Published in final edited form as:

Pediatr Blood Cancer. 2011 May ; 56(5): 825–836. doi:10.1002/pbc.22875.

Prospective Medical Assessment of Adults Surviving Childhood Cancer: Study Design, Cohort Characteristics, and Feasibility of the St. Jude Lifetime Cohort Study

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Abstract

Background—To facilitate prospective medical assessment of adults surviving pediatric malignancies and advance knowledge about long-term childhood cancer survivor health, St. Jude Children's Research Hospital (SJCRH) is establishing a lifetime cohort of survivors.

Methods—Eligibility criteria for inclusion in the St. Jude Lifetime Cohort (SJLIFE) study include: 1) diagnosis of childhood malignancy treated at SJCRH; 2) survival ≥ 10 years from diagnosis; and 3) current age ≥ 18 years. Three levels of participation are offered: 1) comprehensive evaluation on SJCRH campus; 2) limited home evaluation; or 3) completion of health surveys only. A systematic recruitment structure based upon blocks of 50 patients initially focused on leukemia and lymphoma survivors and patients eligible for pilot studies.

Results—As of 01/01/2010, 1625 (42%) of 3900 eligible ≥ 10 year survivors have been contacted. Among the first 1000 potentially eligible survivors selected for recruitment, 971 were subsequently confirmed to fulfill eligibility criteria. To date, 898/971 (92.5%) have been successfully contacted of whom 825 (91.8%) have agreed to participate. Among participants, 88.6% agreed to comprehensive medical evaluation, 0.4% limited local evaluation, and 11.0% survey only. Anticipated minimum overall participation rate for medical evaluation is 75.3% (731/971). Comparison of those contacted who agreed versus declined to participate revealed a greater proportion of males who declined participation ($p = 0.001$).

Conclusions—Early results of the SJLIFE study support its feasibility to recruit aging childhood cancer survivors to research investigations evaluating late health outcomes by medical assessments.

Keywords

Childhood cancer; late effects; long-term follow-up

INTRODUCTION

Contemporary therapy will result in the survival of more than 80% of children and adolescents diagnosed with a malignancy.¹ This treatment success has provided the opportunity and responsibility to evaluate health outcomes in long-term adult childhood cancer survivors. Because curative therapy administered for cancer affects growing and developing tissues and produces subclinical toxicity that may worsen over time, many survivors develop chronic health problems that may not become clinically apparent until decades after therapy.² Late effects are commonly experienced after childhood cancer with two-thirds of survivors reporting at least one chronic or late-occurring complication related to cancer therapy, of which approximately one-third are described as serious or life-threatening.^{3–7} Adverse effects related to cancer or its treatment impact virtually every organ system.² Without intervention, chronic or subclinical changes following cancer treatment result in premature onset of common diseases associated with aging such as obesity,^{8–10} diabetes mellitus,^{11, 12} cardiovascular disease,^{13–17} hypertension,^{18–20} and cancer.^{21–26} Consequently, cancer-related effects predispose the long-term survivor to significant morbidity and early mortality.^{27–30}

Despite the wealth of information published about childhood cancer outcomes, our current understanding of several important areas of long-term survivor health is limited. Most single institutions, consortia and pediatric cooperative groups do not have the resources, infrastructure, or flexibility to undertake comprehensive research investigations of health outcomes in meaningful numbers of adults surviving childhood cancer. The Childhood Cancer Survivor Study (CCSS), a longitudinal retrospective cohort of nearly 15,000 long-term survivors diagnosed with cancer at one of twenty-six participating institutions from 1970 through 1986, has overcome many of these limitations.³¹ Research findings from the CCSS cohort (now at median age of 37.7 [range, 23.2–60.7] years old and at median of 29.1 [range, 23.2–41.2] years from diagnosis) have substantially enhanced our understanding of the childhood cancer survivor experience and the long-term effects of chemotherapy, radiotherapy, and surgery.^{25, 32–37} However, with the exception of subsequent malignancies, which are routinely validated through retrieval of medical records and/or pathological specimens, the CCSS is limited to a self-report method of outcome ascertainment. The few institutions reporting the prevalence of adverse health outcomes in adults surviving childhood cancer based on medical assessments have largely focused on diagnostically heterogeneous cohorts of survivors whose median follow-up time from cancer diagnosis is less than 20 years.^{4, 7, 38}

To advance knowledge about long-term childhood cancer survivor health, St. Jude Children's Research Hospital (SJCRH) is establishing a lifetime cohort of survivors treated at SJCRH to facilitate prospective medical assessment of health outcomes among adults surviving pediatric malignancies. Comprehensive clinical evaluations of adults participating in the St. Jude Lifetime (SJLIFE) Cohort study will permit more accurate quantification of risk for cancer-related morbidity by validating organ function outcomes with state-of-the-art objective measures. Knowledge gained from these investigations offers the potential to 1) improve quality of life of cancer survivors and their families; 2) guide health care providers as they develop new treatment approaches and monitor long-term survivors; and, 3) facilitate approval of screening and remedial services by insurance companies and legislators. This report provides an extensive description of the SJLIFE study objectives,

design and methodology for future research featuring this cohort of very long-term childhood cancer survivors.

METHODS

Study Site

SJCRH, the only NCI-designated comprehensive cancer center dedicated solely to the treatment of childhood cancer and other catastrophic diseases, provides comprehensive medical services for children and adolescents with pediatric malignancies, regardless of the family's ability to pay. The institutional commitment to patient care services, which includes provision of all aspects of clinical care as well as financial support for meals, domiciliary care and transportation, facilitates comprehensive ascertainment of treatment sequelae and research initiatives evaluating late health outcomes in pediatric cancer survivors.

Survivors who remain in remission at least 2 years following completion of antineoplastic therapy and 5 years from diagnosis of childhood cancer are eligible for transfer into the After Completion of Therapy (ACT) Clinic for late effects monitoring.³⁹ Most survivors are evaluated annually by the clinic staff until they are 18 years of age and at least 10 years post-diagnosis; discharge may be delayed until graduation from high school. After "alumni" survivors are discharged to the care of community physicians, the SJCRH Cancer Registry continues to perform periodic follow-up for the lifetime of the patient.

