Analysis Concept Proposal

Study Title: Sleep in long-term survivors of childhood cancer: Cross-sectional comparison and longitudinal follow-up.

Working groups: Psychology (primary); Chronic Disease and Second Malignancy (secondary)

Investigators:

Lauren Daniel	daniell@email.chop.edu
Tara Brinkman	tara.brinkman@stjude.org
Kathy Ruble	rubleka@jhmi.edu
Eric Zhou	eric_zhou@dfci.harvard.edu
Oxana Palesh	opalesh@stanford.edu
Robyn Stremler	robyn.stremler@utoronto.ca
Rebecca Howell	rhowell@mdanderson.org
Yutaka Yasui	yutaka.yasui@stjude.org
Daniel Mulrooney	Daniel.mulrooney@stjude.org
Wendy Leisenring	wleisenr@fhcrc.org
Kevin Oeffinger	kevin.oefinger@duke.edu
Joseph Neglia	jneglia@umn.edu
Leslie Robison	les.robison@stjude.org
Greg Armstrong	greg.armstrong@stjude.org
Kevin Krull	kevin.krull@stjude.org

Background and Rationale:

Sleep disturbances are common across the continuum of cancer treatment,[1,2] posing a significant threat to health and quality of life for long-term survivors. Preliminary data suggest that impaired sleep is associated with earlier mortality in the general[3] and cancer populations[4,5]. Although sleep disturbances may resolve in some survivors following completion of therapy, prevalence rates of symptoms of obstructive sleep apnea and insomnia persist in approximately 5%-25% of long-term childhood cancer survivors, rates that are higher than among siblings.[6] Sleep disturbances are related to impairments in both mental and physical health in the general population.[7,8] However, the trajectory of sleep disturbances across survivorship and the long-term impact of sleep disturbances on the health of childhood cancer survivors remains understudied.

Cross-sectional data from our prior work with the Childhood Cancer Survivor Study (CCSS) suggests that survivors exhibit greater risk for insomnia, daytime sleepiness, snoring, and fatigue relative to siblings.[6,9] Survivors who reported poor sleep were also at risk for increased or persistent emotional distress and more likely to develop migraines over time. However, these results were collected in 2002 from a randomly-selected subset of survivors in the original CCSS cohort diagnosed 1970-1986 (survivors n=1933; siblings n=369), over-representative of Hodgkin lymphoma due to reports of excessive fatigue in this population, and did not include survivors of solid tumors or non-Hodgkin lymphoma. These relationships warrant follow-up in the full cohort, particularly so that survivors treated on more modern protocols are included. Understanding the continued risk for symptoms of sleep disorders in childhood cancer survivors is important for development of interventions to improve health and functional outcomes.

There are several possible underlying mechanisms leading to increased difficulties with sleep after cancer treatment: (1) a bidirectional relationship between mental health and cancer survivorship increasing the likelihood of developing or perpetuating insomnia[10], (2) central hypothalamic damage due to treatment or tumor location which alters circadian regulation of sleep[11], and (3) airway obstruction related to excess weight[12] or treatment related changes to the upper airway[13] or pulmonary functioning[14] (i.e., head/neck or thoracic radiation). These mechanisms likely interact to exacerbate sleep disturbances for some survivors. The current analyses proposed will focus on these three primary measures (symptoms of insomnia, delayed sleep phase which may indicate a circadian delay, and symptoms of obstructive sleep apnea).

Symptoms of insomnia[15] and obstructive sleep apnea[16] increase steadily with age. The association between aging and sleep is bidirectional, with aging affecting sleep architecture, neurotransmitter control, and circadian rhythmicity, while disrupted sleep hastens the aging process.[17] Insufficient sleep due to insomnia is a risk factor for poor quality of life and depression.[18] Obstructive sleep apnea places adults at risk for cardiovascular morbidity, most notably hypertension.[16] For childhood cancer survivors who are already at greater risk of depression[19] and cardiovascular conditions,[20] it is important to understand if childhood cancer increases risk for sleep problems so that intervention efforts could be implemented earlier in the survivorship trajectory. Furthermore, increased prevalence rates of chronic health conditions in cancer survivors may also heighten the risk of poor sleep in long term survivors.[20]

Longitudinal analysis of sleep disturbances within the subset of the CCSS survivors and siblings who have participated in both sleep surveys will help to identify age-related changes to sleep and how these changes compare to siblings. Furthermore, examining demographic, treatment, and health correlates of survivors with persistent sleep disturbances is important for identifying those at greatest risk of poor sleep.

