Circadian Rhythm Disruption and its Role in Colorectal Cancer

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Received: 8 July 2021 Revised: 11 July 2021 Accepted: 23 November 2021 Published:11 December 2021

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Abstract

Circadian rhythms are sleep-wake cycles that show a 24-h oscillating pattern in almost all species' metabolic, physiological and behavioral functions. There is a rhythmic synchronization in transcriptional expression of various clock-controlled genes organized in a network of the biochemical cycle in the suprachiasmatic nucleus and peripheral tissue making cell-autonomous clock pacemakers. Cellular functions like cell division and proliferation are also regulated by Clock-genes. Disturbance in this synchronicity can cause several pathologic conditions, including various cancer progression. According to International Agency for Research on Cancer (IARC), shift work that interferes with the circadian cycle can be carcinogenic to humans. Period genes (Per2, Per1) are essential circadian clock genes, which regulate β-catenin and cell proliferation in colorectal cancer cells. The mechanisms liable for the connection between the circadian clock and cancer are not well defined. Shift work and nocturnal light exposure are related to circadian clock disruption and increased cancer risk. This review discusses how disrupted circadian rhythm or "Biological Clock" could be involved in colorectal cancer development.

Keywords

Circadian rhythm, Colorectal cancer, Suprachiasmatic nucleus, *period genes.*

Introduction

There has been a recent surge of research evaluating sleep disturbances and their correlation with the health of an individual. Acute sleep impairment raises the risk of hormonal imbalance, like Elevated levels of evening cortisol, Reduced levels of glucose tolerance and Growth hormone, high estrogen, and low testosterone. It can also cause a significant increase in markers of systemic inflammation, increased blood pressure, and cognitive dysfunction. [1, 2]Emerging research outcomes suggest that circadian rhythm disruption may also increase the risk of several types of cancer. In particular, night shift workers are at higher risk of developing cancer in the breast, endometrium, prostate, and colorectum. [1]Whereas many research studies suggest the direct association of circadian rhythm and tumor progression. Quality of sleep and its relation to cancer development duration has been under-researched. Most studies reported till now are restricted to breast cancer.

Colorectal cancer (CRC) is one of the most widespread cancers with the highest mortality rates in western countries. [3] CRC is the most common cancer with the highest mortality in European countries. Black community of America and Africa are most likely suffered from Colorectal cancer. While North America and Asian countries had similar CRC incidents. Africa had the lowest incidence in the world. Among Asian countries China, Korea, Japan had the highest prevalence than other countries. India had a relatively low incidence and mortality rate. [41,42,44] 70-80% cases of CRC occur sporadically. In comparison, approximately 15% of CRC cases develop due to inherited factors, such as familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal carcinoma (HNPCC). [3-5] Sporadic human CRC can be due to various environmental and lifestyle factors, such as dietary habits, obesity, sleep disturbance, and physical inactivity. [3,5] Individuals with less than 6 hours sleep duration per day are having a 50 percent higher risk of developing colorectal cancer than those sleeping more than 7 hours. [1] Currently, Circadian Dysfunction and overall sleep quality on the risk of colorectal cancer are poorly understood. [6,7-9]

The sleep-wake cycle is regulated by two processes circadian rhythm of sleep (process S) and wakefulness (process C).[10]Process S is sleep-wake homeostasis is like a timer that creates a need for sleep. The need for sleep increases before bedtime. Process S is associated with neuronal communication inhibition in the hypothalamus, which turns off arousal mechanisms in sleep. Disorders that affect process S promotion are associated with insomnia. Process C is known as Clock-dependent alertness or circadian process that controls and

regulates the timing of sleep and its coordination with the light-dark cycle (Day-Night), which promotes wakefulness is responsible for promoting alertness, physical activity, muscle tone, and hormone secretion over 24 hours. Process S builds pressure to fall asleep. While process C regulates daily sleep rhythm causes the body to wake up. These two processes work together to create a balanced sleep-wake cycle.[9,10]