Study Eligibility and Recruitment

Eligibility criteria for inclusion in the SJLIFE cohort include: 1) diagnosis of childhood malignancy treated at SJCRH; 2) survival of ≥ 10 years from diagnosis; and, 3) current age ≥ 18 years. Alumni survivors who are followed by the SJCRH Cancer Registry and ACT survivors scheduled for alumnus discharge are invited to participate in the study; attendance in the ACT Clinic is not a requisite for recruitment. As St. Jude has made a long-term commitment to the SJLIFE study, the numbers entering the pool of potential recruits will increase over time as survivors are discharged from annual follow-up in the ACT Clinic. Thus, the cohort characteristics, including demographics, diagnoses, and treatment will continually be changing.

Three levels of participation are offered in the SJLIFE study: 1) comprehensive evaluation on the SJCRH campus; 2) limited local evaluation by Examination Management Services, Inc. (EMSI) for survivors who decline to return to SJCRH; or, 3) completion of health surveys by mail or phone interview for those survivors who decline to return to SJCRH or undergo a local evaluation. For survivors declining any level of study participation, information regarding the reason for study refusal is collected to inform the need for modification of recruitment procedures. A detailed description of the recruitment protocol is provided in supplemental Appendix 1.

The Baseline Evaluation

Recruitment—The cohort's initial baseline evaluation will provide data for a cross-sectional examination of the ≥ 10 -year alumnus survivor cohort. This protocol is in progress and utilizes a staged recruitment strategy to fully characterize groups of 50 survivors in targeted diagnostic or treatment categories. This staged approach facilitates early comparison of survivors agreeing or declining to study participation and more rapid reporting of outcomes. Recruitment over the initial years of the study is prioritized to survivors of hematological malignancies (specifically acute lymphoblastic leukemia survivors diagnosed when younger than age 10 years and who are age 30 years or older, and Hodgkin lymphoma survivors who are age 35 years or older), survivors treated with whole

lung radiation, and survivors eligible for priority pilot studies. Survivors of acute lymphoblastic leukemia and Hodgkin lymphoma were targeted for recruitment in the early years of the study because they represented the most prevalent primary malignancies among long-term survivors who were > 20 years from diagnosis and groups for whom the least amount of clinically-based information is available. Subsequent enrollment focuses on survivors of central nervous system tumors, retinoblastoma, Wilms' tumor, neuroblastoma, and bone/soft tissue sarcomas.

Medical Record Abstraction—Medical record abstraction for eligible SJLIFE participants is performed using a protocol similar to that utilized in the CCSS.⁴⁰ This includes abstraction of all chemotherapy received, including cumulative doses for 32 specific chemotherapeutic agents [5-Azacytidine, Bleomycin, Busulfan, Carboplatin, Carmustine, Cisplatin, Cyclophosphamide (IV, PO), Cytarabine (IV, IM, IT, SubQ), Dacarbazine, Dactinomycin, Daunorubicin, Dexamethasone, Doxorubicin, Etoposide (IV, PO), Fludarabine, Fluorouracil, Hydroxyurea, Idarubicin, Ifosfamide, L-Asparaginase, Lomustine, Melphalan, Methotrexate (IV, IM, IT), Nitrogen Mustard, Prednisone, Procarbazine, Teniposide, Thioguanine, Thiotepa, Tretinoin, Vinblastine, Vincristine], surgical procedures, and radiation treatment fields, dose, and energy source. To assure comprehensive ascertainment of health outcomes related to specific treatment exposures, key health events, especially life-threatening organ toxicity, and subsequent malignancies are also obtained. The sources of this information include medical records, Cancer Registry follow-up, and/or contact with next-of-kin for SJCRH patients who survived 10 or more years from diagnosis but subsequently died or are lost to follow-up.

Comprehensive Health Questionnaires—Participants complete a series of health questionnaires that include constructs and measures identified as important in previous assessments of survivors in the CCSS and SJCRH ACT Clinic. Questionnaire items are drawn from published and validated scales or index items from previous surveys such as the CCSS or Behavioral Risk Factor Surveillance System. The questionnaires include a total of 883 items that assess major domains of: 1) health history and status; 2) social and demographic factors; 3) health behaviors; 4) psychosocial functioning; and, 5) psychosexual health. Health outcomes and status include medical service utilization, medication use, current and past health problems, reproductive status, and pregnancies, as well as evaluation of attention deficit, pain, and quality of life. Social and demographic factors include marital status, living arrangements, academic achievement, employment status, insurance access, income, and financial hardship. Health behaviors include tobacco use, alcohol intake, illicit substance use, physical activity, sedentary behavior, sun exposure behaviors, participation in health screening, use of complementary and alternative medicine and dieting behavior. Dietary intake is assessed using a food frequency methodology. Psychosocial constructs include health perceptions, motivation for behavior change, body image/weight concerns, perceived stress, cancer impact, post-traumatic stress, depression, anxiety, and somatization.⁴¹ Psychosexual outcomes include fertility, onset of puberty, sexual development, relationship/marital satisfaction, and sexual health/functioning. Male participants are also asked about history of testosterone therapy, sperm banking, and erectile dysfunction. In addition, a measure of social desirability is administered to assess potential response bias.

As part of the risk-based medical assessment, all survivors identified to be at risk for cognitive difficulties, due to a history of exposure to either cranial radiation therapy or antimetabolite chemotherapy, undergo neurocognitive assessments that include measurement of intelligence, reading skills, memory, attention, processing speed and higher level executive functions. For survivors who demonstrate cognitive deficits severe enough to limit their ability to complete these direct neurocognitive assessments, structured interviews

with their parents/guardians are conducted for formal adaptive behavior assessment. This assessment provides specific measurement of developmental abilities, including communication, socialization, and daily living skills, in a form similar to an IQ index. The comprehensive health questionnaires include coding of whether the questionnaire was completed by the survivor or a surrogate respondent, with coding of the relationship of this respondent to the survivor in question. We will have the ability to link respondent type to the neurocognitive outcome data.