The current proposal is the first analysis of the sleep data collected in Follow-up 6. The previous CCSS manuscripts on sleep were conducted using the 2002 Sleep Survey, which included responses from selected subset of 1,897 survivors and 369 siblings from the Original cohort. This new data collection includes all survivors and siblings in the Original and Expansion cohorts. It offers a unique opportunity to understand sleep in an aging cohort relative to controls, as well the trajectory of sleep disturbances since the original sleep assessment roughly 18 years ago, using the same measure. The cross-sectional analysis from Follow-up 6 is the largest assessment of sleep in childhood cancer survivors anywhere to date, and the longitudinal analyses will be the largest and longest follow-up of a cohort of childhood cancer survivors. Sleep is central to quality of life and health, and better understanding trajectories and risk factors will directly inform interventions that may improve multiple outcomes in long-term cancer survivors.

Proposal team:

The project team is comprised of researchers with expertise in cancer survivorship, child sleep, and adult sleep. Drs. Daniel, Palish, Ruble, Stremler, and Zhou all specialize in behavioral sleep medicine in pediatrics and/or adults and the intersection of sleep and health outcomes in cancer, which complements the expertise of the CCSS team members, Drs. Brinkman, Krull, and Mulrooney, who are well versed in sleep in this cohort. Together with team members with background in cancer treatments, late effects, and statistics in survivorship, this project team is well positioned to analyze the sleep data collected in Follow-Up 6.

Specific aims/objectives/research hypotheses:

Cross-sectional analysis (all survivors and siblings; N=13,085):
Aim 1*:* Examine prevalence of sleep problems (e.g., poor sleep quality, symptoms of insomnia, symptoms of sleep disordered breathing, delayed sleep phase, sleep medication use) in survivors compared to siblings.

Hyp 1: Survivors will report poorer sleep quality, more symptoms of insomnia, greater symptoms of sleep disordered breathing, more delayed sleep phase, and more sleep medication use than siblings. Group differences will be maintained when adjusting for age, sex, and BMI.

Aim 2: Within the survivor group, identify demographic, treatment-related, and chronic health condition predictors of sleep problems.

Hyp 2a: Female survivors will report more symptoms of insomnia, while male survivors will report more sleep disordered breathing.

Hyp 2b: Survivors of CNS tumor and Hodgkin lymphoma will report the highest frequencies of sleep problems relative to other cancer diagnoses.

Hyp 2c: Survivors who received chest radiation will be at higher risk for sleep disordered breathing.

Hyp 2: Survivors who received cranial radiation will be at higher risk for poor sleep quality.

Hyp 2e: Risk of insufficient sleep, symptoms of insomnia, poor sleep quality, and increased symptoms of sleep disordered breathing will increase with age.

Hyp 2f: The number of chronic health conditions will be related to sleep quality, such that more chronic conditions (≥2) and severe chronic conditions (grades 3-4) will be related to worse sleep quality in comparison to those with <2 conditions or grades 1-2, respectively.

Hyp 2g (exploratory): Chronic conditions by organ group (e.g., pulmonary, cardiac, endocrine neurological) will be differentially associated with sleep outcomes (symptoms of insomnia, symptoms of sleep disordered breathing, delayed sleep phase, sleep quality).

Longitudinal analysis (survivors (n=1140) and siblings (n=215) who completed 1st sleep survey in 2002 and the 2nd sleep survey, attrition of 757 survivors and 154 siblings between the two sleep surveys):
Aim 3: Examine the trajectories of change in reported sleep problems with age.

Hyp 3a: The prevalence of sleep problems in survivors will increase more with age compared to that in siblings, controlling for age differences.

Exploratory Aim: Explore the association between persistence of sleep problems from the original sleep survey in 2002 to FU6 with new onset health conditions (e.g., hypertension,

migraines/headaches, menopause onset, subsequent malignancies [ICDO 5th digit of/3), subsequent meningiomas (benign and malignant), mortality] that have developed since 2002.

