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Demographic and Clinical Characteristics Associated with Perceptions of Follow-up Care in 2-Year Survivors of Childhood and Adolescent Cancer

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B.S., Armstrong Atlantic State University, 2014

Thesis Committee Chairs: Dr. Ann Mertens, PhD and Dr. Karen Effinger, MD MSc

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

Demographic and Clinical Characteristics Associated with Perceptions of Follow-up Care in 2-Year Survivors of Childhood and Adolescent Cancer

By Zachary C. Owens

Background: Survivor care focused on screening and prevention can help attenuate childhood cancer survivors' increased risk for morbidity, diminished quality of life, and premature mortality. Patients' perceptions regarding how long they need follow-up care for potential late effects can affect their motivation to attend a survivor clinic.

Methods: Baseline data from patients or parents of patients <18 years enrolled in the Children's Healthcare of Atlanta Childhood, Adolescent, and Young Adult Cancer Survivor Study (CHOA-CAYACSS) were linked with treatment information from medical records. Eligible subjects were ≥ 2 years off-therapy and ≤ 22 years of age at the time of the survey. We used univariate and bivariate analyses to identify demographic and clinical factors associated with patient perceptions of necessary length of follow-up care. The independent effects were then assessed using multivariable logistic regression.

Results: The sample included 655 survivors (53% male, 72% Caucasian, 33% exposed to radiation). Mean age at diagnosis and survey completion were 5.4 years (range: 0-18) and 13.4 years (range: 3-22), respectively. Of these survivors, 85% attended the Cancer Survivor Clinic during the previous twelve months. When evaluating their perceptions, 411 (64%) believed that they needed lifelong follow-up care; 76% stated this follow-up care should be annually. After controlling for gender, race, and age at survey completion, exposure to radiation (adjusted odds ratio (aOR) 1.7, 95% CI 1.0-2.4), time off therapy (aOR 1.1, 95% CI1.0-1.5), and preference to receive follow-up care from a cancer survivor program (aOR 1.7, 95% CI1.0-2.7) were associated with the perceived need for lifelong follow-up care versus limited duration or no follow-up care.

Conclusion: While the majority of survivors had attended a survivor clinic in the past year, only two-thirds believed that they needed lifelong follow-up care and screening for potential treatment-related late effects. Education strategies are needed to improve survivors' awareness of the importance of lifelong survivor care.

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Introduction

Childhood and Adolescent Cancer

According to the United States (US) National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program, approximately 16,000 children and adolescents in the US are diagnosed with cancer each year (1). This equates to an annual age-adjusted incidence rate of 17.8 cancer diagnoses per 100,000 individuals 0 to 19 years old (2). While this makes up just 1% of the total annual cancer diagnoses in the US, this population represents a unique subgroup with respect to cancer type and etiology, response to treatment, and long-term health outcomes (2, 3). While there are differences in incidence, mortality, and survival rates between children and adolescents, they are often studied together because of similarities in cancer etiology and treatment relative to adult cancers (1). Compared to adult cancers, which are largely associated with lifestyle factors that act over a long period of time to influence cancer risk, the majority of childhood and adolescent cancers do not have known preventable causes (1). Some evidence suggests that exposure to certain environmental factors may increase the risk of childhood cancer; however, it is believed that the majority of cancers in this population are due to randomly acquired gene mutations that occur during the complex developmental process (1).

Treatment of childhood and adolescent cancer can vary from patient to patient and is dependent on the type of cancer and the stage at which it is diagnosed (4). Cancers in this population are generally treated with a combination of therapies, which commonly include surgery, radiation therapy, chemotherapy, and/or targeted therapy (4). Treatment usually takes place at specialized cancer centers and is coordinated by a team of health professionals, which can include pediatric oncologists, radiation oncologists, pediatric surgeons, advanced practice nurse practitioners and physician assistants, psychologists, and social workers (4). While these treatments play a central role in the curative process, they can also have negative physical and psychosocial effects on the patient, especially as the survivor ages (5). These treatment-associated “late effects” can affect virtually every organ system and increase the survivors’ risk of morbidity and early mortality compared with the general population (5). To mitigate this increased risk for adverse health outcomes, it is recommended that childhood cancer survivors participate in ongoing, comprehensive follow-up care tailored to their individual treatment history (5). Additionally, survivors should receive counseling on behavioral and lifestyle factors that can reduce the risk of health problems that commonly present during adulthood (5).

Epidemiology of Childhood and Adolescent Cancer

While childhood and adolescent cancers share many similarities, there are notable differences in the types of cancer and in incidence, mortality, and survival rates (1). Childhood cancer refers to cancers that occur between birth and 14 years of age and adolescent cancer refers to cancers that occur between 15 and 19 years of age. Data published from SEER in 2016 show that the most common cancers among children include leukemia (30%), brain and other nervous system cancers (26%), soft tissue sarcomas (7%), and non-Hodgkin lymphomas (NHL) (6%) (6). Compared to children, among adolescents leukemia is less common and a larger proportion of cases are lymphomas (6). Brain and other nervous system cancers (20%) were the most common adolescent cancers, followed by leukemia (14%), Hodgkin lymphoma (HL) (13%), and gonadal germ cell tumors (12%) (6). The incidence of cancer is lower in children than adolescents, with incidence rates of 16.2 and 22.4 diagnoses per 100,000 respectively (2). Survival rates are similar between the two groups, but mortality is slightly higher among adolescents (2).

Cancer incidence, mortality, and survival rates among children and adolescents also vary based on gender and race/ethnicity (1). In children, the overall incidence rate is higher in boys than girls, while mortality and survival rates are approximately the same (1). Among adolescents, incidence rates are similar for boys and girls, however mortality is higher and survival is lower in boys (1). Within each age group, overall cancer incidence rates are the highest in non-Hispanic whites and Hispanics, however they have mortality rates that are comparable to other race/ethnicities due to high survival rates (1). Additionally, non-Hispanic black children and adolescents have lower overall incidence rates, but lower survival makes their mortality rates similar other race/ethnicities (1). Generally, American Indian/Alaska Native and Asian/Pacific Islander children and adolescents have the lowest incidence and mortality rates, with survival being comparable to other racial/ethnic groups (1, 7). The reasons for these gender and racial differences are not completely understood. Gender differences are thought to be due to differences in the types of cancers that occur in child and adolescent boys compared to girls and racial differences are through to be attributable to a combination of factors including socioeconomic status, quality of treatment and supportive care, knowledge about past diagnosis and treatment, adherence to therapies, and genetic differences (1, 7, 8).

Trends in Incidence, Mortality, and Survival Rates

Between 1975 and 2013, the incidence of childhood and adolescent cancer across all sites increased by an average of 0.6% per year (2). However, during this same time period, advances in treatment and supportive care regimens have led to substantial improvements in mortality and survival rates (2). Changes in incidence and mortality rates between 1975 and 2013 for all major cancer sites are displayed in Figure 1A and 1B, respectively. Across all cancer sites, mortality in children and adolescents diagnosed with cancer decreased from 5.1 to 2.3 deaths per 100,000; a total decrease of over 50% (9). The largest declines in mortality were observed for HL, NHL, and acute lymphoblastic leukemia (ALL) and site-specific mortality did not increase for any site (9). Additionally, 5-year relative survival rates for childhood and adolescent cancers increased from 62% to 85% for cancers diagnosed between 1975-1977 and 2006-2012, respectively (2). The largest improvement was observed among children and adolescents diagnosed with acute myelogenous leukemia (AML), where the 5-year survival rate increased from 54% to 91% (2). Other sites that experienced significant increases in survival include NHL (43% increase), ALL (37% increase), bone and joint cancer (24% increase), and neuroblastoma (24% increase) (2). There were no tumors that did not experience increases in 5-year survival (2). Data from the Childhood Cancer Survivor Study (CCSS) suggests that the majority (82%) of those who reach the five year milestone will become long-term survivors and that this proportion continues to increase steadily (10, 11).

Childhood Cancer Survivorship as a Public Health Concern

As a result of this increase in survival rates and decrease in mortality, the number of childhood and adolescent cancer survivors living in the US has grown rapidly. According to SEER data, there are currently over 380,000 childhood and adolescent cancer survivors living in the United States and this number is expected to approach 500,000 by 2020 (2, 5, 12) . This growing population reflects a group of individuals that are highly vulnerable to a range of adverse health outcomes and impaired quality of life as a result of their prior cancer treatment (3, 13-15). These treatment-associated late effects are extremely common among childhood and adolescent cancer survivors and their incidence increases as a survivor ages (14). Data from the CCSS indicates that at some point during their life, approximately two out of every three survivors will be diagnosed with at least one chronic health condition and over 25% will experience a condition that is severe or life-threatening (13). Depending on the survivors' treatment exposures, they can be at risk for a range of late effects, including problems with organ function, growth and development, fertility and reproduction, neurocognitive function, second malignancies, and premature mortality (13-18) . Additionally, survivors commonly experience psychosocial problems that can impact their mental health, interpersonal relationships, functional status, and level of educational attainment (3, 19).

There is variability in the latency period for treatment-associated late effects and it may take decades for some effects to become clinically apparent (3). However, it is possible to reduce the risk and severity of treatment-associated late effects through a combination of lifelong, risk-based follow-up care and implementation of healthy lifestyle behaviors (3, 20-23). According to Oeffinger, et al., this risk-based follow-up care should include a systematic plan for lifelong screening, regular disease surveillance, and prevention that incorporates risks based on previous cancer, cancer therapy, genetic predispositions, lifestyle behaviors, and comorbid health conditions (24). In concordance with the growing body of evidence linking specific treatments with specific late effects, the Children's Oncology Group (COG) created and regularly updates guidelines for providers to consider when providing risk-based follow-up care to childhood and adolescent cancer survivors (25). These guidelines are designed to facilitate early detection and timely intervention for these complications, standardize follow-up care, provide guidance to healthcare professionals that provide care to this population, and ultimately improve health outcomes and quality of life in survivors (25).

While the benefits of risk-based follow-up care for childhood and adolescent cancer survivors are widely accepted, the large majority of survivors are not receiving that type of care (20, 26). Data from the CCSS indicates that while close to 90% of survivors receive some form of general medical care, only 18% of survivors received care that involves advice about risk reduction and screening tests (20). Additionally, most survivors receive their care from primary care physicians who have limited knowledge of how to care for patients with such complex needs (20, 27). Since access to medical care is not an issue for most childhood and adolescent cancer survivors, understanding the factors that influence survivors' participation in lifelong, risk-based follow-up care is important for improving long term health outcomes and quality of life in survivors.