Risk-Based Medical Assessment—Each SJLIFE participant undergoes a periodic risk-based assessment based on primary diagnosis, age at diagnosis, and therapeutic interventions according to the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancer (COG Guidelines)*.⁴² Risk-based evaluations of the SJLIFE cohort are therefore limited to screening and diagnostic evaluations to characterize cancer-related health complications. The SJLIFE Clinic staff assists patients who have established or newly-identified cancer-related health problems with referrals to community health care providers for ongoing care. Disciplines represented among the SJLIFE clinical staff include pediatric oncology, medical oncology, radiation oncology, family medicine, internal medicine, cardiology, endocrinology, gastroenterology, nephrology, neurology, ophthalmology, pulmonology, reproductive endocrinology, diagnostic imaging, nursing, social work, neuropsychology, clinical psychology, and rehabilitative medicine.

The composition of the group targeted for onsite prospective follow-up at SJCRH is anticipated to change over time based on research findings about late health outcomes and the desire to investigate the impact of newer therapeutic approaches. Survivors in diagnostic/treatment groups designated to be of high research priority will be invited for more frequent follow-up. In general, most survivors will have medical assessments scheduled every 2 to 5 years based on our desire to monitor the impact of aging on organ function and health status.

Neuromuscular Functional Assessment—All SJLIFE participants undergo evaluation of physical performance status including formal assessments of sensation, flexibility, balance, muscle strength, mobility and gross and fine motor function. Vital signs, electrocardiography, anthropometrics, body composition and aerobic capacity measures are also included in the neuromuscular functional assessment to correlate with risk-based medical assessments.

Collection, Processing, and Storage of Biological Specimens—After informed consent is obtained, samples of blood and urine are collected for storage and future utilization for research investigations through an IRB-approved tissue banking protocol.

Investigator-Initiated Research

In addition to risk-based evaluations recommended by the *COG Guidelines*, the SJLIFE cohort serves as a resource for investigator-initiated research. This includes current and future hypothesis-driven research projects supported by externally funded grants. In addition, a series of small (typically 20 patients) pilot studies have been organized in survivors identified by SJLIFE investigators to be at high risk for cancer-related morbidity based on specific demographic, diagnostic, therapeutic, or genetic/familial factors. These SJLIFE participants undergo more extensive assessment beyond the screening recommendations outlined in the *COG Guidelines* to more thoroughly characterize specific treatment complications, as well as define the need for further study.

Prospective Longitudinal Cohort Study

After completion of a baseline clinical evaluation of cohort participants, prospective medical screening and evaluations will be undertaken using the risk-based strategies recommended in the *COG Guidelines*. Additionally, information gained from the baseline evaluations and high priority pilot studies of survivors will be used to inform changes in the types or frequency of onsite evaluations performed as the cohort is followed over time.

Retention of Cohort Participants

A newsletter is distributed on a semi-annual basis to: 1) maintain contact (mailings include an address correction request from the post office that can identify individuals who have moved from their last known address and may require additional tracing to re-establish contact); 2) provide an update on the status of the project; 3) maintain and enhance relationships with participants and 4) educate survivors about selected topics of health-related importance. In addition, a website has been developed to provide updates on SJLIFE activities. These procedures have historically been successful in maintaining contact with participants in the CCSS cohort.

Human Subjects Protection

The SJLIFE protocol and component pilot studies have been approved by the SJCRH Institutional Review Board. Informed consent is obtained from all participants before initiation of any of the study procedures.

RESULTS

Participation and Participant Characteristics

A total of 3,900 survivors met eligibility criteria for SJLIFE participation as of January 1, 2010 (Figure 1A). Among these survivors, less than 10% are considered “lost to follow-up” and have been forwarded for tracing. Figure 2 illustrates the geographic distribution by known last residence of eligible survivors from the continental United States. Table I summarizes the distribution of childhood cancer histological subtypes for the potentially eligible cohort subjects in relation to time from diagnosis. Table II provides agent-specific percentile distributions for cumulative chemotherapy dosage among study participants with completed medical record abstractions. Table III summarizes key radiation treatment fields. Table IV summarizes the demographic and cancer characteristics of all potentially eligible study subjects as of January 1, 2010, by current study status. Relying upon the last known address available in the medical record, a total of 303 (8%) required tracing to locate the eligible survivor. To date, almost 42% (1625/3900) of eligible study participants have been contacted; 93% of those contacted (1518/1625) have agreed to some level of study participation (1351 SJCRH campus evaluation, 10 local EMSI evaluation, 157 survey only). Recruitment is ongoing for the remaining survivors. Of the ≥ 10 year survivors eligible for the SJLIFE cohort, just over 60% are 30 years of age or older. Their median age is 32.3 years (range, 18 to 65 years). The cohort’s distribution by age and years from diagnosis is summarized in Table V.

Participation Among All Eligible Survivors

Among the 1351 survivors who agreed to return for risk-based assessments, 908 (67%) SJLIFE participants have completed their evaluations, another 161 (12%) have scheduled evaluations, and the remainder are in the scheduling queue (Figure 1A). Time required (i.e., days on the SJCRH campus) to complete the SJLIFE visit, including risk-based medical assessment and participation in investigator-initiated research, has ranged from 1–5 days (mean days=3.3; median days=3) as of January 1, 2010. Ninety percent or more of survivors

have completed the protocol questionnaires assessing chronic health conditions, health care utilization, psychosocial and quality of life outcomes and health habits. In addition, 70% of male survivors and 79% of female survivors completed a survey specifically evaluating psychosexual health. Among study participants who have completed evaluations, 54% are female and 89% are white, non-Hispanic. Their median age at diagnosis was 6.0 years (range, 0–22.0). Their median age at the baseline evaluation was 35.6 years (range, 20.0–60.6), and their median time from diagnosis was 28.0 years (range, 11.2–47.8). As expected, based on the initial recruitment strategy, the primary diagnoses among the first group of evaluated survivors include leukemia (n=458), lymphoma (n=194), and solid tumor (n=256).

