Cancer Patients Circadian Rhythm Assessment Based on Morningness-Eveningness Preference

Ghazal Daftari[1], Nasim Khajavirad[1], Mahsa Abbaszadeh[1], and Sahar Karimpour Reyhan[1]

[1]Tehran University of Medical Sciences

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Abstract

Background: The circadian rhythm regulates various physiological processes, including sleep-wake cycle, cell division and cancer development. Aims: This study aimed to investigate circadian rhythm patterns in cancer patients. Methods and results: In this cross-sectional study, 150 cancer patients admitted to the internal ward of Tehran's Imam Khomeini Hospital Complex in the fall of 2022 were evaluated. The demographic characteristics of patients were collected using a checklist. Patients also completed a morningness-eveningness questionnaire (MEQ). Utilizing Analysis of Variance (ANOVA) and Fisher's exact test, circadian rhythm types with continuous and categorical variables were compared. The mean age of the study's participants was 49.83 ± 14.53 years. A total of 82.7% (n=124) had non-hematological cancers, and breast cancer was the most prevalent type of cancer among patients (23.3%). The MEQ of the patients studied ranged from 41 to 74, with a mean score of 56.6 ± 6.34. Conclusion: According to the findings of this study, the circadian rhythm is distributed normally among the participants.

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Ghazal Daftari[a], Nasim khajavirad?*, Mahsa Abbaszadeh?, Sahar Karimpour Reyhan?

[a]School of Medicine, Tehran University of Medical Science, Tehran, Iran.

?Department of Internal Medicine, Imam Khomeini Hospital Complex, Tehran University of Medical Science, Tehran, Iran.

*Corresponding author:

Nasim khajavirad

Address: Department of Internal Medicine, Imam Khomeini Hospital Complex, Keshavarz Boulevard, Tehran, Iran, Postal Code:1419733141

Email: Ghazall.daftari@gmail.com

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was 49.83 ± 14.53 years. A total of 82.7% (n=124) had non-hematological cancers, and breast cancer was the most prevalent type of cancer among patients (23.3%). The MEQ of the patients studied ranged from 41 to 74, with a mean score of 56.6 ± 6.34.

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Keywords: Cancer, Circadian Rhythm, MEQ, Chronotype, clock genes

Introduction

The circadian clock with a 24-hour period is an essential biological and behavioral system that persists in plants, animals, and humans and regulates a variety of processes, including the cell cycle, body temperature, immunity, heartbeat, basal metabolism, blood pressure, hormone secretion, sleep-wake cycle, feeding, and glucose homeostasis (1). The system is coordinated with environmental stimuli such as food intake, light, and temperature (2). In humans, the circadian rhythm consists of two components: the brain clock in the anterior hypothalamus, supra chiasmatic nucleus (SCN), and the peripheral clock in the individual cells (3, 4, 5, 6). The brain clock regulates the peripheral clock of cells and functions as a pacemaker (3, 4, 5, 6). Cellular clocks have autonomous rhythms and answer to intermittent signals from the SCN (3, 4, 5, 6). Additionally, circadian pathway genes control the circadian rhythm (7, 8).

In 1917, 1978, 1997, and 2001, the clock genes were reported for the first time in the fruit fly *Drosophila* , the fungus*Neurospora* , the rat, and finally the human, respectively (9). In 2017, the Nobel prize was awarded to scientists who discovered critical molecular mechanisms that control the circadian rhythm (10, 11). The *Per* (period homolog)1, 2, 3, *Clock* ,*BMall* , and *Cry* (cryptochrome) 1,2 genes and their products constitute a transcription-translation feedback loop (TTFL) associated with the circadian rhythm (12). During the day, *Clock* and *BMall* interact to initiate the transcription of the *Cry* and *Per* genes (12). The*Cry* and *Per* proteins are subsequently linked in the cytoplasm (12). This complex migrates to the nucleus and inhibits*BMall* and *Cry* gene-mediated transcription (12). The*Cry-Per* complex is destroyed at night, and the cycle begins again (12).

Cancer is a significant cause of death worldwide (13). Cancer incidence has increased due to aging, changes in associated risk factors, and socioeconomic developments (14). Furthermore, some mutations in DNA replication and exogenous or endogenous DNA damage are associated with cancer (15, 16). Several studies showed that disruption in circadian rhythm results in metabolic syndrome, endocrine disorders, and cancer (17). In circadian patterns, individuals are typically classified as morning or evening types (18). Morning types wake up early and function better in the morning (18). Evening types stay up late and perform best at night (18). Dysregulation of circadian rhythms in humans is associated with different cancers such as hepatocellular carcinoma (19), colon (20), ovarian cancers (21), prostate (22), and lung (23). Consequently, the proper function of clock proteins and circadian rhythm plays a crucial role in cancer prevention and treatment (24). In this study, we aimed to assess the circadian rhythm types using MEQ in cancer patients.

