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Authors

Rogers, Valerie E
Mowbray, Catriona
Zhu, Shijun
et al.

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SCIENTIFIC INVESTIGATIONS

Circadian activity rhythms and fatigue of adolescent cancer survivors and healthy controls: a pilot study

Valerie E. Rogers, PhD, RN[1,*]; Catriona Mowbray, PhD, RN[2]; Shijun Zhu, PhD[1]; Lianqi Liu, MD[3]; Sonia Ancoli-Israel, PhD[3]; Erik A. Barr, MS[1]; Pamela S. Hinds, PhD, RN[2,4]

*[1]University of Maryland, Baltimore, Maryland; [2]Children's National Health System, Washington, DC; [3]University of California, San Diego, California; [4]George Washington University, Washington, DC; *Retired*

Study Objectives: The primary objective of this study was to compare circadian activity rhythms (CARs) of adolescents within 5 years of completing cancer treatment (survivors) with that of healthy adolescent controls. Secondary objectives were to explore differences in the relationship of CARs and fatigue between survivors and controls and between early survivors (<12 months posttreatment) and late survivors (≥12 months posttreatment).

Methods: Twenty-nine survivors and 30 controls, aged 13–18 years, participated in this prospective, descriptive pilot study. Adolescents and their parents completed a baseline measure of adolescents' fatigue. Adolescents wore a wrist actigraph continuously for 7 days and concurrently kept a sleep diary. Activity data recorded by actigraphy were fitted to an extended cosine model to calculate six CAR variables: acrophase, amplitude, midline estimating statistic of rhythm (MESOR), up-MESOR, down-MESOR, and *F*-statistic. Linear mixed models explored the relationship between CARs and fatigue.

Results: There were no group differences on CAR or fatigue measures. Among survivors, earlier down-MESOR was associated with greater parent-reported fatigue ($P = .020$), and earlier acrophase ($P = .023$) and up-MESOR ($P = .025$) were associated with greater adolescent-reported fatigue. Significant CAR-by-time posttreatment interaction effects were found on fatigue between early and late survivors. Among controls, greater parent-reported fatigue was associated with greater MESOR ($P = .0495$).

Conclusions: Survivors within the first 5 years posttreatment were similar to controls in CARs and fatigue, suggesting robust recovery of circadian rhythms posttreatment. Different CAR characteristics were associated with fatigue in survivors and controls. Time posttreatment influenced the relationship between CARs and fatigue for survivors, with significant effects only for early survivors.

Keywords: actigraphy, adolescents, cancer survivorship, circadian activity rhythms, fatigue

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Little is known about disruption of circadian activity rhythms (CARs) resulting from childhood cancer and its treatment, or recovery posttreatment; yet disturbed CARs in adults with cancer have been associated with poorer outcomes, including fatigue and shortened survival, and can persist for years. This study presents preliminary findings on CARs of adolescents within 5 years of completing cancer treatment; compares them with findings in healthy adolescents; and explores the relationship between CARs, time posttreatment, and fatigue.

Study Impact: Raising awareness of the potential for circadian disturbances after treatment of childhood cancers may encourage providers to regularly screen patients for sleep and CAR disorders and intervene to support circadian health and potentially improve long-term outcomes of childhood cancer survivors.

INTRODUCTION

Survival of childhood cancer has improved tremendously, reaching an 83% 5-year survival rate across all cancers.[1] As survival rates improve, however, more long-term health consequences of treatment emerge. Among the more troubling symptoms reported by childhood cancer survivors are disturbances in the sleep-wake cycle[2] and fatigue.[3]

Sleep-wake cycles are reflections of our circadian rhythms, which work together to maintain consolidated sleep during the night and wake during the day. They can be measured via rest-activity rhythms, calculated directly from activity counts recorded by actigraphy. A variety of circadian rest-activity rhythms (CARs) can be modeled using time-series analytic techniques that reflect different characteristics of the rest-activity pattern, such as timing, height, shape, and robustness.[4]

CARs have been studied frequently in adults, particularly those with cancer, in whom disturbances are associated with poorer quality of life, fatigue, reduced treatment responsiveness, shortened time to relapse, and lower survival rates.[5–8] CARs are less well characterized in children. The few published studies describing CAR values of healthy children or adolescents report disparate CAR variables, generally derived from small samples with broad age ranges.[9,10] Thus, no normative CAR values or cut-points indicating circadian dysregulation have yet been established against which to compare children with serious

health issues or to compare differences by developmental age groups. Nevertheless, adolescence is a time of flux in the circadian timing system, with a lengthening of the circadian period and a delay in the circadian phase. Coupled with exposure to electronic media near bedtime and early school start times, circadian disturbances among adolescents are common.[11,12]

