Childhood Cancer Survivor Study - Analysis Concept Proposal for Consideration as a High Priority Analysis from the Epidemiology/Biostatistics Working Group

Title: Characteristics of the Expanded Childhood Cancer Survivor Study Cohort: 5-Year Survivors Diagnosed from 1970-1999

Working Group & Investigators: Epidemiology and Biostatistics Working Group

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Background & Rationale:

Numerous reports and reviews have been published on the late effects of cancer and its treatment among childhood cancer survivors [1-3]. This literature describes outcomes occurring across the spectrum of survivorship, ranging from events present at or shortly following the end of therapy to very long-term events in aging survivors. Most studies of late sequelae focus on medical outcomes, although psychosocial and economic outcomes are also being evaluated among adult survivors of childhood cancer. These studies have shown that type and intensity of therapy, demographics such as age at diagnosis/treatment and sex all contribute to survival and risk of late effects. Well-designed epidemiologic investigations of pediatric cancer survivors are providing a strong research-base on which clinical practice guidelines and future clinical trials are being proposed.

With the expansion of the Childhood Cancer Survivor Study (CCSS) to include a more recent cohort of pediatric cancer survivors, it will be important to characterize this cohort. The original CCSS cohort has been well described. As we begin to examine outcomes in the expanded cohort, it will be important to fully describe the socio-demographic characteristics of the expansion cohort and to identify any similarities/differences between the eligible (where possible) as well as the participating members of the two cohorts. In addition, treatment factors in the original CCSS cohort have been well described. Identical medical record abstraction in the expanded cohort will allow treatment factors to be similarly well described in the expansion cohort, so it will be important to fully characterize these treatments, noting similarities/ differences between the two cohorts and across eras encompassed by the fully combined original and expansion cohorts.

Study participants for the expanded cohort met the following criteria: a) diagnosis of leukemia, central nervous system (CNS) tumors (all histologies), Hodgkin lymphoma, non-Hodgkin lymphoma, kidney tumor, neuroblastoma, soft tissue sarcoma, or bone tumor with survivors of acute lymphoblastic leukemia (ALL) who were <1 and >10 years of age sampled at a 3:1 ratio in relation to those ages 1-10; b) diagnosis and initial treatment at one of the collaborating CCSS institutions; c) diagnosis date between January 1, 1987 and December 31, 1999; d) age less than 21 years at diagnosis; e) survival five or more years from diagnosis.

Specific Aims and Hypotheses:

This proposed analysis will look at demographic and socioeconomic information to fully characterize the entire CCSS cohort (1970-99), with a focus on determining the differences and similarities between the initial (1970-1986) and expanded (1987-1999) cohorts. We propose the following objectives:

- **Objective 1**: Summarize the patient characteristics and treatment exposures of the overall eligible CCSS cohort (1970-99) and compare characteristics of participants and non-participants.
- **Objective 2:** Compare characteristics of participants in the initial and expanded cohorts, including detailed summary of geographical distribution of expansion cohort members' residences.
- **Objective 3**: Describe temporal patterns in treatment-related exposures by cancer diagnosis.
- **Objective 4:** Develop methods/strategies that will take into account identified differences between cohorts, for use in subsequent CCSS analyses which utilize data from both cohorts.

Analysis Framework:

a) Population of interest: All patients eligible to participate in the two CCSS cohorts (original: diagnosed 1970-1986; expanded: diagnosed 1987-1999; total = 35,990).

B) Outcome Measures: overall participation rates (agree, decline, LTFU), primary cancer diagnosis, age at diagnosis, HIPAA consent, treatment factors (specific chemotherapy (anthracyclines, alkylating agents, epipodophyllotoxins, bleomycin, platinum), specific radiation sites (brain, chest, gonads), specific surgeries (amputations, solid organ transplant), demographic factors (alive/dead status at time of recruitment into cohort , age, gender, race/ethnicity), psychosocial factors (insurance, marriage, education, employment, residential status, income)

C) Explanatory Variables: participant vs. non-participant, original cohort vs. expanded cohort, 5-year year of diagnosis intervals across both eras.

D) Statistical approach: A descriptive analysis, summarizing the characteristics of the expansion cohort in detail and comparing the original and expansion cohorts, will be performed, looking at the demographic, cancer related and treatment characteristics mentioned above. In addition to specific comparisons between cohorts, to elucidate differences, characterizations of key changes in treatment over time intervals spanning the full cohort will be carried out.