Analysis Framework:
Outcome of interest.

Sleep parameters and subjective report of sleep.

The Pittsburgh Sleep Quality Index (PSQI) describes sleep habits over the past month on a 4-point scale with higher scores indicating worse sleep, with total scores of >5 indicating poor sleep quality[15]. PSQI items will be dichotomized to indicate clinically significant cut-points. Items from this measure that will be used in analyses are:

Sleep Parameters (used to describe sample's sleep and calculate other variables)

- Bedtime (PSQI Item 1)
- Wake time (PSQI Item 3)
- Sleep duration (PSQI Item 4)
  - Dichotomize into <6 hours or ≥6 hours based on evidence of poor health outcomes related to short sleep duration[21]

Insomnia Symptoms

- Sleep onset latency (PSQI Item 2)
  - Dichotomize into <30 minutes vs. ≥30
  - 30 minutes is a diagnostic criterion for insomnia[22]
- Sleep efficiency—percent of time in bed spent asleep.
  - Difference between item 3 and 1 divided by item 4
  - Dichotomize result into <85% and ≥85%
  - < 85% sleep efficiency is a diagnostic criterion for insomnia[22]
- Night awakening/early morning awakenings
  - Dichotomize into "not at all," "< once per week," "1-2 times per week" vs. "3 or more times"

Sleep Management

- Sleep medication use (PSQI Item 7a).
  - Dichotomized as no use vs any use.

Delayed Sleep/Wake Timing

- Sleep onset after 1 am (PSQI Item 1)
  - Dichotomize into before 1 am AND after 1 am
- Wake time after 10 am (PSQI Item 3)
  - Dichotomize into before 10 am AND after 10 am

Sleep Quality. PSQI Total Score. A total scores of >5 indicating clinically significant poor sleep quality[15].

Symptoms of Sleep Disordered Breathing (i.e., Snoring.)

- Self-report of snoring (PSQI Item 5e) and bed partner report of long pauses in breathing (PSQI Item 10b). Snoring/long pauses in breathing more than 3 nights per week is suggestive of obstructive sleep apnea[23].
- Dichotomize into “not at all,” “< once per week,” “1-2 times per week” VERSUS “3 or more times”

Chronic Health Conditions.

Common Terminology Criteria for Adverse Events (CTCAE, v4.03) grades for chronic health conditions. Conditions were graded as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4), or fatal (grade 5). The maximum score for each participant will be used to define two outcome variables. The first categorized as no chronic conditions, only/at least mild-moderate condition (grades 1 and 2), at least one severe or life-threatening condition (grade 3 or 4) and the second defined as 0, 1, or ≥ 2 chronic conditions (grades 1-4).

Chronic conditions will also be classified by organ system (cardiac, pulmonary, neurological, endocrine) for exploratory analyses comparing survivors with each high chronic conditions in that system (2-4 conditions) vs low conditions (0-1) in each organ group system.

Exploratory: Health outcomes/Medical conditions to assess new onset medical concerns in survivors with and without sleep concerns.

Common Terminology Criteria for Adverse Events (CTCAE, v4.03) grades for chronic health conditions with age of onset occurring after completion of the first Sleep Survey (2002). Hypertension with onset occurring after completion of the first Sleep Survey. Migraines/headaches occurring after completion of the first Sleep Survey. Second malignant neoplasm with onset occurring after completion of the first Sleep Survey. All cause mortality after completion of the first Sleep Survey. Menopause occurring after the completion of the first Sleep Survey.

Potential Covariates.

Treatment exposures.

Chemotherapy exposures: Cyclopospham ide Equivalent Dose (0, >0 to <4,000, ≥4,000 to <8,000, ≥8,000), anthracyclines (none, 1-249, ≥250 mg/m^2), platinum (yes/no), vincristine (yes/no), vinblastine (yes/no)

Corticosteroid treatment (yes/no)

Radiation: Cranial (none, < 20 Gy, ≥20 Gy), neck (none, <30 Gy, ≥30 Gy), chest (none, <30 Gy, ≥30 Gy), abdominal (none, <30 Gy, ≥30 Gy)

Study Population. *Cross-sectional analysis*-CCSS Follow-up 6 data will be used to describe the occurrence of specific sleep problems, behaviors, and sleep management strategies cross-sectionally in childhood cancer survivors and sibling controls. *Longitudinal analysis*-To assess longitudinal trajectories of sleep, the subset of survivors and siblings who completed the original Sleep Survey and the most recent Follow-up 6.