Increased colon and breast cancer cases in developed countries are found, despite advanced screening and prevention techniques.[18] Exposure to light at night exposure suppresses melatonin production, reducing the possible nonspecific oncostatic effect of the pineal gland, thus increasing the risk of colorectal cancer. Melatonin is a potent anticarcinogenic molecule, and the relation between light exposure at night and CRC risk through the melatonin pathway could give one plausible explanation .[19,24]

Environment and Molecular regulation of circadian rhythm

Most physiological and behavioral functions in humans are regulated across days and nights in a synchronized pattern. They automatically exhibit the regular sleep and wake-up cycle. In visual perception light intensity is detected by photoreceptors in retina and process the vision at any time of the day or night. The mammalian, there is a distinct circadian photoreception pathway that is quite different from visual perception that is light-dependent non-visual (NV) responses such as suppression of melatonin, increase in body temperature due to excessive heat and heart rate, and cortical brain activity. Light through non visual retinal projections will stimulate control of alertness, sleep and mood. Melanopsin-expressing retinal ganglion cells are responsible for recognition of light, transmitted to the Suprachiasmatic Nuclei SCN clock via the retinohypothalamic tract. [11-14] Melatonin release and its circulating level are suppressed when light information is conveyed to SCN. For the adaptation to earth's rotation, there is a complete 24 hours' oscillation pattern for regulating metabolic, physiological, and behavioral functions. [14 16 18-13]Apart from SCN, there are some extra-SCN brain regions in certain organ tissues. Peripheral oscillators or slave oscillators are circadian oscillators located outside of SCN (master oscillator in a mammal) in peripheral organs (Lungs, liver, GI tract, kidneys, and other organs). [12,13] Peripheral oscillators contain certain functional circadian oscillators that respond to various non-photic stimuli like temperature, environmental or chemical cues.[12-15]

The molecular generation of circadian rhythms regulates biochemical pathways in the suprachiasmatic nucleus and peripheral tissues. [11-14] (Figure 1: Mammalian molecular circadian clock machinery Light-dark phase)

i. When the retina perceives light, positive and negative auto regulatory feedback loops in SCN Clock.
ii. The SCN oscillator contains interlocking transcription/translational feedback loops which regulate and control circadian timing.
iii. The master genes CLOCK: BMAL1 or CLOCK: NPAS2 heterodimer are the positive elements called "core loop" and transcribe Per, Cry, and Dec through E-box–mediated transcription.[12-14]
iv. The accumulation of PER-CRY heterodimer in cytoplasm acts as a negative element as they phosphorylate and translocate into the nucleus for the inactivation of the BMAL1: CLOCK BMAL1:NPAS2 E-box–mediated transcription and transcription of their genes.[12,13]
v. Degradation of PER: CRY adequately allows a new transcription cycle. While DECs bind to the E-box element and directly inhibit their transcription. (Figure 1) [12,13,15,43]
vi. Core circadian gene's (CLOCK: BMAL1 or CLOCK: NPAS2) primary feedback loop cannot maintain 24-hour rhythms, hence some other additional clock genes (REV-Erba, Period; PER, Cryptochrome; CRY, and Circadian Controlled Genes; CCGs) are associated that form a secondary auto-regulatory feedback loop. [14,15]
vii. The competitive activity of REV -Erba on the retinoic acid-related orphan receptor response element (RORE) inhibits transcription of BMAL-1, which is a stabilizing/auxiliary loop. (Figure 1) [13,14,43]
viii. Cyclic accumulations of clock-controlled gene (CCG) mRNA species by regulation of clock components via Core and stabilizing/auxiliary loops generates various physiological outputs in a cell (cell cycle and arrest, immune function, hormonal regulations, maintaining body temperature, cellular metabolism, DNA replication/repair and response action to anti-cancer drugs). [12,15,16]