Primarily, statistical analyses will be descriptive. Comparisons will be carried out using standard statistical methods, both univariate comparisons of mean values for continuous outcomes and comparisons of proportions for binary events. Similarly, appropriate regression analyses (linear

and logistic) to evaluate adjusted comparisons may be carried out as differences are characterized and needed adjustment factors identified. Stratification by original cancer diagnosis will be applied and sampling weights reflecting that ALL survivors who were aged <1 and >10 were oversampled will be utilized in all analyses (sampling weights for ALL: 0.275 for diagnosis ages 1-10 and 0.826 for ages <1 and >10; weights are 1.0 for all other subjects).

Geographical distribution of participants and non-participants will be mapped to illustrate representativeness of participating subjects as will summaries of participation rates by census tract.

With regard to Aim 4, our goal will be to assist future CCSS proposals/analyses that intend to evaluate late effects in the presence of the differences we observe in Aims 1, 2 and 3. Specifically, the differences in study design and response rates, in addition to the treatment differences identified in Aims 1, 2 and 3, should be accounted for in the combined-cohort analysis. We aim to make methodological recommendations regarding which differences may be best accounted for via statistical adjustment, or other methods. Note that the impact of some changes on outcomes, such as treatment differences, will constitute the comparison groups for many key analyses within CCSS over the coming years: thus, the recommendations will consider scenarios where the treatment differences are the main variable interest and where the treatment exposures are to be adjusted for in assessing effects of main variable(s) of interest.

Tables:

Table 1. Demographic and Cancer Characteristics of Eligible Study Subjects in the Expansion Cohort by Participation Status as of 9/30/2014

Characteristic		Eligible* N (%)	Participants** N (%)	Non-Participants N (%)	Non-Participants		
					Active Refusal N (%)	Passive Refusal N (%)	Lost To Follow-up N (%)
Total Population							
Sex	Male						
	Female						
Race/Ethn	White						
	Black						
	Hispanic						
	Asian/PI						
	Other						
Diagnosis	ALL						
	AML						
	Other leukemia/NOS						
	Astrocytomas						
	Medullo/PNET						
	Other CNS						
	Hodgkin's						
	NHL						
	Kidney tumors						
	Neuroblastoma						
	Soft tissue sarcoma						
	Ewing's sarcoma						

	Osteosarcoma						
	Other bone						
Age at diagnosis	<1						
	1-3						
	4-7						
	8-10						
	11-14						
	15-20						
Status at Date TBD	Alive						
	Dead						
Age at Date TBD	<20						
	20-29						
	30-39						
	40-49						
	50-59						
	60+						
Treatment Modality	Surgery Only (S)						
	Chemo only (C)						
	Radiation only (R)						
	C + R						
	C + S						
	R + S						
	C + R + S						

*Eligible:Five-year cancer survivors diagnosed between 1987 and 1999 at ages 0-20 with Leukemia, CNS tumor, Hodgkin Lymphoma, Non-Hodgkin Lymphoma, Wilms tumor, Neuroblastoma, Soft Tissue Sarcoma or Bone Cancer at one of the CCSS institutions. Note: for this table, eligible subject lists are not currently available from UCSF and Dana Farber so they are excluded from both eligible and participant columns for the purposes of this table, though they contribute XXXX and XXXX participants, respectively.

**Participant: An eligible subject who completed HIPAA and for whom a baseline questionnaire was received.

Table 2. Demographic and Cancer Characteristics of Eligible Study Subjects in the Overall Cohort By Participation Status as of (Freeze Date)

Characteristic		Eligible N (%)	Participants N (%)	Non-Participants N (%)	Non-Participants		
					Active Refusal N (%)	Passive Refusal N (%)	Lost To Follow-up N (%)
Total Population							
Sex	Male						
	Female						
Diagnosis	ALL						
	AML						
	Other leukemia/NOS						
	Astrocytomas						
	Medullo/PNET						
	Other CNS						
	Hodgkin's						
	NHL						
	Kidney tumors						
	Neuroblastoma						
	Soft tissue sarcoma						
	Ewing's sarcoma						
	Osteosarcoma						
	Other bone						
Age at diagnosis	<1						
	1-3						
	4-7						

	8-10						
	11-14						
	15-20						
Date at diagnosis	1970-79						
	1980-89						
	1990-99						
Status at Date TBD	Alive						
	Dead						
Age at Date TBD	<20						
	20-29						
	30-39						
	40-49						
	50-59						
	60+						
Treatment Modality	Surgery Only (S)						
	Chemo only (C)						
	Radiation only (R)						
	C + R						
	C + S						
	R + S						
	C + R + S						

*Eligible: Five-year cancer survivors diagnosed between 1970 and 1999 at ages 0-20 with Leukemia, CNS tumor, Hodgkin Lymphoma, Non-Hodgkin Lymphoma, Wilms tumor, Neuroblastoma, Soft Tissue Sarcoma or Bone Cancer at a CCSS institutions.

