06-02

CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal
January 9, 2006

1. STUDY TITLE:

Obesity in Survivors of Childhood Acute Lymphoblastic Leukemia: A Follow Up Report from the Childhood Cancer Survivor Study

2. WORKING GROUP AND INVESTIGATORS:

Proposed publication will be within the chronic disease working group. Principal Investigators to include:

Edward Garmey	garmeye@mskcc.org	212-639-2000
Kevin Oeffinger	oeffingk@mskcc.org	212-639-8469
Charles Sklar	sklarc@mskcc.org	212-639-8138
Ann Mertens	mertens@epi.umn.edu	612-626-2187
Marilyn Stovall	mstovall@mdanderson.org	
Lillian Meacham	lillian.meacham@oz.ped.emory.edu	
Yutaka Yasui	yutaka.yasui@ualberta.ca	780-492-4220
Les Robison	les.robison@stjude.org	

3. BACKGROUND AND RATIONALE:

Acute Lymphoblastic Leukemia (ALL) is the single most common childhood malignancy, accounting for approximately 75% of all childhood leukemias and 25% of all childhood cancers.[1] ALL is also among the most curable childhood malignancies with ten-year event-free survivorship rates now exceeding 80%.[1]

The implications for health and health-care costs of obesity in the United States are manifold. More specifically, obesity in childhood, adolescence, and young adulthood is a well-described risk-factor for the development of adult-onset diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, and cancer.[2,3] Furthermore, the risk of death from all causes increases throughout the ranges of overweight and obesity in both men and women.[4] Given that both the primary and secondary prevention of obesity has been demonstrated to reduce morbidity and mortality related to cardiovascular (as well as other) disease,[5] it is imperative that efforts continue to be made to identify and assist those populations at risk for developing obesity.

In 1986, Zee and colleagues reported the excess weight gain (in comparison to age-matched population norms) they observed among 414 survivors of childhood ALL who received treatment at the St. Jude Children's Research Hospital.[6] Subsequently and over the past twenty years numerous other studies suggest a role for ALL therapy in the increased risk for overweight and obesity observed among survivors of childhood ALL.[7-21] Factors limiting the generalizability of these studies include: their small sample sizes (often drawn from a single institution and minimizing the diversity of treatment regimens to which study participants were exposed); the absence in many cases of adequate

comparison or control groups; and a reliance on cross-sectional design strategies with little ability to track obesity patterns into young adulthood of childhood ALL survivors.

Following up on these studies and recognizing their limitations, in 2003 Oeffinger and colleagues published results of their analysis of self-reported heights and weights acquired from Childhood Cancer Survivor Study (CCSS)-participating survivors of childhood ALL (all of whom were at the time of enrollment in CCSS a minimum of five years post conclusion of cancer therapy).[19] Calculated body mass indices (BMI; kg/m^2) were used to determine the prevalence of obesity (BMI $\geq$ 30.0) among 1,765 adult survivors of childhood ALL and 2,565 adult sibling controls. These authors reported that cranial radiotherapy (CRT) $\geq$ 20 Gy employed in the therapy of childhood ALL was associated with an increased prevalence of obesity among both women (OR 2.59, 95% CI= 1.88-3.55, $p<0.001$) and men (OR 1.86, 95% CI= 1.33-2.57, $p<0.001$) in comparison to age and race-matched siblings. Among women, furthermore, the prevalence of obesity experienced by individuals who received CRT $\geq$ 20 Gy appeared to be modified by their age at diagnosis, with those female participants diagnosed between 0-4 years of age experiencing the highest risk (OR 3.81, 95% CI= 2.34-5.99, $p<0.001$). No significant increases in the prevalence of obesity were observed among: survivors who received CRT $\geq$ 20 Gy and were diagnosed in mid-to-late adolescence (15-21 years of age); survivors who received CRT less than 20 Gy; and survivors who received chemotherapy without CRT.

Recently, new self-reported height and weight data collected from CCSS participants and sibling controls between 2003 and 2004 have become available for analysis. This new data provide the unique opportunity to assess longitudinally BMI in adult survivors of childhood ALL, with an average of 7-8 years of interval time. To date, there exists no published literature describing longitudinal changes and trends in BMI experienced in this population.