Exploratory Variables: Age at both sleep questionnaire completion times (categorical 18-29, 30-39, 40-49, 50+), sex, education, income, body mass index (BMI), "other reasons" for awakening during the night as reported on the PSQI item B5j (e.g., presence of an infant in the home), and race will be examined as covariates between groups.

Data Analysis

Aim 1*: Examine prevalence of sleep problems (e.g., poor sleep quality, symptoms of insomnia, symptoms of sleep disordered breathing, delayed sleep phase, sleep medication use) in survivors compared to siblings.*

Descriptive statistics of categorical demographic (age, sex, race, BMI) and treatment variables will be calculated in both the survivors and siblings and will be compared using logistic regression models with generalized estimating equations to account for intra-family correlation[24]. Means of continuous variables will be compared between survivors and siblings using generalized linear mixed models, also with generalized estimating equations to address intra-family correlation.

To test hypothesis 1, we will compare sleep quality (dichotomized PSQI raw scores), symptoms of insomnia (dichotomized sleep onset latency, dichotomized sleep efficiency, dichotomized night awakenings), symptoms of sleep disordered breathing (dichotomized snoring), delayed sleep phase (dichotomized sleep onset/offset), and sleep medication use (dichotomized use vs no use) between survivors and sibling controls.

Dichotomized sleep behaviors listed above will be compared between survivors and controls using multivariable logistic regression models with robust sandwich variance estimates to account for intra-family correlations and adjusting for demographic confounding variables (age, sex, race, BMI). If outcomes are rare (<10%), we will use a logistic regression models to estimate odds ratios as an approximation to prevalence ratios (PR) estimates. If not rare, we will use a log link with Poisson error structure to directly estimate PRs. PRs for clinically significant sleep behaviors will be reported with corresponding 95% confidence intervals. All analyses will be adjusted for age, sex and race. **Aim 2:** *Within the survivor group, identify demographic, treatment-related, and chronic health condition predictors of sleep problems.*

Analyses to address Aim 2 will use the same dichotomized sleep variables used in Aim 1. Survivors with clinically significant sleep problems will be compared to survivors without such problems. The hypotheses will be tested as follows: (Hyp 2a) Insomnia symptoms (dichotomized sleep onset latency, dichotomized sleep efficiency, dichotomized night awakenings) and symptoms of sleep disordered breathing (dichotomized snoring) will be compared between groups defined by sex. (Hyp 2b) We will compare the dichotomized versions of insomnia symptoms, sleep disordered breathing, and delayed sleep phase (dichotomized sleep onset/offset variables) between diagnostic groups (leukemia, CNS malignancy, Hodgkin lymphoma, soft tissue sarcoma, and bone cancer). (Hyp 2c) We will compare symptoms of sleep disordered breathing (dichotomized snoring) between chest radiation exposure groups (None, <30 Gy, ≥30 Gy). (Hyp 2d) We will compare dichotomized sleep quality (PSQI total score) between cranial radiation exposure groups (None, <20 Gy, ≥20 Gy). (Hyp 2e) We will test whether categorical age at questionnaire (18-29, 30-39, 40-49, 50+) predicts dichotomous sleep variables (sleep duration dichotomized above/below 6 hours, symptoms of insomnia, symptoms of sleep disordered breathing, and symptoms of delayed sleep phase). (Hyp 2f) Categorical number of chronic health conditions (0-2 vs ≥2) and severe chronic conditions (grades 3-4 vs

grades 1-2) will be related to sleep quality (dichotomized PSQI total score). (Hyp2g) Categorical number of chronic conditions (0-1 vs 2-4) in each organ system (pulmonary, cardiac, endocrine, neurological) will be examined as predictors of dichotomized versions of insomnia symptoms, sleep disordered breathing, delayed sleep phase, and poor sleep quality.