Barriers to Follow-up Care in Survivors

Barriers to follow-up care in survivors of childhood and adolescent cancer can be divided into three categories: health system-related barriers, provider-related barriers, and survivor-related barriers (28). Health system-related barriers generally refer to long term follow-up programs not being covered under a survivor's health plan or lack of health insurance (28). Many childhood cancer survivors age out of their parents' health plan once they enter adulthood and are no longer covered by public assistance programs funded by the government. Data from the CCSS found that 16% of survivors older than18 years at the time of enrollment did not have health coverage (26). Additionally, survivors without health insurance were less likely to have a cancer-related medical visit within the past 2 years and almost twice as likely to report no medical contact at all (26).

Provider-level barriers include the small number of long-term follow-up programs in the US, poor communication between cancer institutions and primary care physicians, and primary care physicians' lack of knowledge and unfamiliarity with the health risks and needs of childhood and adolescent cancer survivors (28). Surveys of general internists in the US indicate that most primary care providers have seen a childhood cancer survivor in the past 5 years (29). Additionally, they suggest that these providers are willing to follow survivors; however, they are not familiar with published guidelines and would prefer to follow survivors in collaboration with a cancer center (27, 29). In a 2004 publication, Mertens et al. ranked primary care physicians lack of familiarity with late effects and management of childhood cancer as the most important barrier to the healthcare of childhood and adolescent cancer survivors (30).

Survivor-level barriers include lack of knowledge regarding past cancer diagnosis and treatment history and lack of awareness regarding potential late effects and future health risks (28). In the same 2004 publication, Mertens et al. also identified these factors as the two primary survivor-related barriers (30). In a cross-sectional survey of CCSS participants, 74% could provide a general summary of their diagnosis and treatment history, but none could provide a detailed history (31). Additionally in the same report, only 15% ever received a report from their oncologist outlining their medical and treatment history (31). Lack of knowledge of potential health risks and lower vulnerability to late effects are associated with decreased attendance at long term follow-up clinics (32, 33).

Context and Significance of this Project

Understanding survivor-level factors that can improve follow-up clinic attendance and adoption of risk-based care recommendations is crucial to improving long-term health outcomes and quality of life in childhood and adolescent cancer survivors. Survivors who lack detailed and accurate knowledge about their past cancer diagnosis and treatment are less likely understand their risk for treatment-associated late effects and adverse health outcomes. Additionally, survivors who have low perceived vulnerability to treatment-associated late effects are less likely to be motivated to participate in risk-based follow-up care. To date, there have been several studies looking at the relationship of perceived vulnerability to late effects and follow-up clinic attendance. However, there have been no analyses exploring survivors’ perception regarding follow-up care length. This thesis has three aims:

1) To characterize survivor perceptions regarding follow-up care length and provider preference in a population of childhood and adolescent cancer survivors enrolled in a cancer survivor program
2) To explore the bivariate and multivariate association of demographic and clinical characteristics associated with perceptions of follow-up care length

3) To investigate how these factors are related to the type of provider survivors prefer to receive their follow-up care from.

We hypothesized that exposure to radiation, having a high-risk cumulative anthracycline dose, or having a high-risk cumulative alkylating agent dose would be associated with a greater likelihood that a survivor would perceive lifelong follow-up care as necessary. Additionally, we hypothesized that exposure to radiation, having a high-risk cumulative dose of anthracyclines, and having a high-risk cumulative dose of alkylating agents would be associated with a greater likelihood to prefer to receive follow-up care from a cancer survivor program and a decreased likelihood to prefer to receive follow-up care from a primary care provider or oncologist.

Methods

Study Setting

This study uses data from a subset of childhood and adolescent cancer survivors enrolled in the Aflac Cancer Survivor Program (CSP) at Children's Healthcare of Atlanta's (CHOA). The CSP is a specialized clinic that provides patient-centered multidisciplinary care to survivors who are in disease remission and have been off therapy for at least two years. The multidisciplinary team at the CSP includes specialists in pediatric oncology, endocrinology, psychology, and social work. Once survivors are enrolled in the program, members of the CSP team work with them and their parents to provide personalized education about late effects for which the survivor is at increased risk. All information provided is tailored to survivors based on their previous cancer diagnosis, treatment history, family history, and current health status with an emphasis placed on the importance of disease prevention, early detection, and the establishment of healthy behaviors. Each survivor is given a Survivor Health Plan (SHP) that outlines their previous treatment information, personalized risk profile, and late effects surveillance plan based on guidelines created by the COG (25). Most survivors are seen at the CSP annually until age 21, when their care is transitioned to adult providers. However, since the risk of late effects varies between survivors, the frequency of follow-up visits can vary.

Survey Methods

Survivors receiving care at the CSP are invited to enroll in the CHOA Childhood, Adolescent, and Young Adult Cancer Survivor Study (CHOA-CAYACSS), which has been enrolling patients since 2008. CHOA-CAYACSS is an institutional cohort study that uses longitudinal surveys to explore long-term treatment-associated medical and psychosocial effects of patients enrolled in the CSP. Upon entering the CAYACSS cohort, survivors are asked to complete a detailed, 23-page baseline survey that explores demographic characteristics as well as the chronology of medical, social, and psychological problems commonly experienced by childhood and adolescent cancer survivors. Specific survey items in the baseline CAYACSS survey assess demographics and family information, academic history and performance, patient perceptions regarding their health and follow-up care, healthcare utilization, and medical problems. Parents of survivors who are younger than 18 years old complete the survey and survivors 18 years and older complete the survey themselves. Following completion of the baseline enrollment survey, an abbreviated follow-up survey is administered on an annual basis. All CAYACSS surveys are administered either on a paper form or using Research Electronic Data Capture (REDCap) software, and are stored in a CAYACSS Survey Database. For the purposes of this analysis, only baseline CAYACSS survey responses were used.

Study Population

Some hematology patients who receive blood or bone marrow transplants are seen in the CSP before they are two years off therapy and some survivors are seen past the age of 22. Additionally, survivors of brain and other central nervous system cancers are treated in a separate clinic. These patients do not accurately reflect the overall population in the CSP and thus were excluded from the analysis. The final population of survivors included in this analysis consisted of patients from the CSP who were enrolled in CAYACSS, in disease remission and off therapy for at least two years, less than or equal to 22 years old at the time of baseline CAYACSS survey completion, and diagnosed with non-central nervous system tumors. Institutional Review Board (IRB) approval was obtained through Emory University and CHOA, and all subjects provided informed consent to participate in CAYACSS.

Survivor Electronic Health Records

Additional medical information on survivors enrolled in CAYACSS is stored in the CHOA Aflac Cancer Center Survivor Database, referred to as the Survivor Database. Data are abstracted from the survivors' medical records and uploaded to the Survivor Database. These records include previous oncology diagnosis or diagnoses, radiation exposure and cumulative doses by site, chemotherapeutic agent exposure and dose, diagnostic testing results, an updated problem list, and additional treatment-related variables such as date of diagnosis and date when therapy was completed. All survivors enrolled in CAYACSS have a Survivor Database identification number that was used to link survey responses from the CAYACSS Survey Database with relevant medical information from the Survivor Database.

Dependent Variables

There were four binary dependent variables of interest for this analysis: one primary outcome and three secondary outcomes. Figure 2 shows the questions in the baseline CAYACSS survey that were used to ascertain the outcome variables and the possible response options for each. The primary outcome variable was survivor perception of how long it is necessary to be followed for potential treatment-associated late effects. For the analysis, response options for this question were collapsed into two categories – survivors who believed they needed lifelong follow up care versus those who did not. The secondary outcomes for this analysis were the types of provider survivors would prefer to receive their follow-up care from. The possible choices for providers included (1) primary care provider, (2) oncologist, and (3) cancer survivor program. These categories were not mutually exclusive, so survivors were able to select more than one provider.

Independent and Derived Variables

Predictor variables selected for this analysis included demographic, clinical, and treatment-related variables obtained through baseline responses to the CAYACSS survey and the Survivor Database. Demographic variables included age at survey completion, gender, race and ethnicity, maternal and paternal education level, total annual household income, exercise frequency, perceived health status, and health insurance status. Clinical and treatment-related variables included age at diagnosis, time off therapy, previous cancer diagnosis, exposure to radiation, cumulative anthracycline dose, cumulative alkylator dose, heavy metal exposure, frequency of follow-up care visits, history of hematopoietic stem cell transplant, 19 different educational and behavioral problems, 39 different symptoms, and healthcare utilization over the past 12 months. Predictors were selected based on their hypothesized association with each outcome and their potential to identify important relationships that could lead to improvement in survivor care. Several independent variables had to be derived using existing variables in our dataset. These included the following: age at survey completion, age at diagnosis, time off therapy, chemotherapeutic agent exposure, and cumulative radiation exposure by site. Age at survey completion was derived using the date the survivor completed the baseline CAYACSS survey and their date of birth. Age at cancer diagnosis was calculated using the date of the survivors' original cancer diagnosis as recorded in the Survivor Database and their date of birth. Time off therapy was calculated at the time of survey completion using the date the baseline CAYACSS survey was completed and the date therapy was completed from the Survivor Database.

Chemotherapeutic agent and radiation exposure were assessed using information on each survivor that was present in the Survivor Database. For chemotherapeutic agents, three different types of exposures were considered: cumulative alkylating agent dose, cumulative anthracycline dose, and any exposure to heavy metals. Cumulative alkylating agent dose, in cyclophosphamide equivalents, was calculated using methods described by Green, et al.(34). Individual alkylating agents used in the calculation included cyclophosphamide, ifosfamide, procarbazine, chlorambucil, carmustine, lomustine, melphalan, thiotepa, nitrogen mustard, and busulfan. Individual doses for each agent were transformed to a common unit of measure (mg/m^2), summed, and then multiplied by standardized coefficients to convert cumulative doses for each agent to cyclophosphamide equivalents. The cyclophosphamide equivalent dose (CED) for each alkylating agent were summed to create a cumulative CED for each survivor. For anthracyclines, cumulative anthracycline dose, in doxorubicin equivalents, was derived using methods outlined in the COG Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancer (25). Individual anthracyclines used in the calculation included daunorubicin, doxorubicin, epirubicin, idarubicin, and mitoxantrone. The same procedure described above for cumulative alkylating agent dose was used to generate cumulative anthracycline dose for each survivor. For cumulative alkylating agent and anthracycline doses, survivors were categorized as having high exposure, low exposure, or no exposure as determined by the COG and Childhood Cancer Guideline Harmonization Group (35). High and low cumulative doses were defined as ≥7500 and <7500 mg/m^2 for alkylating agents and ≥250 and <250 mg/m^2 for anthracyclines. No exposure indicated that the survivor never received that treatment. Exposure assessment for heavy metal agents included carboplatin and cisplatin and was defined as the presence or absence of exposure.

