Cancer Survivorship: Resilience Across the Lifespan

Supplement to ***Cancer***

Long-Term Outcomes of Adult Survivors of Childhood Cancer

Results from the Childhood Cancer Survivor Study

Leslie L. Robison, Ph.D.[1,2]
Daniel M. Green, M.D.[3]
Melissa Hudson, M.D.[4]
Anna T. Meadows, M.D.[5]
Ann C. Mertens, Ph.D.[1]
Roger J. Packer, M.D.[6]
Charles A. Sklar, M.D.[7]
Louise C. Strong, M.D.[8]
Yutaka Yasui, Ph.D.[9]
Lonnie K. Zeltzer, M.D.[10]

[1] Department of Pediatrics, University of Minnesota Medical School and Cancer Center, Minneapolis, Minnesota.

[2] Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, Tennessee.

[3] Department of Pediatrics, Roswell Park Cancer Institute, Buffalo, New York.

[4] Department of Hematology/Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee.

[5] Department of Medicine, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania.

[6] Department of Neurology, Children's National Medical Center, Washington, DC.

[7] Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, New York.

[8] Cancer Genetics, University of Texas, M.D. Anderson Cancer Center, Houston, Texas.

[9] Department of Public Health Sciences, University of Alberta, Edmonton, Alberta, Canada.

[10] Departments of Pediatrics, Anesthesiology and Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California.

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Address for reprints: Leslie L. Robison, Ph.D., Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, 332 N. Lauderdale Street, Memphis, TN 38105-2794; Fax: (901) 495-3048; E-mail: les.robison@stjude.org

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During the past 30 years, changes in the treatment of children and adolescents with cancer have led to substantial improvements in survival. Although treatment-related factors have been shown to impact subsequent health status and quality of life, there is limited information on survivors who are now two or more decades after treatment. The Childhood Cancer Survivor Study (CCSS) was established as a resource for investigating the long-term outcomes of a cohort of 5-year survivors of childhood and adolescent cancer, diagnosed between 1970–1986. The CCSS cohort has more than 14,000 active participants, including survivors of leukemia, brain tumors, Hodgkin disease, non-Hodgkin lymphoma, Wilms tumor, neuroblastoma, soft-tissue sarcoma, and bone tumors. Study participants, extensively characterized by their cancer therapy, have provided self-reported sociodemographic- and health-related information. Although the survivor population has been found to be at significantly increased risk of several adverse outcomes, such as late mortality, second cancers, pulmonary complications, pregnancy loss, low birth weight of offspring, and decreased education, the overall proportion of survivors affected is relatively small. Subgroups at high risk of adverse outcomes, defined by treatment-related, demographic, or medical factors, can be identified. The ongoing evaluation of large and diverse cohorts of cancer survivors will aid in further identifying individuals who should be the target of innovative intervention strategies. ***Cancer*** **2005;104(11 Suppl):2557–64.** © *2005 American Cancer Society.*

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For several decades, it has been well recognized that survival rates for many childhood cancers are improving at a remarkable pace. Because children have potential for many more years of productive life, these improvements in survival have led investigators to consider long-term morbidity and mortality associated with treatments responsible for increased survival.

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Approximately 1 of every 640 individuals in the United States between the ages of 20 and 39 years is a survivor of childhood cancer.[1] For most children diagnosed with cancer, cure is a likely outcome. The overall probability of 5-year survival has changed from $< 30\%$ in 1960 to $> 70\%$ in 1990.[2] According to data from the Surveillance, Epidemiology and End Results program of the National Cancer Institute for patients diagnosed since 1985, there has been only a modest improvement in the proportion of patients achieving 5-year survival. Long-term survival rates vary with cancer diagnosis and frequently by demographic characteristics, such as age, gender, and race; and by tumor characteristics, such as location and extent of disease, morphology, and genetic alterations. Attempts to improve survival rates in poor prognosis groups have led to therapeutic protocols that use more intensive therapy, thus increasing the probability of long-term adverse outcomes should such patients survive.

The subject of late effects among children treated for cancer has been the topic of numerous reviews.[3–7] To varying degrees, long-term survivors are at risk of developing adverse outcomes, including early death, second neoplasms, organ dysfunction (e.g., cardiac, gonadal), reduced growth and development, decreased fertility, impaired intellectual function, difficulties obtaining employment and insurance, and overall reduced quality of life. Because of the young age of these cancer survivors, and thus their potential longevity, delayed consequences of therapy may have a greater impact on their lives and on society at large than the acute complications of cytotoxic therapies that they have already experienced.