**Participant: An eligible subject for whom we received a baseline questionnaire.

Table 3. Demographic and Cancer Characteristics of Participants in the Expansion, Original and Overall Cohorts

Characteristic		*Expansion Cohort N (%)*	*Original Cohort N (%)*	*Overall Cohort N (%)*
Total population				
Sex	Male			
	Female			
Race	White			
	Black			
	Hispanic			
	Asian/Pacific Islander			
	Other/Unknown			
Diagnosis	Acute lymphoblastic leukemia			
	Acute myeloid leukemia			
	Other leukemia			
	Astrocytomas			
	Medulloblastoma, PNET			
	Other CNS tumors			
	Hodgkin lymphoma			
	Non-Hodgkin lymphoma			
	Wilms tumor			
	Neuroblastoma			

	Rhabdomyosarcoma			
	Other soft tissue sarcoma			
	Ewing sarcoma			
	Osteosarcoma			
	Other bone tumors			
Age at Diagnosis	<1			
	1-3			
	4-7			
	8-10			
	11-14			
	15-20			
Status at 06/01/14	Alive			
(date TBD)	Deceased			
Age at Baseline Survey	<20			
	20-29			
	30-39			
	40+			
Year at Diagnosis	1970-79			
	1980-89			
	1990-99			
Treatment modality	Surgery only (S)			

	Chemotherapy only (C)			
	Radiation only (R)			
	C + R			
	C + S			
	R + S			
	C + R + S			

Table 4. Exposure to Specific Treatment Agents During First 5 Years After Primary Cancer by Cancer Diagnosis among Participants in the Expansion Cohort With Complete Abstraction of Medical Records (N=xxx)

Agent	*Participants N (%)*	*Leukemia N (%)*	*CNS N (%)*	*HD N (%)*	*NHL N (%)*	*Kidney N (%)*	*Neuro blastoma N (%)*	*Soft tissue sarcoma N (%)*	*Bone cancer N (%)*
All cases									
Radiation Therapy									
Any Radiation (yes/no)									
Max Dose to Head (not brain)									
≥50 Gy ≥30-50 Gy 1-30 Gy									
Whole Brain									
≥30 Gy ≥20 Gy to 30 Gy 1-≥20 Gy None									
Max Dose to Brain ≥50 Gy ≥30-50 Gy 1-30 Gy Craniospinal ≥30 Gy ≥20 Gy to 30 Gy 1-≥20 Gy None									

Neck (Yes/No)									
Chest ≥30 Gy ≥20 Gy -30 Gy 1-20 Gy None Abdomen (yes/no)									
Pelvis (yes/no)									
Limb (yes/no)									
TBI (yes/no)									
Chemotherapeutic Exposures									
Alkylating agents (cyclophosphamide equivalent dose, mg/m^2)									
None									
0 - <4,000									
≥4000-<8000									
≥8000-12,000									
≥12,000-<16,000									
≥16,000-<20,000									
≥20,000									
Anthracycline cumulative dose (mg/m^2)									
None									
0-100									

101-250									
251-400									
>400									
Specific Agents									
5-Azacytadine									
ARA-G									
Bleomycin									
Busulfan									
Carboplatin									
Carmustine (BCNU)									
Chlorambucil									
Cisplatin									
Cyclophosphamide-All									
Cyclophosphamide-IV/IM									
Cyclophosphamide-PO									
Cytarabine									
Dacarbazine (DTIC)									
Dactinomycin									
Daunorubicin									
Dexamethasone									
Doxil									
Doxorubicin									
Epirubicin									
Etoposide (VP-16)-All Routes									
Etoposide (VP-16)-IV/IM									
Etoposide (VP-16)-PO									
Fludarabine phosphate									
Fluorouracil (5-FU)									
Gemcitabine									
Gemtuzimab (Mylotarg)									

Gleevec									
Hydroxyurea									
Idarubicin									
Ifosfamide									
Irinotecan									
L-Asparaginase									
Lomustine (CCNU)									
Mechlorethamine (N.									
Melphalan-All Routes									
Melphalan-IV/IM									
Melphalan-PO									
Mercaptopurine (6-MP)									
Methotrexate-All Routes									
Methotrexate-IM									
Methotrexate-IT/Ommaya									
Methotrexate-IV									
Methotrexate-PO									
Mitoxantrone									
Prednisone									
Procarbazine									
Taxol									
Taxotere									
Temozolomide									
Teniposide (VM-26)									
Thioguanine (6-TG)									
Thiotepa-All Routes									
Thiotepa-IT									
Thiotepa-IV/IM									
Topotecan									
Vinblastine									
Vincristine									