Radiation exposure was also assessed using information from the Survivor Database. The database includes information on individual radiation exposure events, including the date of exposure, radiation site, and total dose administered. Categories for site were determined using recommendations outlined in the COG Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancer (25). These categories included cranial, neck, thorax, abdomen, pelvis, skeletal, testes, and total body irradiation. When radiation site data were not clear, a Pediatric Oncologist from the CSP team made the final determination as to the site category. Once radiation exposure events were correctly classified, cumulative radiation exposure, in grays (Gy), was calculated for each specific site.

Statistical Methods

Descriptive statistics for demographic, clinical, and treatment-related variables were calculated using counts and percentages for categorical variables and means with standard deviations for continuous variables. The chi-square test of proportions was used to compare categorical variables and two-sample t-tests were used to compare continuous variables. Simple logistic regression was used to determine the crude association of each independent variable with each study outcome. Odds ratios (OR), 95% confidence intervals (95% CI), and Wald p-values were calculated. For our primary outcome, we modeled the probability of a survivor perceiving lifelong follow-up care as necessary versus the probability of a survivor perceiving anything less than lifelong follow-up care as necessary. Variables significantly associated with our primary outcome ($p<0.05$) were included in a multivariable logistic regression model. Age at cancer diagnosis, gender, and race and ethnicity were selected *a priori* as control variables and radiation exposure, cumulative anthracycline dose, and cumulative alkylator dose were included in each model because of their important influence on risk of late effects and follow-up care recommendations. Step-wise backwards elimination was used to eliminate variables that did not have significant independent effects on our primary outcome and to generate a final multivariable logistic regression model. For our secondary outcomes, three multivariable logistic regression models were fit, one for each provider preference. Each model estimated the probability that a survivor preferred to receive their follow-up care from a specific provider versus the probability that a survivor did not prefer to receive follow-up care from that same provider. The same *a priori* control variables and treatments included in the analysis of the primary outcome were also included these models. Additionally, variables with significant bivariate associations with each provider preference were included in the multivariable models. Each of these final multivariable models contained the same clinical and demographic factors so that the independent effects could be compared across provider types. Goodness of fit was assessed using the Hosmer-Lemeshow chi-square test and adjusted odds ratios (aOR), 95% confidence intervals, and Wald p-values were calculated. Tests of significance were set at the $\alpha=0.05$ significance level and all analyses were conducted using SAS 9.4 (Cary, NC).

Results

Study Population

Survivors or their parents completed the baseline CAYACSS survey between January 2008 and September 2016. The CAYACSS population initially consisted of 744 survivors of childhood and adolescent cancer, excluding brain and central nervous system tumors. Sixty-four (8.6%) were excluded because they were not two or more years off therapy or because their time off therapy was unknown. Additionally, 25 (3.4%) were excluded because they were older than 22 years at the time of survey completion. The remaining 655 (88.0%) survivors composed the final study population and were included in all subsequent analyses. Of these, 548 (83.7%) were younger than 18 years at the time of the baseline CAYACSS survey and had a parent or guardian complete the survey. There were 474 (86.5%) baseline CAYACSS surveys completed by the survivor's mother, 48 (8.8%) by the survivor's father, and 21 (3.8%) by another family member or guardian. The remaining 107 (16.3%) surveys were completed by survivors themselves. Supplementary Table S1 displays a comparison of survey responses stratified according to who completed the survey. Briefly, mothers were more likely to report lower education for fathers compared to fathers themselves and survivors (p=0.030). Both mothers and fathers reported that survivors had better general health and exercised more frequently compared to survivors (p=0.046 and p<0.001, respectively). Fathers were more likely to report that the survivor had seen a primary care provider in the past 12 months compared to mothers and survivors (p<0.001). Fathers and survivors were more likely to report that they do not perceive follow-up care as necessary or do not know the proper frequency of follow-up care visits compared to mothers (p<0.001). Additionally, mothers were more likely to prefer that the survivor receive follow-up care from a cancer survivor program compared to survivors and fathers (p=0.007).

Demographic Characteristics

Table 1 provides an overview of the baseline demographic characteristics of the eligible survivors enrolled in the CAYACSS cohort. Three hundred forty-five (52.7%) survivors were male, 310 (47.3%) were female, and the median age (interquartile range [IQR]) at survey completion was 12.7 years (9.3-16.4). Survivors were mostly of non-Hispanic white race and ethnicity (71.7%), but our population also included a proportion of non-Hispanic black (13.8%) and Hispanic (8.9%) survivors. Two hundred fifty-five (39.5%) survivors have mothers and fathers with at least a college degree, 73% of families had a total household income of $40,000 or greater, and nearly all (93.4%) spoke English as their primary language at home. Of the 643 (98.8%) survivors with health insurance, 436 (67.8%) received insurance through their parent’s work and 198 (30.8%) through Medicaid or another public assistance program.

Clinical Characteristics and Treatment History

Survivors were diagnosed between September 1988 and October 2013. They had a median age at diagnosis of 3.9 years (IQR=2.2-7.6), with 397 (60.6%), 149 (22.8%), and 109 (16.6%) diagnosed at less than 5 years, between 5 and 9 years, and 10 years of age and older, respectively (Table 2). Leukemia was the most common cancer diagnosis, occurring in 46.3% of survivors, followed by sarcomas, renal tumors, lymphomas, and neuroblastoma. Of those with a leukemia diagnosis, 81.7% had acute lymphoblastic leukemia and 18.3% had acute myeloblastic leukemia. There were 590 (90.1%) survivors who underwent a routine check-up, sports physical, or school physical in the 12 months prior to completion of the CAYACSS survey. Additionally, in the past 12 months, 559 (85.3%) survivors saw a provider at a cancer survivor clinic, 579 (88.4%) had a routine dental exam, and 307 (46.9%)had a routine off therapy visit with an oncologist.

Table 2 provides a complete summary of the clinical characteristics and treatment-related exposures of eligible survivors enrolled in the CAYACSS cohort. Survivors completed therapy between June 1990 and January 2014 and had a median time off therapy of 5.0 years (IQR=3.3-8.2). Six hundred forty-five (98.5%) survivors received chemotherapy and 216 (33.0%) were exposed to radiation as part of their treatment. Of these, 435 (66.1%) received chemotherapy only, 6 (0.9%) received radiation only, and 210 (32.1%) received both chemotherapy and radiation. There were 539 (89.1%), 467 (75.2%), and 127 (20.5%) survivors who received an anthracycline, alkylating agent, or heavy metal, respectively, as part of their chemotherapy. Of those that received anthracyclines, 389 survivors had a cumulative dose that put them at low risk for cardiovascular late effects (<250 mg/m^2) while 139 had a cumulative dose that put them at high cardiovascular risk (≥ 250 mg/m^2). There were 11 survivors that received chest radiation and a high-risk dose of anthracyclines, 128 who received a high-risk dose of anthracyclines alone, and 3 who received chest radiation alone. Of those that received alkylating agents, 311 had a cumulative dose that put them at low risk for gonadotoxic late effects (<7500 mg/m^2) and 134 had a cumulative dose that placed them in the high gonadotoxic risk group (≥ 7500 mg/m^2).

Perceptions of Follow-up Care and Provider Preference

Table 3 displays a univariate analysis of survivor perceptions regarding length, frequency, and provider preference for follow-up care. Four hundred eleven (64.3%)

survivors perceived lifelong follow-up as necessary in order to screen for potential treatment-associated late effects. One hundred ten (17.2%) survivors perceived some follow-up care as necessary, but did not believe follow-up needed to be lifelong. Additionally, 118 (18.5%) survivors perceived follow-up care as unnecessary or did not know how long follow-up care needed to be. The majority of survivors perceived that annual late effect screening was necessary (78.9%), while 7.2% and 7.5% believed follow-up screening needed to be more frequent and less frequent than annually, respectively. An additional 9.5% perceived follow-up care as unnecessary or did not know how frequent follow-up screenings needed to be. There were 343 (54.1%) survivors that perceived lifelong follow-up care and annual screenings as necessary and 44 (6.9%) that were unsure about both the length and frequency of follow-up care.

Four hundred ninety (74.8%) survivors preferred to receive their follow-up care from a specialized cancer survivor program, while 254 (39.8%) and 55 (8.4%) survivors said they would prefer to receive follow-up care from an oncologist or primary care provider, respectively. There were 152 (24.4%) survivors that selected multiple providers from which they would prefer to receive follow-up care. Three hundred forty-two (52.2%) survivors preferred to receive their follow-up care from a cancer survivor program only, 115 (17.6%) preferred an oncologist only, and 110 (16.8%) preferred to receive care from both.

Predictors of Survivor Perceptions of Follow-up Care Length

Crude and adjusted associations of demographic and clinical variables with survivor perception of follow-up length were assessed using binary logistic regression models. Results from this analysis are presented in Table 4. Based on crude associations, survivors who were exposed to radiation (vs no radiation, OR=1.61, 95% CI=1.13-2.31, p=0.009), preferred to receive follow-up care from a cancer survivor program (vs another provider, OR=1.73, 95% CI=1.19-2.50, p=0.004), currently were experiencing behavioral problems (vs no behavioral problems, OR=2.67, 95% CI=1.36-5.26, p=0.004), currently were experiencing anxiety (vs no anxiety, OR=1.70, 95% CI=1.11-2.62, p=0.016), or had problems with headaches (vs no headaches, OR=2.04, 95% CI=1.36-5.05, p=0.001) were more likely to perceive lifelong follow-up care as necessary. Survivors that perceived follow-up care as unnecessary or that were unsure about follow-up frequency were 92% less likely to perceive lifelong follow-up as necessary (vs annual follow-up screening, OR=0.08, 95% CI=0.04-0.17, p<0.001). We expected cumulative anthracycline dose and cumulative alkylating agent dose to be associated with survivors perceiving lifelong follow-up care as necessary; however, they were not. Additionally, gender, race and ethnicity, cancer diagnosis, time off therapy, and history of hematopoietic stem cell transplant were not significant bivariate predictors of survivors' perception of follow-up care length.