Although single institutions, some limited consortia, and, occasionally, cooperative clinical trials groups pursue investigations of late sequelae, it is clear that there are strengths and limitations inherent in each of these approaches. The Childhood Cancer Survivor Study (CCSS) was designed to overcome some of these limitations and to be a resource for future investigations of childhood cancer survivors. The current article addresses selected results from the CCSS and illustrates the broad range of outcomes that have been studied in this large cohort of childhood cancer survivors. Although this population has been shown to experience a variety of adverse outcomes, including some that are associated with considerable morbidity and/or mortality, this article also demonstrates that, at this point in time, most childhood and adolescent survivors are not experiencing serious late effects stemming from their cancer diagnosis and therapy.

The Childhood Cancer Survivor Study

The CCSS cohort comprises individuals with a confirmed diagnosis of cancer who participated in The Long-Term Follow-Up Study. A detailed description of the CCSS study design and characteristics of the cohort have been previously published.[8] Presented here is a brief description of this resource, funded by the National Institutes of Health, for the study of survivors of cancer during childhood and adolescence.

The CCSS was established as the largest and most comprehensively characterized epidemiological research cohort of childhood cancer survivors ever assembled in North America. Results presented in this article are derived from a group of 20,304 individuals who were treated for cancer during childhood or adolescence at 26 centers across the United States and Canada (Table 1). Members of the CCSS cohort fulfilled the following eligibility criteria, 1) diagnosis of leukemia, CNS malignancies (all histologies), Hodgkin disease, non-Hodgkin lymphoma, kidney cancer, neuroblastoma, soft tissue sarcoma, or malignant bone tumor; 2) diagnosis and initial treatment at one of the 26 collaborating CCSS institutions; 3) diagnosis date between January 1, 1970 and December 31, 1986; 4) age younger than 21 years at the time of diagnosis; and 5) survival of at least five years from the time of diagnosis.

Of the 20,304 childhood cancer survivors included in the cohort, 2996 (14.8%) could not be located after an extensive tracing process and are currently considered lost to follow-up, although there are ongoing attempts to locate these individuals. Among the 17,308 subjects initially located, 14,193 (82%) completed a baseline questionnaire. The outcome data available for the cohort consist of self-reports obtained by mailed questionnaires or telephone interviewers. A 24-page baseline questionnaire, completed by survivors and parents for those younger than 18 years of age, provided information on demographics, personal and family medical history, functional limitations, psychological outcomes, work history, and living circumstances. In addition, questionnaires have been designed and distributed to obtain additional detailed information relating to topics such as pregnancy outcomes, family history, healthcare utilization, teen concerns, psychosocial function, quality of life, and intimacy. Study questionnaires including two for prospective follow-up and special projects can be viewed and downloaded at www.cancer.umn.edu/ccss. A process of medical record abstraction, according to a structured protocol, was conducted at each CCSS center and included detailed information on

TABLE 1
CCSS Contributing Institutions and Original Principal Investigators

Institution	Investigator
Children's Health Care, Minneapolis, MN	Maura O'Leary, M.D.
Children's Hospital, Denver, CO	Brian Greffe, M.D.
Children's Hospital and Medical Center, Seattle, WA	Debra Friedman, M.D., M.P.H.
Children's Hospital Los Angeles, CA	Kathy Ruccione, R.N., M.P.H.
Children's Hospital of Philadelphia, PA	Anna T. Meadows, M.D.
Children's Hospital of Pittsburgh, PA	A. Kim Ritchey, M.D.
Children's National Medical Center, Washington, DC	Gregory Reaman, M.D.
Columbus Children's Hospital, OH	Amanda Termuhlen, M.D.
Dana Farber Cancer Institute, Boston, MA	Lisa Diller, M.D.
Emory University, Atlanta, GA	Lillian Meacham, M.D.
Hospital for Sick Children, Toronto, ON	Mark Greenberg, M.B., Ch.B.
Mayo Clinic, Rochester, MN	W. Anthony Smithson, M.D.
Memorial Sloan Kettering Cancer Center, New York, NY	Charles Sklar, M.D.
Riley Hospital for Children, Indianapolis, IN	Terry A. Vik, M.D.
Roswell Park Cancer Institute, Buffalo, NY	Daniel M. Green, M.D.
St. Jude Children's Research Hospital, Memphis, TN	Melissa Hudson, M.D.
St. Louis Children's Hospital, MO	Robert Hayashi, M.D.
Stanford University School of Medicine, CA	Michael P. Link, M.D.
Texas Children's Center, Houston, TX	Zoann Dreyer, M.D.
University of Alabama, Birmingham, AL	Roger Berkow, M.D.
University of California Los Angeles, CA	Lonnie Zeltzer, M.D.
University of California San Francisco, CA	Arthur Ablin, M.D.
University of Michigan, Ann Arbor, MI	Raymond Hutchinson, M.D.
University of Minnesota, Minneapolis, MN	Leslie L. Robison, Ph.D.
UT M. D. Anderson Cancer Center, Houston, TX	Louise Strong, M.D.
UT Southwestern Medical Center at Dallas, TX	George R. Buchanan, M.D.