Studies reporting CARs of children and adolescents with cancer have begun to emerge. Rogers et al[13] reported on CARs of 82 children and adolescents aged 1–18 years with acute lymphoblastic leukemia. Actigraphy was measured over a 10-day period during maintenance chemotherapy. Compared with a 5-day period before initiation of dexamethasone, peak activity, amplitude, and midline estimating statistic of rhythm (MESOR) all declined significantly, and acrophase advanced to a significantly earlier clock time during the subsequent 5-day period on dexamethasone.[13] This group also reported on CARs of 33 children and adolescents aged 4–19 years with central nervous system tumors admitted to the hospital for high-dose chemotherapy.[14] Compared with published adult or pediatric CAR values, participants experienced disturbed amplitude, 24-hour autocorrelation, and dichotomy index, and CAR disturbances increased with age.[14] Most recently, Steur et al compared CARs of 71 children and adolescents aged 2–18 years with acute lymphoblastic leukemia measured at home after their first treatment phase (induction/reinduction) compared with 85 healthy children. Interdaily stability, relative amplitude (nonparametric equivalent of amplitude), and activity counts of the most active 10 hours of the day (M10 counts, a nonparametric equivalent of MESOR) were all significantly lower in children with cancer compared with controls.[15] Preliminary evidence suggests, then, that cancer treatments adversely affect CARs of children and adolescents, similar to their effect on adults.

Fatigue is a common complaint among both adult[16] and childhood[17] cancer patients, and emerging evidence suggests a relationship between circadian rhythms and fatigue.[18,19] Both Steur et al[15] and Rogers et al[14] found that disturbed CARs were significantly associated with parent-reported fatigue, and Rogers et al[13] found that this relationship held for both self- and parent-reported fatigue.

No studies have yet evaluated the recovery of circadian rhythms after childhood cancer treatment in adolescents. Yet disturbances in CARs have been identified in adult and pediatric cancer patients during treatment,[13–15] and evidence suggests that CAR disruption in adult cancer survivors can persist as long as 5 years postdiagnosis.[20] This finding suggests that disturbance of CARs may persist after completion of childhood cancer treatment, too. Identifying and treating circadian dysregulation are important, as it has been linked to multiple chronic diseases.[21,22] Survivors of childhood cancers are at increased risk for developing many of these diseases,[23,24] and intervention to improve circadian health during early survivorship may help mitigate their development.[22,25,26]

Thus, this was a hypothesis-generating study, with the primary aim to compare CARs of adolescents within 5 years of completing cancer treatment (survivors) with those of healthy adolescents who never had cancer. We hypothesized that disturbances in CARs would be present in both groups but would be significantly greater in survivors. Secondary aims were to investigate the relationship between CARs and fatigue, and differences between survivors and controls and between early survivors (<12 months posttreatment) and late survivors (≥12 months posttreatment). We hypothesized that this relationship, which has been identified in children during cancer treatment, would be stronger among survivors than among controls and that greater time posttreatment would attenuate this relationship. This study adds to our current limited knowledge of CARs in childhood cancer patients by evaluating adolescents for evidence of circadian disturbances during the first 5 years of survivorship.

METHODS

Study design and sample

This was a prospective, descriptive 7-day pilot study. Participants were a convenience sample of adolescents living, attending school, and working in the community setting. Inclusion criteria were English-speaking adolescents aged 13–18 years and their parent. Survivors were within 5 years of completing cancer treatment for any type of cancer. Exclusions were major psychiatric diagnosis and pregnancy. History of cancer was an additional exclusion for controls. Recruitment of survivors took place at three pediatric oncology clinics in the mid-Atlantic region of the United States at the time of their follow-up appointment. Because of the difficulty of recruiting healthy adolescents in a health care setting, survivors were encouraged to "invite a friend" or sibling to participate with them as a control. Controls were screened via telephone, and were consented and completed baseline measures in their home.

Study protocol

This study was approved by the Children's National Health System Institutional Review Board, which served as the institutional review board of record. Before participation, parents and participants 18 years of age or older signed informed consent forms, and adolescents 17 years and younger signed their assent. Baseline questionnaires were completed by adolescents and their parent following consent/assent. Adolescents were instructed on use of a sleep diary and actigraph, which was worn on their nondominant wrist continuously for 7 days. Incentives for participation were provided on return of equipment and diaries via prepaid priority mail envelopes.