Predictors of Participation in First 20 Recruitment Blocks

Evaluation of predictors of participation was limited to the first 20 recruitment blocks of 50 survivors so as to fully characterize the participating and non-participating survivors. Figure 1B and Table VI detail recruitment outcomes as of January 1, 2010 in the first 20 recruitment blocks of 50 survivors identified as potentially eligible for study participation. Eighty-five percent of those determined to be eligible agreed to participate in SJLIFE; 75% (731/971) agreed to a comprehensive medical assessment, and 60% (587/971) completed this evaluation. Anticipated minimum overall participation rate for medical evaluation is 75.3% (731/971). Comparison of those contacted versus those not contacted for study participation showed that a significantly greater proportion of black survivors ($p=0.02$) and a lower proportion of those treated with radiation ($p=0.01$) were unable to be contacted. Among those contacted, males were significantly less likely to participate ($p=0.001$). Further comparison suggests that a greater proportion of older survivors (age 40–49 years) opted for a local evaluation or completion of surveys only compared to returning to the SJCRH campus for a comprehensive medical assessment ($p=0.06$).

DISCUSSION

Through comprehensive, risk-based evaluation and correlation with pertinent host- and disease-related factors, the SJLIFE study is in a unique position to advance knowledge about the impact of aging on childhood cancer-related morbidity and mortality. We aim to define the prevalence and cumulative incidence of selected late treatment complications following predisposing therapeutic exposures. We anticipate that our findings will inform more accurate risk profiles for adverse outcomes in adults surviving childhood cancer and insights into mechanisms of cancer-related morbidity in an aging population. Knowledge gained will be critical for the development of follow-up guidelines and timely interventions to prevent or ameliorate cancer-related sequelae and their adverse effects on quality of life.

The progress achieved in curing childhood malignancies has created unique challenges for health outcomes research in childhood cancer survivors. The required transition of care of aging survivors from pediatric oncology to community medical providers often poses significant barriers to the evaluation of childhood cancer's impact on health during adulthood. Because many adverse effects of treatment may not become clinically apparent until the survivor attains maturity or begins to age, continued follow-up during adulthood is essential to accurately characterize very late cancer-related sequelae and determine if complications resulting from cancer therapy will be exacerbated by the organ dysfunction associated with aging. Prospective medical assessment of survivors offers the opportunity to accurately characterize long-term survivor health and identify clinical groups at high risk for cancer-related morbidity who may benefit from health promoting interventions. However, most research programs involving medical assessment of health outcomes in adults surviving childhood cancer are limited by substantial participation bias as insurance coverage typically determines the medical assessments undertaken. Only one previous study has undertaken medical assessments in a cohort of comparable magnitude to the SJLIFE

cohort.⁷ Dutch investigators were successful in recruiting 1362 (94.3% of eligible) five-year survivors of childhood cancer treated between 1966 and 1996. Substantial morbidity (both clinical and subclinical) was observed in this group who had attained a median age of 24.4 years and median follow-up of 17 years. This study was facilitated by a robust national health care system and cancer registry. In contrast, the SJLIFE cohort is older (median age 32.3 years) and has longer follow-up (median time, 24.3 years) from diagnosis. Because of the challenges faced by providers supervising follow-up care of childhood cancer survivors in the United States, the SJLIFE study is designed to facilitate prospective and comprehensive risk-based medical assessment of long-term survivors by eliminating key barriers to participation identified by survivors through pre-recruitment surveys. Insurance coverage does not dictate the study evaluations undertaken since all SJLIFE medical assessments are supported entirely by institutional funds. Likewise, travel and lodging are provided for study participants, who are also reimbursed a per diem rate to compensate for miscellaneous costs such as missed days at work or childcare expenses. Providing this type of assistance may alleviate barriers to study participation, such as low socioeconomic status (SES), and explain the excellent participation rates (which are currently > 92%) following study invitation.

Late sequelae of therapy for childhood cancer can be anticipated based on therapeutic exposures, but the magnitude of risk and the manifestations in an individual patient are influenced by numerous factors.² History pertinent to the host (age at diagnosis, time from therapy, sex, genetic/familial characteristics, premorbid health conditions, tolerance to therapy, socioeconomic status, health habits) and cancer (location, histology/biology, treatment modality) must be considered in the risk assessment for cancer-related morbidity. However, few health outcomes investigations have access to a large and well-characterized clinical cohort of survivors to address the multi-factorial nature of cancer-related morbidity, particularly in regards to the impact of aging on long-term childhood cancer survivor health. This information is essential to guide the development of health screening recommendations and health-preserving interventions for children who present with a new diagnosis of malignancy as well as for those who have already achieved long-term survival. Better understanding of the nature and severity of long-term adverse effects of treatment will also inform the development of newer treatment strategies for childhood cancer.

While cancer-related morbidity is anticipated to adversely impact the natural course of organ senescence during adulthood, factors contributing to the risk of premature organ dysfunction and secondary carcinogenesis require continued investigation as treatment approaches evolve. This is particularly relevant to health risks associated with contemporary risk-adapted treatment regimens that have been modified to reduce therapy intensity for clinically and biologically favorable presentations of pediatric malignancies. Subclinical effects on vital organ function--cardiovascular, pulmonary, hepatic, and renal function--are frequently observed in these cohorts; the impact of these subclinical changes on long-term health in aging survivors has not been established. Characterization of long-term survivor health is also critical to establish if contemporary treatment modalities have been successful in their aims to reduce late cancer-related morbidity. For example, technical advances in therapeutic radiation have largely focused on optimizing protection of normal tissues, but research confirming the effectiveness of these approaches in reducing morbidity in long-term survivors is lacking. Likewise, late health outcomes resulting from more intensive interventions like hematopoietic stem cell transplantation undertaken for children with relapsed and high risk malignancies have not been established. Through a scientifically-rigorous research protocol, the SJLIFE cohort will provide important new information regarding characterization of long-term outcomes in these individuals, which is necessary to determine the true costs of achieving long-term disease-free survival in regards to health status and quality of life. Evaluation of the impact of treatment modifications over time is a

priority objective of the SJLIFE study that should be facilitated by recruitment of a large cohort of survivors with diverse pediatric cancer diagnostic types treated over the last 48 years.

Research is also needed to promote the early identification of survivors at risk for cancer-related morbidity using both conventional and novel clinical and laboratory-based methods. Potential novel laboratory investigations utilizing the biologic specimens of the SJLIFE cohort include, but are not limited to, more extensive analyses of: vital organ function, biomarkers of metabolic function, micronutrient levels, cancer-predisposing genetic mutations, cancer susceptibility genes relating to phase I enzymes (that activate or deactivate carcinogens depending on the experimental conditions) and phase II enzymes, (that are more likely to detoxify pharmaceuticals). Correlation of results from these laboratory evaluations with other diagnostic assessments and cancer treatment exposures may enhance understanding of the pathophysiology underlying cancer treatment toxicity. The ability to identify survivors with subclinical changes of treatment-related toxicity then may provide an opportunity for early detection, rehabilitation, and prevention of cancer-related morbidity.