cancer type, treatments received, and clinical characteristics of the survivor.

Nearest age siblings of randomly selected survivors were invited to participate as a control population. Of the 5800 siblings selected, 3585 have to date completed a questionnaire. Four hundred seventy-two siblings chose not to participate in the study.

The study was approved by the institutional review boards of all participating institutions. All participants were informed that participation in the study was voluntary, and all respondents provided informed consent.

Selected Results From The CCSS

Late mortality

By using the 20,227 5-year survivors eligible for the CCSS cohort, a detailed evaluation of cause-specific mortality was undertaken.[9] Deaths occurring 5 or more years from diagnosis of cancer were ascertained through participating institutions, reports from family members, and a search conducted through the National Death Index. Death certificates were then requested, and underlying cause of death was coded and categorized as either (1) recurrent disease, (2) sequelae of cancer treatment, or (3) noncancer-related. Age- and gender-standardized mortality ratios (SMR) were calculated by using United States population mortality data. At the time of the analysis (including deaths occurring through 1996), 2030 (10%) members of the cohort had died, representing a 10.8-fold excess mortality (95% CI of the SMR, 0.3–11.3). Recurrence of the original cancer was the leading cause of death, accounting for 67% of deaths. Statistically significant elevated mortality rates were found for treatment-related causes, including second and subsequent cancers (SMR = 19.4), cardiac conditions (SMR = 8.2), and pulmonary conditions (SMR = 9.2).

Although the magnitude of risk of late death was significantly elevated relative to age- and sex-specific rates in the general population, the observed cumulative proportion of survivors experiencing treatment-related mortality was low. For example, at 25 years from diagnosis of the original cancer, the cumulative probability of death from a second or subsequent malignancy was less than 3%. The cumulative probability of death from cardiac or pulmonary conditions was less than 1%.

Second malignancies

Second and subsequent malignancies in members of the cohort have been continuously ascertained through reports from participating institutions, survivors or surrogate respondents who complete questionnaires, or the National Death Index. All reported second or subsequent malignancies were verified by review of pathology reports. The initial CCSS report on subsequent malignant neoplasms (SMN) was based upon 314 SMNs occurring among 298 members of the cohort.[10] The standardized incidence ratio (SIR) for SMN was 6.38 (95% CI, 5.69–7.13), with the largest observed excesses for bone and breast cancers (SIR = 19.1 and 16.2, respectively). A 10-fold or greater risk was also observed for subsequent cancer of the central nervous system and thyroid. Independent risk factors for SMN (adjusted for radiation exposure) included female gender, original cancer diagnosed at a younger age, original diagnosis of Hodgkin disease or soft-tissue sarcoma, and exposure to alkylating agents.

The analyses of SMN, similar to those of late mortality, demonstrated high relative risks but low cumulative or absolute risks. The cumulative incidence of SMN 20 years from the time of original cancer diag-

nosis was 3.2% overall and varied by diagnostic subgroups; Hodgkin disease (7.6%), soft-tissue sarcoma (4.0%), bone sarcoma (3.3%), leukemia (2.1%), central nervous system cancer (2.1%), neuroblastoma (1.9%), non-Hodgkin lymphoma (1.9%), and kidney tumor (1.6%). These data demonstrate that most survivors are not expected to experience SMN in the first 2 decades after their original cancer; however, there is an expectation that new cancers will occur as the members of the cohort age. This cohort is expected to enable many critical questions to be addressed: What is the excess cancer risk in this population and how does it relate to host, disease, and therapeutic factors?

