Received: 7 May 2018 | Revised: 10 August 2018 | Accepted: 13 August 2018

DOI: 10.1002/pon.4862

PAPER

WILEY

Depressive symptoms and actigraphy-measured circadian disruption predict head and neck cancer survival

Elizabeth Cash[1,3,4] | C. Riley Duck[2] | Courtney Brinkman[1] | Whitney Rebholz[1] | Christy Albert[1] | Mary Worthen[1] | Mia Jusufbegovic[1] | Liz Wilson[1,3] | Jeffrey M. Bumpous[1,3]

[1] Department of Otolaryngology-Head and Neck Surgery and Communicative Disorders, University of Louisville School of Medicine, Louisville, KY, USA

[2] University of Louisville School of Medicine, Louisville, KY, USA

[3] James Graham Brown Cancer Center, Louisville, KY, USA

[4] Department of Psychological and Brain Sciences, University of Louisville, Louisville, KY, USA

Correspondence
Cash, Elizabeth, 529 S Jackson St., 3rd Floor ENT Suite, Louisville, KY 40202, USA.
Email: liz.cash@louisville.edu

Funding information
University of Louisville, Grant/Award Number: Multidisciplinary Research Incentive Grant

Abstract

Objective: Depressive symptoms have demonstrated prognostic significance among head and neck cancer patients. Depression is associated with circadian disruption, which is prognostic in multiple other cancer types. We hypothesized that depressive symptoms would be associated with circadian disruption in head and neck cancer, that each would be related to poorer 2-year overall survival, and that relationships would be mediated by tumor response to treatment.

Methods: Patients (N = 55) reported on cognitive/affective and somatic depressive symptoms (PHQ-9) and wore an actigraph for 6 days to continuously record rest and activity cycles prior to chemoradiation. Records review documented treatment response and 2-year survival. Spearman correlations tested depressive symptoms and circadian disruption relationships. Cox proportional hazard models tested the predictive capability of depressive symptoms and circadian disruption, separately, on survival.

Results: Depressive symptoms were significantly associated with circadian disruption, and both were significantly associated with shorter survival (somatic: hazard ratio [HR] = 1.325, 95% confidence interval [CI] = 1.089-1.611, P = .005; rest/activity rhythm: HR = 0.073, 95% CI = 0.009-0.563, P = .012; nighttime restfulness: HR = 0.910, 95% CI = 0.848-0.977, P = .009). Tumor response to treatment appeared to partly mediate the nighttime restfulness-survival relationship.

Conclusions: This study replicates and extends prior work with new evidence linking a subjective measure of depression and an objective measure of circadian disruption—2 known prognostic indicators—to shortened overall survival among head and neck cancer patients. Continued examination should elucidate mechanisms by which depressive symptomatology and circadian disruption translate to head and neck cancer progression and mortality.

KEYWORDS

cancer, circadian disruption, depressive symptoms, head and neck cancer, nighttime restfulness, oncology, overall survival, rest/activity rhythm

1 | BACKGROUND

Head and neck cancer patients experience some of the highest rates of clinical depression among cancer patients.[1] Depressive symptomatology is increasingly being recognized as prognostic for early head and neck cancer mortality.[2-5] Our prior work revealed that depressive symptoms predicted significantly higher 2-year mortality rates and that this relationship was partly mediated by poorer tumor

 © 2018 John Wiley & Sons, Ltd.

response to treatment.[6] Effects were not explained by the efficacy of treatment or the typical prognostic factors of patient age, stage or site of tumor, or type of treatment received.

Depression and head and neck cancer survival may be linked via biological pathways. There is strong evidence implicating links between circadian disruption and depressive symptomatology.[7,8] While the causal nature of these relationships remains under investigation, shifts in circadian activity peaks may be depressogenic.[8] Circadian gene polymorphisms have been implicated in depression relapses and rest/activity rhythm disruption among individuals with bipolar disorder, suggesting that clock gene effects extend to psychological well-being.[9]

Strong coordination of the body's circadian clocks with environmental time-givers appears to be crucial for tumor suppression.[10] Murine and cellular data conclusively demonstrate that circadian disruption is tightly linked to tumor initiation and progression.[11] In humans, endogenous circadian signaling, indicated by actigraphy-measured rest/activity rhythm and nighttime restfulness, has strong prognostic significance for early mortality among metastatic colorectal cancer patients.[12,13] Similarly, circadian activity phase shifts play a role in tumor initiation: Individuals living in western time zones have increased cancer risk, likely related to adherence to eastern social and occupational schedules creating subtle circadian activity phase shifts.[10] Data are so convincing that the World Health Organization considers shift work to be potentially carcinogenic (level 2A).[14]

