02-09

CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal
REVISED October 10, 2002

1. **STUDY TITLE:** Prevalence and severity of physical late effects in adult survivors of childhood cancer.

2. **WORKING GROUP AND INVESTIGATORS:** This proposed publication will be within the Chronic Disease Working Group. Proposed Investigators will include:

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3. **BACKGROUND AND RATIONALE:**

It is well recognized that survivors of childhood cancer may experience a variety of different late effects secondary to their previous chemotherapy, with problems ranging from relatively benign conditions, such as radiation-induced alopecia to life-threatening diseases such as a second malignancy. Most studies to date have focused either on a single cancer group or have been conducted in single institutions with small sample sizes, thus limiting estimates regarding the prevalence and severity of different late effects. In five single institution studies reporting about 704 childhood cancer survivors with a median age ranging from 15 – 23 years, 58 to 69% had at least one late effect of therapy, with 25 to 30% experiencing a moderate to severe late complication.[1-5]

A descriptive analysis of the CCSS cohort would provide a much needed improvement on these estimates. Further, the format of the CCSS questionnaire provides a method to grade the severity of many of the physical late effects. Because of the large sample size available, analysis of important modifying factors, such as age, gender, race/ethnicity, age at diagnosis, and cancer- and treatment-related variables, can be assessed.

The purpose of this descriptive study is to estimate the extent of morbidity associated with cancer treatment in a representative population of long-term survivors of childhood cancer. The

intent is to provide an overall picture of the population and then to look at higher risk populations (based on cancer group, exposure, or sociodemographics) in subsequent analyses.

This descriptive study will focus on physical late effects reported by survivors who were 18 years or older at the time of interview. Physical late effects are defined as either a chronic disease or an outcome of the cancer or treatment with a potential for a more serious disability that occurs or persists five or more years from the cancer diagnosis.

In determining and reporting these the findings, the working group recognizes the importance of (a) limitations of an estimate based on self-report of health problems by a lay population, (b) avoiding over estimating the prevalence by double counting similar or overlapping problems, (c) avoiding overestimating the severity of the late effects, (d) assessing the significant influence of age and time from diagnosis.

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

Specific Aims:

To determine the prevalence of long-term survivors of childhood cancer who report single, multiple, and severe/life threatening physical late effects;

To identify factors that modify the prevalence and/or severity of physical late effects;

To determine the odds for these outcomes in comparison with sibling controls;

5. ANALYSIS FRAMEWORK:

The prevalence of physical late effects, listed in Tables 1 and 2, will be determined. This list is not an 'all-inclusive' list of potential physical late effects that survivors may report, but covers the primary physical late effects seen in follow-up. It is recognized that these outcomes are based on self-report by a lay population. There are a variety of methods to 'cross-check' many of the outcomes. Algorithms are briefly described in the notes following Table 1. To assist the statistical analysis, the working group will develop and test these algorithms to ensure the highest level of accuracy possible.

Simply reporting the prevalence of physical late effects does not give much depth to the picture of the health of the population. Grading the physical late effects by some reproducible and accepted method will provide more information. There is not perfect scoring system. The NCI/CTEP is currently revising the Common Toxicity Criteria (CTC) to include late effects. Late effects are scored with a grade ranging from 1-4: mild, moderate, severe, life-threatening or disabling. The greatest point of separation is between grades 1/2 and grades 3/4.

1 = mild
2 = moderate
3 = severe
4 = life threatening or disabling problem

Though this set of criteria is evolving and can be subjective, it represents the best option for scoring late effects. Cindy Schwartz, the chair of the COG committee that is making recommendations to CTEP/NCI for CTCv3, is a member of this working group. Also, a number of the members of the COG committee are on this working group and are familiar with the strengths, limitations, and process of the CTC. Recognizing these limitations, the working group feels that it is better to include an estimate of severity rather than reporting only prevalence.

The severity of the physical late effects, listed in Tables 1 and 2, will be scored according to the criteria of the most recent draft of CTCv3. Where available, medications and/or associated surgical procedures will be used in the algorithms to refine the scoring. When this information is unavailable and a severity score cannot accurately be assigned, the item will be given a score of 1 so that it is counted in the overall prevalence while avoiding overestimating the severity.