The final multivariable logistic regression model contained the variables age at diagnosis, gender, race and ethnicity, exposure to radiation, cumulative alkylating agent dose, cumulative anthracycline dose, time off therapy, frequency of follow-up care visits, preference to receive follow-up care from a cancer survivor program, and problems with headaches. When controlling for all other variables in the model, gender, exposure to radiation, having a low- or high-risk cumulative anthracycline dose, time off therapy, preference to receive follow-up care from a cancer survivor program, and problems with headaches independently increased the likelihood that a survivor perceived lifelong follow-up care as necessary. Of these predictors, exposure to radiation, time off therapy, preference to receive follow-up care from a cancer survivor program, and currently experiencing headaches had effects that were statistically significant. Exposure to radiation independently increased the likelihood of survivors perceiving lifelong follow-up care as necessary by 67% compared to survivors that were not exposed to radiation (aOR=1.67, 95% CI=1.01-2.74, p=0.044). For every additional year off therapy, a survivor's odds of perceiving lifelong follow-up care as necessary increased by 7% (aOR=1.07, 95% CI=1.00-1.15, p=0.049). Preference to receive follow-up care from a cancer survivor program (vs another provider, aOR=1.68, 95% CI=1.04-2.70, p=0.035) and problems with headaches (vs no headaches, aOR=2.02, 95% CI=1.25-3.28, p=0.004) increased the likelihood that a survivor perceived lifelong follow-up care as necessary. When controlling for all other variables in the model, age at diagnosis; race and ethnicity; having a low- or high-risk cumulative alkylating agent dose; and frequency of follow-up care visits independently decreased the likelihood that a survivor perceived lifelong follow-up care as necessary. Of these variables, frequency of follow-up care was the only effect that was statistically significant. Survivors who perceived follow-up care as unnecessary or did not know how frequently screening events should be spaced apart were 90% less likely to perceive lifelong follow-up as necessary compared to those that thought screening should be conducted on an annual basis (aOR=0.10, 95% CI=0.04-2.70, p<0.001).

Predictors of Provider Preferences

Multivariable logistic regression models were used to identify clinical and demographic factors that were associated with survivor preference to receive follow-up care from a primary care provider, oncologist, or cancer survivor program, respectively. The final variables in each model included age at diagnosis, gender, race and ethnicity, exposure to radiation, cumulative alkylating agent dose, cumulative anthracycline dose, time off therapy, frequency of follow-up care visits, and total household income. The results from the multivariable analyses are presented in Table 5.

The first provider preference model we investigated looked at clinical and demographic characteristics that predicted survivor preference to receive their follow-up care from a primary care provider. When controlling for all other variables in the model, older age at diagnosis, female gender, black, non-Hispanic race and ethnicity, radiation exposure, perceiving follow-up visits should be less frequent than annually, perceiving follow-up care as unnecessary or not knowing the proper frequency of follow-up visits, and medium total annual household income were independently associated with survivors preferring to receive follow-up care from their primary care provider. However, none of the effects were statistically significant. Variables that were independently associated with a decreased likelihood of preferring to receive follow-up care from a primary care provider included choosing “other” as their race and ethnicity, receiving a low- or high-risk cumulative anthracycline dose, longer time off therapy, perceiving follow-up screening events should be more frequently than annually, and low total annual household income. Of these, having a low-risk cumulative anthracycline dose was the only statistically significant effect. Survivors with a cumulative anthracycline dose less than 250 mg/m^2 were 63% less likely to prefer to receive follow-up care from their primary care provider compared to survivors that never received an anthracycline does agent (aOR=0.37, 95% CI=0.15-0.93, p=0.034).

The second provider preference model we investigated looked at clinical and demographic characteristics that predicted survivor preference to receive their follow-up care from an oncologist. Age at diagnosis, female gender, black, non-Hispanic or other race and ethnicity, having a low- or high-risk cumulative anthracycline dose, perceiving that follow-up visits should be less frequent than annually, perceiving follow-up care as unnecessary or not knowing the proper frequency of follow-up visits, and higher total annual household income were independently associated with survivors preferring to receive follow-up care from their oncologist when controlling for all other variables in the model. Of those variables, the only statistically significant effect was among survivors who perceived that follow-up care events should be more frequent than annually. These survivors were 2.9 times more likely to prefer to receive their follow-up care from an oncologist compared to survivors that perceived follow-up screening visits should occur annually (aOR=2.94, 95% CI=1.40-6.16, p=0.004). When holding all other variables in the model constant, exposure to radiation and having a low- or high-risk cumulative alkylating agent dose were independently associated with a decreased likelihood that survivors would prefer to receive follow-up care from an oncologist. Of these, having a low-risk cumulative alkylating agent dose was the only statistically significant effect. Survivors with a cumulative alkylating agent dose less than 7500 mg/m^2 were 42% less likely to prefer to receive follow-up care from an oncologist compared to those who did not receive any alkylating agent (aOR=0.58, 95% CI=0.35-0.97, p=0.037).

The third provider preference model we investigated looked at clinical and demographic characteristics that predicted survivor preference to receive their follow-up care from a cancer survivor program. When controlling for all other variables in the model, variables that independently increased the likelihood that a survivor would prefer to receive follow-up care from a cancer survivor program included exposure to radiation and having a low- or high-risk cumulative alkylating agent dose. Of those variables, having a low-risk cumulative alkylating agent dose was the only statistically significant effect. Survivors who had a cumulative alkylating agent dose less than 7500 mg/m^2 were 86% more likely to prefer to receive their follow-up care from a cancer survivor program compared to those that never received an alkylating agent (aOR=1.86, 95% CI=1.03-3.37, p=0.041). Variables that independently decreased the likelihood that a survivor would prefer to receive follow-up care from a cancer survivor program, when all other variables in the model were held constant, included older age at diagnosis, black, non-Hispanic or “other” race and ethnicity, having a low or high-risk cumulative anthracycline dose, longer time off therapy, perceiving follow-up visits should occur more or less frequent than annually, perceiving follow-up care as unnecessary or not knowing the proper frequency of follow-up screenings, and lower total annual household income. Of these, frequency of follow-up care visits and total annual household income had statistically significant effects. Survivors who perceived that follow-up screening events should occur more frequently than on an annual basis were 80% less likely to prefer to receive follow-up care from a cancer survivor program compared to those who though screening events should occur on an annual basis (aOR=0.20, 95% CI=0.09-0.41, p<0.001). Survivors who perceived follow-up care as unnecessary or did not know the proper frequency of screening events were 68% less likely to prefer to receive their follow-up care from a cancer survivor program (vs annual screening, aOR=0.32, 0.16-

0.65, p=0.002). Compared to survivors who had a total annual household income of at least \$100,000, those with total annual household income less than \$40,000 were 54% less likely to prefer to receive follow-up care from a cancer survivor program (aOR=0.46, 95% CI=0.25-0.85, p=0.014).

Discussion

Perceptions of Follow-up Care Length

To our knowledge, this study is the first to assess how clinical and demographic characteristics are associated with perceptions of follow-up care length in survivors of childhood and adolescent cancer. Specifically, we investigated how these variables are related to whether or not a survivor perceived lifelong follow-up care as necessary compared to follow-up care that is less than lifelong in duration. Understanding these factors can have important implications for identifying groups of survivors that will benefit from further education about their risk of treatment-associated late effects.

We identified that only 64% of survivors in our study perceived lifelong follow-up care as necessary. Considering that over 85% of these patients had been seen by a cancer survivor program in the 12 months prior to survey completion, this was significantly lower than we expected. In concordance with our initial hypothesis, survivors who were exposed to radiation therapy as part of their treatment were significantly more likely to perceive lifelong follow-up care as necessary. This finding is consistent with literature from the CCSS that shows survivors who receive radiation are more likely to have received risk-based follow-up care compared to general medical care (20). A longer time off-therapy was also significantly associated with survivor perception of lifelong follow-up care as necessary. Survivors who have been off-therapy for a longer amount of time may have experienced a late effect or had more contact with clinicians that have explained the importance of routine lifelong follow-up care; it is also possible that these patients had been seen at the CSP several times prior to completing their baseline CAYACSS survey. Additionally, survivors that preferred to receive their follow-up care from a cancer survivor program were more likely to perceive lifelong follow-up care as necessary. This finding makes sense considering survivors who are seen regularly at a CSP are likely to have received additional education regarding late effects and see the benefit of this type of routine follow-up. The only independent factor associated with decreased likelihood that a survivor would perceive lifelong follow-up care as necessary was survivor perception of follow-up frequency. Survivors who perceived follow-up care as unnecessary or did not know how frequently screenings should occur were significantly less likely to perceive lifelong follow-up care as necessary. This finding is reasonable considering these survivors may have less knowledge regarding their vulnerability to treatment-associated late effects.

Contrary to our initial hypotheses, exposure to a high-risk cumulative dose of anthracyclines or alkylating agents was not significantly associated with survivors perceiving lifelong follow-up care as necessary. Interestingly, survivors who received any dose of anthracyclines or alkylating agents were not more likely to perceive lifelong follow-up care as necessary compared to those who received none. This finding was surprising to us since patients who receive these chemotherapeutic agents are generally informed about the potential long-term health risks associated with the treatments and recommended to undergo screenings regularly. Demographic characteristics such as gender, race/ethnicity, parent education level, and total annual household income were not significantly associated with survivors' perception that lifelong follow-up care is necessary. This is consistent with other literature that indicates most demographic factors are not associated with gaps in survivor knowledge about their past diagnosis and treatment (31).

Provider Preferences

Data from the CCSS suggest that the majority of survivors receive their medical care from general practitioners and that this care is usually not related to their history of cancer (20). Additionally, survivors who received care from general practitioners are much less likely to receive regular screening tests for the treatment-associate late effects for which they are at risk (20). Understanding factors that influence the type of provider that survivors prefer to receive their follow-up care from can identify groups of survivors that may not know they are at increased risk for potential late effects.

While 85% of survivors reported being seen by a cancer survivor program in the 12 months prior to completion of their baseline CAYACSS survey, only 75% preferred to receive follow-up care from a cancer survivor program. Following our original hypothesis, exposure to radiation was associated with greater likelihood that a survivor would prefer to receive follow-up care from a cancer survivor program and decreased likelihood they would prefer to receive care from a primary care provider or oncologist. Additionally, survivors who received low- or high-risk cumulative doses of alkylating agents were more likely to prefer to receive follow-up care from a cancer survivor program and less likely to prefer to receive follow-up care from a primary care provider or oncologist. Interestingly, survivors who received low- or high-risk cumulative doses of anthracyclines were more likely to prefer to receive follow-up care from an oncologist and less likely to prefer to receive care from a cancer survivor program.