One prior study has employed actigraphy among head and neck cancer patients, and revealed rest/activity rhythm disruption, decreased nighttime restfulness, and circadian phase shifts compared to controls.[15] Because of the growing propensity for desynchronization of human activity with the earth's rotation, circadian disruption and resultant oncogenic sequelae are likely to impact large numbers of people. Combined with burgeoning evidence that depressive symptoms portend poorer head and neck cancer survival, it is critical that we gain mechanistic insight into relationships among mood, circadian factors, and cancer control mechanisms. We hypothesized that depressive symptoms would be associated with circadian disruption, that depressive symptoms and circadian disruption would each be related to poorer 2-year overall survival, and that significant relationships would be mediated by tumor response to treatment.

2 | METHODS

2.1 | Participants and procedures

After university institutional review board approval was obtained (reference number 14-0607), patients with a new primary head and neck cancer were invited to participate at a treatment-planning visit. After providing written informed consent, participants received psychometric questionnaires and instructions for actigraphy collection. Study assistants arranged to meet with participants the following week to collect data and provide compensation. Those who did not speak English, had benign disease, would be treated elsewhere, lived >120 mi away, were immunocompromised, abusing alcohol, or had severe psychiatric illness were excluded.

2.2 | Measures

2.2.1 | Clinical variables

Demographics including age at diagnosis/enrollment, biological sex, marital status, income, and alcohol and smoking history were collected from intake forms. American Joint Commission on Cancer, Seventh Edition, staging was determined utilizing all available clinical, pathologic, and radiographic data. Viral status was determined by either human papillomavirus (HPV; in situ hybridization) or p16 (immunohistochemistry) results. Tumors were classified into oral, oropharyngeal, laryngeal, hypopharyngeal, and other sites.

Medical records were reviewed for treatment regimen (surgery, radiotherapy, chemotherapy), clinical and/or radiographic evidence of tumor response 3-6 months post treatment completion, and 2-year follow-up as this is when the vast majority of treatment failures occur. To indicate treatment response, patients were coded as poorly responsive if there was evidence of stable, persistent, or progressive disease. Otherwise, patients were coded as optimally responsive. Survival was calculated from date of enrollment.

2.2.2 | Depressive symptoms

The Patient Health Questionnaire (PHQ-9) was used to indicate frequency of depressive symptoms during the previous 2 weeks on a 0 to 3 scale.[16] The PHQ-9 has demonstrated adequate internal consistency, reliability, and validity,[16] and has been utilized in studies among head and neck cancer patients.[4,17] Sum scores were generated for all 9 items (range 0-27) and for items representing a 2-factor structure[18]: cognitive/affective symptoms (mood, anhedonia, feelings of failure, trouble concentrating, psychomotor perturbations, and suicidality; range 0-18) and somatic symptoms (sleep, appetite and energy level changes; range 0-9).

2.2.3 | Circadian disruption

Patients wore an actigraph (Mini-Motionlogger; Ambulatory Monitoring Systems, Inc., Ardsley, NY) at home for 6 days. Data were scored utilizing self-reported sleep and wake times logged by participants. In the few instances where the watch was briefly removed, these minutes were deleted. This protocol has been deemed sufficient for estimating circadian disruption in cancer populations.[12,13]

Three indices were calculated: rest/activity rhythm, the autocorrelation coefficient of activity for each minute on the first day compared to the same minute on each subsequent day. This is considered a measure of circadian consistency or similarity across days.[12,13] Nighttime restfulness is the ratio of time in bed during which activity falls below median activity for time out of bed. It indicates the frequency of movement during time in bed. Both rest/activity rhythm and nighttime restfulness are prognostic for overall survival in metastatic colorectal cancer patients.[12,13] Acrophase, the average minute at which peak activity occurs each day indicates circadian phase shifts, is implicated in cancer risk and progression.[10,14]

Daytime sedentary behavior was also assessed, but because of skewed data and fewer prognostic findings in extant literature, this index was not analyzed.