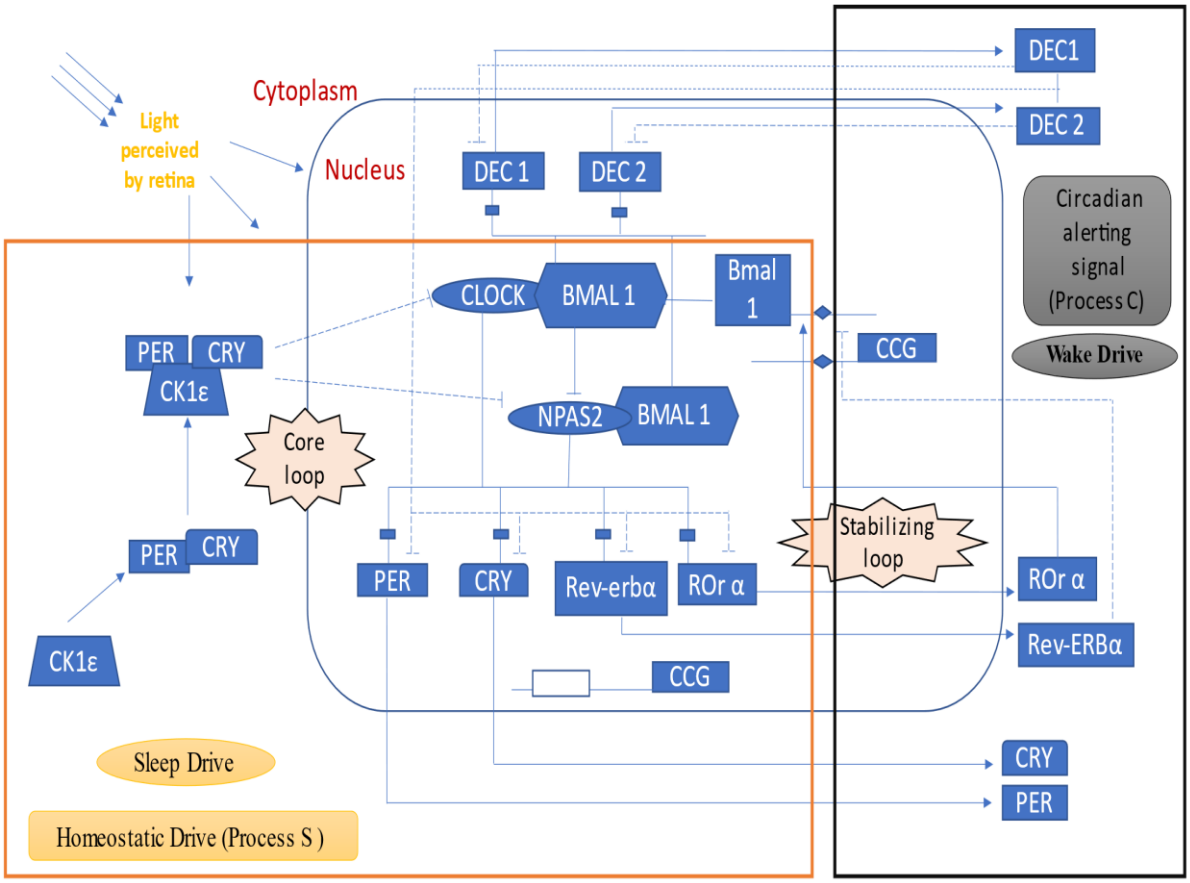

Figure 1: Mammalian molecular circadian clock machinery (Light-dark phase)