We found that survivors with lower income were more likely to prefer to receive follow-up care from a general practitioner or oncologist and less likely to prefer to receive follow-up care from a cancer survivor program, suggesting that the cost associated with survivor care is a barrier for some patients. Additionally, we found that perceived frequency of follow-up visits was associated with provider preference. Survivors that perceived that follow-up screenings should be more frequent than on an annual basis were more likely to prefer to receive follow-up care from an oncologist and less likely to prefer follow-up care from a primary care provider or cancer survivor program. Consistent with our expectation, survivors who perceived follow-up care as unnecessary or were unsure about how frequently follow-up screenings should be spaced were more likely to prefer to receive follow-up care from a primary care provider or an oncologist and less likely to prefer to receive follow-up care from a cancer survivor program. It is likely these survivors have not had as much education regarding follow-up screenings for late effects and do not understand the benefit of attending specialized CSP.

Limitations

The results of this analysis are subject to several limitations. First, the data collected from the baseline CAYACSS survey were self-reported by survivors or parents or guardians of survivors. Over half the surveys were completed by someone other than the survivor and, as Table S1 shows, responses to some questions may have been biased depending on who completed the survey. Second, a significant proportion of survivors in the study were of non-Hispanic, white race/ethnicity and nearly all survivors had health insurance. This limited data on racial and ethnic minorities and individuals without health insurance eliminate a proportion of survivors that may have different perceptions of follow-up care compared to those present in our study and limits generalizability of our findings. Third, data were gathered from patients who have been seen in a CSP and do not reflect the perceptions of patients who have never attended a CSP. Fourth, sample size limitations forced us to collapse variable categories for our primary dependent variable and some independent variables and hindered our ability to look at how receiving combinations of therapies, such as high-risk anthracycline dose and chest radiation, impacts perceptions of follow-up care.

Strengths

The primary strength of this analysis is its novelty. First, to date, we were unable to find any studies of childhood and adolescent cancer survivors that investigated how demographic and clinical characteristics are associated with survivor perceptions of follow-up care and provider preferences. Problems and limitations in this analysis can be used to inform future projects investigating these associations and improve the design of future studies. Second, we utilized data collected from two distinct sources in our analysis. Our dependent variables were collected as part of the baseline CAYACSS survey, while covariates and independent variables of primary interest were collected from the Survivor Database. This decreases the likelihood that our results are biased due to differential misclassification. Third, we had a relatively low proportion of missing data.

Conclusions

Although 85% of survivors had been seen by a cancer survivor program in the past year, only 64% perceived lifelong follow-up care as necessary. Survivors who received low- or high-risk cumulative doses of anthracyclines and alkylating agents did not perceive lifelong follow-up care as necessary. Additionally, those receiving anthracyclines were less likely to prefer to receive their follow-up care from a cancer survivor program. This suggests a significant proportion of survivors, some who have received high-risk therapies, are not aware of their increased risk of late effects and need for lifelong follow-up care. Education strategies are needed to improve survivors' and survivors' parents' awareness of the vulnerability to treatment-associated late effects and the importance of lifelong follow-up care.

Summary, Public Health Implications, and Future Directions

Summary

Advances in treatment and supportive care regimens over the past 40 years have resulted in a current survival rate of over 85% for childhood and adolescent cancers. However, survivors are at increased risk for morbidity, diminished quality of life, and premature mortality associated with their previous cancer diagnosis and treatment. Risk-based follow-up care mediates this risk and improves health outcomes and quality of life. Survivors' perceptions regarding how long they need to be followed for potential late effects can affect their motivation to attend a survivor clinic. We used baseline data from a cohort of childhood and adolescent cancer survivors enrolled in a cancer survivor program to identify demographic and clinical factors associated with survivor perceptions of follow-up care. Our results suggest that while 85% of survivors have attended the cancer survivor program in the past year, only 64% perceive lifelong follow-up care as necessary. Additionally, some survivors who received high-risk treatments were less likely to perceive lifelong follow-up care as necessary and more likely to prefer to receive follow-up care from a provider other than a cancer survivor program. This underscores the importance of survivor education regarding late effects and follow-up care guidelines and suggests that additional education strategies are needed to improve survivors' knowledge.

Public Health Implications

Our results support findings from other studies suggesting that a large number of childhood and adolescent cancer survivors are unaware of their increased risk for adverse health outcomes and their need for lifelong follow-up care. In the larger public health context, this study suggests that additional education strategies are necessary in order to improve survivors’ knowledge about their cancer history, treatment-history, increased risk of adverse health outcomes as they age, and need for lifelong follow-up care. Our analysis was unique in that it included survey responses from both survivors and survivors’ parents and our results indicate that there is a lack of knowledge among both groups. Therefore, education strategies should be targeted towards improving the knowledge of both. Data from this analysis can be used to support the need for educational programs or trials looking at the effectiveness of various educational strategies to improve survivors’ and parents of survivors’ knowledge about treatment-associated late effects and the importance of lifelong follow-up care.

Future Directions

Future analyses should consider including a larger sample size to investigate how a wider range of treatment exposures and combinations of treatments are related to survivor perceptions of follow-up care. They should also consider incorporating a longitudinal measure of survivor preferences regarding follow-up care length and provider preferences to see how these outcomes change over time and if any factors are associated with changes over time. The CAYACSS follow-up surveys include the same questions regarding perceptions of follow-up length and provider preference, so that type of analysis is possible with the same population. Additionally, it would be interesting to conduct a prospective, observational or randomized controlled trial looking at how different educational strategies impact survivor perceptions and preferences for follow-up care.

Tables

Table 1. Demographic Characteristics of Eligible Survivors Enrolled in the CAYACS Cohort (n=655)

	N	Percent
Age at Survey Completion, Years		
Less than 7	64	9.77
7 to 12	279	42.6
13 to 17	206	31.45
18 to 22	106	16.18
Gender		
Male	345	52.67
Female	310	47.33
Race and Ethnicity		
White, non-Hispanic	468	71.67
Black, non-Hispanic	90	13.78
Other*	95	14.55
Mothers Education Level		
Less than College Degree	272	42.04
College Degree or Higher	375	57.96
Fathers Education Level		
Less than College Degree	293	47.33
College Degree or Higher	326	52.67
Household Income		
Less than $40,000	157	26.75
$40,000 to 99,999	237	40.37
$100,000 or more	193	32.88
Speak English at Home		
No	44	6.73
Yes	610	93.27
General Health		
Poor to Good	110	16.85
Very Good to Excellent	543	83.15
Insurance Status		
No	8	1.23
Yes	643	98.77

*Other race includes Hispanics, Asian and Pacific Islanders, and American Indian/Alaska Natives.

Table 2. Clinical and Treatment Related Characteristics of Eligible Survivors Enrolled in the CAYACS Cohort (n=655)

	N	Percent
Age at Diagnosis, Years		
Less than 5 Years	397	60.61
5 to 9 Years	149	22.75
10 Years or Older	109	16.64
Diagnosis		
Leukemia	303	46.26
Lymphoma	76	11.60
Renal Tumor	81	12.37
Sarcoma	86	13.13
Neuroblastoma	65	9.92
Other*	44	6.72
Providers Seen in Last 12 Months		
Primary Care or Routine Check-up	566	86.41
Sports or School Physical	181	27.63
Cancer Survivor Clinic	559	85.34
Routine Off-therapy with Oncologist	307	46.87
Dental Routine Check-up	579	88.40
Experienced the Following in Past 12 Months		
Illness Requiring Doctors Visit	360	54.96
Illness Requiring ER Visit	136	20.76
Illness Requiring Hospitalization	27	4.12
Illness Requiring Surgery	68	10.38
Time off Therapy, Years		
Less than 5 Years	327	49.92
5 to 9 Years	227	34.66
10 Years or More	101	15.42
Radiation Exposure		
No	441	67.33
Yes	214	32.67
Chemotherapy Exposure		
No	10	1.53
Yes	645	98.47
Cumulative Alkylator Dose, mg/m^2		
None	151	32.06
<7500	311	47.48
≥7500	134	20.46
Cumulative Anthracycline Dose, mg/m^2		
None	64	19.39
<250	389	59.39

≥250	139	21.22
Heavy Metal Exposure**		
No	494	79.55
Yes	127	20.45
Hematopoietic Stem Cell Transplant		
No	571	87.18
Yes	84	12.82
Currently Experiencing Behavioral Problems		
No	578	90.45
Yes	61	9.55
Currently experiencing Headaches		
No	456	73.42
Yes	164	26.58
Currently experiencing Depression		
No	587	91.43
Yes	55	8.57
Currently experiencing Anxiety		
No	502	79.30
Yes	131	20.70

*Other cancer diagnoses include Carcinomas, Germ Cell Tumors, Liver Tumors, and Retinoblastomas

**Defined as exposure to either carboplatin or cisplatin

Table 3. Patient Perceptions of Follow-up Care After Cancer Treatment in the CAYACS Cohort (n=655)

	N	Percent
Perceived Length of Follow-up		
Lifelong	411	64.32
Less than lifelong follow-up	110	17.21
No follow-up needed or do not know	118	18.47
Perceived Frequency of Follow-up		
More frequently than annually	46	7.17
Annually	487	75.86
Less frequently than annually	48	7.48
No follow-up needed or do not know	61	9.50
Preferred Provider of Follow-up Care*		
Oncologist	254	38.78
Primary Care Doctor	55	8.40
Cancer Survivor Program	490	74.81
No follow-up needed or do not know	19	2.91

*Categories were not mutually exclusive

Table 4. Bivariate and Multivariate Associations of Clinical and Demographic Factors with Patient Perception of Receiving Lifelong Follow-up for Treatment-associated Late Effects

	Frequency	**Bivariate Association**			**Multivariate Association**		
	N	OR	95%CI	p-value	aOR	95%CI	p-value
Age at Diagnosis, Years	655	0.98	0.94, 1.01	0.204	0.99	0.94, 1.04	0.716
Gender of Survivor							
Male	345	1.00	Reference		1.00	Reference	
Female	310	1.36	0.98, 1.88	0.068	1.40	0.94, 2.10	0.102
Race of Survivor							
White, non-Hispanic	468	1.00	Reference		1.00	Reference	
Black, non-Hispanic	90	0.69	0.44, 1.11	0.123	0.69	0.38, 1.26	0.230
Other*	95	0.73	0.46, 1.18	0.197	0.83	0.47, 1.48	0.533
Radiation Exposure							
No	441	1.00	Reference		1.00	Reference	
Yes	214	1.61	1.13, 2.31	**0.009**	1.67	1.01, 2.74	**0.044**
Gonadotoxic Agent Dose, mg/m^2							
None	151	1.00	Reference		1.00	Reference	
<7500	311	0.92	0.61, 1.39	0.686	0.94	0.53, 1.64	0.819
≥7500	134	1.19	0.72, 1.96	0.503	0.87	0.47, 1.63	0.663
Anthracycline Dose, mg/m2							
None	64	1.00	Reference		1.00	Reference	
<250	389	1.14	0.66, 1.97	0.645	1.35	0.69, 2.68	0.384
≥250	139	1.27	0.68, 2.37	0.448	1.81	0.84, 3.90	0.131
Mothers Education Level							
Less than College Degree	272	1.00	Reference				
College Degree or Higher	375	1.32	0.95, 1.84	0.096			
Diagnosis							
Leukemia	303	1.00	Reference				