Initial comparisons will be univariate, we will build multivariable logistic regression models (or above mentioned modified Poisson models) will examine treatment predictors of these outcomes, *a priori* retaining age, sex, race, and BMI in the models. Prevalence Ratios (PRs) for factors associated with clinically significant sleep behaviors will be reported with corresponding 95% confidence intervals. We will also build multivariable logistic regression models (or above mentioned modified Poisson models) to examine chronic conditions as predictors of these outcomes, *a priori* retaining age, sex, race, and BMI in the models. We will then build a single multivariable logistic regression model (or above mentioned modified Poisson models) combining treatment predictors and chronic conditions of these outcomes, *a priori* retaining age, sex, race, and BMI in the models. In addition to analyses conducted using the entire group of survivors, we will examine the possibility of stratified analyses within some of the larger diagnostic groups (e.g., ALL, CNS tumor, Hodgkin lymphoma). We will also conduct an exploratory sensitivity analysis of chemotherapy effects in those survivors not treated with radiation.

Aim 3: *Examine the trajectories of change in reported sleep problems with age.*

Survivors and siblings who responded to both the 2002 and FU6 sleep surveys will be identified and their characteristics will be compared to those individuals who only answered the original sleep survey to determine whether the longitudinal cohort is representative and identify potential biases. We will compare the 1140 survivors with two timepoints to the 757 survivors with one timepoint on demographic (age at diagnosis, sex, race, BMI) and clinical variables (diagnosis, treatment), and we will compare the 215 siblings with two timepoints to the 154 siblings with one timepoint on demographic variables (age at diagnosis, sex, race, BMI) to evaluate selection bias. If such bias is determined to exist, we can consider options for adjusting (e.g., inverse probability weighting). We will also examine whether those who did not complete FU6 died prior to completion, their sleep metrics from baseline and the cause of death.

Outcomes for each sleep variable will be defined by dividing individuals into 4 groups (using PSQI total score of above/below 5, sleep efficiency above/below 85%, snoring >3 nights per week or <3 nights) at the two time points (original sleep survey and FU6):

(1) persistent no sleep problem
(2) new onset sleep problem
(3) persistent sleep problem
(4) improved sleep problem

For each primary sleep variable (PSQI total score, sleep efficiency, snoring) we will compare the percentage in each of these 4 groupings between survivors and siblings. Sleep behaviors will be compared between survivors and siblings using multinomial logistic regression models with robust sandwich variance estimates to account for intra-family correlations and adjusting for demographic confounding variables. All analyses will be adjusted for age, sex, race, and BMI.

Within the survivor group we will examine demographic and clinical predictors of new onset sleep problems by comparing the above groups 1 (persistent no sleep problems) to 2 (new onset sleep problems). We will also examine clinical predictors of resolution of sleep problems by comparing groups 3 (persistent sleep problems) with 4 (improved sleep problems). If outcomes are rare (<10%), we will use a logistic regression models to estimate odds ratios as an approximation to prevalence ratios (PR) estimates. If not rare, we will use a log link with Poisson error structure to directly estimate PRs. PRs for clinically significant sleep behaviors will be reported with corresponding 95% confidence intervals. Similarly, logistic regression models with the appropriate link function will be used to assess the impact of treatment related factors on sleep behavior outcomes among survivors.

Exploratory Aim: *Explore the association between persistence of sleep problems from the original sleep survey in 2002 to FU6 with new onset health conditions (e.g., hypertension, migraines/headaches, menopause onset, subsequent malignancies [ICDO 5th digit of/3), subsequent meningiomas (benign and malignant), mortality] that have developed since 2002.*

Within the survivor group, we will examine the association between the change in sleep quality from the original sleep survey to FU6 using the 4 groups (persistent no problem, new onset sleep problem, persistent problem, resolved sleep,) for PSQI (Total Score above/below 5), with the new onset health conditions (e.g., hypertension, migraines/headaches, menopause onset, second malignant neoplasms, mortality) that have developed since 2002. Again, logistic regression models or Poisson models with the appropriate link function will be used to assess the relationship of change in sleep group membership with new onset health conditions from between the time of the 2002 sleep survey and the FU6 survey. Similar pairwise comparisons as described for the latter part of Aim 3 will be used here.