Disruption of Circadian rhythm

Disruption of the circadian clock or any alterations in clock genes results in abnormalities in various function cellular functions like proliferation, apoptosis, DNA damage response, and metabolism, which can lead to cancer initiation and progression. [13] Disturbed circadian rhythms are directly or indirectly linked for causing or promoting various forms of cancer in humans. According to the past few research studies sleep dysfunction is associated with the pathogenesis of cancer and its progression. [12,13,14] This Endogenous timekeeping circadian clock regulates the system to controls multiple peripheral clocks present in peripheral tissues of the body. Dysfunction of the circadian clock gene accelerates tumor progression, and potentially restoring circadian rhythms should improve prognosis. [6,13,14,16]

Clock genes and colorectal cancer

Circadian oscillation of Per1 and Per2 is found in the oral mucosa and colon crypt cells independent of the SCN. [17,25,26] PERIOD proteins play a significant role in the circadian clock and tumor suppression. Per1 and Per2 mutations have been detected in the sequencing of colorectal tumors. PERIOD proteins regulate cell cycle progression via circadian gated expression of cell cycle proteins (WEE1, cyclins, p21, p53), controls cell cycle regulators (b-catenin, vascular endothelial growth factor [VEGF], cyclin D, c-Myc), regulate DNA damage response, and also modulate other clock genes (*Per1*, *Bmal1*). [12,15,25] Per2 mutation and ApcMin/+, the mutation act together to potentiate intestinal polyp formation. [12] In colorectal cancer cell lines increase in expression of PER1 leads to DNA damage-induced apoptosis, whereas its inhibition causes blunted apoptosis by disrupting circadian control of b-catenin-dependent pathways and alterations in the DNA damage response. CTNNB1 is a controlled clock gene functions as an oncogene, influencing cell proliferation in colon cancer cells. PER1 and PER2 encoded by CTNNB1 participate in ATM-Chk1/Chk2 DNA damage response pathways and modulating ß-catenin, whose promoter shows BMAL1. [12-14] Melatonin hormone is secreted by the pineal gland regulated by a rhythm-generating system located in the SCN, which is in turn regulated by photo stimuli. Melatonin acts as a darkness signal, providing feedback to the SCN oscillators. Melatonin has both induce sleep and an ability to entrain the sleep-wake rhythm.[6,20]Melatonin has been proven to show anti-cancer properties in animal models to reduce DNA adducts and promote DNA repair by reducing the overall DNA damage and inhibiting the cell cycle to decrease cell proliferation. [20-23]Exogenous melatonin could restrict tumor growth and restore circadian rhythmicity. [23,31,32]Alteration of rhythmic motor activity and adrenocortical secretion is associated with poor survival of patients with metastatic colorectal.

In an experiment with mice, SCN was destroyed before transplanting tumor; transplanted tumors grew twice to thrice faster than in operated mice. 12-hours of light and dark phases to maintain SCN-independent photoperiodic synchronization. [2936,28]When rhythms of clock genes were suppressed in jet-lagged mice, down-regulation of p53 and overexpression of c-myc occurred, and both contribute to tumor progression. [26-28]

Disturbance in the peripheral intestinal circadian clock can lead to intestinal epithelial neoplastic transformation of human CRC.[33] Circadian disruption is classified as "probably

carcinogenic," according to humans by the International Agency Research on Cancer (IARC). Sleep disturbance affects the secretion of melatonin and is associated with a decrease in removing free radicals and protecting against oxidative DNA damage. [33-35]

Inadequate sleep may reduce the release of immune-stimulating hormones, such as growth hormone, prolactin, and dopamine, and affects functions of pro-inflammatory cytokine genes, including interleukin-6 (IL6) and tumor necrosis factor-α (*TNFA*). [36,37] These alterations can lead to cellular and genomic markers of inflammation and contribute to CRC development. [38,39,43] These above-mentioned pathophysiological factors may explain the association between circadian rhythms disruption and CRC.