2.3 | Statistical analyses

Potential covariates included age at diagnosis, biological sex, marital status, income, tobacco history, pain level at study entry, site of disease, T and N classification and summary stage, viral status, postoperative status, and treatment received. Those that correlated with both depressive symptoms and overall survival, or with both circadian disruption and overall survival, were considered possible proxies in their respective statistical models.[19] When this occurred, Cox models were constructed to include the hypothesized predictor, the possible proxy, and their interaction term.

Descriptive and summary statistics characterized clinical and demographic features. For primary analyses, Spearman correlations assessed relationships between depressive symptoms and circadian disruption. Relationships between depressive symptoms and survival, as well as circadian disruption and survival, were tested using separate Cox proportional hazard models.

Secondary analyses employed Spearman correlations to assess associations of 3 variables—depressive symptoms, circadian disruption, and overall survival—with tumor response to treatment. For those significantly associated with treatment response, Cox models were repeated to include the predictor, treatment response, and their interaction term.

Because of skewness, rest/activity rhythm and income were dichotomized at the median to meet Cox regression analytic assumptions. All other statistical tests utilizing these variables, and statistical tests for all other analyses, entered mean-centered continuous data. Tests were 2-sided, $\alpha = .05$, and conducted in SPSS version 25 (IBM; Armonk, NY). Power analysis indicated that unadjusted Cox models would have 95%[6] and 79%[13] power to detect effects of depressive symptoms (n = 55) and circadian disruption (n = 38), respectively, on overall survival.

3 | RESULTS

3.1 | Patient and clinical characteristics

Of 197 patients screened, 77 met criteria and 55 (71%) were enrolled. Those who declined had more advanced T classification ($t = 2.917$, $P = .004$), but no differences in age, tumor site, or N classification were observed. Patients had typically received notification of their diagnosis 1 to 4 weeks prior to presentation. While 11 (21%) had undergone surgical procedure to confirm extent of malignancy and extirpation, postoperative status was not associated with any study variable. None had yet received radiation or chemotherapy. We followed every patient until death or for 2 years. When death date was unavailable in records, obituaries were reviewed. Sample characteristics are presented in Table 1. We observed a 33% mortality rate (n = 18 deaths), which is higher than national estimates of 25% 2-year mortality rates for head and neck cancer, and higher than reported in prior studies.[2,4] Actigraphy data were provided by 38 participants: 4 could not wear the devices due to occupational or band sizing issues, 5 declined, and 8 returned partial or unusable data.

3.2 | Primary analyses

3.2.1 | Associations between depressive symptoms and circadian disruption

Spearman correlations revealed that cognitive/affective symptoms of depression were associated with rest/activity rhythm disruption ($r_s = -.338$, $P = .041$). Both overall ($r_s = .339$, $P = .040$) and somatic depressive symptoms ($r_s = .370$, $P = .024$) were significantly associated with activity phase shifts, with peaks shifting from morning to evening hours.

3.2.2 | Associations between depressive symptoms and overall survival

Neither the total depressive nor cognitive/affective symptom scores were associated with survival. However, greater somatic depressive symptoms significantly predicted poorer 2-year overall survival (hazard ratio [HR] = 1.325; 95% confidence interval [CI] = 1.089-1.611; $P = .005$; Table 2; Figure 1A). No proxies were associated with depressive symptoms.

3.2.3 | Associations between circadian disruption and overall survival

Both rest/activity rhythm disruption (HR = 0.073; 95% CI = 0.009-0.563; $P = .012$) and lower nighttime restfulness (HR = 0.910; 95% CI = 0.848-0.977; $P = .009$), but not acrophase (HR = 1.196; 95% CI = 0.860-1.665; $P = .288$), were associated with 2-year overall survival. Income was the only proxy significantly associated with nighttime restfulness ($r_s = .502$, $P = .002$) and survival ($r_s = .419$, $P = .006$). Statistical tests were repeated using a Cox model stratified at the median income level. Poorer nighttime restfulness remained significantly associated with poorer overall survival (HR = 0.930; 95% CI = 0.865-0.999; $P = .049$).

3.3 | Secondary analyses

3.3.1 | Mediation by tumor response to treatment

Of the depressive symptom and circadian disruption measures, only nighttime restfulness was associated with tumor response to treatment ($r_s = -.348$, $P = .038$). Tumor response was also associated with overall survival ($r_s = -.332$, $P = .005$). A Cox model with 3 predictors (nighttime restfulness, tumor response to treatment, and their interaction term) revealed that the relationship between nighttime restfulness and overall survival was mediated by tumor response to treatment (Figure 1B). According to MacArthur criteria for mediation,[19] nighttime restfulness (X) at study entry preceded tumor response to treatment (Y), X was significantly associated with Y, the interaction term was not significant, and there was a significant main effect of Y.

