer), filter for 2012. This search was executed in May 2013.
[17] IMPACC II data was retrieved using the QVR system, Search details: IC, CA; Project status, awarded; Fiscal year, 2000–2006; Terms, pediatric AND Cancer were searched in Abs/Aims, Title, Summary Statement, and CRISP/RCDC Terms. Intramural projects are not captured with this search strategy.

Table 2. NCI Projects Acknowledged by 2012 Pediatric Cancer Articles

Code	Coding Source	Number of Projects	Percent of Total Projects
"Childhood Cancer" SIC	NFRP FY 2007–2012	216	43
Pediatric relevant*	IMPAC II accessed by QVR, FY 2000–2006	100	20
Other Projects	Manual Review	182	
General cancer		77	15
Leukemia		22	4
Brain/ONS		16	3
Gastrointestinal/liver		12	2
Lung		11	2
Pediatric		10	2
Lymphoma		9	2
Breast		8	2
Other sites**		10	2
Training/educational		4	1
Unknown		2	< 1
Unawarded		1	< 1
TOTAL		**498**	

* Query, View, Report (QVR) search criteria: IC, NCI (CA); Project status, awarded; Fiscal year, 2000–2006; Terms, "pediatric AND cancer" searched in Abstract/Aims, Title, Summary Statement, and CRISP/RCDC Terms. Intramural projects not captured.

** "Other sites" includes cervical, anal, pancreatic, germ cell, Kaposi sarcoma, and myeloma.

To determine whether the remaining 182 projects had any relevance to pediatric cancer, the abstracts and titles of all projects were manually reviewed, and the projects were evaluated for their relevance to pediatric cancer. This review identified 10 additional grants (2%) that were relevant.[18] The remaining 172 projects were coded to a major cancer site by reviewing existing cancer site codes in the NFRP or by a manual abstract and title review. If a major site was not apparent, projects with applicability to cancer in general (e.g., basic science or general prevention/survivorship studies) were coded as "general cancer," and training or educational program grants (T and R25 mechanisms) were coded as "training/educational." Many of the remaining 172 projects were relevant to cancer in general (77), and the majority of the major cancer sites associated with the projects were relevant to pediatric or adolescent cancers (compare sites in Figure 3 and Table 2).

[18] Of the 10 pediatric projects identified through manual review, 5 predated FY2000; 4 were funded through ARRA, intramural, or L40 mechanisms that would not be captured in the NFRP or QVR searches; and 1 is a probable coding error.

For interpretation of the pediatric literature analysis, a few caveats should be considered. First, because intramural researchers may not cite their NCI project number and because the IMPAC II search did not include intramural projects,[8] this approach does not capture all intramural projects or publications. Thus, these results primarily reflect NCI's extramural portfolio. Also, this approach is simply an estimate of the pediatric research landscape; it does not capture projects that have not published results or publications that did not properly acknowledge their NCI funding.

Given these caveats, it is notable that only 43% of NCI projects that published results relevant to pediatric cancer are represented by the "childhood cancers" SIC (Table 2). This finding suggests that NCI funding estimates for research relevant to pediatric cancer may underestimate the Institute's true investment in relevant projects. It is also notable that 37% (n = 182) of the 498 projects that published results relevant to research on pediatric cancer are contributing to pediatric research, even though the research project as proposed was not obviously relevant to pediatric cancer or coded to "childhood cancers" (Table 2). This finding underscores the notion that research in cancer sites that are relevant to pediatric cancer and the findings of basic research each contribute to our collective knowledge in the pediatric cancer field.

CONCLUSION

NCI's investment in research on pediatric cancer has increased 20% in the past 5 years. The discoveries from these investments have improved our knowledge of the complex set of diseases that constitute pediatric cancers and will likely contribute to reductions in mortality and improvements in treatment over time.

NCI acknowledges that there are specific areas of research that have lagged behind. For example, drug development for pediatric cancer patients has been slow over the past few decades. Many challenges exist in this particular area, including a lack of testing agents, limited patient cohorts, and insufficient preclinical models for pediatric cancers. NCI researchers, through initiatives like the Pediatric Preclinical Testing Program (PPTP), Therapeutically Applicable Research to Generate Effective Treatments (TARGET), and the Children's Oncology Group, are focusing their efforts on finding effective treatments for children despite these challenges.

NCI is not the sole supporter of relevant research projects in the pediatric cancer research field, as important contributions are being made through private research funds as well. NCI's collaborations with these organizations is essential. Working together, the pediatric cancer research community can better identify scientific areas in need of further exploration and develop high-quality initiatives to address research opportunities. Moving forward, although enormous challenges in our understanding and treatment of pediatric cancer remain, the continued commitments of NCI and our research partners will continue to improve outcomes for pediatric cancer patients.