Measures

The rest-activity rhythm has been considered a suitable noninvasive and robust marker of circadian timing[25] owing to its rhythmic expression and endogenous (genetic) underpinnings. It is measured using an actigraph (AW2, Philips, Inc., Murrysville, PA), which converts wrist activity into activity counts that represent the amplitude and frequency of acceleration events occurring over user-defined epochs.[27] A minimum of 72 hours of recording is required for reliable calculations.[28] Published studies have reported a variety of CARs, the choice of which can be influenced by the statistical capabilities of the manufacturer's software. For this study, six variables modeling a range of CAR characteristics (height, circadian timing, and

robustness) were chosen. They were calculated from activity counts downloaded from the actigraph, using a five-parameter extended cosine model that applies an antilogistic transformation of the standard cosine curve.[29] This model better accommodates human rest-activity rhythms, which exhibit a square-like waveform, than the standard cosine curve and has demonstrated its usefulness in studies of CARs in adult cancer patients.[30,31] Variables included amplitude, MESOR, acrophase, up-MESOR, down-MESOR, and *F*-statistic (defined in **Table 1**). To capture typical rest-activity patterns, actigraphy data collection was avoided during major holidays, travel vacations, the 2 days after daylight savings time changes, and acute illness.

The sleep diary was kept concurrently with actigraphy, completed at bedtime and wake time daily. Recorded information included bedtimes, wake times, nap start and end times, off-wrist times, school and job attendance, and illness.

Fatigue was measured by self-report using the Patient-Reported Outcomes Measurement Information System Pediatric Fatigue—Short Form, which includes versions for children 8–18 years of age, and for parents as proxy reporters for their child. It includes 10 items that assess fatigue over the past 7 days. Standardized *t* scores are calculated from the final summed score, with scores ≤50 considered within normal limits for fatigue and higher scores indicating greater than normal fatigue.[32] In our study, the cut-point for significant fatigue was considered the mean *t* score plus 1 SD of our healthy controls (score >53.9). Cronbach's alpha for parent report in the present study was 0.91 and for adolescent report was 0.86.

Table 1—Circadian activity rhythm definitions.

Variables	Definition
Acrophase	Clock time of peak activity. Represents the timing of the rest-activity rhythm. Change to earlier or later time during treatment can indicate an advanced or delayed circadian period.
Amplitude	Difference between the peak and trough of the cosine-fitted curve of activity counts. Represents the height of the rest-activity rhythm. Higher values indicate a more robust rhythm with higher activity level during the day and lower activity during the night.
Down-MESOR	Time of day of switch from high to low activity (from above MESOR to below MESOR). Represents the timing of the rest-activity rhythm. Lower (earlier) values indicate decline in activity earlier in the day, suggesting a more advanced circadian phase.
F-statistic	Represents adjustment of the R^2 goodness-of-fit statistic to account for the number of observations and the number of parameters in the cosine model. Represents the robustness of the rest-activity rhythm. Higher values indicate greater rhythmicity.
MESOR	The mean activity count of the cosine fitted 24-hour rest-activity pattern. Represents the height of the rest-activity rhythm. Higher values indicate more robust mean activity levels.
Up-MESOR	Time of day of switch from low to high activity (from <MESOR to >MESOR). Represents the timing of the rest-activity rhythm. Lower (earlier) values indicate increase in activity earlier in the day and suggest a more advanced circadian phase.

MESOR = midline estimating statistic of rhythm.

Statistical analysis

Descriptive statistics (mean ± SD, percent) were used to describe the sample and measures. Normality of variables and missing data patterns were evaluated, and *t* tests were used to test unadjusted group differences between sample characteristics. Age-adjusted linear mixed models were used to explore the effect of CARs on fatigue between survivors and controls. Linear mixed models included a random intercept to account for nonindependence between siblings. Linear regression, adjusting for age, was used to test for potential interactions between CAR variables and time posttreatment (time) in survivors, dichotomized as "early" survivors (<12 months posttreatment) and "late" survivors (≥12 posttreatment) on fatigue outcomes. Analyses were carried out with IBM SPSS Statistics, version 21 (IBM Corp, Armonk, New York) and SAS 9.3 (SAS Institute, Inc., 2012, Cary, North Carolina). Significance was $P < .05$. No corrections were made for multiple comparisons as this was an exploratory study, and clinically meaningful directions for future research might otherwise be missed.[33]