4. SPECIFIC RESEARCH AIMS/HYPOTHESES:

Aim 1: For the interval from Baseline to Follow-Up 2 Study, determine if the rate of BMI increase and the change in proportion (normal weight, overweight, obese) in ALL survivors is greater than that of sibling controls.

Aim 2: Identify factors among ALL survivors that are significantly associated with obesity or a greater rate of BMI increase.

Hypothesis 1: The rate of BMI increase in ALL survivors who received $\geq$ 20 Gy CRT is greater than those rates of BMI increase observed among:

1. Adult siblings of childhood cancer survivors;
2. ALL survivors who received 10.0 – 19.9 Gy CRT;
3. ALL survivors who received chemotherapy alone.

Hypothesis 2: The rate of BMI increase among ALL survivors who received ≥ 20 Gy CRT and were non-obese at Baseline is greater than that of sibling controls who were non-obese at Baseline.

Hypothesis 3: The rate of BMI increase in ALL survivors who received 10.0 – 19.9 Gy CRT is greater than that of sibling controls.

Hypothesis 4: The rate of BMI increase in ALL survivors who received chemotherapy alone is greater than that of sibling controls.

5. ANALYSIS FRAMEWORK:

A. Subject population:

Childhood ALL survivors enrolled in CCSS who completed Baseline and Follow-Up 2 questionnaires (n = 1765).

B. Comparison group:

Siblings of childhood cancer survivors who completed Baseline and Follow-Up 2 questionnaires (n = 2565).

C. Outcomes of interest:

1. Mean BMI among subjects and comparison controls.
2. Prevalence of obesity (BMI $\geq$ 30 kg/m^2) among subjects and comparison controls.
3. Rate of change in mean BMI among subjects and comparison controls occurring between Baseline and Follow-Up 2 (Δ mean BMI/# interval days).
4. Absolute change in prevalence of obesity among subjects and comparison controls occurring between Baseline and Follow-Up 2 (Δ % individuals with BMI $\geq$ 30 kg/m^2).

D. Independent variables of interest:

1. Age at study;
2. Gender;
3. Race/ethnicity;
4. Age at time of diagnosis (continuous by 5-year intervals);
5. History of cranial radiation therapy (categorical);
6. History of cranial radiation therapy (categorized by dosage intervals 10.0 – 19.9 Gy; 20.0 – 29.9 Gy; ≥30.0 Gy);
7. History of corticosteroid therapy (categorical)

E. Statistical analysis:

Two types of analyses will be conducted: cross-sectional analysis using Follow-up 2 data and longitudinal analysis using Baseline and Follow-up 2 data.

Cross-sectional Analysis:
The methodology used in the original obesity analysis of Baseline data will be used for the cross-sectional Follow-up 2 data. Descriptive univariate analyses will be performed to assess the relationship of demographic and treatment variables with BMI and prevalence of being overweight or obese. Analysis will be stratified by gender and adjusted for attained age at follow up and race. The influence of each chemotherapeutic agent used for ALL will be analyzed individually and in combination. Cumulative doses of CRT will be grouped by 5-Gy intervals. An adjusted 3-level (normal weight, overweight, obese) polytomous logistic regression analysis will be conducted to estimate the odds ratios and 95% confidence intervals for being overweight or obese rather than being normal weight in ALL survivors and the associations will be compared with those in the siblings. To account for potential within-family correlation, a bootstrap method will be used by resampling the family units. Significant factors identified in the univariate analysis will be tested in the logistic regression.

Longitudinal Analysis:
A Generalized Estimating Equation (GEE) model will be used to model the BMI at Baseline and Follow-up 2. The within-person correlation between the two time points as well as the within-family correlations will be accounted for in the GEE using an unstructured working correlation matrix. As above, this comparison will be stratified by gender and adjusted for attained age at study and race. The main variable of interest will be the effect of time (i.e., change in BMI between the two time points) and its interaction with the subgroups of ALL survivors and controls. Other factors of interest will also be crossed with the time variable to assess what characteristics are associated with at steeper slope/change. The three-weight category polytomous model will also be extended to fit the longitudinal data with the similar covariate set as the GEE model. Here the statistical inference will use bootstrap.