Lymphoma	76	0.72	0.43, 1.21	0.213			
Renal Tumor	81	1.07	0.63, 1.82	0.796			
Sarcoma	86	1.11	0.66, 1.87	0.688			
Neuroblastoma	65	1.07	0.60, 1.91	0.812			
Other**	44	0.72	0.37, 1.34	0.316			
Time off Therapy, Years	655	1.05	1.00, 1.10	0.050	1.07	1.00, 1.15	**0.049**
Hematopoietic Stem Cell Transplant							
No	571	1.00	Reference				
Yes	84	1.60	0.95, 2.69	0.075			
Frequency of Follow-up Care Visits							
More frequently than annually	46	0.65	0.34, 1.23	0.183	0.79	0.37, 1.71	0.549
Annually	487	1.00	Reference		1.00	Reference	
Less frequently than annually	48	0.60	0.33, 1.12	0.105	0.64	0.29, 1.42	0.272
No follow-up needed or do not know	61	0.08	0.04, 0.17	**<0.001**	0.10	0.04, 0.22	**<0.001**
Preference to Receive Follow-up Care from a Cancer Survivor Program							
No	165	1.00	Reference		1.00	Reference	
Yes	490	1.73	1.19, 2.50	**0.004**	1.68	1.04, 2.70	**0.035**
Currently Experiencing Behavioral Problems							
No	578	1.00	Reference				
Yes	61	2.67	1.36, 5.26	**0.004**			
Currently experiencing Headaches							
No	456	1.00	Reference		1.00	Reference	
Yes	164	2.04	1.36, 3.05	**0.001**	2.02	1.25, 3.28	**0.004**

Currently experiencing Depression				
No	587	1.00	Reference	
Yes	55	1.79	0.94, 3.42	0.079
Currently experiencing Anxiety				
No	502	1.00	Reference	
Yes	131	1.70	1.11, 2.62	**0.016**

OR: Odds Ratio, aOR: adjusted odds ratio, CI: confidence interval
Multivariable mode: age at diagnosis, gender, and race were selected a priori as control variables; radiation exposure, cumulative alkylator dose, and cumulative anthracycline dose were included in the model because they are important factors in determining a patients risk for treatment-associated late effects; all other statistically significant bivariate associations were included in the multivariable model and stepwise backwards elimination was used to eliminate variables that did not have statistically significant independent effects

*Other race includes Hispanic, Asian and Pacific Islander, and American Indian/Alaska Native

**Other cancer diagnoses include Carcinomas, Germ Cell Tumors, Liver Tumors, and Retinoblastomas

Table 5. Multivariate Associations of Clinical and Demographic Factors with Whom Survivors Prefer to Receive Follow-up Care for Treatment-associated Late Effects

	Preferred Provider								
	Primary Care Provider (n=55)			Oncologist (n=254)			Cancer Survivor Program (n=490)		
	aOR	95%CI	p-value	aOR	95%CI	p-value	aOR	95%CI	p-value
Age at Diagnosis, Years	1.06	0.98, 1.15	0.155	1.03	0.98, 1.09	0.225	0.95	0.89, 1.01	0.077
Gender of Survivor									
Male	1.00	Reference		1.00	Reference		1.00	Reference	
Female	1.45	0.75, 2.80	0.271	1.06	0.72, 1.54	0.779	1.00	0.64, 1.58	0.998
Race of Survivor									
White, non-Hispanic	1.00	Reference		1.00	Reference		1.00	Reference	
Black, non-Hispanic	1.48	0.60, 3.64	0.393	1.38	0.78, 2.46	0.274	0.70	0.37, 1.35	0.289
Other*	0.92	0.35, 2.42	0.858	1.59	0.92, 2.74	0.097	0.83	0.44, 1.59	0.581
Radiation Exposure									
No	1.00	Reference		1.00	Reference		1.00	Reference	
Yes	1.03	0.48, 2.21	0.954	0.78	0.50, 1.23	0.288	1.56	0.90, 2.72	0.115
Gonadotoxic Agent Dose, mm/kg^2									
None	1.00	Reference		1.00	Reference		1.00	Reference	
<7500	0.52	0.22, 1.20	0.127	0.58	0.35, 0.97	**0.037**	1.86	1.03, 3.37	**0.041**
≥7500	0.73	0.29, 1.79	0.485	0.70	0.40, 1.23	0.215	1.57	0.81, 3.05	0.185
Anthracycline Dose, mm/kg^2									
None	1.00	Reference		1.00	Reference		1.00	Reference	
<250	0.37	0.15, 0.93	**0.034**	1.38	0.72, 2.64	0.335	0.59	0.26, 1.32	0.200
≥250	0.40	0.14, 1.16	0.093	1.19	0.58, 2.45	0.641	0.76	0.32, 1.83	0.541
Time off Therapy, Years	0.91	0.81, 1.03	0.141	0.95	0.89, 1.01	0.081	0.98	0.91, 1.06	0.591

Frequency of Follow-up Care Visits									
More frequently than 1 year	0.19	0.03, 1.49	0.114	2.94	1.40, 6.16	**0.004**	0.20	0.09, 0.41	**<0.001**
Every year	1.00	Reference		1.00	Reference		1.00	Reference	
Less frequently than 1 year	1.56	0.47, 5.22	0.472	1.16	0.52, 2.57	0.715	0.80	0.32, 2.01	0.632
No follow-up needed/ do not know	1.60	0.56, 4.54	0.379	1.19	0.60, 2.35	0.623	0.32	0.16, 0.65	**0.002**
Total Household Income									
Less than $40,000	1.79	0.75, 4.27	0.189	1.46	0.88, 2.44	0.144	0.46	0.25, 0.85	**0.014**
$40,000 to 99,999	0.93	0.41, 2.13	0.863	1.13	0.72, 1.78	0.598	0.66	0.37, 1.16	0.149
$100,000 or greater	1.00	Reference		1.00	Reference		1.00	Reference	

OR: odds ratio, aOR: adjusted odds ratio, CI: confidence interval

Multivariable models: age at diagnosis, gender, and race were selected a priori as control variables; radiation exposure, cumulative alkylator dose, and cumulative anthracycline dose were included in each model because they are important factors in determining a survivors risk for treatment-associated late effects; other predictors that had statistically significant bivariate associations with each outcome were added to multivariable models

*Other race includes Hispanic, Asian and Pacific Islander, and American Indian/Alaska Native

Figures

Figure 1A. Age-Adjusted SEER Cancer Incidence Rates, Birth to 19 Years, 1975-2013

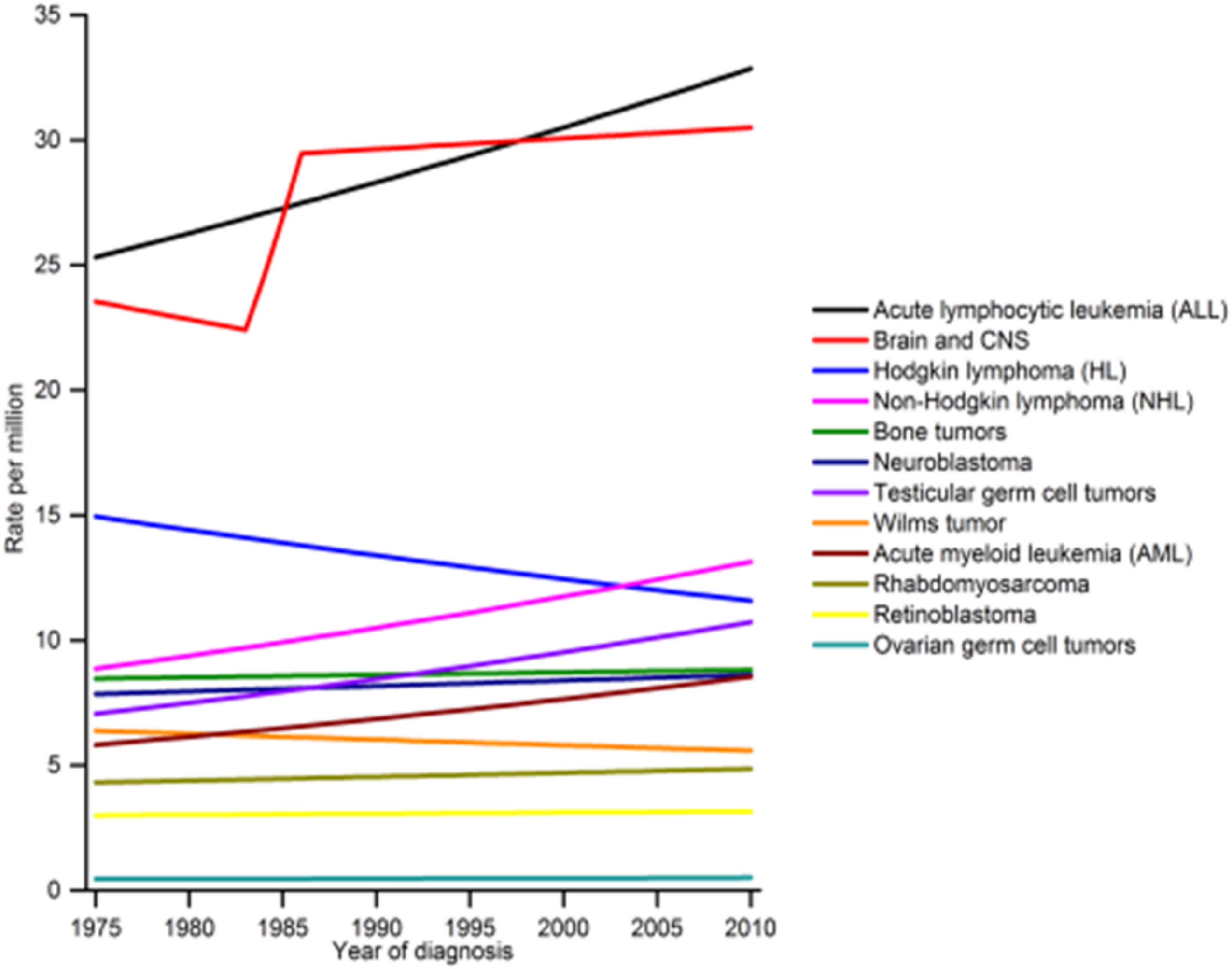


Figure 1B. Age-Adjusted SEER Cancer Mortality Rates, Birth to 19 Years, 1975-2013