Pregnancy outcomes

Adult survivors of childhood cancer report a great concern regarding their fertility and the health of their future offspring. Pregnancy outcome information provided by female participants in CCSS was evaluated to determine the impact of prior treatment on the frequency of live birth, stillbirth, miscarriage, abortion, and birth weight of offspring.[11] Of 1953 women included in this analysis, 4029 pregnancies were reported and consisted of 63% live births, 1% stillbirths, 15% miscarriages, 17% abortions, and 3% unknown or in gestation. No statistically significant associations were observed between treatment factors and pregnancy outcomes, although risk of miscarriage was higher among women whose ovaries were in the radiation therapy field (relative risk [*RR*] = 1.86, $P = 0.14$) or near the radiation field ($RR = 1.64$, $P = 0.06$). Individual chemotherapeutic agents were evaluated, but none was found to be significantly associated with an increased risk of an adverse pregnancy outcome. Lower birth weight (i.e., $<$ 2500 grams) was associated with pelvic irradiation ($RR = 1.84$, $P = 0.03$).

The results of this analysis are reassuring in that prior exposure to chemotherapy does not appear to negatively affect pregnancy outcome. Currently, an in-depth evaluation of adverse pregnancy outcomes is underway and includes precise gonadal radiation dosimetry and validation of reported outcomes including offspring birth defects.

Knowledge of cancer diagnosis and treatment

Adult survivors of childhood cancer, especially those who were very young at diagnosis, may have received limited information about their cancer diagnosis and treatment. To evaluate the level of knowledge of past diagnosis and treatment, a 5% sample ($n = 635$) of CCSS participants was selected and interviewed.[12] The information obtained from survivors was compared with the information abstracted from their medical records. Overall, 72% named their diagnosis with precision, and 19% were accurate but not precise. Survivors of central nervous system (CNS) malignancies and neuroblastoma were significantly less likely to know their cancer diagnosis. Although participants' accuracy rates for reporting their treatment history were generally high (94% for chemotherapy, 89% for radiation therapy, 93% for splenectomy), only 30% of those who received daunorubicin and 52% of those who received doxorubicin recalled having been treated with these agents even after these survivors were prompted with the drugs' generic and proprietary names.

A high proportion (91%) of adult survivors of childhood cancer know what type of cancer they had. However, important knowledge deficits exist among long-term survivors in the CCSS cohort, including 1) the correct name of their cancer, 2) specifics of their cancer treatment history; and 3) potential long-term health risks associated with cancer treatment. Lack of accurate information could negatively impact survivors' ability to seek and receive appropriate long-term follow-up care. Accordingly, strategies need to be developed and tested to address these deficits.

Tobacco use

The CCSS evaluated the use of tobacco, primarily cigarettes, among 9709 members of the cohort who were older than 18 years of age at the time they completed their baseline questionnaire.[13] Information was obtained on history of tobacco use, including the tobacco type, age at initiation of use, frequency and duration of use, and current use. Twenty-eight percent of those older than 18 years of age reported having been a smoker, and 17% indicated that they currently smoked. When smoking rates were standardized to U.S. population rates (observed to expected ratio [O/E]), it was found that survivors overall were smoking at significantly lower rates than expected (O/E = 0.72; 95% CI, 0.69–0.75), as well as among Whites and non-Whites (O/E = 0.71 and 0.81, respectively) and males and females (O/E = 0.73 and 0.70, respectively). Moreover, those who reported smoking were more likely to report that they had quit smoking (O/E = 1.22; 95% CI, 1.15–1.30).

Although it is encouraging that smoking is less frequent among CCSS survivors than would be expected, the overall proportion who have been or currently are smokers is not reassuring. This is especially worrisome because survivors who received treatment that places them at high risk for cardiovascular and/or pulmonary complications were not substantially different in their incidence of tobacco use. Based upon these data, individuals in the CCSS cohort were invited to participate in a tobacco cessation intervention study, the results of which are currently under analysis or in press.