The analysis will be conducted by Dr. Yasui and his group in Alberta. Drs. Yasui, Oeffinger, Sklar, and Mertens collaborated on the first obesity analysis in ALL survivors.

6. REFERENCES:

1. Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, Mariotto A, Feuer EJ, Edwards BK (eds). *SEER Cancer Statistics Review, 1975-2002*, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2002/, based on November 2004 SEER data submission, posted to the SEER web site 2005.
2. Flegal KM, Carroll MD, Ogden CL and Johnson CL. Prevalence and trends in obesity among US adults, 1999–2000. JAMA 2002; 288(14):1723–7.

3. Calle EE, Thun MJ, Petrelli JM, et al. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med 1999; 341:1097-1105.
4. National Task Force on the Prevention and Treatment of Obesity. Overweight, obesity and health risk. Arch Int Med 2000; 160:898-904.
5. National Institutes of Health. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the Evidence Report. Obes Res 1998; 6: Suppl 2:51S-209S.
6. Zee P, Chen CH. Prevalence of obesity in children after therapy for acute lymphoblastic leukemia. Am J Pediatr Hematol Oncol 1986; 8:294-299.
7. Schell MJ, Ochs JJ, Schriock EA, et al. A method of predicting adult height and obesity in long-term survivors of childhood acute lymphoblastic leukemia. J Clin Oncol 1992; 10:128-133.
8. Odame I, Reilly JJ, Gibson BE, et al. Patterns of obesity in boys and girls after treatment for acute lymphoblastic leukaemia. Arch Dis Child 1994; 71:147-149.
9. Didi M, Didcock E, Davies HA, et al. High incidence of obesity in young adults after treatment of acute lymphoblastic leukemia in childhood. J Pediatr 1995; 127:63-67.
10. Dongen-Melman JE, Hokken-Koelega AC, Hahlen K, et al. Obesity after successful treatment of acute lymphoblastic leukemia in childhood. Pediatr Res 1995; 38:86-90.
11. Birkebaek NH, Fisker S, Clausen N, et al. Growth and endocrinological disorders up to 21 years after treatment for acute lymphoblastic leukemia in childhood. Med Pediatr Oncol 1998; 30:351-356.
12. Craig F, Leiper AD, Stanhope R, et al. Sexually dimorphic and radiation dose dependent effect of cranial irradiation on body mass index. Arch Dis Child 1999; 81:500-504.
13. Nysom K, Holm K, Michaelsen KF, et al. Degree of fatness after treatment for acute lymphoblastic leukemia in childhood. J Clin Endocrinol Metab 1999; 84:4591-4596.
14. Warner JT, Evans WD, Webb DKH, et al. Body composition of long-term survivors of acute lymphoblastic leukaemia. Med Pediatr Oncol 2002; 38:165-172.
15. Mayer EI, Reuter M, Dopfer RE, et al. Energy expenditure, energy intake and prevalence of obesity after therapy for acute lymphoblastic leukemia during childhood. Horm Res 2000; 53:193-199.
16. Shaw MP, Bath LE, Duff J, et al. Obesity in leukemia survivors: the familial contribution. Pediatr Hematol Oncol 2000; 17:231-237.
17. Sklar CA, Mertens AC, Walter A, et al. Changes in body mass index and prevalence of overweight in survivors of childhood acute lymphoblastic leukemia: role of cranial irradiation. Med Pediatr Oncol 2000; 35:91-95.
18. Oeffinger KC, Buchanan GR, Eshelman DA, et al. Cardiovascular risk factors in young adult survivors of childhood acute lymphoblastic leukemia. Am J Pediatr Hematol Oncol 2001; 23:424-430.
19. Oeffinger KC, Mertens AC, Sklar CA, et al. Obesity in adult survivors of childhood acute lymphoblastic leukemia: a report from the childhood cancer survivor study. J Clin Oncol 2003; 21: 1359-1365.
20. Meacham LR, Gurney JG, Mertens AC, et al. Body mass index in long-term survivors of childhood cancer. Cancer 2005; 103: 1730-39.
21. Reilly JJ, Ventham JC, Newell J, Aitchison T, Wallace WH, Gibson BE. Risk factors for excess weight gain in children treated for acute lymphoblastic leukaemia. Int J Obes Relat Metab Disord 2000;24(11):1537–41.