4 | DISCUSSION

Somatic symptoms of depression measured prior to chemoradiation predict shortened survival among patients with head and neck cancer. Our findings are consistent with prior work, including our own results from a separate patient sample,[6] showing that even mild to moderate

TABLE 1 Patient clinical and demographic characteristics (N = 55)

Patient characteristics		N	%
Male		33	60
Marital status	Single, never married	8	14.5
	Married/domestic partnership	31	56.4
	Widowed	4	7.3
	Divorced	11	20.0
	Separated	1	1.8
Annual income[a]	<$15 000	7	17.1
	$15 000-$40 000	7	17.1
	$40 000-$50 000	7	17.1
	$50 000-$70 000	6	14.5
	$70 000-$100 000	7	17.1
	>$100 000	7	17.1
Tobacco history	Never smoked	21	38.9
	Quit	19	35.2
	Current	14	25.9
Disease characteristics			
Site of disease	Oral	17	30.9
	Oropharyngeal	16	29.1
	HPV−	2	12.5
	HPV+	12	75.0
	Undetermined	2	12.5
	Hypopharyngeal	4	7.3
	Laryngeal	8	14.5
	Other	10	18.2
Summary stage	Not completely staged or unknown primary	5	9.1
	Stage I	11	20.0
	Stage II	4	7.3
	Stage III	10	18.2
	Stage IV	25	45.4
Treatment received	Declined/observation only	2	3.6
	OR only	5	9.1
	XRT only	3	5.5
	OR + XRT and/or CT	28	50.9
	XRT + CT	15	27.3
Tumor response to treatment	Optimal	36	65.5
	Suboptimal	19	34.5

Patient characteristics		Mean	SD	Median	Range
Age at diagnosis, years		58.5	10.6	58	24-82
Pack-years		28.9	20.2	30	1-80
Depressive symptoms					
Total		5.5	5.0	5.0	0-23
Cognitive/affective		2.4	3.3	1.0	0-14
Somatic		3.1	2.6	3.0	0-9
Circadian disruption					
Rest/activity rhythm, correlation coefficient		.132	.086	.119	−.058-.282
Nighttime restfulness, proportion		92.829	6.459	95.040	74.162-99.503
Acrophase, clock hour		14:46	1:52	14:31	10:37-20:01
Two-year overall survival, days	Events = 18 (33.3%)	537	233	642	12-741

Abbreviations: OR, operative procedure; XRT, radiation therapy; CT, chemotherapy.

[a]Income data are missing for n = 14 participants who declined to report this information.

depressive symptoms predict early mortality in head and neck cancer patients.[2-6] We previously demonstrated that depressive symptom relationships to survival are mediated by tumor response to treatment. We did not replicate this in the current study, which could be explained by the use of a different instrument to measure depressive symptoms. However, we did observe that circadian rest/activity rhythm disruption and less restful nights each predicted poorer overall survival. We believe this to be the first study linking a subjective measure of depression, an objective measure of circadian disruption, and clinical outcomes (overall survival) in head and neck cancer patients.

In our prior study, the most frequently endorsed depression item on the Hospital Anxiety and Depression Scale (HADS) was the somatic symptom of "feeling slowed down."[6] The current study utilized the PHQ-9, which allowed a more refined look at different aspects of depressive symptomatology. We again observed that somatic

TABLE 2 Summaries of Cox proportional-hazard survival statistics

	N	B	Hazard ratio	95% Confidence interval	*P* Value
Primary analyses					
Depressive symptoms	55				
Total		0.066	1.068	0.976-1.170	.153
Cognitive/affective		−0.005	0.995	0.853-1.162	.953
Somatic		0.281	1.325	1.089-1.611	.005
Circadian disruption	38				
Rest/activity rhythm		−2.617	0.073	0.009-0.563	.012
Nighttime restfulness		−0.094	0.910	0.848-0.977	.009
Adjusted for income		−0.073	0.930	0.865-0.999	.049
Acrophase		0.179	1.196	0.860-1.665	.288
Secondary analyses					
Survival mediation	38				
Nighttime restfulness		−0.121	0.886	0.798-0.984	.024
Tumor response to treatment		2.605	13.534	2.613-70.085	.002
Nighttime restfulness × tumor response		−0.066	0.936	−0.770-1.140	.512