Materials and Methods

2.1. Study participants

This cross-sectional study was conducted on 150 patients with hematologic and non-hematologic cancers, ages 16 to 80, admitted to the internal ward of Tehran's Imam Khomeini Hospital Complex in the fall of 2022. Initial estimates placed the sample size at 145 patients, based on a study indicating that circadian rhythm disturbances and sleep disorders were prevalent in 30-75% of cancer patients, or nearly twice the rate in the general population (25). Five additional patients were added for a total of 150 to prevent losses. Inclusion criteria were age 15 or older, a cancer diagnosis, consent to participate in the study, absence of comorbidities, and absence of intubation. Exclusion criteria were using Melatonin, sedative, and hypnotic medications, significant cognitive impairment, night-shift workers, and end-stage patients. This study was conducted per the Declaration of Helsinki and was approved by the Imam Khomeini Hospital Complex, Tehran University

of Medical Science, Tehran, Iran, Ethics Committee (ethics number: IR.TUMS.IKHC.1398.28). All patients were informed of the study, and consent forms were obtained.

2.2. Clinical and demographic evaluation

Researchers designed a questionnaire to collect demographic and clinical information, including gender, age, weight, height, marital status, education, occupation, type of cancer, duration of illness, number of hospitalizations, and history of chemotherapy or/and radiotherapy or/and surgery. The questionnaire's content was evaluated by specialists and deemed suitable for use.

2.3. The morningness-eveningness questionnaire

The circadian type of participants was evaluated using MEQ, which was initially presented by Östberg and Horne (26). MEQ is a self-assessment questionnaire comprising 19 questions; the scores range from 16 to 86. The score weighting of the questions is not equal. This questionnaire describes five behavioral types: definitely morning type (70-86 scores), moderately morning type (59-69 scores), neither type (42-58 scores), moderately evening type (31-41 scores), and definitely evening type (31-41 scores) (27). The Persian form of MEQ's validity and reliability have been established ($\alpha = 0.79$) (28).

2.4. Statistical analysis

Statistical Package Software for Social Science (SPSS) version 18 was used to analyze the data, and $P < 0.05$ was considered statistically significant. Continuous variables were assessed using the mean and standard deviation, while categorical variables were evaluated using frequency and percentage. The Analysis of Variance (ANOVA) test was used to examine the relationship between means of age, time of cancer diagnosis, hospital admissions, chemotherapy and radiotherapy sessions, and circadian rhythm types. Furthermore, Fisher's exact test was used to determine the relationship between chronotype and gender, educational level, marital status, patient condition, treatment methods, occupation, and type of cancer. Kolmogorov-Smirnov analysis was used to verify the normality of the variable distribution.

Results

The age and body mass index (BMI) of 150 patients in this study ranged from 16 to 80 y (49.83 ± 14.53) and 12.41 to 41.79 kg/m^2 (25.09 ± 5.32), respectively. Tables 1 and 2 show the participants' demographic, clinical, and medical characteristics.

Table 1 near here.

Among the participants, 17.3% (n=26) had hematologic cancers. Cancer incidence ranged from 1 to 180 months (23.26 ± 29.3). The frequency of chemotherapy and radiotherapy sessions varied from 1 to 13 (3.61 ± 2.37), 0 to 70 (8.24 ± 9.79), and 0 to 50 (5.50 ± 11.5) times, respectively, for patients admitted to the hospital due to cancer.

Table 2 near here.

Total MEQ scores ranged between 41 and 74 (56.6 ± 6.34). In this study, 2% (n=3) of patients were definitely morning types, 38% (n=57) were moderately morning types, 59.3% (n=89) were neither types, 0.7% (n=1) was moderately evening types, and no patients were definitely evening types. Normal distribution was observed for MEQ scores among the participants (Figure 1).

Figure 1 near here.

According to Table 3 and 4, the mean ages of completely and moderately morning types were greater than those of all other types. The distribution of circadian rhythms was nearly identical between male and female participants. Employed and unemployed individuals, as well as patients with varying levels of education, were frequently morning and neither types. The ANOVA test did not reveal significant associations between chronotype and age, time of cancer onset, cancer-specific hospitalization, chemotherapy, or radiotherapy

sessions. Furthermore, Fisher's exact test revealed no correlation between employment status, marital status, gender, treatment methods, level of education, patient condition, and types of circadian rhythm.

Table 3 and 4 near here.

Discussion

Several cancers are associated with circadian clock dysfunction, highlighting the connection between circadian rhythm dysregulation and oncogenesis (29). Epidemiological studies have linked cancers to night shift work and light pollution that disrupt chronotype (2, 30). In mice, dysregulated circadian gene expression may cause lymphoma, osteosarcoma, and hepatocellular carcinoma (HCC), according to Kettner et al. (31). Jiang et al. reported that circadian gene disruption is associated with the onset of HCC (11). Methylation of single nucleotide polymorphisms (SNPs) or clock gene promoters is a known molecular mechanism (30). Consideration of this issue could lead to cancer prevention and treatment in the future.