References

1. Ancoli-Israel S, Moore PJ, Jones V. The relationship between fatigue and sleep in cancer patients: A review. *European Journal of Cancer Care.* 2001;10(4):245-255.
2. Lee K, Cho M, Miaskowski C, Dodd M. Impaired sleep and rhythms in persons with cancer. *Sleep Medicine Reviews.* 2004;8(3):199-212.
3. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. *Sleep.* 2010;33(5):585-592.
4. Collins KP, Geller DA, Antoni M, et al. Sleep duration is associated with survival in advanced cancer patients. *Sleep medicine.* 2017;32:208-212.
5. Palesh O, Aldridge-Gerry A, Zeitzer JM, et al. Actigraphy-measured sleep disruption as a predictor of survival among women with advanced breast cancer. *Sleep.* 2014;37(5):837-842.
6. Daniel LC, Wang M, Srivastava DK, et al. Sleep behaviors and patterns in adult survivors of childhood cancers: A report from the childhood cancer sruvivor study (CCSS). Associate Professional Sleep Socities; 2018; Baltimore, MD.
7. Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: A longitudinal epidemiological study of young adults. *Biological Psychiatry.* 1996;39(6):411-418.
8. Lund HG, Reider BD, Whiting AB, Prichard JR. Sleep patterns and predictors of disturbed sleep in a large population of college students. *Journal of Adolescent Health.* 2010;46(2):124-132.
9. Mulrooney DA, Ness KK, Neglia JP, et al. Fatigue and sleep disturbance in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). *Sleep.* 2008;31(2):271.
10. Savard J, Morin CM. Insomnia in the Context of Cancer: A Review of a Neglected Problem. *Journal of Clinical Oncology.* 2001;19(3):895-908.
11. Innominato PF, Roche VP, Palesh OG, Ulusakarya A, Spiegel D, Lévi FA. The circadian timing system in clinical oncology. *Annals of Medicine.* 2014;46(4):191-207.
12. Mandrell BN, Wise M, Schoumacher RA, et al. Excessive daytime sleepiness and sleep-disordered breathing disturbances in survivors of childhood central nervous system tumors. *Pediatric blood & cancer.* 2012;58(5):746-751.
13. Saesen K, van der Veen J, Buyse B, Nuyts S. Obstructive sleep apnea in head and neck cancer survivors. *Supportive Care in Cancer.* 2021;29(1):279-287.
14. Mandrell BN, Lewis W, Ogg S, et al. A pilot study of sleep-related breathing disorders and hypersomnia in adult survivors of childhood Hodgkin lymphoma treated with thoracic radiation. In: American Society of Clinical Oncology; 2019.
15. Buysse DJ, Angst J, Gamma A, Ajdacic V, Eich D, Rössler W. Prevalence, course, and comorbidity of insomnia and depression in young adults. *Sleep.* 2008;31(4):473.
16. Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc.* 2008;5(2):136-143.
17. Zhong H-H, Yu B, Luo D, et al. Roles of aging in sleep. *Neurosci Biobehav Rev.* 2019.
18. Roth T. Insomnia: definition, prevalence, etiology, and consequences. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine.* 2007;3(5 Suppl):S7-S10.
19. Zeltzer LK, Lu Q, Leisenring W, et al. Psychosocial Outcomes and Health-Related Quality of Life in Adult Childhood Cancer Survivors: A Report from the Childhood Cancer Survivor Study. *Cancer Epidemiology Biomarkers & Prevention.* 2008;17(2):435-446.
20. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *New England Journal of Medicine.* 2006;355(15):1572-1582.

21. Itani O, Jike M, Watanabe N, Kaneita Y. Short sleep duration and health outcomes: a systematic review, meta-analysis, and meta-regression. *Sleep medicine.* 2017;32:246-256.
22. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults. *Journal of Clinical Sleep Medicine.* 2008;4(5):487-504.
23. Epstein LJ, Kristo D, Strollo Jr PJ, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med.* 2009;5(3):263-276.
24. Verbeke G, Molenberghs G. *Linear mixed models for longitudinal data.* Springer Science & Business Media; 2009.