RESULTS

Sample

Recruitment was conducted from April 2016 through January 2019. Thirty-five survivors were approached for recruitment, and 31 consented. One survivor dropped out because of family issues, and actigraphy for another survivor was recorded for only 2 days owing to technical issues, and so this survivor was excluded from analysis. Control participants were invited into the study by their participating survivor friend, and so no record was kept of the number of adolescents approached for participation, but all consented controls completed the study. Analysis included 30 controls and 29 survivors, of which 15 were early survivors and 14 were late survivors. A description of the sample is presented in **Table 2**. No significant differences were found in any sample characteristics between controls and survivors or between early and late survivors. Medications reported by survivors included trimethoprim-sulfamethoxazole (n = 6), pentamidine (n = 1), proton pump inhibitor (n = 2), albuterol (n = 2), inhaled corticosteroid (n = 1), antihistamine (n = 2), levothyroxine (n = 1), oral contraceptive (n = 1), rivaroxaban (n = 1), and melatonin (n = 1) and among controls included doxycycline (n = 1), valproic acid (n = 1), and melatonin (n = 1).

Circadian activity rhythms

CAR variables are presented by group in **Table 3**. Comparison of CARs between adolescents with leukemia and lymphoma, our two best represented cancer types, showed no differences; so all survivors were considered together, regardless of diagnosis. No significant differences were noted between survivors and controls for any CAR variable, before or after adjusting for age; however, group means obscured individual variations, as

Table 2—Description of the sample.

Variable	Mean ± SD or N (%)		
	Survivors	Controls	*P*
Age (y)	16.2 ± 1.6	15.5 ± 1.6	.10
Sex (female)	16 (55.2)	20 (66.7)	.37
Race			.09*
White	15 (51.7)	22 (73.3)	
Black/African American	7 (24.1)	3 (10.0)	
Non-black Hispanic	4 (13.8)	4 (13.3)	
Asian	2 (6.9)	0	
Multiracial	1 (3.4)	1 (3.3)	
Cancer type (survivors)			
Leukemia	14 (48.3)		
Lymphoma	10 (34.5)		
Cranial/brain	2 (6.9)		
Bone	3 (10.3)		
Relapse (yes)	4 (13.4)		
Cranial radiation (yes)	3 (10.3)		
Months posttreatment	19.1 ± 18.0		

*Chi-square test of white vs other.

survivors showed disturbances in several CAR variables compared with controls. For example, using a cut-point for disturbed CARs of >1 SD below the mean for healthy controls, amplitude was disturbed in 31.0% of survivors compared with 20.0% of controls, and MESOR was disturbed in 27.6% of survivors compared with 10.0% of controls. **Figure 1** depicts activity counts graphed across the study for a survivor with a robust rest-activity rhythm compared to one with a disturbed rhythm.

For the full sample, higher age was significantly associated with lower amplitude ($r = -.267$, $P = .041$) and MESOR ($r = -.367$, $P = .004$), later acrophase ($r = .296$, $P = .023$), and down-MESOR ($r = .425$, $P = .001$), and with lower *F*-statistic ($r = -.427$, $P = .001$). Post hoc analysis showed significant correlations between age and CARs only for survivors. In analysis of additional factors that may affect CAR outcomes among survivors, down-MESOR was significantly later (66 minutes) in males than in females ($t_{(27)}$ 2.478, $P = .020$). White adolescents had a significantly earlier acrophase ($t_{(19.70)}$ −3.433, $P = .003$), up-MESOR ($t_{(19.10)}$ −2.869, $P = .010$), and down-MESOR ($t_{(27)}$ −3.221, $P = .003$) than adolescents of other races or ethnicities.

Fatigue and circadian activity rhythms

Although the average parent-reported fatigue scores were higher for survivors than for controls, they did not differ significantly between survivors and controls for either measure. Significant fatigue was identified in seven (11.7%) participants (five survivors, two controls) by parent report and nine (15%) participants (four survivors, five controls) by adolescent report.

Controlling for age, among survivors, earlier down-MESOR was associated with greater parent-reported fatigue ($P = .020$). Earlier acrophase ($P = .023$) and up-MESOR ($P = .025$) were associated with greater adolescent-reported fatigue. Among controls, greater MESOR was associated with greater parent-reported fatigue ($P = .0495$), and no CAR variables were associated with adolescent-reported fatigue (**Table 4**).