Vinorelbine									
ATG									
Alemtuzumab (Campath)									
Cyclosporine (CSA)									
Mycophenolate (CellCept)									
Rituximab (Rituxan)									
Sirolimus									
Tacrolimus									
Erythropoietin (EPO)									
GCSF									
GMCSF									
Interferon									
Interleukin-2									
Mesna									
Retinoic Acid									
Zinecard (Dexrazoxane)									

*This format is one possibility and shows the information we want to display, but we are also considering a different format in which the numbers for the 3 cohorts (expansion, overall, original) would be displayed in adjacent columns for easy comparison. For example, there would be three columns for “Participants”, three columns for “Leukemia”, three columns for “CNS”, etc.

Table 5. Exposure to Specific Treatment Agents by Cancer Diagnosis among the Overall Cohort Participants With Complete Abstraction of Medical Records (N=xxx)

Agent	*Participants N (%)*	*Leukemia N (%)*	*CNS N (%)*	*HD N (%)*	*NHL N (%)*	*Kidney N (%)*	*Neuro blastoma N (%)*	*Soft tissue sarcoma N (%)*	*Bone cancer N (%)*
Agent	*Participants N (%)*	*Leukemia N (%)*	*CNS N (%)*	*HD N (%)*	*NHL N (%)*	*Kidney N (%)*	*Neuro blastoma N (%)*	*Soft tissue sarcoma N (%)*	*Bone cancer N (%)*
All cases									
Radiation Therapy									
Any Radiation (yes/no)									
Max Dose to Head (not brain)									
≥50 Gy ≥30-50 Gy 1-30 Gy									
Whole Brain									
≥30 Gy ≥20 Gy to 30 Gy 1-≥20 Gy None									
Max Dose to Brain ≥50 Gy ≥30-50 Gy 1-30 Gy									

Craniospinal ≥30 Gy ≥20 Gy to 30 Gy 1-≥20 Gy None Neck (Yes/No)									
 Chest ≥30 Gy ≥20 Gy -30 Gy 1-20 Gy None Abdomen (yes/no)									
Pelvis (yes/no)									
Limb (yes/no)									
TBI (yes/no)									
Chemotherapeutic Exposures									
Alkylating agents (cyclophosphamide equivalent dose, mg/m^2)									
None									
0 - <4,000									
≥4000-<8000									
≥8000-12,000									
≥12,000-<16,000									
≥16,000-<20,000									

≥20,000									
Anthracycline cumulative dose (mg/m^2)									
None									
0-100									
101-250									
251-400									
>400									
Chemotherapeutic Agents									
Alkylating agents (cyclophosphamide equivalent dose, mg/m^2)									
None									
0 - <4,000									
≥4000-<8000									
≥8000-12,000									
≥12,000-<16,000									
≥16,000-<20,000									
≥20,000									
Anthracycline cumulative dose (mg/m^2)									
None									
0-100									
101-250									
251-400									
>400									

5-Azacytadine									
ARA-G									
Bleomycin									
Busulfan									
Carboplatin									
Carmustine (BCNU)									
Chlorambucil									
Cisplatin									
Cyclophosphamide-All Routes									
Cyclophosphamide-IV/IM									
Cyclophosphamide-PO									
Cytarabine									
Dacarbazine (DTIC)									
Dactinomycin									
Daunorubicin									
Dexamethasone									
Doxil									
Doxorubicin									
Epirubicin									
Etoposide (VP-16)-All Routes									
Etoposide (VP-16)-IV/IM									
Etoposide (VP-16)-PO									
Fludarabine phosphate									
Fluorouracil (5-FU)									
Gemcitabine									
Gemtuzimab (Mylotarg)									
Gleevec									
Hydroxyurea									
Idarubicin									
Ifosfamide									