Significant gaps in the research

Considering the evidence mentioned above from various studies, light reduces circulating melatonin levels, increasing colorectal cancer risk, especially in night-shift workers.[19] EM waves have also been considered another pertinent modern environmental influence that suppresses melatonin levels as low exposure to low-frequency EM fields can increase colon cancer risk.[29] Apart from disrupting circadian rhythm, EM waves can directly interact with colon tumor cells and affect their proliferation. [30,40]Disruption of circadian rhythms is majorly due to the Modern lifestyle. Any genetic variations and their interaction with certain environment cues (even Disruption of circadian due to exposure to light during the night) can lead to cancer development. Primarily colorectal cancer could be explained by any of these mechanisms. Complete understanding of molecular mechanisms that form an interrelation between disruption of Clock controlled genes and Colorectal cancer development is still understudied. A comprehensive evaluation of how a disrupted circadian peripheral clock contributes to tumor formation in intestines is essential for developing future circadian clock–based strategies to prevent colorectal cancer and development. [22,35,40]

Underlying Molecular mechanisms that associate sleep duration with colorectal cancer initiation are largely under-researched. Less than 6 hours of sleep can disrupt circadian rhythm and suppress the production of melatonin which leads to the development of colorectal adenomas are evaluated; till now, there is no study proving how sleep quality affects human health and cancer progression.

Future Directions

Circadian rhythms disruption has a substantial impact on gastrointestinal diseases and colorectal cancer development. Conversely, many gastrointestinal disease processes influence the sleep-wake cycle and sleep quality. It is considering recent research that has shown a vital significance of sleep and its impact on colorectal cancer development and progression. Research has shown that treating a patient's underlying sleep disorder may result in improvement in their gastrointestinal symptoms. Furthermore, control of gastrointestinal disease states will result in improved sleep quality and can prevent cancer initiation. Therefore, gastroenterologists need to take a detailed sleep history to identify any underlying gastrointestinal diseases and colorectal cancer early diagnosis to better care for patients.

Glossary

- **Systemic inflammation**: inflammation in the whole body
- **familial adenomatous polyposis (FAP):** genetic cancer predisposition of a precancerous polyp
- **hereditary nonpolyposis colorectal carcinoma (HNPCC):** a dominant genetic condition that causes the highest risk of colon cancer.
- **Hypothalamus**: region of the brain at the base of pituitary gland responsible for regulating hormones and body temperature.
- **Suprachiasmatic nucleus SCN**: region of the brain in hypothalamus situated above optic chiasma
- **Retinohypothalamic tract**: photic neural input passage from eyes to hypothalamus
- **Apoptosis:** Programmed cell death pathway. This process to remove damaged cell in normal physiology.
- **Vascular endothelial growth factor (VEGF):** a protein that promotes the formation of new blood vessels
- **Cyclins**: protein family that control cell progression associated in cell cycle
- **EM:** Electromagnetic Radiation