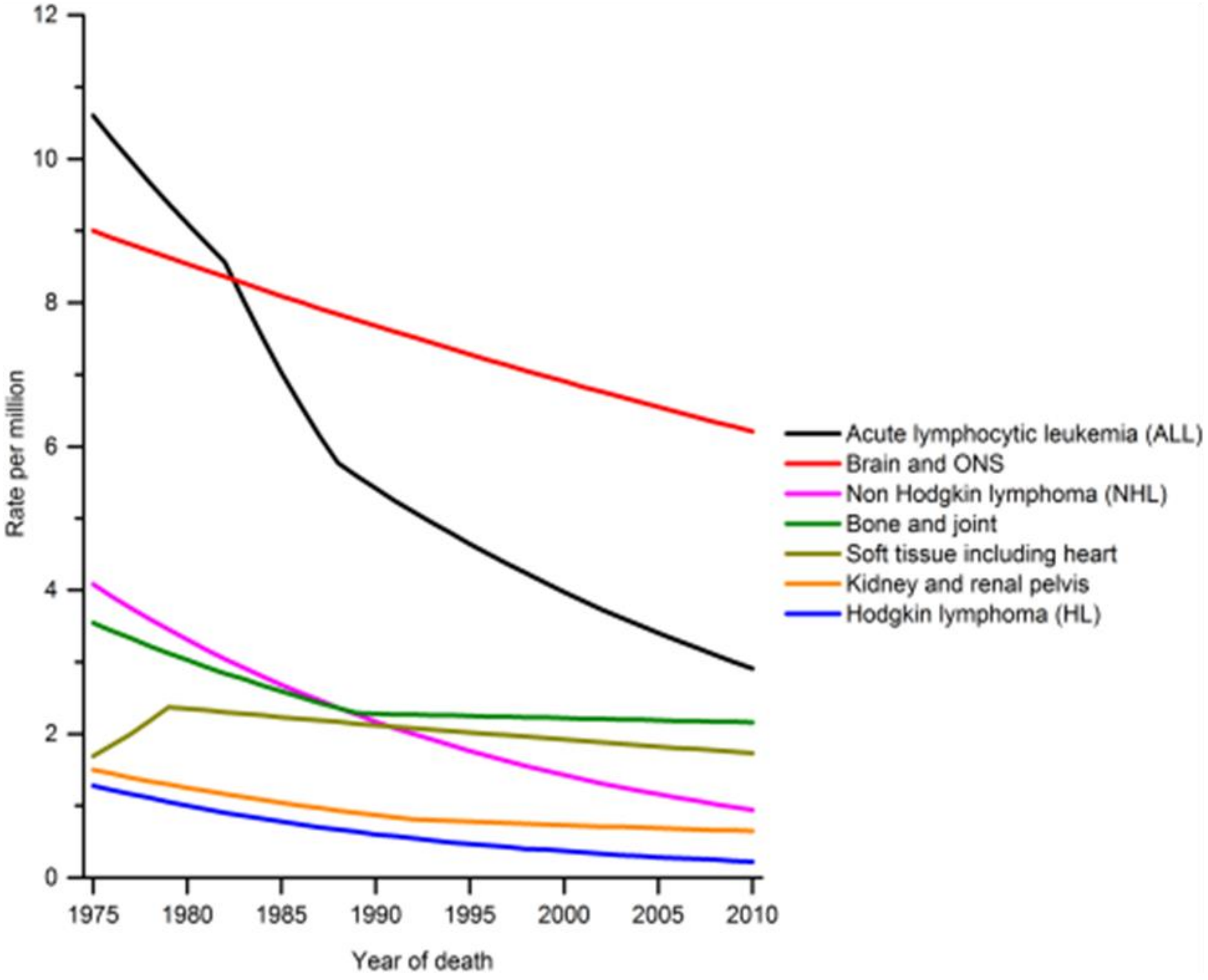
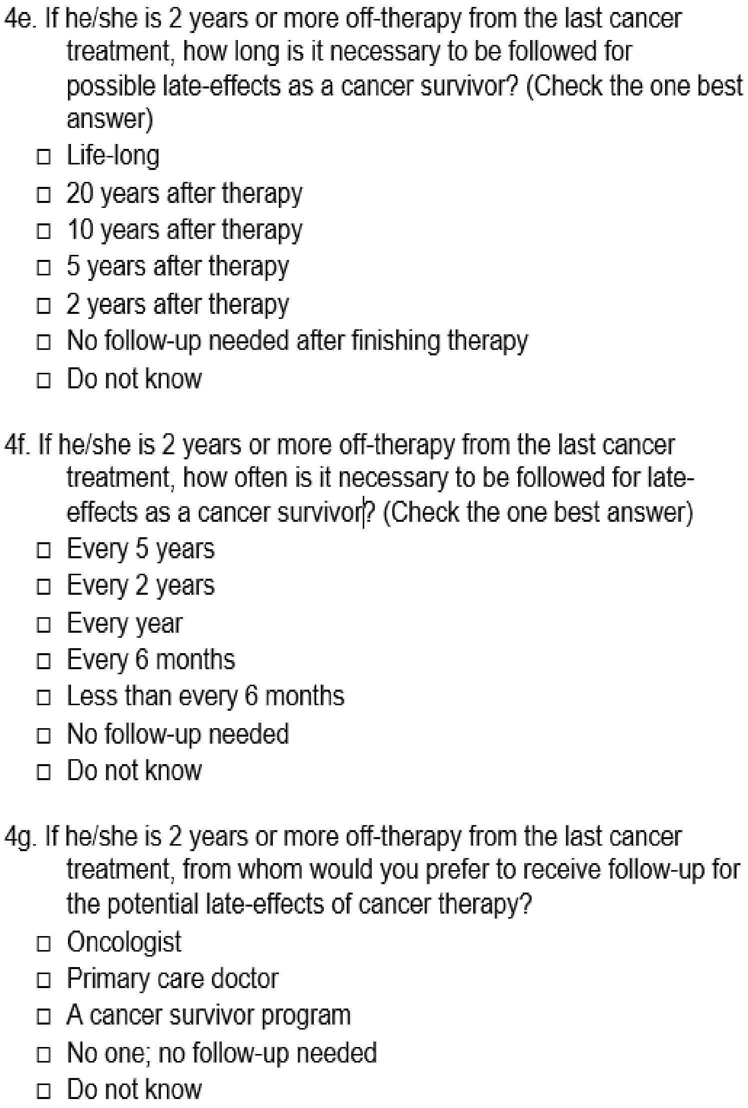


Figure 2. CAYACS Survey Questions used as Outcome Variables



4e. If he/she is 2 years or more off-therapy from the last cancer treatment, how long is it necessary to be followed for possible late-effects as a cancer survivor? (Check the one best answer)

- ☐ Life-long
- ☐ 20 years after therapy
- ☐ 10 years after therapy
- ☐ 5 years after therapy
- ☐ 2 years after therapy
- ☐ No follow-up needed after finishing therapy
- ☐ Do not know

4f. If he/she is 2 years or more off-therapy from the last cancer treatment, how often is it necessary to be followed for late-effects as a cancer survivor? (Check the one best answer)

- ☐ Every 5 years
- ☐ Every 2 years
- ☐ Every year
- ☐ Every 6 months
- ☐ Less than every 6 months
- ☐ No follow-up needed
- ☐ Do not know

4g. If he/she is 2 years or more off-therapy from the last cancer treatment, from whom would you prefer to receive follow-up for the potential late-effects of cancer therapy?

- ☐ Oncologist
- ☐ Primary care doctor
- ☐ A cancer survivor program
- ☐ No one; no follow-up needed
- ☐ Do not know

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Supplementary Appendix

Additional Tables

Table S1. Baseline CAYACS Responses Stratified by who Completed the Survey

	Survivor (n=107)		Mother (n=474)		Father (n=48)		P-value
	N	**Percent**	**N**	**Percent**	**N**	**Percent**	
Race of Survivor*							0.328
White, non-Hispanic	82	76.64	337	71.25	30	62.5	
Black, non-Hispanic	14	13.08	65	13.74	7	14.58	
Other	11	10.28	71	15.01	11	22.92	
Mothers Education Level*							0.545
Less than College Degree	46	44.66	188	40	22	45.83	
College Degree or Higher	57	55.34	282	60	26	54.17	
Fathers Education Level*							**0.030**
Less than College Degree	38	39.58	224	49.67	16	33.33	
College Degree or Higher	58	60.42	227	50.33	32	66.67	
Household Income*							0.187
Less than $40,000	14	17.28	121	27.69	8	17.78	
$40,000 to 99,999	34	41.98	176	40.27	19	42.22	
$100,000 or more	33	40.74	140	32.04	18	40	
Speak English at Home*							0.073
No	3	2.8	33	6.98	6	12.5	
Yes	104	97.2	440	93.02	42	87.5	
General Health**							**0.046**
Good, fair, or poor	25	23.58	75	15.86	4	8.33	
Very Good or Excellent	81	76.42	398	84.14	44	91.67	

Exercise Frequency*							**<0.001**
None or some days	56	53.85	107	22.96	14	30.43	
Most Days	33	31.73	148	31.76	12	26.09	
Everyday	15	14.42	211	45.28	20	43.48	
Providers Seen in Last 12 Months*							
Primary Care or Routine Check-up	80	74.77	428	90.3	35	72.92	**<0.001**
Sports or School Physical	25	23.36	135	28.48	14	29.17	0.549
Cancer Survivor Clinic	94	87.85	404	85.23	38	79.15	0.371
Routine Off-therapy with Oncologist	46	42.99	225	47.47	23	47.92	0.694
Dental Routine Check-up	87	81.31	428	90.3	41	85.42	**0.026**
Participant Experienced the Following in Past 12 Months							
Illness Requiring Doctors Visit*	51	47.66	267	56.33	26	54.14	0.266
Illness Requiring ER Visit*	26	24.3	100	21.1	5	10.42	0.138
Illness Requiring Hospitalization**	4	3.74	20	4.22	1	2.08	0.938
Illness Requiring Surgery*	14	13.08	44	9.28	5	10.42	0.494
Perceived Necessary Follow-up Care Length*							0.151
Lifelong	69	64.49	304	65.66	23	51.11	
Less than lifelong	38	35.51	159	34.34	22	48.89	
Perceived Necessary Follow-up Frequency**							**<0.001**
More frequently than annually	8	7.55	31	6.67	5	10.87	
Annually	58	54.72	378	81.29	30	65.22	
Less frequently than annually	27	25.47	16	3.44	3	6.52	
Don't know or don't need follow-up care	13	12.26	40	8.6	8	17.39	
Follow-up Care Provider Preference							
Oncologist*	42	39.25	185	39.03	17	35.42	0.882
Primary Care Provider*	12	11.21	36	7.59	4	8.33	0.470
Cancer Survivor Clinic*	73	68.22	369	77.85	29	60.42	**0.007**
No one / no follow-up needed**	1	0.93	1	0.21	1	2.08	0.087