To avoid 'double counting' some of the overlapping conditions, algorithms will be developed and tested. The highest severity score for the groupings will be used. Groupings will include:

1. Cataracts or cataract surgery
2. Dialysis or kidney transplant
3. Thyroid nodules or removal of thyroid gland
4. Coronary heart disease, angina, heart attack or CABG/angioplasty
5. Congestive heart failure or heart transplant
6. Chronic cough or lung fibrosis or emphysema or currently using oxygen
7. Hepatitis or cirrhosis
8. Amputation or walking with a limp

Table 1 includes similar or overlapping conditions on a single row.

Age and time from diagnosis/treatment may be very important confounders in the analysis. Initially, the analysis will be stratified by age categories (by 5 yr increments). Depending upon the confounding of age, these groups may be collapsed into larger periods of time or regressions simply adjusted for age. We will assess the time interval from diagnosis with the same approach.

The following independent variables will be used to assess modification of prevalence and severity of chronic diseases:

1. Age, gender, race/ethnicity
2. Sociodemographics (income, education level, health insurance)
3. Cancer-related variables (cancer group/type, age at diagnosis, interval from diagnosis to study)
4. Treatment-related variables:
    a. surgery – site
    b. radiation – site (possibly dose; dosimetry not necessary)
    c. chemotherapy – agents (will group alkylating agents together, will group anthracyclines together and use cumulative dose)

As noted above, the goal is to determine the proportion of the survivor population with single, multiple, or severe physical late effect. The number and severity of physical late effects will be calculated for the individual survivor. For example a female Hodgkin's survivor may report (a) hypothyroidism and be on Synthroid (score 2), (b) cardiomyopathy and be on lisinopril (score 3), and have ovarian failure (score 3). This survivor would have 3 physical late effects, one with a score of 2 and two with a score of 3. These scores are NOT added together, but treated as individual outcomes.

In the multivariate analysis assessing factors associated with having a single, multiple, or severe physical late effects, logistic regression will be used with the dichotomous outcome of yes/no (for each of the respective groups). Thus, in assessing factors associated with severe to life-threatening physical late effects, all survivors would fall in to one of two groups: presence or absence of a score 3 or 4 physical late effect.

Analysis will be performed at the Fred Hutchinson Cancer Research Center; the Working Group will assist in the development and testing of algorithms to cross-check items and to avoid double counting.

6. REFERENCES

1. Garre ML, Gandus S, Cesana B, Haupt R, De Bernardi B, Comelli A et al. Health status of long-term survivors after cancer in childhood. Results of an uniinstitutional study in Italy. Am J Pediatr Hematol Oncol 1994; 16(2):143-152.
2. Vonderweid N, Beck D, Caflisch U, Feldges A, Wyss M, Wagner HP. Standardized assessment of late effects in long-term survivors of childhood cancer in Switzerland: Results of a Swiss Pediatric Oncology Group (SPOG) pilot study. International Journal of Pediatric Hematology/Oncology 1996; 3:483-490.
3. Stevens MC, Mahler H, Parkes S. The health status of adult survivors of cancer in childhood. Eur J Cancer 1998; 34(5):694-698.
4. Sklar CA. Overview of the effects of cancer therapies: the nature, scale and breadth of the problem. Acta Paediatr Suppl. 1999; 88:1-4.
5. Oeffinger KC, Eshelman DA, Tomlinson GE, Buchanan GR, Foster BM. Grading of late effects in young adult survivors of childhood cancer followed in an ambulatory adult setting. Cancer 2000; 88(7):1687-1695.

Table 1. Categories of physical late effects by severity.

Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening or disabling
	Basal cell carcinoma		Second malignant neoplasm
Problems hearing, not requiring a hearing aid	Hearing loss requiring a hearing aid	Deafness, not completely corrected by hearing aid	Complete deafness in either ear
Cataracts, not requiring surgery		Cataracts, requiring surgery	
Glaucoma, not requiring medication	Glaucoma, requiring medication		
Double vision			
			Legally blind or loss of an eye
Stammering or stuttering			
Abnormal taste			
Problems chewing or swallowing			
		Hyperthyroid	
Hypothyroid, not requiring medication	Hypothyroid, requiring medication		
	Thyroid nodules, not requiring surgery	Thyroid nodules, requiring surgery	
Chronic cough or shortness of breath or Lung fibrosis, not requiring oxygen or Emphysema, not requiring medication[1]		Lung fibrosis, requiring oxygen or Emphysema, requiring medication	
		Heart attack, angina, or coronary heart disease not requiring a cardiac catheterization but on anti-anginal medication[2]	Heart attack, requiring cardiac catheterization, or angioplasty or CABG
	Congestive heart failure, not requiring medication	Congestive heart failure, requiring medication	Heart transplant
Arrhythmia, not requiring medication		Arrhythmia, requiring medication	
Hypertension, not requiring medication	Hypertension, requiring medication		
Stiff or leaky valves[3]			
		Blood clot in head, lung, arm, leg, or pelvis	
	Hepatitis[4]	Cirrhosis[5]	
	Rectal or anal fistula	Rectal or anal stricture	
		Surgery for intestinal obstruction	
Repeated bladder infections or repeated kidney infections[6]			
	Kidney stones		
			Dialysis or kidney transplant
Amputation or walking with a limp, with mild limitations[7]	Amputation or walking with a limp, with moderate limitations		
		Joint replacement	
			Mental retardation[8]
Epilepsy/seizures, not requiring medications	Epilepsy/seizures, requiring medications		
Problems with balance or vertigo			
Tremors or problems with movement			
Weakness in leg(s), mild limitation[9]	Weakness in leg, moderate limitation		Paralysis
Weakness in arm(s)[10]			
Sensory neuropathy[11]			
Persistent hair loss[12]	Scarring or disfigurement of chest or abdomen or of arms or legs	Scarring or disfigurement of head or neck region (including face)	
Diabetes, no medications	Diabetes, pills	Diabetes, insulin	
	Growth hormone injections		
	Osteoporosis	Ovarian dysfunction, requiring HRT Testicular dysfunction, requiring male hormones	

Notes on following page

Notes for Table 1:

[1] Lung fibrosis and emphysema (COPD) are different problems, but may be overlapping. To avoid double counting, only one will be scored.

[2] Self-reported heart attacks are not very reliable. Patients often are admitted for two days for a "rule-out MI", ruled out, another etiology for the chest pain is found, but the patient still thinks s/he had a 'mild' heart attack. Given the age of these respondents, general standard of care would recommend that all have a cardiac catheterization to assess their anatomy. Thus, a survivor who reports an MI and yet does not have a cardiac cath is less likely to truly have had an MI. Recognizing the difficult access some survivors may have in getting a catheterization, if some one reports an MI and is on anti-anginal medications, it is reasonable to score him/her as a grade 3.

[3] There is not a good way to score this item with the given information.

[4] If H4/hepatitis and J38/hepatitis both = yes

[5] If reports a liver biopsy (I21)

[6] Patients often do not know the difference between upper and lower tract infections, and tend to over-report 'kidney infections'. Will group together.

[7] Survivors with a bone tumor of the lower extremity may have had either an amputation or a limb salvage procedure. Limitations of activity (question N14e - walk one block) will be used to score severity of problem. If limited for more than 3 months, will score 2; If N14e not limited, will score 1.

[8] Include if (a) treated with cranial/head RT, (b) age at first occurrence was after date of diagnosis, (c) Question O3 (education) was reported as yes for special education and yes for low scores on tests.

[9] Limitation graded as in note #7

[10] Information is lacking to score arm limitations, so score = 1.

[11] Sensory neuropathy – "Decreased sense of touch or feeling in hands, fingers, arms, or legs/prolonged pain or abnormal sensation in arms, legs, or back"; J12/J13

[12] If treated with cranial/head RT

Table 2. Physical late effects, with a severity score, by organ or system categories.