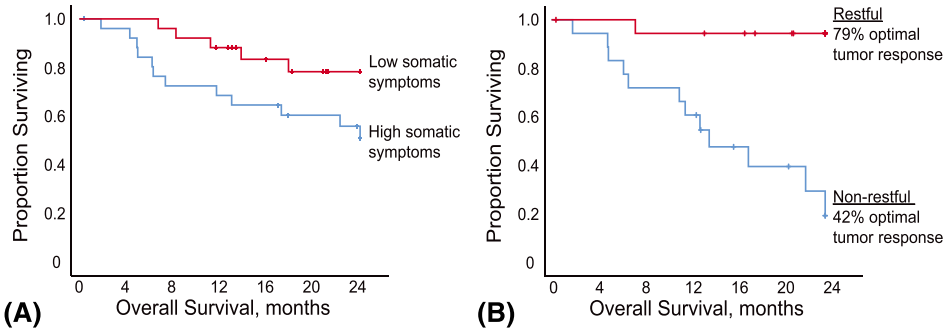

FIGURE 1 A, For descriptive (not analytic) purposes, Kaplan-Meier curves are shown for 2 groups of patients with high (mean = 5) vs low (mean = 1) somatic symptoms of depression based on a median split. Greater somatic depressive symptoms, reported prior to beginning cancer treatment, significantly predicted poorer 2-year overall head and neck cancer survival. B, Kaplan-Meier curves showing high (mean = 97.7%) vs low (mean = 88.2%) actigraphy-measured nighttime restfulness score split at the median, again for descriptive (not analytic) purposes. Nighttime restfulness measured prior to the start of cancer treatment significantly predicted 2-year overall head and neck cancer survival. We also observed that tumor response mediated the circadian-survival relationship. Patients experiencing high nighttime restfulness prior to undergoing cancer treatment had a 79% (n = 15) optimal tumor response rate (red line). Among patients who were experiencing less restful nights, only 42% (n = 8) achieved a subsequent optimal tumor response to treatment (blue line)

symptoms might be driving survival associations. However, while 33% of participants scored above clinical cutoff for major depression in our prior study, a smaller proportion (25%) met criteria in this study (PHQ-9 sum score >9). This narrower distribution in total depression scores may explain why we did not observe a significant effect on overall survival. This also likely precluded tests for mediation by tumor response in the depression-survival relationship.

Response pattern differences may partly have arisen from measurement characteristics. Many items on the HADS inquire about ability to engage in prototypical activities rather than about diagnostic symptoms. The HADS may be suitable for use among patients with a tendency toward social desirability, as may often be the case with older adult populations, or where the stigma of expressing mental health concerns may be high. Though we did not observe associations between depressive symptoms and biological sex in proxy examinations, it is important to consider the observation that male patients may be less likely to report symptoms.[20] The HADS may generally be better suited to elicit responses among more reticent or hesitant patients.

While cognitive/affective symptoms on the PHQ-9 were not associated with overall survival, increases in these symptoms were correlated with younger age (r_s = −.373, *P* = .012) and being widowed, divorced, or separated (r_s = −.418, *P* = .007). Younger patients may have been experiencing greater cognitive and/or affective symptoms, or they perhaps felt more comfortable endorsing them. Marital status may also confer protection against the experience of depressive symptomatology during cancer treatment[21] as well as reduced cancer mortality.[22] Although neither proxy was associated with survival, prior observations suggest their potential relevance to head and neck cancer, warranting ongoing consideration.

Somatic depressive symptoms can include changes in appetite, sleep, and energy levels, with either an increase or decrease in symptoms thought to be potentially indicative of depressed states. While decreased appetite, sleep, and energy level may result from the

burden of the tumor itself, increases in these symptoms (hypersomnia, overeating, and increased energy) are also common and not indicative of head and neck tumor burden. While the PHQ-9 does not require respondents to characterize the nature of their experiences, we observed no significant correlations between somatic scores and stage (T and N classification) or site of disease, or with viral etiology. This lack of association suggests that somatic endorsements in our sample may be distinct from tumor-driven somatic symptomatology.