Special education and attainment level of education

Reduced education attainment level and diminished cognitive functioning encompassing memory, quantitative skills, and abstract reasoning have been well documented in selected groups of survivors of childhood cancer. Deficits have been seen most often in children with acute leukemia or CNS tumors who received cranial radiation and/or intrathecal therapy. Assessment of 12,430 survivors of the CCSS cohort and 3410 siblings was undertaken to expand upon previous reports by: 1) evaluating the educational history for a broad distribution of cancer diagnoses; 2) describing rates of entry into special education programs; 3) characterizing stated reasons for entry into special education; and 4) ascertaining the ultimate level of education attainment after special education placement.[14] Use of special education services were reported by 23% of survivors and 8% of siblings, with the greatest differences observed among survivors of CNS tumors, leukemia, and Hodgkin disease diagnosed at young ages (*RR* = 18.8; 95% CI, 15.0–23.5, *RR* =4.4; 95% CI, 3.8–5.2, *RR* = 4.4; 95% CI, 2.6–7.2, respectively). Cranial radiation and intrathecal methotrexate, either alone or in combination, were found to significantly increase a survivor's risk of having to use special education services. Moreover, a dose-response relation existed between doses of cranial radiation and use of special education. Compared with the sibling cohort (graduation rate of 93%), the rate of high school graduation was significantly lower for survivors of leukemia (86%), CNS tumors (82%), non-Hodgkin lymphoma (87%), and neuroblastoma (85%). The subgroup of survivors who received special education services was found to have high school graduation rates similar to those of the sibling cohort, with the only exception being survivors of CNS cancers and Wilms tumor. Although a high proportion of childhood cancer survivors will successfully complete high school, the results of this CCSS analysis provides support for closely monitoring survivors and for early identification of signs of learning disabilities so that special education intervention can be planned.

Obesity in survivors of childhood acute lymphoblastic leukemia

An analysis was undertaken to evaluate weight and body mass index of adult survivors 1) todetermine whether adult survivors (≥ 18 yrs of age) of childhood acute lymphoblastic leukemia (ALL) are at increased risk for obesity and 2) to assess patient and treatment variables that influence risk.[15] Whereas previous reports demonstrate that survivors of childhood ALL, as a group, are more likely to be overweight, there is a lack of data on very long-term survivors who are now adults in the third and fourth decades of life. The 1765 adult survivors of childhood ALL were compared with 2565 adult siblings of childhood cancer survivors. Body mass index (BMI kg/m^2), calculated from self-reported heights and weights, was used to determine the prevalence of overweight ($25.0 \leq$ BMI < 30.0) or obese (BMI ≤ 30.0) survivors. The age- and race-adjusted relative risk for being obese in survivors treated with cranial radiation doses ≥ 20 Gy in comparison with siblings was 2.59 for females (95% CI, 1.88–3.55, $P \leq 0.001$) and 1.86 for males (95% CI, 1.33–2.57; $P < 0.001$). The risk for obesity was greatest among females diagnosed before 4 years of age and treated with radiation doses ≥ 20 Gy (*RR* = 3.81; 95% CI, 2.34–5.99; $P \leq 0.001$). Obesity was not associated with treatment consisting of chemotherapy only or with cranial radiation doses of 10-19 Gy.

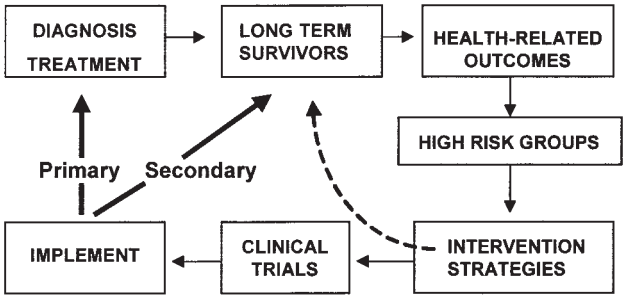

FIGURE 1. Impact of late effects research on possible prevention and intervention strategies among childhood cancer survivors.

The population of cancer survivors identified as being substantially overweight or obese are a prime target for intervention strategies because of their potential increased risk for cardiovascular disease. For some survivors, this risk may be compounded by their previous cancer therapy with modalities that can compromise cardiac function. It is important that healthcare professionals recognize this risk and develop strategies for weight control among this highly susceptible population.