Preliminary SJLIFE investigations will broadly evaluate “at risk” survivors based on treatment exposures to establish prevalence and severity of specific cancer-related toxicities. The prevalence of late treatment complications detected by risk-based screening will provide important information regarding the appropriateness of the *COG Guidelines* recommendations in at risk survivor populations after specific therapeutic exposures. Notably, the health surveillance measures recommended by the *COG Guidelines* are derived from the clinical consensus of late effects experts who have identified “at risk” groups based on late effects research. Research is needed to assess the yield from this risk-based screening approach, particularly in very long-term survivors who may have other co-morbid conditions exacerbating cancer-related toxicity. In subsequent investigations, we plan to focus on the specific outcomes associated with therapeutic exposures that have been understudied in cohorts of adults surviving childhood cancer. Potential topics for investigation may range from global assessment of health status and quality of life, to focused evaluations of a specific tissue or organ system, or of a particular treatment complication in a given diagnostic group, e.g., stroke after Hodgkin lymphoma. In particular, we are interested in advancing knowledge about the cancer-related health complications that may present in adulthood or that may be exacerbated with organ senescence. Early results will inform future investigations that will extend beyond the initial risk-based evaluation outlined by the *COG Guidelines*. Potential objectives of these investigations include evaluation of novel screening methods for early detection of health conditions predisposed by cancer and intervention trials to remediate or prevent cancer-related complications. In this way, the anticipation is that SJLIFE will serve as a conduit for recruitment of adult survivors to other late health outcomes investigations.

As St. Jude is remarkable in its ability to engage survivors and families in research and maintain long-lasting follow-up of research participants, future SJLIFE investigations will need to consider the generalizability of results derived from the cohort to outcomes reported by pediatric cancer survivors across North America. In this regard, we compared and noted no substantial difference in the diagnostic subtypes and treatment exposures of survivors eligible for the SJLIFE study to those of non-St. Jude survivors eligible for the Childhood Cancer Survivor Study.⁴⁰ We also compared the racial distribution of eligible survivors in the SJLIFE cohort to that of childhood cancer survivors 10 to 32 years since diagnosis from the Surveillance, Epidemiology and End Results Program (SEER).⁴³ According to the SEER Cancer Statistics Review (1975–2007) the estimated US prevalence of childhood cancer survivors of all races is 158,284, of which, 136,588 (86%) are white and 14,290 (9%) are black. Among participants of SJLIFE, 89% of participants are white and 10% of participants

are black. These numbers are remarkably similar to what is seen in SEER suggesting generalizability with regards to race. Considering that the current contact and participation rates are significantly lower among black compared to white survivors, future analyses will need to address the potential impact of differential contact and response rates by race.

Demographic similarities between survivors treated at St. Jude and the US population extend to SES. Previous characterization of SES among ACT patients in 2006 found that 32%, 44% and 24% fell in low, middle and high SES categories, respectively, based on the Hollingshead Four Factor Index of Social Status, whereas 29%, 45%, and 26% of Americans fell in the lower, middle and upper income quintiles among familial households as reported by the US Census Bureau in 2008.^{44–46} Although SES was not significant in models predicting ACT Clinic attendance, future analyses will examine the impact that SES may have on SJLIFE participation. It is possible that the clinical services routinely provided to St. Jude survivors, compared to survivors treated at other pediatric institutions, foster greater health consciousness that translates into a willingness to collaborate in research. Future investigations will need to consider how medical care, insurance access and adherence to medical follow-up impact outcomes of the SJLIFE cohort compared to those reported by other survivor cohorts.

In summary, the objective of the SJLIFE study is to establish a lifetime cohort of childhood cancer survivors treated at St. Jude Children's Research Hospital to be used for investigation of the multi-factorial etiology of adverse health outcomes in aging adults surviving pediatric cancer. Our hypothesis is that a multidimensional, comprehensive risk assessment will permit more accurate definition of risk profiles for morbidity in aging childhood cancer survivors, inform the development of long-term follow-up screening guidelines, and facilitate the development of risk-reducing intervention measures. If study recruitment is maintained at the present level, SJLIFE study progress to date suggests its feasibility to recruit aging childhood cancer survivors to research investigations evaluating late health outcomes by medical assessments. While successful recruitment to the cohort is proceeding well, it is equally important to maintain ongoing participation of survivors. A number of mechanisms, beyond the newsletters and website, have been implemented to help retain study subjects. These include having survivors complete a survey after their clinical evaluation to determine satisfaction with all aspects of study participation with modifications in process and procedures based upon responses. In addition, each participant receives a detailed written summary of their visit including the results of evaluations performed and recommendations for follow-up. Those individuals with events detected during their visit also receive follow-up calls and counseling from the study healthcare team to facilitate referral to local healthcare providers. Lastly, in all interactions with study participants, the view is that everyone is part of the research team and contributing knowledge that will help improve the health and well-being of all pediatric cancer patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Research grant support: Supported by the Cancer Center Support (CORE) grant CA 21765 from the National Cancer Institute and by the American Lebanese Syrian Associated Charities (ALSAC).

We are grateful for the considerable efforts of the research, clinical and administrative staff who support the SJLIFE study and the survivors and their families from whom it is our privilege to learn.

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Figure 1.

To facilitate early comparison of survivors agreeing or declining to study participation and more rapid reporting of outcomes, the SJLIFE study utilizes a staged recruitment strategy to fully characterize groups of 50 survivors in targeted diagnostic or treatment categories. The figure illustrates recruitment outcomes as of January 1, 2010 among all survivors (A) and among survivors in the first 20 recruitment blocks (B) identified as potentially eligible for SJLIFE study participation. “One-year hold” in the “Not Contacted” block refers to participants the study team has not been able to directly contact, but for whom addresses and/or telephone numbers have not been determined to be inaccurate.

