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Differential patterns of circadian rhythmicity in women with malignant versus benign gynecologic tumors

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Wearable activity trackers that measure rest and physical activity have become widely available commercially and are of increasing interest in early identification of disease. No studies to our knowledge have examined whether wearable activity trackers can be used in conjunction with patient-reported symptomatology to identify cancer early in the cancer continuum. This state of affairs is surprising because a sizable body of evidence suggests that circadian patterns of sleep and activity (i.e., circadian rhythmicity) are associated with oncogenesis. [1,2] Moreover, circadian cortisol dysregulation in patients with gynecologic cancer is associated with greater fatigue and worse self-reported functional status.[3] Among women with suspected gynecologic cancer, self-reported pain and fatigue are more severe and frequent in patients with malignant tumors as compared to patients with benign tumors.[3] Thus, circadian rhythms and patient-reported symptomatology may help to discriminate early between malignant versus benign tumors.

The aim of the current study was to explore whether circadian rhythmicity prior to diagnostic surgery differed between women with malignant versus benign gynecologic tumors. We hypothesized that: 1) patients who were later diagnosed with a malignant tumor would exhibit more circadian dysregulation and worse symptomatology prior to surgery (i.e., fatigue, psychological distress, and pain) than those later diagnosed with a benign tumor, and 2) circadian dysregulation would be independently associated with malignancy over and above the effects of self-reported symptomatology.

Methods

Participants

Women were recruited as part of a larger, IRB-approved study of quality of life in gynecologic cancer patients. Eligibility criteria included: 1) age ≥18 years; 2) scheduled

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Conflict of interest

The authors declare no conflict of interest.

surgery for suspected gynecologic cancer at Moffitt Cancer Center; 3) no prior chemotherapy or radiation within 30 days of recruitment; 4) no psychiatric or neurological disorders that could interfere with study participation (e.g., dementia); 5) absence of immune-related disease; 6) ability to speak and read English, and 7) ability to provide informed consent.

Procedures

Eligible women were recruited during an outpatient clinic visit at least four days prior to surgery. Recruitment occurred between March 2013 and February 2018. All participants provided informed consent, completed a battery of self-report questionnaires, and began actigraphic monitoring upon study enrollment. Participants were asked to wear the actigraph continuously on their non-dominant wrist until surgery.

Measures

Demographic information included: self-reported age, race, ethnicity, marital status, education, and income. Comorbid medical conditions were self-reported via the Charlson Comorbidity Index.[4] Cancer diagnosis and stage were obtained from medical charts.

Fatigue was assessed with the four-item severity subscale of the Fatigue Symptom Inventory (FSI)[5] at the end of actigraphic monitoring, with higher scores indicating greater fatigue severity. Psychological distress was assessed with the Hospital Anxiety and Depression Scale (HADS),[6] with higher scores indicating greater distress. Pain was assessed with the bodily pain subscale of the acute (i.e., one week) form of the Medical Outcomes Study Short Form-12 (SF-12)[7] version 2.0, with higher scores indicating less pain.

Actigraph (Pensacola, FL) activity monitors (wActisleep+, wGT3X-BT, and GT9X Link) were used to objectively assess circadian dysregulation. Each actigraph uses a three-axis piezoelectric accelerometer to measure and record wrist movement, averaged over every minute. Consistent with evidence-based practice parameters,[8] circadian data were only included from participants who continuously wore the actigraph for ≥72 hours. Raw continuous accelerometer data for the first 72 hours of wear time (when participants were most likely to wear the actigraph; starting at 12:00 AM) were obtained using Actilife 6.13.3 (Actigraph LLC, Pensacola, FL). Clock time and vector magnitude were then input into a five-parameter extended cosine model with an antilogistic transformation of the standard cosine program[9] in SAS 9.4 to derive circadian parameters.. These parameters included: the difference between the maximum and minimum levels of daily activity (amplitude), average 24-hour activity level (mesor), the fraction of the day that activity is above the mesor (width ratio), and overall circadian rhythmicity (f-statistic) (see Supplemental Figure 1).

Data Analysis

Independent samples t-tests were used to evaluate differences in circadian rhythmicity and symptomatology between patients with malignant versus benign tumors. Logistic regressions were used to examine independent associations of circadian rhythmicity with tumor malignancy above and beyond symptomatology. All analyses were conducted in SAS Version 9.4 (Cary, NC). All tests were two-sided and alpha was set at $P<0.05$.

Results

One hundred and fourteen patients with suspected gynecologic cancer consented to participate in the study. Of these, 28 participants were excluded from analyses due to insufficient patient reported data (n=8) or actigraphy data (n=20). Excluded patients were less likely to be married (*P*=.04) compared with those who were included. The final sample consisted of 86 patients (66 with malignant tumors) with complete data.

Most participants were white, non-Hispanic, married, high school graduates, and reported an annual household income of ≥$40,000 per year (Table 1). Patients with and without malignant tumors did not differ on sociodemographic factors (i.e., age, marital status, ethnicity, race, education, income, or comorbidities) (*p*s>.16). Among patients with malignant tumors, most (70%) had early stage (I or II) cancers originating in the endometrium or ovary (85%). Patients with benign tumors had a variety of diagnoses, including endometriosis, leiomyoma, retroperitoneal fibroid, and benign cystadenoma.