Summary

Knowledge of the late effects associated with cancer in children and adolescents continues to increase. However, much of the available information is on outcomes within the first decade after treatment, with a paucity of data addressing the longer term outcomes and those that occur beyond the third decade of life. It is critical that we improve our knowledge of the long-term impact of cancer therapy if we are to effectively counsel survivors and offer effective intervention strategies to prevent or minimize the impact of ad-

TABLE 2
Summary of Published Results from the Childhood Cancer Survivor Study

Reference	Outcome	Study population	Selected findings
Mertens et al. (2001)[9]	Mortality	Full CCSS cohort	10-fold excess in overall mortality; SMR for second cancer, cardiac and pulmonary, 19.4, 8.2, and 9.2, respectively.
Neglia et al.[10]	Second malignancy	Full CCSS cohort	6.4-fold excess in cancer occurrence; SIR highest for bone and breast cancers, 19.1 and 16.2, respectively.
Sklar et al. (2000)[16]	Thyroid function	Hodgkin disease	Relative risk of hypothyroidism (17.1) and hyperthyroidism (8.0); cumulative risk of hypothyroidism for those treated with 4500 cGy or more was 50% at 20 yrs from dia gnosis.
Rauck et al.[18]	Marriage or divorce	Full CCSS cohort	32% reported being married or living as married, 6% divorced or separated; compared with population rates, survivors were less likely to have ever married.
Emmons et al.[13]	Tobacco use	Full CCSS cohort	28% reported ever smoking with 17% current smokers; based on general population rates male and female survivors smoked at lower rates (0.73 and 0.70, respectively); survivors who smoked were more likely to quit.
Green et al. (2002)[11]	Pregnancy outcomes	Female survivors	4029 reported pregnancies with 63% live births; no significant differences in pregnancy outcome by treatment; ovarian RT associated with increased risk of miscarri age; lower birthweight associated with pelvic RT.
Green et al. (2003)[21]	Pregnancy outcomes	Male survivors	2323 pregnancies with 69% live births; significantly less likely to result in live birth compared with siblings; no significant differences in pregnancy outcome by t reatment; significant difference in male/female ratio of offspring (1.0:1.3).
Kadan-Lottick et al.[12]	Knowledge of previous cancer history	Subset of CCSS cohort	72% accurately reported previous cancer diagnosis; brain tumor and neuroblastoma more likely not to know their previous cancer; accuracy of reporting hist ory of chemotherapy, RT and splenectomy was 94%, 89%, 93%, respectively.
Mertens et al. (2002)[20]	Pulmonary function	Full CCSS cohort	Increased risk of lung fibrosis, recurrent pneumonia, chronic cough, pleurisy, use of supplemental oxygen, abnormal chest wall, exercise-induced shortness of br eath; 4.3-fold increased risk of fibrosis associated with chest RT; BCNU, CCNU, bleomycin, busulfan, cyclophosphamide associated with recurrent pneumonia.
Sklar et al. (2002)[17]	Growth hormone	Full CCSS cohort	No increased risk of disease recurrence or death among 361 survivors treated with growth hormone; 3.2-fold increased risk of second malignancy among growth hormone tre ated survivors.
Zebrack et al.[19]	Psychological status	Leukemia and lymphoma	Compared with siblings, survivors were significantly more likely to report symptoms of depression and somatic distress; history of exposure to intensive chemotherapy predicted scores indicative of somatic distress.
Gurney et al. (2003)[22]	Endocrine and cardiac outcomes	Brain tumors	43% reported one or more endocrine conditions and 18% reported one or more cardiovascular conditions; compared with siblings, increased risk of hypothyroi dism (14.3), growth hormone deficiency (277.8), required medications to induce puberty (86.1), osteoporosis (24.7), stroke (42.8), blood clots (5.7), angina-like symptoms (2.0).
Mitby et al.[14]	Education attainment and special education services	Full CCSS cohort	Compared with sibling controls, survivors of leukemia non-Hodgkin lymphoma and neuroblastoma were significantly less likely to graduate from high schoo l. Use of special education services was reported in 23% of survivors compared with 8% of sibling controls. Use of special education services was highest among those diagnosed at a younger age (< 6 yrs) and those with a diagnosis of CNS tumor or Hodgkin disease, intrathecal methotrexate and cranial radiation significantly increased the risk of use of special education services.
Nagarajan et al.[24]	Psychosocial status	Lower extremity bone tumor	Amputation status (i.e., amputation vs. limb salvage) and age at diagnosis did not significantly influence any of the measures of psychosocial outcomes (i.e., educational attainment, employment, health insurance, and marriage). Compared with siblings, amputees had significant deficits in education, employment, and insurance.