Proposed Tables—Cross-Sectional Analysis

Table 1. Sample Demographics

	Survivor	**Sibling**	***p* value**
	N (%)	**N (%)**	
Sex Male Female			
Race/Ethnicity White Black Hispanic Asian American Indian/Alaska Native Other			
Age at Questionnaire 18-29 30-39 40-49 50+			
Body Mass Index Normal/underweight Over weight Obese			
Age at Diagnosis 0-4 5-9 10-14 15+			
Diagnosis Leukemia CNS malignancy Hodgkin lymphoma Soft tissue sarcoma Bone cancer			
Chemotherapy Yes No			
Cyclophosphamide Equivalent Dose (mg/m^2) 0 >0 to < 4,000 ≥ 4,000 to < 8,000 ≥ 8,000 Unknown			
Anthracyclines, mg/m^2			

None 1-249 ≥ 250			
Platinum Yes No			
Corticosteroids Yes No			
Cranial radiation dose None < 20 Gy ≥ 20 Gy			
Neck Radiation None < 30 Gy ≥ 30 Gy			
Chest radiation None < 30 Gy ≥ 30 Gy			
Abdominal radiation None < 30 Gy ≥ 30 Gy			

Table 2. Aim 1— Generalized linear models for comparison of frequency of sleep behaviors between survivors and sibling controls.

Sleep Domain	**Sleep Variable**	**Survivor vs. Sibling**	
		Unadjusted PR (95% CI)	**Adjusted PR (95% CI)***
Sleep Quality	PSQI Total Score >5		
Insomnia Symptoms	Sleep Onset Latency >30 minutes OR 5a >3 times per week		
	Sleep Efficiency <85%		
	Night awakening/early morning awakening >3 times per week		
Sleep Disordered Breathing Symptoms	Snoring >3 times per week		
	Pauses in breathing >3 times per week		
Delayed Sleep Timing	Sleep onset after 1 am		
Sleep Management Strategies	Medication Use		

* Adjusted for Age, sex, race and BMI.

Table 3. Multivariable associations between treatment exposures and sleep behaviors in survivors.

Variable	Category	Sleep Quality PSQI>5	Snoring ≥3 times per week	Pauses in Breathing	Bedtime After 1 am	Sleep Medication use ≥1 time per week
		PR(95% CI)	PR(95% CI)	PR(95% CI)	PR(95% CI)	PR(95% CI)
Sex	Female					
	Male					
Body Mass Index	Normal/ underweight					
	Overweight					
	Obese					
Age	15-29					
	30-39					
	40+					
Chemotherapy	No					
	Yes					
Cyclophosphamide Equivalent Dose (mg/m^2) 0 >0 to < 4,000 ≥ 4,000 to < 8,000 ≥ 8,000	0					
	>0 to < 4,000					
	≥ 4,000 to < 8,000					
	≥ 8,000					
	Unknown					
Anthracyclines, mg/m^2	None					
	1-249					
	≥ 250					
Vincristine	No					
	Yes					
Vinblastine	No					
	Yes					
Platinum	No					
	Yes					
Corticosteroids	No					
	Yes					
Cranial radiation	None					
	< 20 Gy					
	≥20 Gy					
Neck radiation	None					
	<30 Gy					
	≥30 Gy					
Chest radiation	None					
	<30 Gy					
	≥30 Gy					

Variable	Category	Sleep Quality PSQI>5	Snoring ≥3 times per week	Pauses in Breathing	Bedtime After 1 am	Sleep Medication use ≥1 time per week
		PR(95% CI)	PR(95% CI)	PR(95% CI)	PR(95% CI)	PR(95% CI)
Abdominal radiation	None					
	<30 Gy					
	≥30 Gy					

Table 4. Associations among Chronic Conditions and Sleep Outcomes, adjusted for sex and age.