We also considered the potential impact of pain and found significant associations with both somatic symptoms (r_s = .321, P = .045) and nighttime restfulness (r_s = −.377, P = .023). However, pain scores did not meet proxy criteria for survival models, and so, we do not expect pain to have confounded those relationships. The absence of this and other (e.g., age, stage, biological sex, marital status, tobacco history, T and N classification, viral status, postoperative status, treatment regimen) proxy threat to our statistical models suggests that links between somatic symptoms, and circadian disruption, with overall head and neck cancer survival are robust to the effects of other clinical and demographic prognostic indicators.

The circadian disruption indicator, nighttime restfulness, describes the proportion of physical activity recorded while in bed that falls below the median physical activity level recorded during daytime hours. Restless nights are associated with early mortality in metastatic colorectal cancer patients.[12,13] The index does not offer an indication of sleep per se, as favorable ratios may also exist among highly active individuals who suffer fragmented sleep. Its freedom from variance introduced by homeostatic sleep mechanisms and demonstrated prognostic significance[12,13] led to its consideration. We extend existing literature with our observation among a smaller subset of patients, that those experiencing less restful nights also demonstrate poorer overall survival. Secondary findings suggest that this may hold true for patients with nonresponsive tumors. This observation should be considered fodder for future hypotheses rather than a confirmatory finding. These initial data suggest that the deleterious effects of circadian disruption, demonstrated in multiple prior cancer studies, may hold true for patients with head and neck cancer.

Depressive symptoms were associated with circadian phase shifts in timing of peak daily activity levels to later hours, consistent with observations among advanced non-small cell lung cancer patients planning for chemotherapy.[23] We did not find circadian phase shifts to be significantly associated with overall survival, however. Though phase shifts may portend higher risk for tumor initiation, our measurement of acrophase occurred after the onset of disease, potentially limiting generalizability to existing epidemiological data. In the context of an established malignancy, shifts in activity may be less consequential for survival than restlessness and rhythm disruption.

The degree of inherent variability in different measures of circadian disruption also suggests the possibility that single markers may be more or less suited for circadian analysis in different populations. Circadian systems respond differently to stimuli, may become dysregulated to varying degrees, and may become further disrupted by tumor progression[24] and associated treatments.[25] Further examination of endogenous host rhythm disruption indicators in a larger sample of head and neck cancer patients is warranted.

4.1 | Clinical implications

In light of evidence that circadian disruption portends poorer cancer survival,[11] interventions that target circadian re-entrainment may hold promise for head and neck cancer patients. Bright light exposure can prevent actigraphy-measured circadian disruption in breast cancer patients undergoing chemotherapy.[26] Melatonin supplements may re-entrain host circadian rhythms for patients with untreatable metastatic cancers.[27] Among head and neck cancer patients, taking melatonin during chemoradiation may stave off mucositis and reduce opiate dependence.[28] Spurred partly by the notion that circadian disruption plays a role in treatment outcomes,[29] the strategy of chronotherapy (shifting treatment to hours where healthy cells are more resilient) has been gaining popularity. Clinical observations comparing morning versus afternoon administration of head and neck cancer treatment hold promise for reduced toxicity.[30,31] Optimal intervention efficacy requires a better understanding of circadian disruption in head and neck cancer patients. Addressing this knowledge gap may add to our ability to predict treatment resistance and early mortality, and potentially lead to refined therapeutic treatment strategies for head and neck cancer patients.

4.2 | Future directions

While we assessed depressive symptoms at 1 time point, the emergence of depressive symptoms several months after a major medical event may also adversely impact health outcomes.[32] A longitudinal view of a depressed individual's changes in biology—before, during, and after cancer treatment—may help elucidate mechanisms underlying relationships between depressive symptoms and survival in head and neck cancer patients.

Examining other, well-established measures of circadian disruption is another important next step. Depression has been associated with flattened diurnal cortisol expression,[33] which in turn predicts shortened survival across multiple cancer types.[34-37] Further study will help to uncover how these biological processes relate to impaired host defenses against cancer.

4.3 | Study limitations

Depressive symptoms were assessed at study entry, but no further psychometric information was collected as patients progressed through treatment. There is likely some selection bias present, as 1 of the most common reasons for declining was being too busy or too distressed. The small sample, especially for actigraphy data, means that replication of these novel observations is required before any definitive conclusions can be drawn.

5 | CONCLUSIONS

Taken as a whole, our findings reinforce the notion that cognitive/affective symptoms are distinguishable from the somatic experiences of depression among head and neck cancer patients. This study represents the first step in filling an important knowledge gap by demonstrating that 2 robust prognostic indicators—depressive

symptoms and circadian disruption—are significantly linked, and that both may associate with poorer head and neck cancer outcomes. Continued examination of the varying manifestations of depressive symptomatology and circadian disruption in larger samples, potentially utilizing repeated measurement, will more clearly determine the mechanisms by which these factors may influence head and neck cancer progression and mortality.