Figure 2.
Geographic distribution by last known residence of 3900 eligible survivors from the continental United States meeting eligibility criteria for SJLIFE participation as of January 1, 2010. Does not include 3 survivors residing in Alaska and 2 residing in Hawaii.

Table I

Distribution of St. Jude 10-year Survivors by Time from Diagnosis*

Primary Diagnosis	Years from Diagnosis			Total
	≥ 10 < 20	≥ 20 < 30	≥ 30	
Acute lymphoblastic leukemia	280	591	396	1267
Acute myeloid leukemia	54	51	22	127
Hodgkin lymphoma	177	179	125	481
Non-Hodgkin lymphoma	103	160	77	340
CNS tumor	203	100	11	314
Wilms' tumor	59	127	86	272
Neuroblastoma	21	100	69	190
Retinoblastoma	10	39	62	111
Germ cell tumor	32	52	23	107
Hepatoblastoma	4	15	10	29
Osteosarcoma	49	65	34	148
Rhabdomyosarcoma	37	62	45	144
Ewing Sarcoma Family of Tumors	36	47	25	108
Non-rhabdomyosarcoma soft tissue sarcoma	48	37	17	102
Other malignancies	75	46	39	160
Total No. Patients	1188	1671	1041	3900

* Data from 3900 survivors eligible for study participation as of January 1, 2010.

TABLE II

Chemotherapy -Specific Percentile Dose Distributions Among SJLIFE Participants with Complete Medical Record Abstraction (n = 3,612)

Chemotherapy agent	N	Cumulative dose percentiles				
		10th	25th	50th	75th	90th
5-Azacytidine	37	572.5	600.0	601.7	1,615.2	1,811.0
Bleomycin	162	29.7	40.2	60.0	79.7	127.3
Busulfan	8	236.1	323.1	494.0	533.3	917.3
Carboplatin	134	1,115.0	2,100.0	2,761.1	3,512.5	5,441.8
Carmustine	16	95.2	100.0	111.8	268.8	457.1
Cisplatin	245	182.1	298.3	400.0	485.2	719.6
Cyclophosphamide (IV)	1,764	1,714.3	3,635.7	7,301.9	10,095.6	15,001.7
Cyclophosphamide (PO)	352	3,500.0	4,274.8	7,196.5	13,356.7	22,142.9
Cytarabine (IT)	794	191.0	336.0	468.0	576.0	828.0
Cytarabine (IV/IM)	1,093	1,188.0	2,752.4	8,085.6	10,618.3	13,993.1
Cytarabine (SQ)	46	1,270.6	1,983.9	5,750.1	8,672.7	10,355.3
Dacarbazine (DTIC)	120	1,254.5	1,502.1	1,968.0	2,470.6	7,034.0
Dactinomycin	558	2.9	5.3	8.0	11.6	15.8
Daunorubicin (daunomycin)	795	49.3	50.3	98.0	105.0	185.7
Dexamethasone (decadron)	157	159.7	185.0	541.8	941.2	1,610.0
Doxorubicin (adriamycin)	1,263	120.5	153.4	199.0	310.8	384.5
Etoposide (IV)	836	892.6	1,996.3	6,033.2	10,066.3	14,104.8
Etoposide (PO)	22	614.7	714.3	1,105.2	2,100.0	3,200.0
Fludarabine	7	44.3	56.1	59.7	60.4	69.5
Fluorouracil (5FU)	31	2,387.5	2,736.5	9,000.0	15,437.9	17,767.9
Hydroxyurea	8	27,741.9	27,741.9	89,310.3	157,723.6	157,723.6
Idarubicin	11	9.0	10.8	20.3	24.1	36.2
Ifosfamide	201	12,069.0	23,679.6	39,878.8	53,959.2	69,509.2
L-Asparaginase	1,148	20,000.0	39,888.3	59,761.9	92,400.0	170,000.0
Lomustine	11	222.2	302.5	461.5	700.8	753.8
Melphalan	5	88.1	89.8	91.3	92.5	140.2
Mercaptopurine	1,374	2,000.0	6,000.0	16,859.6	42,735.6	53,857.6
Methotrexate (IM)	319	621.4	985.5	1,252.2	3,038.8	3,908.0

Chemotherapy agent	N	Cumulative dose percentiles				
		10th	25th	50th	75th	90th
Methotrexate (IT)	1,442	40.0	76.0	132.0	180.0	254.5
Methotrexate (IV)	1,416	162.7	2,400.0	4,115.4	16,227.5	26,289.7
Methotrexate (PO)	547	182.7	883.8	2,100.0	2,970.0	4,115.2
Nitrogen mustard	44	11.9	23.9	36.2	70.5	106.5
Prednisone	1,595	482.6	785.4	1,143.8	3,866.5	9,110.4
Procarbazine	280	2,414.9	3,602.2	4,229.5	6,294.6	8,790.7
Teniposide	706	605.6	1,375.0	3,214.1	5,370.3	6,629.2
Thioguanine	37	300.0	1,714.1	2,978.0	11,458.3	16,225.0
Thiotepa	19	33.1	65.0	400.0	550.0	900.0
Tretinoin (retin A)	5	895.3	1,861.4	3,000.0	5,484.3	16,207.5
Vinblastine	288	27.8	35.8	46.7	50.3	72.0
Vincristine	2,528	5.7	7.5	21.9	50.0	60.0

IV, intravenous; PO, oral; IT, intrathecal; IM, intramuscular; SQ, subcutaneous.