Don’t know**	3	2.8	10	2.11	2	4.14	0.463

Note: 26 surveys were completed by adult guardians other than the survivors parents

*Chi-square test of proportions

**Fisher's exact test

Table S2. Demographic Characteristics of Eligible Subjects in the CAYACS Cohort Stratified by Perceived Length of Follow-up Care for Possible Late Effects (n=655)

	Life-long Follow-up Care (n=411)		Less than life-long Follow-up Care (n=228)		P-value
	N	Percent	N	Percent	
Age of Survivor at Survey Completion, Years*					0.610
Less than 7	43	10.46	18	7.89	
7 to 12	169	41.12	104	45.61	
13 to 17	130	31.63	69	30.26	
18 or Older	69	16.79	37	16.23	
Gender of Survivor*					0.068
Male	207	50.36	132	57.89	
Female	204	49.64	96	42.11	
Race of Survivor*					0.176
White, non-Hispanic	308	75.12	155	68.28	
Black, non-Hispanic	51	12.44	37	16.30	
Other**	51	12.44	35	15.42	
Mothers Education Level*					0.096
Less than College Degree	158	38.73	102	45.54	
College Degree or Higher	250	61.27	122	54.46	
Fathers Education Level*					0.475
Less than College Degree	179	45.55	103	48.58	
College Degree or Higher	214	54.45	109	51.42	
Household Income*					0.558
Less than $40,000	92	24.47	53	26.90	
$40,000 to 99,999	153	40.69	84	42.64	
$100,000 or more	131	34.84	60	30.46	
Speak English at Home*					0.615
No	23	5.60	15	6.58	
Yes	388	94.40	213	93.42	
General Health*					0.784
Good, fair, or poor	70	17.07	37	16.23	
Very Good or Excellent	340	82.93	191	83.77	
Insurance Status***					0.972
No	7	1.72	1	0.44	
Yes	401	98.28	226	99.56	

*Chi-square test of proportions

**Other race includes Hispanic, Asian and Pacific Islander, and American Indian/Alaska Native

***Fisher's exact test

Table S3. Demographic Characteristics of Eligible Subjects in the CAYACS Cohort Stratified by Preference of Receiving Follow-up Care from a Cancer Survivor Program or Not (n=655)

	Prefer Cancer Survivor Program (n=490)		Do Not Prefer Cancer Survivor Program (n=165)		P-value
	N	Percent	N	Percent	
Age of Survivor at Survey Completion, Years*					0.121
Less than 7	49	10.00	15	9.09	
7 to 12	219	44.69	60	36.36	
13 to 17	151	30.82	55	33.33	
18 or Older	71	14.49	35	21.21	
Gender of Survivor*					0.844
Male	257	52.45	88	53.33	
Female	233	47.55	77	46.67	
Race of Survivor*					0.156
White, non-Hispanic	360	73.62	108	65.85	
Black, non-Hispanic	62	12.68	28	17.07	
Other**	67	13.70	28	17.07	
Mothers Education Level*					**0.011**
Less than College Degree	190	39.18	82	50.62	
College Degree or Higher	295	60.82	80	49.38	
Fathers Education Level*					0.977
Less than College Degree	219	47.30	74	47.44	
College Degree or Higher	244	52.70	82	52.56	
Household Income*					**0.007**
Less than $40,000	106	23.71	51	36.43	
$40,000 to 99,999	183	40.94	54	38.57	
$100,000 or more	158	35.35	35	25.00	
Speak English at Home*					0.078
No	28	5.73	16	9.70	
Yes	461	94.27	149	90.30	
General Health*					0.725
Good, fair, or poor	84	17.14	26	15.95	
Very Good or Excellent	406	82.86	137	84.05	
Insurance Status***					0.990
No	6	1.23	2	1.22	
Yes	481	98.77	162	98.78	

*Chi-square test of proportions

**Other race includes Hispanic, Asian and Pacific Islander, and American Indian/Alaska Native

***Fisher's exact test

Table S3. Demographic Characteristics of Eligible Subjects in the CAYACS Cohort Stratified by Perceived Length of Follow-up Care for Possible Late Effects (n=655)

	Life-long Follow-up Care (n=411)		Less than life-long Follow-up Care (n=228)		P-value
	N	Percent	N	Percent	
Age at Diagnosis, Years*					0.358
Less than 5 Years	256	62.29	129	56.58	
5 to 9 Years	90	21.90	56	24.56	
10 Years or Older	65	15.85	43	18.86	
Diagnosis*					0.652
Leukemia	194	47.20	104	45.61	
Lymphoma	43	10.46	32	14.04	
Renal Tumor	52	12.65	26	11.40	
Sarcoma	56	13.63	27	11.84	
Neuroblastoma	42	10.22	21	9.21	
Other**	24	5.84	18	7.89	
Providers Seen in Last 12 Months*					
Primary Care or Routine Check-up	361	87.83	193	84.65	0.256
Sports or School Physical	119	28.95	55	24.12	0.189
Cancer Survivor Clinic	358	87.10	189	82.89	0.147
Routine Off-therapy with Oncologist	196	47.69	107	46.93	0.854
Dental Routine Check-up	367	89.29	197	86.40	0.277
Experienced the Following in Past 12 Months*					
Illness Requiring Doctors Visit	244	59.37	112	49.12	**0.013**
Illness Requiring ER Visit	88	21.41	48	21.05	0.916
Illness Requiring Hospitalization	21	5.11	6	2.63	0.136
Illness Requiring Surgery	47	11.44	20	8.77	0.292
Time off Therapy, Years*					**0.022**
Less than 5 Years	199	48.42	119	52.19	
5 to 9 Years	137	33.33	86	37.72	
10 Years or Older	75	18.25	23	10.09	
Radiation Exposure*					**0.009**
No	263	63.99	169	74.12	
Yes	148	36.01	59	25.88	
Chemotherapy Exposure*					0.262
No	5	1.22	5	2.19	
Yes	406	98.78	223	97.81	
Cumulative Alkylator Dose, mg/m^{2*}					0.514
None	94	25.20	52	25.00	
<7500	191	51.21	115	55.29	
≥7500	88	23.59	41	19.71	

Cumulative Anthracycline Dose, mg/m^{2*}					0.739
None	39	10.37	24	11.94	
<250	246	65.43	133	66.17	
≥250	91	24.20	44	21.89	
Heavy Metal Exposure* **					0.586
No	310	78.88	172	80.75	
Yes	83	21.12	11	19.25	
Hematopoietic Stem Cell Transplant*					0.073
No	351	85.40	206	90.35	
Yes	60	14.60	22	9.65	

*Chi-square test of proportions

**Other cancer diagnoses include Carcinomas, Germ Cell Tumors, Liver Tumors, and Retinoblastomas

***Defined as exposure to either carboplatin or cisplatin

Table S4. Demographic Characteristics of Eligible Subjects in the CAYACS Cohort Stratified by Preference of Receiving Follow-up Care from a Cancer Survivor Program or Not (n=655)

	Prefer Cancer Survivor Program (n=490)		Do Not Prefer Cancer Survivor Program (n=165)		P-value
	N	Percent	N	Percent	
Age at Diagnosis, Years*					0.429
Less than 5 Years	304	62.04	93	56.36	
5 to 9 Years	108	22.04	41	24.85	
10 Years or Older	78	15.92	31	18.79	
Diagnosis*					0.660
Leukemia	230	44.94	73	44.24	
Lymphoma	58	11.84	18	10.91	
Renal Tumor	60	12.24	21	12.73	
Sarcoma	65	13.27	21	12.73	
Neuroblastoma	49	10.00	16	9.70	
Other**	28	5.57	16	9.70	
Providers Seen in Last 12 Months*					
Primary Care or Routine Check-up	428	87.35	138	83.64	0.229
Sports or School Physical	132	26.94	49	29.70	0.493
Cancer Survivor Clinic	423	86.33	136	82.42	0.220
Routine Off-therapy with Oncologist	220	44.90	87	52.73	0.081
Dental Routine Check-up	434	88.57	145	87.88	0.810
Experienced the Following in Past 12 Months*					
Illness Requiring Doctors Visit	279	56.94	81	49.09	0.080
Illness Requiring ER Visit	98	20.00	38	23.03	0.407
Illness Requiring Hospitalization	22	4.49	5	3.03	0.415
Illness Requiring Surgery	50	10.20	18	10.91	0.797
Time off Therapy, Years*					0.507
Less than 5 Years	246	50.20	81	49.09	
5 to 9 Years	173	35.31	54	32.73	
10 Years or Older	71	14.49	30	18.18	
Radiation Exposure*					0.057
No	320	65.31	121	73.33	
Yes	170	34.69	44	26.67	
Chemotherapy Exposure*					0.921
No	6	1.22	4	2.42	
Yes	484	98.78	161	97.57	
Cumulative Alkylator Dose, mg/m^{2*}					0.116
None	104	23.21	47	31.76	
<7500	241	53.79	70	47.30	

≥7500	103	22.99	31	20.95	
Cumulative Anthracycline Dose, mg/m^{2*}					0.406
None	52	11.58	12	8.39	
<250	296	65.92	93	65.03	
≥250	101	22.49	38	26.57	
Heavy Metal Exposure* **					0.110
No	380	81.02	114	75.00	
Yes	89	18.98	38	25.00	
Hematopoietic Stem Cell Transplant*					0.165
No	149	86.12	16	9.70	
Yes	422	68.00	68	13.88	

*Chi-square test of proportions

**Other cancer diagnoses include Carcinomas, Germ Cell Tumors, Liver Tumors, and Retinoblastomas

***Defined as exposure to either carboplatin or cisplatin