ACKNOWLEDGEMENTS

The authors wish to thank Sandie Sephton, PhD, and Paula Bates, PhD, for their editorial guidance and advice in preparing the manuscript. University of Louisville Intramural Multidisciplinary Research Incentive Grant.

CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflicts of interest to disclose.

ORCID

Elizabeth Cash http://orcid.org/0000-0003-4148-6927
Whitney Rebholz http://orcid.org/0000-0002-6857-3070

REFERENCES

1. Massie MJ. Prevalence of depression in patients with Cancer. *J Natl Cancer Inst Monogr*. 2004;2004(32):57-71.
2. Lazure KE, Lydiatt WM, Denman D, Burke WJ. Association between depression and survival or disease recurrence in patients with head and neck cancer enrolled in a depression prevention trial. *Head Neck*. 2009;31(7):888-892.
3. Kim SA, Roh JL, Lee SA, et al. Pretreatment depression as a prognostic indicator of survival and nutritional status in patients with head and neck cancer. *Cancer*. 2016;122(1):131-140.
4. Shinn EH, Valentine A, Jethanandani A, et al. Depression and oropharynx cancer outcome. *Psychosom Med*. 2016;78(1):38-48.
5. Rieke K, Schmid KK, Lydiatt W, Houfek J, Boilesen E, Watanabe-Galloway S. Depression and survival in head and neck cancer patients. *Oral Oncol*. 2017;65:76-82.
6. Zimmaro LA, Sephton SE, Siwik CJ, et al. Depressive symptoms predict head and neck cancer survival: examining plausible behavioral and biological pathways. *Cancer*. 2018;124(5):1053-1060.
7. Salgado-Delgado R, Tapia Osorio A, Saderi N, Escobar C. Disruption of circadian rhythms: a crucial factor in the etiology of depression. *Depress Res Treat*. 2011;2011:839743.
8. Zaki NFW, Spence DW, BaHammam AS, Pandi-Perumal SR, Cardinali DP, Brown GM. Chronobiological theories of mood disorder. *Eur Arch Psychiatry Clin Neurosci*. 2018;268(2):107-118.
9. Bollettini I, Melloni EM, Aggio V, et al. Clock genes associate with white matter integrity in depressed bipolar patients. *Chronobiol Int*. 2017;34(2):212-224.
10. Gu F, Xu S, Devesa SS, et al. Longitude position in a time zone and cancer risk in the United States. *Cancer Epidemiol Biomarkers Prev*. 2017;26(8):1306-1311.
11. Eismann EA, Lush E, Sephton SE. Circadian effects in cancer-relevant psychoneuroendocrine and immune pathways. *Psychoneuroendocrinology*. 2010;35(7):963-976.
12. Levi F, Dugue PA, Innominato P, et al. Wrist actimetry circadian rhythm as a robust predictor of colorectal cancer patients survival. *Chronobiol Int*. 2014;31(8):891-900.
13. Innominato PF, Giacchetti S, Bjarnason GA, et al. Prediction of overall survival through circadian rest-activity monitoring during chemotherapy for metastatic colorectal cancer. *Int J Cancer*. 2012;131(11):2684-2692.
14. Straif K, Baan R, Grosse Y, et al. Carcinogenicity of shift-work, painting, and fire-fighting. *Lancet Oncol*. 2007;8(12):1065-1066.
15. Pati AK, Parganiha A, Kar A, Soni R, Roy S, Choudhary V. Alterations of the characteristics of the circadian rest-activity rhythm of cancer inpatients. *Chronobiol Int*. 2007;24(6):1179-1197.
16. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613.
17. Britton B, Clover K, Bateman L, et al. Baseline depression predicts malnutrition in head and neck cancer patients undergoing radiotherapy. *Support Care Cancer*. 2012;20(2):335-342.
18. Guo B, Kaylor-Hughes C, Garland A, et al. Factor structure and longitudinal measurement invariance of PHQ-9 for specialist mental health care patients with persistent major depressive disorder: exploratory structural equation Modelling. *J Affect Disord*. 2017;219:1-8.
19. Kraemer HC, Kiernan M, Essex M, Kupfer DJ. How and why criteria defining moderators and mediators differ between the Baron & Kenny and MacArthur approaches. *Health Psychol*. 2008;27(2, Suppl):S101-S108.
20. Miaskowski C. Gender differences in pain, fatigue, and depression in patients with cancer. *J Natl Cancer Inst Monogr*. 2004;2004(32):139-143.
21. Morgan S, Cooper B, Paul S, et al. Association of personality profiles with depressive, anxiety, and cancer-related symptoms in patients undergoing chemotherapy. *Personal Individ Differ*. 2017;117:130-138.
22. Aizer AA, Chen MH, McCarthy EP, et al. Marital status and survival in patients with cancer. *J Clin Oncol*. 2013;31(31):3869-3876.
23. Du-Quiton J, Wood PA, Burch JB, et al. Actigraphic assessment of daily sleep-activity pattern abnormalities reflects self-assessed depression and anxiety in outpatients with advanced non-small cell lung cancer. *Psychooncology*. 2010;19(2):180-189.
24. Mormont MC, Levi F. Cancer chronotherapy: principles, applications, and perspectives. *Cancer*. 2003;97(1):155-169.
25. Sultan A, Choudhary V, Parganiha A. Worsening of rest-activity circadian rhythm and quality of life in female breast cancer patients along progression of chemotherapy cycles. *Chronobiol Int*. 2017;34(5):609-623.
26. Neikrug AB, Rissling M, Trofimenko V, et al. Bright light therapy protects women from circadian rhythm desynchronization during chemotherapy for breast cancer. *Behav Sleep Med*. 2012;10(3):202-216.
27. Brivio F, Fumagalli L, Fumagalli G, et al. Synchronization of cortisol circadian rhythm by the pineal hormone melatonin in untreatable metastatic solid tumor patients and its possible prognostic significance on tumor progression. *In Vivo*. 2010;24:239-241.
28. Onseng K, Johns NP, Khuayjarernpanishk T, et al. Beneficial effects of adjuvant melatonin in minimizing oral mucositis complications in head and neck cancer patients receiving concurrent chemoradiation. *J Altern Complement Med*. 2017;23(12):957-963.
29. Smolensky MH, Hermida RC, Reinberg A, Sackett-Lundeen L, Portaluppi F. Circadian disruption: new clinical perspective of disease pathology and basis for chronotherapeutic intervention. *Chronobiol Int*. 2016;33(8):1101-1119.
30. Bjarnason GA, Mackenzie RG, Nabid A, et al. Comparison of toxicity associated with early morning versus late afternoon radiotherapy in patients with head-and-neck cancer: a prospective randomized trial of the National Cancer Institute of Canada clinical trials group (HN3). *Int J Radiat Oncol Biol Phys*. 2009;73(1):166-172.
31. Goyal M, Shukla P, Gupta D, et al. Oral mucositis in morning vs. evening irradiated patients: a randomised prospective study. *Int J Radiat Biol*. 2009;85(6):504-509.
32. Morin RT, Galatzer-Levy IR, Maccallum F, Bonanno GA. Do multiple health events reduce resilience when compared with single events? *Health Psychol*. 2017;36(8):721-728.