Exposure to Specific Radiation Treatment Fields by Cancer Diagnosis Among SJLIFE Participants with Complete Medical Record Abstraction (n=3612)

Table III

Diagnosis	Eligible SJLIFE Participants	Radiation treatment field				
		Any N (%)	Brain N (%)	Chest N (%)	Abdomen/pelvis N (%)	None N (%)
Acute lymphoblastic leukemia	1241	803 (65)	784 (63)	30 (2)	51 (4)	438 (35)
Acute myeloid leukemia	94	26 (28)	26 (28)	10 (11)	11 (12)	68 (72)
Hodgkin lymphoma	451	431 (95)	0 (0)	397 (88)	268 (59)	20 (5)
Non-Hodgkin lymphoma	290	147 (51)	47 (16)	48 (17)	36 (12)	143 (49)
Central nervous system	305	208 (68)	189 (62)	1 (<1)	40 (13)	97 (32)
Wilms tumor	253	157 (62)	2 (1)	149 (59)	156 (62)	96 (38)
Neuroblastoma	179	41 (23)	1 (1)	30 (17)	22 (12)	138 (77)
Retinoblastoma	110	49 (45)	3 (3)	0 (0)	0 (0)	61 (55)
Germ cell tumor	91	25 (27)	1 (1)	15 (16)	21 (23)	66 (73)
Hepatoblastoma	26	5 (19)	0 (0)	5 (19)	5 (19)	21 (81)
Osteosarcoma	139	5 (4)	0 (0)	2 (1)	1 (1)	134 (96)
Rhabdomyosarcoma	133	105 (79)	10 (8)	18 (14)	33 (25)	28 (21)
Ewing Sarcoma Family of Tumors	102	82 (80)	3 (3)	24 (24)	25 (25)	20 (20)
Non-rhabdomyosarcoma soft tissue sarcoma	83	33 (40)	0 (0)	6 (7)	5 (6)	50 (60)
Other	115	48 (42)	10 (9)	17 (15)	15 (13)	67 (58)
All patients	3612	2165 (60)	1076 (30)	752 (21)	689 (19)	1447 (40)

Table IV

Demographic and Cancer Characteristics of Survivors Eligible for SJLIFE Study

Characteristic	Eligible N (%)	Contacted/Agreed to Participate* N (%)	Contacted/Declined to Participate* N (%)	Pending Contact** N (%)
Total population	3900 (100)	1518 (39)	107 (3)	2275 (59)
Sex				
Male	2145 (55)	720 (47)	66 (62)	1359 (60)
Female	1755 (45)	798 (53)	41 (38)	916 (40)
Race/Ethnicity				
White	3237 (83)	1353 (89)	96 (90)	1788 (79)
Black	557 (14)	152 (10)	10 (9)	395 (17)
Hispanic	65 (2)	6 (<1)	0 (0)	59 (3)
Asian/Pacific Islander	2 (<1)	0 (0)	1 (1)	1 (<1)
Other	39 (1)	7 (<1)	0 (0)	32 (1)
Diagnosis				
Acute lymphoblastic leukemia	1267 (32)	804 (53)	65 (61)	398 (17)
Acute myeloid leukemia	127 (3)	34 (2)	3 (3)	90 (4)
Hodgkin lymphoma	481 (12)	242 (16)	13 (12)	226 (10)
Non-Hodgkin lymphoma	340 (9)	35 (2)	3 (3)	302 (13)
CNS tumor	314 (8)	39 (3)	4 (4)	271 (12)
Wilms' tumor	272 (7)	87 (6)	1 (1)	184 (8)
Neuroblastoma	190 (5)	42 (3)	2 (2)	146 (6)
Retinoblastoma	111 (3)	70 (5)	2 (2)	39 (2)
Germ cell tumor	107 (3)	10 (1)	0 (0)	97 (4)
Hepatoblastoma	29 (1)	0 (0)	0 (0)	29 (1)
Osteosarcoma	148 (4)	58 (4)	5 (5)	85 (4)
Rhabdomyosarcoma	144 (4)	31 (2)	4 (4)	109 (5)
Ewing Sarcoma Family of Tumors	108 (3)	47 (3)	5 (5)	56 (2)
Non-rhabdomyosarcoma soft tissue sarcoma	102 (3)	3 (<1)	0 (0)	99 (4)
Other malignancies	160 (4)	16 (1)	0 (0)	144 (6)
Age at diagnosis				
Mean	7.9	7.4	7.1	8.2
Median	7.0	6.0	6.0	8.0
Range	0.0–28.0	0.0–24.0	0.0–28.0	0.0–23.0
< 1	250 (6)	79 (5)	7 (7)	164 (7)
1–3	908 (23)	439 (29)	27 (25)	442 (19)
4–7	876 (22)	372 (25)	27 (25)	477 (21)
8–10	513 (13)	169 (11)	18 (17)	326 (14)
11–14	727 (19)	224 (15)	16 (15)	487 (21)

Characteristic	Eligible N (%)	Contacted/Agreed to Participate* N (%)	Contacted/Declined to Participate* N (%)	Pending Contact** N (%)
15–20	593 (15)	220 (14)	11 (10)	362 (16)
20 +	33 (1)	15 (1)	1 (1)	17 (1)
Time since diagnosis				
Mean	25.0	27.5	29.0	23.1
Median	24.3	27.2	29.8	21.8
Range	10.0–47.8	11.2–47.8	14.6–44.5	10.0–46.7
10–19	1188 (30)	249 (16)	15 (14)	924 (41)
20–29	1671 (43)	716 (47)	41 (38)	914 (40)
30 +	1041 (27)	553 (36)	51 (48)	437 (19)
Current Age				
Mean	33.3	35.3	36.6	31.8
Median	32.3	34.7	36.3	30.6
Range	18.0–65.0	19.5–62.9	21.5–63.3	18.0–65.0
< 20	66 (2)	1 (<1)	0 (0)	65 (3)
20–29	1461 (37)	440 (29)	25 (23)	996 (44)
30–39	1543 (40)	651 (43)	52 (49)	840 (37)
40–49	697 (18)	368 (24)	23 (22)	306 (13)
50–59	123 (3)	52 (3)	6 (6)	65 (3)
60+	10 (<1)	6 (<1)	1 (1)	3 (<1)

* As of January 1, 2010;

** Pending contact includes those lost, in tracing, on hold/pending contact.

Table V

Distribution of SJLIFE Cohort by Current Age and Time from Diagnosis*

Current Age by Primary Diagnosis	Years from Diagnosis			Total
	10 to 20	20 to 30	30+	
Leukemia				
< 20	27			27
≥ 20< 25	155	57		212
≥ 25< 30	94	221		315
≥ 30< 35	53	224	50	327
≥ 35< 40	5	94	147	246
≥ 40< 45		43	120	163
≥ 45		3	101	104
Lymphoma				
< 20	6			6
≥ 20< 25	48	4		52
≥ 25< 30	107	33		140
≥ 30< 35	98	82	4	184
≥ 35< 40	21	120	31	172
≥ 40< 45		84	47	131
≥ 45		16	120	136
CNS tumors				
< 20	3			3
≥ 20< 25	102	22		124
≥ 25< 30	68	40		108
≥ 30< 35	25	28	2	55
≥ 35< 40	5	8	2	15
≥ 40< 45		1	2	3
≥ 45		1	5	6
Embryonal tumors [£]				
< 20	20			20
≥ 20< 25	70	77		147
≥ 25< 30	21	146		167
≥ 30< 35	13	77	79	169
≥ 35< 40	2	24	89	115
≥ 40< 45		7	42	49
≥ 45		2	40	42
Bone and soft tissue sarcomas				
< 20	7			7
≥ 20< 25	47	11		58