Comparing early versus late survivors, controlling for age, several significant CAR-by-time interactions were noted (**Table 5**). For parent-reported fatigue models, significant interactions were demonstrated for acrophase ($P = .006$) and down-MESOR ($P = .002$) with post hoc testing showing that these effects were significant only for early survivors. For adolescent-reported fatigue models, a significant CAR-by-time interaction was demonstrated for *F*-statistic ($P = .020$) and marginally for down-MESOR and amplitude (both $P = .051$), which, again, were significant only for early survivors.

Table 3—Circadian activity rhythm values for survivors and controls.

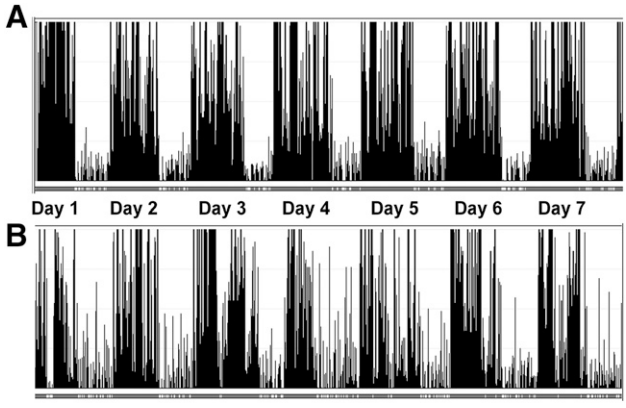
Variable	Survivors	Controls	*P**
Acrophase**	15.63 ± 1.31	15.09 ± 1.24	.11
Amplitude	1.99 ± .28	2.08 ± .22	.17
Down-MESOR**	23.53 ± 1.28	23.09 ± 1.36	.20
F-statistic	2505.7 ± 1293.0	2872.6 ± 1386.3	.30
MESOR	1.17 ± .13	1.21 ± .11	.16
Up-MESOR**	7.73 ± 1.62	7.09 ± 1.37	.11

*Significance for unadjusted group differences; **24-h clock time, with minutes presented as proportion of an hour. MESOR = midline estimating statistic of rhythm.

DISCUSSION

It is encouraging that, in our sample, CARs of most survivors did not differ significantly from those of controls. This finding suggests

Figure 1—Rest-activity patterns of two survivors.



Cumulative activity counts (vertical lines) represent the rest-activity pattern across 7 days. Higher lines indicate higher activity levels. Participant **(A)** demonstrates a robust rest-activity pattern; participant **(B)** demonstrates a lack of a robustness suggested by higher activity during the night and less distinct sleep periods and lower activity during the day.

Table 4—Relationship between circadian activity rhythm (CAR) variables and fatigue for survivors and controls.

CAR variable	Controls			Survivors		
	Beta	SE	*P*	Beta	SE	*P*
Parent-reported fatigue						
Acrophase	−.84	1.22	.495	−2.62	1.37	.066
Amplitude	5.11	6.71	.454	−10.03	6.27	.122
Down-MESOR	−1.03	1.14	.372	−3.54	1.42	.020*
F-statistic	−.0001	.0012	.916	.0007	.0015	.654
MESOR	28.02	13.60	.0495*	2.55	13.49	.852
Up-MESOR	−.43	1.12	.701	−1.28	1.08	.245
Adolescent-reported fatigue						
Acrophase	−1.43	.91	.129	−3.24	1.34	.023*
Amplitude	1.06	5.26	.842	−5.83	6.75	.400
Down-MESOR	−1.57	.84	.073	−2.82	1.58	.085
F-statistic	.001	.0009	.289	.0007	.002	.665
MESOR	9.18	11.18	.419	8.33	13.95	.556
Up-MESOR	−.91	.85	.297	−2.40	1.007	.025*

*Significant *P* values. Linear mixed models were run for each individual circadian activity rhythm (CAR) variable, adjusted for age. MESOR = midline estimating statistic of rhythm, SE = standard error.

Table 5—Interaction of circadian activity rhythms (CARs) and time posttreatment on fatigue among survivors and CAR effects on fatigue by early and late survivor group.