References

1. Thompson, C. L., Larkin, E. K., Patel, S., Berger, N. A., Redline, S., & Li, L. (2011). The short duration of sleep increases the risk of colorectal adenoma. *Cancer*, *117*(4), 841-847. DOI :10.1002/cncr.25507
2. Khanijow, V., Prakash, P., Emsellem, H. A., Borum, M. L., & Doman, D. B. (2015). Sleep dysfunction and gastrointestinal diseases. *Gastroenterology & hepatology*, *11*(12), 817.
3. Wu, H., Liu, J., Yin, Y., Zhang, D., Xia, P., & Zhu, G. (2019). Therapeutic opportunities in colorectal cancer: Focus on melatonin antioncogenic action. *BioMed research international*, *2019*, 9740568. DOI:10.1155/2019/9740568.
4. Bubenik, G. A. (2008). Thirty-four years since the discovery. *Journal of physiology and pharmacology*, *59*(2), 33-51
5. Gil-Martín, E., Egea, J., Reiter, R. J., & Romero, A. (2019). The emergence of melatonin in oncology: Focus on colorectal cancer. *Medicinal research reviews*, *39*(6), 2239-2285. DOI:10.1002/med.21582
6. Muñiz-Calvo, S., Bisquert, R., Fernández-Cruz, E., García-Parrilla, M. C., & Guillamón, J. M. (2019). Deciphering the melatonin metabolism in Saccharomyces cerevisiae by the bioconversion of related metabolites. *Journal of pineal research*, *66*(3), Article e12554. DOI:10.1111/jpi.12554
7. Kato M, Phillips BG, Sigurdsson G, Narkiewicz K, Pesek CA, Somers VK. (2000). Effects of sleep deprivation on neural circulatory control. *Hypertension*, *35*(5), 1173-1175. DOI: 10.1161/01.HYP.35.5.1173
8. Meier-Ewert HK, Ridker PM, Rifai N. (2004). Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. *J Am Coll Cardiol*, *43*(4), 678-683. DOI: 10.1016/j.jacc.2003.07.050
9. Spiegel K, Leproult R, L'hermite-Baleriaux M, Copinschi G, Penev PD, Van Cauter E. (2004). Leptin levels are dependent on sleep duration: relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin. *J Clin Endocrinol Metab*. *89*(11), 5762-5771. DOI: 10.1210/jc.2004-1003
10. Gillette MU Abbott SM. (2009). Biological timekeeping. *Sleep Med Clin*, *4*(2), 99-110. DOI: 10.1016/j.jsmc.2009.01.005
11. Rana, S., & Mahmood, S. (2010). Circadian rhythm and its role in malignancy. *Journal of circadian rhythms*, *8*(1), 1-13. DOI: 10.1186/1740-3391-8-3

12. Savvidis, C., & Koutsilieris, M. (2012). Circadian rhythm disruption in cancer biology. *Molecular medicine*, *18*(9), 1249-1260. DOI: 10.2119/molmed.2012.00077
13. Garcia-Saenz, A., de Miguel, A. S., Espinosa, A., Costas, L., Aragonés, N., Tonne, C., & Kogevinas, M. (2020). Association between outdoor light-at-night exposure and colorectal cancer in Spain. *Epidemiology*, *31*(5), 718-727.
14. Rajendran, S., Barbon, S., & Pucciarelli, S. (2021). Spotlight on Circadian Genes and Colorectal Cancer Crosstalk. *Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders)*, *21*(1), 4-11.
15. Bechtold, D. A., Gibbs, J. E. and Loudon, A. S. (2010). Circadian dysfunction in disease. *Trends Pharmacol Sci*, *31*(5), 191-198. DOI: 10.1016/j.tips.2010.01.002
16. Arendt, J. (2010). Shift work: coping with the biological clock. *Occup Med (Lond)*, *60*(1), 10-20. DOI: 10.1093/occmed/kqp162.
17. Okazaki, F., Matsunaga, N., Okazaki, H., Utoguchi, N., Suzuki, R., Maruyama, K., ... & Ohdo, S. (2010). Circadian rhythm of transferrin receptor one gene expression controlled by c-Myc in colon cancer-bearing mice. *Cancer Research*, *70*(15), 6238-6246. DOI:10.1158/0008-5472
18. Mormont, M. C., & Levi, F. (1997). Circadian-system alterations during cancer processes: a review. *International Journal of Cancer*, *70*(2), 241-247. DOI:10.1002/(SICI)1097-0215(19970117)70:2%3C241::AID-IJC16%3E3.0.CO;2-L
19. Shanmugam, V., Wafi, A., Al-Taweel, N., & Büsselberg, D. (2013). Disruption of circadian rhythm increases the risk of cancer, metabolic syndrome and cardiovascular disease. *Journal of Local and Global Health Science*, *2013*(1), 3. DOI:10.5339/jlghs.2013.3
20. Farriol, M., Venereo, Y., Orta, X., Castellanos, J. M. and Segovia-Silvestre, T. (2000). In vitro effects of melatonin on cell proliferation in a colon adenocarcinoma line. *J Appl Toxicol*, *20*(1), 21-24. DOI: 10.1002/ (SICI)1099-1263(200001/02)20:1%3C21::AID-JAT623%3E3.0.CO;2-M
21. Anisimov, V. N., I. G. Popovich, A. V. Shtylik, M. A. Zabezhinski, H. Ben-Huh, P. Gurevich, V. Berman, Y. Tendler, and I. Zusman. (2000). Melatonin and Colon Carcinogenesis: III. Effect of Melatonin on Proliferative Activity and Apoptosis in Colon Mucosa and Colon Tumors Induced by 1, 2-dimethylhydrazine in Rats. *Experimental and Toxicologic Pathology*,*52*(1),71-76. DOI: 10.1016/S0940-2993(00)80022-6