Category	Wording in Questionnaire	Score
Hearing		
C6	Problems hearing sounds, words, or language in crowds	1
C1	Hearing loss requiring a hearing aid	2
C2	Deafness in or both ears not completely corrected by hearing aid	3
C3	Complete deafness in either ear	4
Vision		
C8	Legally blind	4
B9g	Loss of an eye	4
C9	Cataracts without surgery	1
I28	Cataract surgery	3
C10	Glaucoma on medications	1
C11	Double vision	1
Speech		
C16	Stammering or stuttering	1
C17	Abnormal taste	1
Renal		
D1	Kidney stones	2
D2	Repeated kidney infections	2
D3	Repeated bladder infections	1
D4	Dialysis	4
I25	Kidney transplant	4
Endocrine		
E1	Hyperthyroid	3
E2	Hypothyroid (and on medications in B8.5)	2
E3	Thyroid nodules	2
I15	Removal of thyroid gland	3
E5	Diabetes, diet	1
E6	Diabetes, pills (verified with B8.7)	2
E7	Diabetes, insulin	3
E9	Growth hormone injections	2
E10	Osteoporosis	2
E17	Ovarian dysfunction (verified with B8.3)	3
E15	Testicular dysfunction (verified by B8.4)	3

Category	Wording in Questionnaire	Score
Heart and Circ		
F2, F6, F10, F5	Hardening of the arteries, coronary heart disease, angina, heart attack	
	If F14 (card cath) =1	4
	If F14=0	2
I7, I8	CABG or angioplasty	4
F4	Congestive heart failure (verified with B8.12 - ACE or ARB or carvedilol	3
I23	Heart transplant	4
F3	Arrhythmia requiring medication (verify with B8.12, will review meds)	3
F7	Hypertension, not requiring medication	1
F8	Hypertension, requiring medication (verify with B8.12)	2
F11	Pericarditis, no requiring surgery (I8=0)	2
F12	Pericarditis, requiring surgery (I8=1)	4
F13	Stiff or leaking valves	1
F9	Stroke/CVA	4
F16	Blood clot in head, lung, arm, leg, or pelvis	3
Respiratory		
G8	Chronic cough or shortness of breath for greater than one month	1
G9b	Currently using oxygen	4
G11	Emphysema (will review meds B8.16)	3
G12	Lung fibrosis = 2 if G9b=0; If G9b=1, then count only once	2
GI		
H3	Cirrhosis (If I21=1, then 3; else if I21=0, then don't count)	3
H4	Hepatitis (If J38=yes, then 2; else if J38=no, don't count)	2
H17	Rectal or anal fistula	2
H18	Rectal or anal stricture	3
I11	Surgery for intestinal obstruction	3
Musculoskeletal		
I1 or B9f	Amputation of an arm, leg, hand, foot, finger, or toe	4
B9e	Walk with a limp	3
I2	Scoliosis surgery	3
I4	Leg lengthening or shortening procedure	3
I5	Joint replacement	3
I22	Reconstructive surgery	3
I30	Surgery on jaw	3

Category	Wording in Questionnaire	Score
Neurological		
J2	Paralysis of any kind	4
J3	Mental retardation	4
J4 or J5	Epilepsy/Repeated seizures (verify with B8.11)	3
J8 or C5	Problems with balance, equilibrium, or ability to reach for or manipulate objects/persistent dizziness or vertigo	1
J9	Tremors or problems with movements	1
J10	Weakness or inability to move arm(s)	3
J11	Weakness or inability to move leg(s)	3
J12 or J13	Decreased sense of touch or feeling in hands, fingers, arms, or legs/prolonged pain or abnormal sensation in arms, legs, or back	1
J14	Problems with chewing or swallowing solids or liquids	1
SMN	Any SMN except BCC	4
	BCC	3
Cosmetic		
B9a	Persistent hair loss	1
B9b	Scarring or disfigurement of head or neck region (including face)	3
B9c	Scarring or disfigurement of chest or abdomen	2
B9d	Scarring or disfigurement of arms or legs (including abnormally short arm or leg)	2