CAR Variable	CAR Time			CAR Effect, Early Survivors			CAR Effect, Late Survivors		
	Beta	SE	*P*	Beta	SE	*P*	Beta	SE	*P*
Parent-reported fatigue									
Acrophase	7.10	2.36	.006*	−5.65	1.60	.002*	1.45	1.86	.445
Down-MESOR	7.72	2.21	.002*	−6.47	1.49	.0002*	1.25	1.88	.513
Up-MESOR	3.99	2.16	.078	−2.94	1.41	.049*	1.05	1.65	.528
Adolescent-reported fatigue									
Amplitude	−29.55	14.36	.051	−.21	7.45	.978	−29.76	12.85	.029*
Down-MESOR	5.60	2.72	.051	−4.66	1.82	.017*	0.94	2.44	.703
F-statistic	−.006	.003	.020*	.0045	.0021	.045*	−.0019	.0018	.295

*Significant *P* values. For time posttreatment (time), <12 months was coded as 0, and ≥12 months as 1. Linear regression models were adjusted for age. Only CAR variables with significant or marginally significant interactions are included. MESOR = midline estimating statistic of rhythm, SE = standard error.

that, despite probable disturbance of CARs during cancer treatment, as found in adult and childhood cancer studies,[13,30] most adolescents appear to recover within the first 5 years posttreatment.

Likewise, fatigue did not differ between groups by either parent or adolescent report; however, fatigue was differentially associated with CAR characteristics, depending on whether an adolescent was a survivor or a control. Among survivors, higher fatigue level was associated with earlier acrophase, up-MESOR, and down-MESOR, reflecting an advance in circadian timing. Similar to our findings, an advance in the circadian phase has been identified in both adult cancer patients during treatment[34,35] and in children with leukemia after the start of dexamethasone treatment.[13] Among controls, parent-reported fatigue was associated with greater MESOR, representing greater height of the rest-activity pattern (higher activity levels). It is difficult to explain the latter finding, and it is most likely not a circadian disturbance, as activity was higher, rather than lower, as fatigue increased. Our sample was generally very active and included several athletes. It is possible that parents, observing the high activity level of their child, may have presumed that they would also likely be fatigued. It is noteworthy that the relationship was not present with adolescent-reported fatigue.

Significant interactions between CARs and time emerged among survivors, in which the association between fatigue and several CARs differed between early and late survivors. This appeared to be a time-dependent relationship, with significant effects only for early survivors. The absence of this association among late survivors may indicate reestablishment of the age-related physiological delay in circadian timing[36] as time post-treatment increases. Although these analyses must be considered

exploratory owing to small sample sizes, they suggest that significant changes in the relationship between CARs and fatigue occur within the first 5 years posttreatment, a finding that merits further investigation.

This study had several limitations. Our age range of 13–18 years covered a broad span of adolescence, and many developmental and circadian changes occur between early and late adolescence. Larger studies with narrower age ranges (eg, early, mid-, and late adolescence) are needed to better identify developmental circadian variations and their association with important outcomes, such as fatigue, during different developmental periods. Given that this was a pilot study, we had a relatively small sample of survivors and included adolescents with any type of cancer or treatment, limiting our ability to analyze CARs by cancer type or treatment and therefore limiting the generalizability of our findings. Despite our finding of no differences in CARs between adolescents with leukemias and lymphomas, tumor types, tumor location, and treatment type, intensity and length are all likely to affect circadian health outcomes. These differences are not well understood even in adult cancer research, where the study of CARs has been carried out in larger samples with more targeted cancer types. Large samples are required to account for the effects of these multiple factors and would require integrating sleep and circadian measures into large pediatric oncology clinical trials, a recommendation recently proposed in a position paper on behalf of the International Psycho-Oncology Society Pediatrics Special Interest Group.[37]

In conclusion, on average, survivors did not demonstrate substantial differences in CARs compared with controls, suggesting that if treatment had disturbed their circadian rhythmicity, recovery was relatively rapid for most adolescents once treatment ended. Fatigue also did not differ between survivors and controls, although among survivors, greater fatigue was associated with disturbance of several CAR variables, and these relationships varied by time posttreatment. Studies including larger samples of children and adolescents with more homogeneous cancer diagnoses and narrower age ranges are needed to expand our understanding of CARs, their trajectory of change across survivorship and relationship to health, and the association between CARs and fatigue.

ABBREVIATIONS

CARs, circadian activity rhythms
MESOR, Midline estimating statistic of rhythm

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Address correspondence to: Valerie E. Rogers, PhD, RN, 655 W. Lombard St, Suite 575B, Baltimore, MD 21201; Tel: (410) 794-6485; Email: valerie.e.rogers@gmail.com

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