22. Anisimov, V. N., Kvetnoy, I. M., Chumakova, N. K., Kvetnaya, T. V., Molotkov, A. O., Pogudina, N. A., Popovich, I. G., Popuchiev, V. V., Zabezhinski, M. A., Bartsch, H. and Bartsch, C. (1999). Melatonin and colon carcinogenesis. II. Intestinal melatonin-containing cells and serum melatonin level in rats with 1,2-dimethylhydrazine-induced colon tumors. *Exp Toxicol Patho, l51*(1), 47-52, DOI:10.1016/S0940-2993(99)80062-1
23. Anisimov, Vladmir N., Irina G. Popovich, and Mark A. Zabezhinski. (1997). Melatonin and Colon Carcinogenesis: I. Inhibitory Effect of Melatonin on Development of Intestinal Tumors, Carcinogenesis,*18*(8), 1549-53. DOI:10.1093/carcin/18.8.1549
24. Parkin, D. M., Bray, F., Ferlay, J. and Pisani, P. (2005). Global cancer statistics, 2002. *CA Cancer J Clin*, *55*(2), 74-108. DOI: 10.3322/canjclin.55.2.74
25. Gery, S., Komatsu, N., Baldjyan, L., Yu, A., Koo, D. and Koeffler, H. P. (2006). The circadian gene per1 plays a vital role in cell growth and DNA damage control in human cancer cells. *Mol Cell*, *22*(3), 375-382. DOI: 10.1016/j.molcel.2006.03.038
26. Lee, K., Cho, M., Miaskowski, C., & Dodd, M. (2004). Impaired sleep and rhythms in persons with cancer. *Sleep medicine reviews*, *8*(3), 199-212. DOI:10.1016/j.smrv.2003.10.001
27. Krugluger, W., Brandstaetter, A., Kállay, E., Schueller, J., Krexner, E., Kriwanek, S., ... & Cross, H. S. (2007). Regulation of genes of the circadian clock in human colon cancer: reduced period-1 and dihydropyrimidine dehydrogenase transcription correlate in high-grade tumors. *Cancer Research*, *67*(16), 7917-7922. DOI:10.1158/0008-5472
28. Filipski E, King VM, Li X. (2002). Host circadian clock as a control point in tumor progression. *J Natl Cancer Inst ,94*(9), 690–7. DOI:10.1093/jnci/94.9.690
29. Filipski E, Li XM, Levi F. (2006). Disruption of circadian coordination and malignant growth. *Cancer Causes Control*, *17*(4), 509–14. DOI: 10.1007/s10552-005-9007-4
30. Orbach-Arbouys, S., Abgrall, S. and Bravo-Cuellar, A. (1999). Recent data from the literature on the biological and pathologic effects of electromagnetic radiation, radio waves, and stray currents. *Pathol Biol*, *47*(10), 1085-1093.
31. Cleary, S. F. (1993). A review of in vitro studies: low-frequency electromagnetic fields. *Am Ind Hyg Assoc J*,*54*(4), 178-185. DOI: 10.1080/15298669391354531
32. Otalora BB, Madrid JA, Alvarez N. (2008). Effects of exogenous melatonin and circadian synchronization on tumor progression in melanoma-bearing C57BL6 mice. *J Pineal Res, 44*(3), 307–315. DOI: 10.1111/j.1600-079X.2007. 00531.x