7. TABLES/FIGURES:

Table 1. Demographics of adult survivors of childhood ALL and siblings of childhood cancer survivors

Variable	ALL Survivors N=1765	Siblings N=2565
Age at interview		
Mean, Yrs. (SD)		
Median, Yrs. (range)		
Gender, % female		
Ethnicity, %		
White, NH		
Black, NH		
Hispanic/Latino		
Other		
Age at cancer diagnosis		
Mean, Yrs. (SD)		
Median, Yrs. (range)		
Interval from diagnosis		
Mean, Yrs. (SD)		
Median, Yrs. (range)		
Treatment		
Chemotherapy		
cytarabine		
cyclophosphamide		
daunorubicin		
dexamethasone		
doxorubicin		
L-asparaginase		
6-mercaptopurine		
methotrexate		
prednisone		
thioguanine		
vincristine		
etoposide		
Chemotherapy without CRT		
Chemotherapy with CRT:		
10.0 – 19.9 Gy		
20.0 – 29.9 Gy		
$\geq$ 30.0 Gy		

Table 2. Mean body mass index (BMI) and prevalence of obesity among survivors of childhood ALL and sibling controls

Characteristic	N	BMI Mean (SD)	% Obese BMI ≥ 30 kg./m2
MALES			
Siblings			
Age at Study			
18-24 years			
25-29			
30-34			
35+			
ALL Survivors			
Age at Study			
18-24 years			
25-29			
30-34			
35+			
Age at Diagnosis			
0-4 years			
5-9			
10-14			
15-21			
Therapy			
Chemotherapy only			
Chemo + CRT 10-19 Gy			
Chemo + CRT ≥ 20 Gy			
FEMALES			
Siblings			
Age at Study			
18-24 years			
25-29			
30-34			
35+			
ALL Survivors			
Age at Study			
18-24 years			
25-29			
30-34			
35+			
Age at Diagnosis			
0-4 years			
5-9			
10-14			
15-21			
Therapy			
Chemotherapy only			
Chemo + CRT 10-19 Gy			
Chemo + CRT ≥ 20 Gy			

Table 3. Gender-specific odds ratio (OR) and 95% confidence intervals (95% CI) for being overweight or obese among survivors of childhood ALL in comparison with sibling controls and U.S. adult means, adjusted for age and race

Group	N	Overweight BMI 25-29 (vs. siblings) OR (95% CI)	Obesity (BMI ≥ 30) (vs. siblings) OR (95% CI)
MALES			
Siblings			
ALL survivors			
Chemotherapy only			
age at diagnosis 0-21			
Chemo + CRT 10-19 Gy			
age at diagnosis 0-21			
Chemo + CRT ≥ 20 Gy			
age at diagnosis 0-4			
age at diagnosis 5-9			
age at diagnosis 10-14			
age at diagnosis 15-21			
FEMALES			
Siblings			
ALL survivors			
Chemotherapy only			
age at diagnosis 0-21			
Chemo + CRT 10-19 Gy			
age at diagnosis 0-21			
Chemo + CRT ≥ 20 Gy			
age at diagnosis 0-4			
age at diagnosis 5-9			
age at diagnosis 10-14			
age at diagnosis 15-21			

Table 4. Factors associated with increased rate of BMI change.

Group
MALES
Siblings
ALL survivors
Chemotherapy only
age at diagnosis 0-21
Chemo + CRT 10-19 Gy
age at diagnosis 0-21
Chemo + CRT $\geq$ 20 Gy
age at diagnosis 0-4
age at diagnosis 5-9
age at diagnosis 10-14
age at diagnosis 15-21
FEMALES
Siblings
ALL survivors
Chemotherapy only
age at diagnosis 0-21
Chemo + CRT 10-19 Gy
age at diagnosis 0-21
Chemo + CRT $\geq$ 20 Gy
age at diagnosis 0-4
age at diagnosis 5-9
age at diagnosis 10-14
age at diagnosis 15-21

Figure 1. Change over time in mean BMI among survivors of childhood ALL and sibling controls