TABLE 2
Summary of Published Results from the Childhood Cancer Survivor Study

Reference	Outcome	Study population	Selected findings
Oeffinger et al. (2003)[15]	Obesity	Acute lymphoblastic leukemia	Age- and race-adjusted relative risk of being obese following cranial radiation of > 20 Gy was 2.59 for females and 1.86 for males. Among females with cra nial radiation, risk of obesity was significantly higher when the diagnosis was less than age of 4 yrs.
Oeffinger et al. (2004)[25]	Health care utilization	Full CCSS cohort	Within the previous 2 years, 87% of survivors reported some form of general medical contact, 71.4% a general physical exam, 41.9% a cancer-related medical visit, and 19.2% a visit to a cancer center. Factors found to be associated with no general physical exam included male gender, lack of health insurance, older current age, and lack of concern about future health.
Gurney et al. (2003)[26]	Height and weight	Brain tumors	Nearly 40% of childhood brain tumor survivors were below the 10th percentile for final height, with the most prominent risk factors being young age (< 4 yrs old) at diagnosis and radiation therapy involving the hypothalamic-pituitary axis (dose dependent risk). Distribution of body mass index did not differ from population norms.
Packer et al.[27]	Neurologic and neurosensory	Brain tumors	70% developed neurosensory impairment. Relative to siblings, survivors were at elevated risk ($P < 0.001$) for hearing impairments ($RR = 17.3$), legal blindness in one or both eyes ($RR = 14.8$), cataracts (RR = 11.9), double vision ($RR = 8.8$). Among survivors, coordination and motor control problems were reported in 49% and 26%, respectively. Seizure disorders were reported in 25% of patients, i ncluding 6.5% who had a late recurrence.
Yeazel et al.[28]	Cancer screening practices	Full CCSS cohort	Overall, 27.3% of females reported regularly performing self breast exams, 78.2% had a PAP smear within the previous 3 three period, 62.4% underwent clinical breast examination within the past year, and 20.9% had at least 1 mammogram. Approximately, 17.4% of males reported regularly performing testicular self-examination. Survivors reported higher rates of screening compared with sibling controls.
Hudson et al.[29]	Health status	Full CCSS cohort	40% of survivors reported at least 1 adversely affected health domain. Compared with sibling controls, survivors were significantly ($P < 0.001$) more likely to report adverse gen eral health ($OR = 2.5$), mental health ($OR = 1.8$), activity limitations ($OR = 2.7$), functional impairment ($OR = 5.2$).

verse late effects. Research is needed to more precisely identify survivors at greatest risk for specific outcomes and is essential to the development and testing of rational and effective interventions in high-risk populations (Fig. 1).

The CCSS has proven to be a valuable research resource for investigations of adult survivors of childhood and adolescent cancers. In addition to the selected results presented in this article, the CCSS has addressed the following topics (Table 2), thyroid abnormalities after Hodgkin disease,[16] impact of growth hormone therapy,[17] marriage,[18] psychological outcomes,[19] pulmonary complications,[20] pregnancy outcomes in males,[21] endocrine and cardiac outcomes in brain tumor survivors,[22] effectiveness of tobacco cessation strategies,[23] psychological outcomes among bone tumor survivors,[24] healthcare utilization,[25] final height and weight among brain tumor survivors,[26] neurologic and neurosensory outcomes,[27] cancer screening practices,[28] and health status.[29] Additional analyses completed (manuscripts under review) or nearing completion include family history of cancer, secondary brain tumors, employment, function and quality of life among bone tumor survivors, dental care, psychological status of CNS survivors, secondary breast cancer, genetic susceptibility for second cancers, and leptin-receptor polymorphisms in ALL survivors. Ongoing research efforts are also being directed toward premature menopause, reduced fertility, adverse pregnancy outcomes, fatigue, bone density, quality of life, dental status, and genetic susceptibility to a variety of outcomes.

Whether focusing on children, adolescents, young adults, middle-aged adults, or the elderly, the landscape of cancer survivorship research is continually changing. With the introduction of new agents or

combinations of agents, more focused radiation oncology techniques, improvement in surgical procedures or in supportive care, the potential for late effects of treatment also changes. There will be a continuing need to systematically follow survivors exposed to these new treatment strategies and to conduct high quality and scientifically sound population-based outcomes research.

The Childhood Cancer Survivor Study is a National Cancer Institute funded resource to promote and facilitate research among long-term survivors of cancer diagnosed during childhood and adolecence. Investigators interested in potential uses of this resource are encouraged to visit www.cancer.umn.edu/ccss.

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