33. Miller AH, Ancoli-Israel S, Bower JE, Capuron L, Irwin MR. Neuroendocrine-immune mechanisms of behavioral comorbidities in patients with cancer. *J Clin Oncol*. 2008;26(6):971-982.

34. Sephton SE. Diurnal cortisol rhythm as a predictor of breast cancer survival. *J Natl Cancer Inst*. 2000;92(12):994-1000.

35. Sephton SE, Lush E, Dedert EA, et al. Diurnal cortisol rhythm as a predictor of lung cancer survival. *Brain Behav Immun*. 2013;30(Suppl):S163-S170.

36. Schrepf A, Thaker PH, Goodheart MJ, et al. Diurnal cortisol and survival in epithelial ovarian cancer. *Psychoneuroendocrinology*. 2015;53:256-267.

37. Cohen L, Cole SW, Sood AK, et al. Depressive symptoms and cortisol rhythmicity predict survival in patients with renal cell carcinoma: role of inflammatory signaling. *PLoS One*. 2012;7(8):e42324.

How to cite this article: Cash E, Duck CR, Brinkman C, et al. Depressive symptoms and actigraphy-measured circadian disruption predict head and neck cancer survival. *Psycho-Oncology*. 2018;1–8. https://doi.org/10.1002/pon.4862