Variable	**Category**	**Sleep Quality PSQI>5**	**Snoring ≥3 times per week**	**Pauses in Breathing**	**Bedtime After 1 am**	**Sleep Medication use ≥1 time per week**
		PR(95% CI)	**PR(95% CI)**	**PR(95% CI)**	**PR(95% CI)**	**PR(95% CI)**
Severity of Chronic Condition	None					
	Only Mild/Moderate					
	Severe					
Number of Chronic Conditions	0					
	1					
	≥2					

Longitudinal Analysis

Table 5. Sample Demographics, Longitudinal sample: Sleep Survey 1 and Follow-up 6

	FU-6 Non-Responders		**FU-6 Responders**		**FU-6 group comparison**
	Survivor	**Control**	**Survivor**	**Control**	***p* value**
	N (%)	**N (%)**	**N (%)**	**N (%)**	
Sex Male Female					
Race/Ethnicity White Black Hispanic Asian American Indian/Alaska Native Other					
Age at Questionnaire 18-29 30-39 40-49 50+					
Body Mass Index Normal/underweight Over weight Obese					
Menopause No Yes					
Age at Diagnosis 0-4 5-9 10-14 15+					
Diagnosis Leukemia CNS malignancy Hodgkin lymphoma Soft tissue sarcoma Bone cancer					
Chemotherapy No Yes					
Cyclophosphamide Equivalent Dose (mg/m^2) 0 >0 to < 4,000					

≥ 4,000 to < 8,000 ≥ 8,000 Unknown					
Anthracyclines, mg/m^2 None 1-249 ≥ 250					
Vincristine No Yes					
Vinblastine No Yes					
Platinum No Yes					
Corticosteroids No Yes					
Cranial radiation dose None < 20 Gy ≥ 20 Gy					
Neck Radiation None < 30 Gy ≥ 30 Gy					
Chest radiation None < 30 Gy ≥ 30 Gy					
Abdominal radiation None < 30 Gy ≥ 30 Gy					

Table 6. Longitudinal analysis. Summary of sleep variables by group at original assessment and follow-up 6.

Sleep Domain	**Sleep Variable**	**Survivor**		**Control**	
		Time 1	**Time 2**	**Time 1**	**Time 2**
Sleep Duration	Total sleep time <6 hours				
Sleep Quality	PSQI Total Score >5				
Insomnia Symptoms	Sleep Onset Latency >30 minutes OR 5a >3 times per week				
	Sleep Efficiency <85%				
	Night awakening/early morning awakening >3 times per week				
Sleep Disordered Breathing Symptoms	Snoring >3 times per week				
	Pauses in breathing >3 times per week				
Delayed Sleep/Wake Timing	Sleep onset after 1 am				
Sleep Management Strategies	Medication Use				

Variable	Category	Persistent No Poor Sleep	New Onset Sleep Problems	Persistent Poor Sleep	Resolved Poor Sleep
		PR(95% CI)	PR(95% CI)	PR(95% CI)	PR(95% CI)
Sex	Female				
	Male				
Body Mass Index	Normal/ underweight				
	Overweight				
	Obese				
Age at Diagnosis	15-29				
	30-39				
	40+				
Menopause	No				
	Yes				
Chemotherapy	No				
	Yes				
Cyclophosphamide Equivalent Dose (mg/m^2)	0				
	>0 to < 4,000				
	≥ 4,000 to < 8,000				
	≥ 8,000				
	Unknown				
Anthracyclines, mg/m^2	None				
	1-249				
	≥ 250				
Vincristine	No				
	Yes				
Vinblastine	No				
	Yes				
Platinum	No				
	Yes				
Corticosteroids	No				
	Yes				
Cranial radiation	None/Scatter				
	< 20 Gy				
	≥20 Gy				
Neck radiation	None				
	<30 Gy				
	≥30 Gy				
Chest radiation	None				
	<30 Gy				
	≥30 Gy				
Abdominal radiation	None				
	<30 Gy				
	≥30 Gy				

Hypertension	No				
	Yes				
Migraines/ Headaches	No				
	Yes				
Secondary Malignancies	No				
	Yes				

Table 6. Clinical and treatment predictors of change in sleep.

Table 7. Change in sleep group membership for PSQI total score as a predictor of new onset chronic health conditions.

Group	**N (%) Total in group**	**Hypertension**	**Migraines/ headaches**	**Menopause onset**	**Subsequent Malignant Neoplasms**	**Mortality**
		PR(95%CI)	**PR(95%CI)**	**PR(95%CI)**	**PR(95%CI)**	**PR(95%CI)**
Persistent No Poor Sleep						
New Onset Sleep Problems						
Persistent Poor Sleep						
Resolved Poor Sleep						