In our study, there was no significant correlation between chronotype and gender (P =0.629), age (P =0.135), marital status (P =0.263), occupation (P =0.931), or education level (P =0.899). Definitive and moderate morning types exhibited higher age means than neither and moderate evening types. This finding is consistent with the findings of Montaruli et al., who observed that older adults are typically morning types, possibly due to age-related sleep shortness, whereas younger adults are commonly evening types (32). Furthermore, there is no correlation between age and gender, and circadian rhythm (32, 33, 34). Some studies suggest that there may be gender differences in circadian types due to housework, grooming, and breakfast preparation. In a cohort study conducted by Ramin et al., the average age and BMI of the participants were 59.2 y and 27.5 kg/m^2, respectively, and the most prevalent chronotype was definitely morning type, while neither type was the least prevalent (35).

Neither type increased the risk of breast cancer among participants, but the difference was not statistically significant (35). In our study, breast cancer was the most prevalent type, and neither type comprised the majority, consistent with a previously published study. A dysregulated circadian rhythm in neither species, possibly leading to cancer, may explain this finding. Our study's mean age and BMI were 49 and 25.09 kg/m^2, respectively. All of the participants in the current study were cancer patients; some were in advanced stages and suffered from cachexia, which could explain the differences in BMIs. Bhar et al. found that evening types have a higher BMI, FBS, and HbA1c, resulting in less physical activity, unhealthy eating habits, and sleep disturbances that lead to T2DM (33, 36).

In contrast to our study, the mean BMI is higher for morning types, but no significant difference was observed between circadian types (P =0.317). The participants lacked comorbidities such as diabetes, and we did not evaluate their physical activity and dietary habits; as previously mentioned, some patients were in the cachectic phase. Chronotype was not significantly associated with duration as a cancer patient (P =0.855) or hospital admission (P =0.250). The neither and moderately evening types developed cancer sooner, were hospitalized more frequently, experienced fatigue and weakness, and were in advanced stages; consequently, these groups exhibit a lower BMI. The present study observed normal distribution for chronotype, and the mean MEQ score was 56.6 ± 6.34 (41-74). Neither type was the most chronotype, with the moderately evening type being the least. No evening-only types were detected. In a case-control study conducted by Di Somma et al., the mean MEQ score of craniopharyngioma patients was 47.8 ± 12.6 (34).

Most participants were morning types, and the minority were evening types (34). Definitive and moderate morning types were considered one group, and evening types were considered a second (34). Based on the results, females were predominantly evening and intermediate types, while males were primarily morning types. Different MEQ means and scores may result from the sample size, study design, and various types of cancer. In line with our findings, Kanagarajan et al. demonstrated that the MEQ distribution in bipolar patients aged 25 to 66 was normal, the mean score was 49.2 ± 10.4 (24-74), neither type was the most chronotype, and circadian rhythm was not significantly associated with age and gender (37). The correlation between circadian rhythm and surgery (P =0.933), chemotherapy (P =0.565), and radiotherapy (P =0.326) were not statistically significant.

Most patients who received chemotherapy and radiotherapy were neither morning nor evening types, whereas morning types had more chemotherapy sessions. Multiple studies have suggested that a higher MEQ score for morning types is associated with fewer chemotherapy-related side effects, such as nausea and vomiting (32). Cancer patients were the subject of a case-control study by Sultan et al. (38). The participants' mean age was 46.67 ± 12.51 y (38). Similar to our research, the majority and minority circadian rhythms were neither morning nor evening. The MEQ score was negatively correlated with chemotherapy-induced nausea, vomiting, and diarrhea (38). Unfortunately, we did not assess the side effects of chemotherapy or radiotherapy. Hematologic and non-hematologic cancers (P =0.999), palliative therapy or treatment (P =0.262), treatment method combinations such as chemotherapy + radiotherapy (P =0.457), chemotherapy + surgery (P =0.794), radiotherapy + surgery (P =0.500), and chemotherapy + radiotherapy + surgery (P =0.738) were not significantly correlated to chronotype. The majority of participants in these groups fell into neither category.

Some research indicates that chronochemotherapy and chronoradiotherapy may improve cancer patients' survival and response rate (18). Consequently, chronomodulated chemotherapy or radiotherapy sessions compatible with circadian rhythm may be advantageous to the treatment process (18). Although a disorganized circadian rhythm may result in carcinogenesis, cancer treatments may alter the circadian type. Comparing the chronotype of various cancers requires additional research.

Study limitations

Assessing the circadian rhythm at the time of diagnosis and then comparing it during treatment and follow-up, studying a specific type of cancer, not having a control group, having a small sample size, resulted in limited statistical power.

Conclusion

In conclusion, circadian rhythm distribution in our study was normal. Indeed, cancer is a global concern, and circadian rhythm disruption as a carcinogen is an area of study. Regulated circadian rhythm could be a preventative measure, and targeting the clock genes could improve cancer treatment. Chronomodulated cancer therapies are emerging fields that are anticipated to improve prognosis. Concerning these points, additional research is required to develop effective cancer preventive and therapeutic interventions.

Ethics approval and consent to participate

Informed written consent was obtained from participants. All procedures performed in studies

involving human participants adhered to the ethical standards of the institutional and/or

national research committee and with the 1964 Helsinki declaration and its later amendments

or comparable ethical standards. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and material

The datasets analyzed in the current study are available from the corresponding author on

reasonable request

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Conflict of interest

The authors declare that they have no competing interests.

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