Current Age by Primary Diagnosis	Years from Diagnosis			Total
	10 to 20	20 to 30	30+	
≥ 25–< 30	59	40		99
≥ 30–< 35	39	47	9	95
≥ 35–< 40	16	55	19	90
≥ 40–< 45	2	45	27	74
≥ 45		13	66	79
Other				
< 20	3			3
≥ 20–< 25	11	1		12
≥ 25–< 30	23	4		27
≥ 30–< 35	32	12	2	46
≥ 35–< 40	6	18	5	29
≥ 40–< 45		9	10	19
≥ 45		2	22	24
Total	1188	1671	1041	3900

* Data from 3900 survivors eligible for study participation as of January 1, 2010;

£ Embryonal includes Wilms tumor, neuroblastoma, retinoblastoma, germ cell tumor, and hepatoblastoma

Table VI
Predictors of Participation Among Survivors Allocated to First 20 Recruitment Blocks

Characteristic	Total Eligible N (%)	Contacted N (%)	Not Contacted N (%)	Agreed to Participate in SJLIFE N (%)	Declined to Participate N (%)	Agreed to Clinical Eval N (%)	Agreed to EMSI or Survey only N (%)	P-value			
								Contacted v Not Contacted	Agreed to participate v Declined	Agreed to Clinical Eval v EMSI or Survey only	Agreed to Clinical Eval v Combined (Not contacted + Declined + EMSI or Survey Only)
Total Eligible Population	971 (100.0)	898 (92.5)	73 (7.5)	825 (85.0)	73 (7.5)	731 (75.3)	94 (9.7)				
Sex								P=0.52	P=0.001	P=0.78	P=0.05
Male	497 (51)	457 (51)	40 (55)	406 (49)	51 (70)	361 (49)	45 (48)				
Female	474 (49)	441 (49)	33 (45)	419 (51)	22 (30)	370 (51)	49 (52)				
Race								P=0.02	P=0.93	P=0.72	P=0.87
White	865 (89)	806 (90)	59 (81)	740 (90)	66 (90)	652 (89)	88 (94)				
Black	98 (10)	87 (10)	11 (15)	80 (10)	7 (10)	74 (10)	6 (6)				
Hispanic	3 (<1)	2 (<1)	1 (1)	2 (<1)		2 (<1)					
Other	5 (1)	3 (<1)	2 (3)	3 (<1)		3 (<1)					
Age at Cancer Diagnosis (years)								P=0.56	P=0.83	P=0.98	P=0.62
<5	355 (37)	330 (37)	25 (34)	302 (37)	28 (38)	267 (37)	35 (37)				
5-9	278 (29)	255 (28)	23 (32)	234 (28)	21 (29)	208 (28)	26 (28)				
10-14	201 (21)	182 (20)	19 (26)	167 (20)	15 (21)	146 (20)	21 (22)				
15-19	132 (14)	126 (14)	6 (8)	118 (14)	8 (11)	106 (15)	12 (13)				
20+	5 (1)	5 (1)		4 (<1)	1 (1)	4 (1)					
Age at Contact for SJLIFE (years)								P=0.08	P=0.53	P=0.06	P=0.88
<20											
20-29	242 (25)	215 (24)	27 (37)	199 (24)	16 (22)	185 (25)	14 (15)				
30-39	353 (36)	330 (37)	23 (32)	300 (36)	30 (41)	266 (36)	34 (36)				
40-49	314 (32)	293 (33)	21 (29)	273 (33)	20 (27)	232 (32)	41 (44)				

Characteristic	Total Eligible N (%)	Contacted N (%)	Not Contacted N (%)	Agreed to Participate in SJLIFE N (%)	Declined to Participate N (%)	Agreed to Clinical Eval N (%)	Agreed to EMSI or Survey only N (%)	P-value			
								Contacted v Not Contacted	Agreed to participate v Declined	Agreed to Clinical Eval v EMSI or Survey only	Agreed to Clinical Eval v Combined (Not contacted + Declined + EMSI or Survey Only)
50+	62 (6)	60 (7)	2 (3)	53 (6)	7 (10)	48 (7)	5 (5)				
Cancer Diagnosis								P=0.71	P=0.62	P=0.61	P=0.78
Leukemia	510 (53)	472 (53)	38 (52)	432 (52)	40 (55)	380 (52)	52 (55)				
Lymphoma	242 (25)	226 (25)	16 (22)	211 (26)	15 (21)	186 (25)	25 (27)				
Other	219 (23)	200 (22)	19 (26)	182 (22)	18 (25)	165 (23)	17 (18)				
Cancer Therapy*											
Radiation	688 (71)	646 (72)	42 (58)	594 (72)	52 (71)	522 (71)	72 (77)	P=0.01	P=0.89	P=0.29	P=0.51
Alkylating Agent	739 (76)	685 (76)	54 (74)	632 (77)	53 (73)	553 (76)	79 (84)	P=0.66	P=0.44	P=0.07	P=0.56
Anthracycline	315 (32)	287 (32)	28 (38)	268 (32)	19 (26)	240 (33)	28 (30)	P=0.26	P=0.26	P=0.55	P=0.65
Distance from SJCRH (miles)											
<100	199 (20)	180 (20)	19 (26)	168 (20)	12 (16)	155 (21)	13 (14)	P=0.48	P=0.67	P=0.08	P=0.47
100-299	321 (33)	299 (33)	22 (30)	275 (33)	24 (33)	235 (32)	40 (43)				
300+	451 (46)	419 (47)	32 (44)	382 (46)	37 (51)	341 (47)	41 (44)				

* Based on data from survivors for whom medical abstraction has been completed.