Irinotecan									
L-Asparaginase									
Lomustine (CCNU)									
Mechlorethamine (N. Mustard)									
Melphalan-All Routes									
Melphalan-IV/IM									
Melphalan-PO									
Mercaptopurine (6-MP)									
Methotrexate-All Routes									
Methotrexate-IM									
Methotrexate-IT/Ommaya									
Methotrexate-IV									
Methotrexate-PO									
Mitoxantrone									
Prednisone									
Procarbazine									
Taxol									
Taxotere									
Temozolomide									
Teniposide (VM-26)									
Thioguanine (6-TG)									
Thiotepa-All Routes									
Thiotepa-IT									
Thiotepa-IV/IM									
Topotecan									
Vinblastine									
Vincristine									
Vinorelbine									
ATG									

Alemtuzumab (Campath)									
Cyclosporine (CSA)									
Mycophenolate (CellCept)									
Rituximab (Rituxan)									
Sirolimus									
Tacrolimus									
Erythropoietin (EPO)									
GCSF									
GMCSF									
Interferon									
Interleukin-2									
Mesna									
Retinoic Acid									
Zinecard (Dexrazoxane)									

Optional
Exposure to Specific Treatment Agents by Cancer Diagnosis among the Original Cohort Participants With Complete Abstraction of Medical Records (N=xxx)

- Replicate above tables for the Original Cohort

Table 6. Comparison of cancer and treatment factors by diagnosis year time intervals *

	1970-1974	1975-1979	1980-1984	1985-1989	1990-1994	1995-1999
Signed HIPAA/medical release						
Yes						
no						
Diagnosis						
Acute lymphoblastic leukemia						
Acute myeloid leukemia						
Other leukemia						
Hodgkin lymphoma						
Non-Hodgkin lymphoma						
Medulloblastoma						
Ependymoma						
Glioma						
Other CNS						
Kidney tumors						
Neuroblastoma						
Soft tissue sarcoma						
Ewing sarcoma						
Osteosarcoma						
Other bone tumors						
Age at Diagnosis						
0-4						
5-9						
10-14						
15-21						
Any Radiation (yes/no)						
Max Dose to Head (not brain)						
≥50 Gy ≥30-50 Gy 1-30 Gy						

Whole Brain						
≥30 Gy ≥20 Gy to 30 Gy 1-≥20 Gy None						
Max Dose to Brain ≥50 Gy ≥30-50 Gy 1-30 Gy Craniospinal ≥30 Gy ≥20 Gy to 30 Gy 1-≥20 Gy None Neck (Yes/No)						
 Chest ≥30 Gy ≥20 Gy -30 Gy 1-20 Gy None Abdomen (yes/no)						
Pelvis (yes/no)						
Limb (yes/no)						
TBI (yes/no)						
Any chemotherapy						
Yes						
No						
Alkylating agent (CPM equivalents, mg/m^2)						
None						
0 - <4,000						
≥4000-<8000						
≥8000-12,000						

≥12,000-<16,000						
≥16,000-<20,000						
≥20,000						
Anthracycline (mg/m^2)						
None						
0-100						
101-250						
251-400						
>400						
Epipodophyllotoxin(mg/m^2)						
Yes						
No						
Bleomycin						
Yes						
No						
Platinum						
Yes						
No						
Amputation						
Yes						
No						
Bone Marrow transplant						
Yes						
No						

***** Note: we will also look at treatment by era within each primary diagnosis group, to determine if there are changes over time of interest for particular diagnoses (extra tables by diagnosis not shown).

Figure: Map illustrating geographical distribution of participants / non-participants for full cohort.

References:

1. Robison LL, Mertens AC, Boice JD, Breslow NE, Donaldson SE, Green DM, Li FP, Meadows AT, Mulvihill JJ, Neglia JP, Nesbit NE, Packer RJ, Potter JD, Sklar CA, Smith MA, Stovall M, Strong LC, Yasui Y, Zeltzer LK. Study design and cohort characteristics of the childhood cancer survivor study: a multi-institutional collaborative project. Med Pediatr Oncol 38:229–239, 2002.

2. Robison LL, Armstrong GT, Boice JD, Chow EJ, Davies SM, Donaldson SS, Green DM, Hammond S, Meadows AT, Mertens AC, Mulvihill JJ, Nathan PC, Neglia JP, Packer RJ, Rajaraman P, Sklar CA, Stovall M, Strong LC, Yasui Y, Zeltzer LK. The Childhood Cancer Survivor Study: a National Cancer Institute-supported resource for outcome and intervention research. J Clin Oncol. 27(14):2308-18, 2009.

3. Leisenring WM, Mertens AC, Armstrong GT, Stovall MA, Neglia JP, Lanctot JQ, Boice JD Jr, Whitton JA, Yasui Y. Pediatric cancer survivorship research: experience of the Childhood Cancer Survivor Study. J Clin Oncol. 27(14):2319-27, 2009.