Patients who went on to receive a cancer diagnosis demonstrated less overall circadian rhythmicity (f-statistic) compared to patients with benign tumors (Table 2). Patients with malignant versus benign tumors did not differ on any other circadian parameter (*P*s>.75). There were no significant differences in symptomatology between patients with malignant and benign tumors (*P*s>.15). Patients who were one SD lower on the f-statistic, indicating less rhythmic daily activity patterns, had more than double the risk of malignancy (OR = 2.38; 95% CI: 1.18 to 4.77; *P*=.02) when controlling for symptomatology (Supplemental Table 1). Post hoc, exploratory Spearman's rho correlations were conducted to evaluate associations between symptomatology and circadian rhythmicity (Supplemental Table 2). Analyses revealed that more rhythmic daily activity patterns were associated with less bodily pain (rho=.25, *P*=.02).

Discussion

This study examined relationships among circadian rhythmicity, symptomatology, and presence of malignancy in a group of women with suspected gynecologic cancer. Results indicated that, as hypothesized, patients with malignant tumors had less rhythmic circadian activity patterns compared to patients with benign tumors. Further, less rhythmic circadian activity patterns were associated with over a twofold risk of tumor malignancy after accounting for symptomatology. However, contrary to our hypothesis, self-reported symptomatology was similar between women with benign and malignant tumors. Taken together, these provocative findings suggest that circadian dysregulation may be a unique identifier of tumor malignancy.

Limitations of this study include a small sample size, a heterogeneous sample in terms of gynecologic cancer diagnosis, and a primarily white, non-Hispanic population that limited generalizability. In addition, we did not specify requirements for weekday versus weekend actigraphic monitoring, which may have limited our ability to detect group differences in some circadian rhythmicity parameters. Finally, because these were secondary data analyses,

the sample size was not calculated a priori. Thus, we may have lacked statistical power to detect some associations.

Prior research has identified circadian dysregulation (i.e., cortisol) in patients with ovarian cancer to be associated with worse physical functioning, fatigue, and depression.[3] Results from this study add to this current body of literature and warrant additional research to assess the ability of circadian rhythmicity to help identify cancer early. Gynecologic cancers in particular are often fatal and diagnosed at an advanced stage,[10] and using wearable sensors to detect circadian rhythmicity may facilitate earlier identification of gynecologic disease and initiation of treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- Dysregulated circadian patterns of rest and activity and patient-reported symptomatology (e.g., fatigue, pain, distress) have been observed among patients with cancer.
- No study to our knowledge has examined use of wearable activity trackers in conjunction with patient-reported symptomatology to help identify the presence of gynecologic cancer prior to diagnostic surgery.
- In this analysis, patients later diagnosed with malignant tumors (n=66) had significantly less rhythmic circadian activity patterns (P=.04), but similar self-reported symptomatology prior to surgery compared to patients later diagnosed with benign tumors (n=20) (Ps>.15).
- Dysregulated circadian activity patterns significantly increased the odds of later diagnosis of tumor malignancy, independent of self-reported symptoms.
- Circadian activity patterns may be reliable indicators of gynecologic cancer.

Table 1.

Participant Characteristics, *N*=86

Variable	Benign (n=20)	Malignant (n=66)	*p*-value
Age, mean (SD)	56 (10)	60 (12)	0.16
Married, No. (%)	12 (60)	42 (65)	0.71
Not Hispanic, No. (%)	18 (90)	63 (95)	0.25
White, No. (%)	19 (95)	59 (89)	0.29
High school graduate, No. (%)	20 (100)	63 (97)	0.58
More than $40k, n (%)	10 (63)	40 (74)	0.37
Comorbidities, mean (SD)	2 (.5)	2 (1)	0.23
Cancer type, No. (%)			
Ovarian	-	23 (35)	-
Endometrial	-	33 (50)	-
Uterine	-	5 (8)	-
Other	-	5 (8)	-
Disease stage, No. (%)			
I	-	37 (59)	-
II	-	7 (11)	-
III	-	16 (25)	-
IV	-	3 (5)	-

Table 2.

Circadian rhythmicity and symptomatology variables, raw means, SD, median, interquartile range (25%, 75%)

Variable	Benign (n=20)	Malignant (n=66)	*p*-value	*d*-value
Circadian Rhythmicity				
Amplitude	2.42 (.51) [Mdn: 2.53] [IQR: 2.19, 2.82]	2.38 (.60) [Mdn: 2.41] [IQR: 2.02, 2.67]	0.75	0.07
Mesor	1.56 (.29) [Mdn: 1.56] [IQR: 1.35, 1.86]	1.57 (.28) [Mdn: 1.59] [IQR: 1.46, 1.71]	0.93	0.04
Width ratio	.63 (.07) [Mdn: .62] [IQR: .58, .68]	.63 (.10) [Mdn: .65] [IQR: .59, .69]	0.93	0.00
F-statistic	1024.94 (554.66) [Mdn: 994.62] [IQR: 534.99, 1453.34]	782.02 (419.44) [Mdn: 702.57] [IQR: 439.33, 1028.47]	0.04	0.49
Symptomatology				
Fatigue severity	4.06 (1.80) [Mdn: 4.38] [IQR: 2.88, 5.50]	3.32 (2.08) [Mdn: 3.25] [IQR: 1.75, 4.75]	0.15	0.38
Psychological distress	12.58 (5.30) [Mdn: 13.00] [IQR: 8.5, 16.5]	11.22 (7.01) [Mdn: 9.00] [IQR: 6.00, 16.00]	0.43	0.22
Bodily pain	43.69 (11.58) [Mdn: 47.25] [IQR: 37.06, 57.44]	47.25 (12.00) [Mdn: 47.25] [IQR: 47.25, 57.44]	0.15	0.30