33. Jung-Hynes, B., Reiter, R. J., & Ahmad, N. (2010). Sirtuins, melatonin and circadian rhythms: building a bridge between aging and cancer. *Journal of pineal research*, *48*(1), 9-19. DOI: 10.1111/j.1600-079X.2009. 00729.x
34. Savvidis C and Koutsilieris M. (2012). Circadian rhythm disruption in cancer biology. *Mol Med, 18*(1), 1249-1260. DOI: 10.2119/molmed.2012.00077
35. Stevens, R.G., Hansen, J, Costa, G, Haus, E, Kauppinen, T, Aronson, K.J., Castano-Vinyals, G., Davis, S., Frings-Dresen, M.H., Fritschi, L., Kogevinas, M., Kogi, K., Lie, J.A., Lowden, A., Peplonska, B., Pesch, B., Pukkala, E., Schernhammer, E., Travis, R.C., Vermeulen, R., Zheng, T., Cogliano, V., and Straif, K. (2011). Considerations of circadian impact for defining 'shift work' in cancer studies: IARC Working Group Report. *Occup Environ Med*, *68*(2), 154-l62
36. Sliwinski, T., Rozej, W., Morawiec-Bajda, A., Morawiec, Z., Reiter, R., and Blasiak,J. (2007). Protective action of melatonin against oxidative DNA damage – chemical inactivation *versus* base-excision repair. *Mutat Res*, *634*(1-2), 220-227. DOI: 10.1016/j.mrgentox.2007.07.013
37. Lange, T., Dimitrov, S. and Born,J. (2010). Effects of sleep and circadian rhythm on the human immune system. *Ann NY Acad Sci*, *1193(1*), 48-59. DOI:10.1111/j.1749-6632.2009. 05300.x
38. Irwin, M.R., Wang, M., Campomayor, C.O., Collado-Hidalgo, A. and Cole,S. (2006). Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation *Arch Intern Med*, *166*(16), 1756-1762. DOI:10.1001/archinte.166.16.1756
39. Itzkowitz, S.H., Yio,X. (2004). Inflammation and cancer IV: Colorectal cancer in inflammatory bowel disease: the role of inflammation. *Am J Physiol Gastrointest Liver Physiol*, *287*(1), G7-17. DOI: 10.1152/ajpgi.00079.2004
40. Lin, C. L., Liu, T. C., Wang, Y. N., Chung, C. H., & Chien, W. C. (2019). The association between sleep disorders and the risk of colorectal cancer in patients: A Population-based Nested Case-Control Study. *in vivo*, *33*(2), 573-579. DOI:10.21873/invivo.11513
41. Cao, J., Feng, J., Li, L., & Chen, B. (2015). Obstructive sleep apnea promotes cancer development and progression: a concise review. *Sleep and Breathing*, *19*(2), 453-457. DOI:10.1007/s11325-015-1126-x
42. Wong, M. C., Ding, H., Wang, J., Chan, P. S., & Huang, J. (2019). Prevalence and risk factors of colorectal cancer in Asia. *Intestinal Research*, *17*(3), 317

43. García-Alfonso, P., García-González, G., Gallego, I., Peligros, M. I., Ortega, L., Torres Perez-Solero, G., ... & Martin, M. (2021). Prognostic value of molecular biomarkers in patients with metastatic colorectal cancer: a real-world study. *Clinical and Translational Oncology*, *23*(1), 122-129.
44. Sahar, N. E., Qadir, J., Riaz, S. K., Sultan, A., Arif, A., & Malik, M. F. A. (2021). Dysregulation of core circadian genes, BMAL1 and CLOCK, in colorectal cancer. *Biological Rhythm Research*, 1-14. DOI: 10.1080/09291016.2021.1940623