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A Review on Role of Circadian Rhythms in Management of Prostate Cancer

Shilpa P. Chaudhari[1] and Dhanaji S. Suryavanshi[1*]

[1]Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune- 411 044, Maharashtra, India.

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The circadian clock is a molecular evolutionary mechanism that controls the time of physiology to maintain homeostasis. Circadian disorder in particular has been identified as an independent risk factor for cancer and has been classified as a carcinogen. The circadian rhythm regulates several biological pathways, including oncogenic tumors, metabolism, and cell reproduction. The new data examined in this article suggest that circadian regulatory functions play a key role in various aspects of cancer, including cell proliferation control, cell death, DNA repair, and metabolism. Circadian irregularities are incorrect input signals, such as exposure to night light, variability in circadian rhythm genes, and output changes that regulate circadian behavior, including melatonin. Night work, shift work, workday changes, urinary melatonin levels, and insomnia put older men at risk for prostate cancer. Melatonin has anti-cancer properties. Men with lower melatonin levels in the morning had a higher risk of advanced or fatal prostate cancer. Melatonin, a hormone found in the pineal gland, plays an important role in the functioning of the circadian function. The integration of circadian biology into cancer research opens up new avenues for more effective cancer treatment, including the prevention, diagnosis, and treatment of this destructive disease. This review examines the role of the circadian clock in tumor formation and cancer symptoms, and examines whether pharmacological changes in circadian clock genes may lead to new treatment options.

**Corresponding author: E-mail: dhanajipharma@gmail.com;*

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ABBREVIATIONS

CR : Circadian Rhythms
SCN : Suprachiasmatic Nucleus
NSCLC: Non–Small-Cell Lung Cancer
CRY : Cryptochrome
PER : Repressor Proteins Period

1. INTRODUCTION

Circadian rhythms (CR) (about a day) are at the forefront of our lives, most obviously via the sleep–wake cycle [1,2]. In fact, almost all basic physiology and metabolism are under circadian control [3]. Driven by these cellular "clocks" distributed to the body by these rhythms, they adapt us to the world by preparing the brain and other tissues for very different day-to-day functions, often incompatible, was expected [4]. For example, in everyday species such as humans, neuronal mechanisms that maintain alertness and cognitive abilities during the day are regulated [5,6], and nocturnal readiness activates the pathways needed to improve synaptic sleep and memory [7]. Active nocturnal animals show similar changes in two directions in mice but against light and dark phases. At the cellular level, these rhythms are the result of daily programs for the expression of genes specific to individual tissues [8,9]. Disruption of the circadian program of the brain negatively affects sleep and cognitive performance, as well as associated processes such as synaptogenesis and the elimination of brain metabolites [10,11]. It is therefore not surprising that circadian time disturbances are associated with various psychiatric12, neurological [13], and metabolic diseases [14].

CR are driven by a pacemaker located in the suprachiasmatic nucleus (SCN), which plays crucial roles in maintenance of systemic CR and regulates peripheral tissue clocks through secretion of endogenous regulatory factors [15]. The molecular clock of the CR system, which is present in all cells, is made up of oscillating clock-related proteins that compose TTFLs [16]. The core TTFL is composed of the transcriptional activator proteins CLOCK and BMAL1, and the Repressor Proteins Period-1 (PER1), PER2, PER3, Cryptochrome-1 (CRY1) and CRY2 [16]. Additional loops are attached to the core TTFL to keep oscillation. The primary sub-loop be composed of RORs with nuclear REV-ERB receptors. The second sub-loop comprises D-box-related genes, which include DBP, TEF, and HLF [17,18].

The upper CR is protected by a suprachiasmatic nucleus (SCN) regulator, which plays a key role in maintaining systemic CR and regulating peripheral tissue peripheral cleansing clocks. The molecular clock of the CR system, which is present in all cells, is made up of oscillating clock-related proteins that compose TTFLs [16]. The core TTFL is composed of the transcriptional activator proteins CLOCK and BMAL1, and the repressor proteins Period-1 (PER1), PER2, PER3, Cryptochrome-1 (CRY1) and CRY2 [16]. Additional loops are attached to the TTFL core to maintain fluctuations. The first sub-cycle consists of the ROR and REV-ERB nuclear receptors. The second sub-loop contains D-box-related genes, including DBP, TEF, and HLF17, 18.

Signals from the overhead pacemaker of the circadian clock, the SCN, mediate the oscillation on a cellular level through clock gene expression and feedback [19]. An interruption within these signaling pathways could have a critical influence on the organism exaggerated. Circadian genes may be involved in regulating cancer-related pathways, including cell proliferation, DNA damage response, and apoptosis [20]. Cancer-related genes like *c-myc* and *p53* exhibit a circadian rhythm *in vivo* [21, 22]. Oncogenic activity such as excessive cell proliferation, loss of DNA damage control and increased tumor development has been detected in mice with a loss of functioning circadian genes22. The lifestyle in the twenty-first century has changed due to more industrialization of society, which has altered the endogenous circadian rhythm in ~50% of the world's population. This, among other reasons, has led to increased development of cancer throughout the world [23]. There are studies presenting the consequence of dysfunctional circadian machinery in individuals, for instance mutations, non-standard appearance, and translocation of clock genes, which have lead to diverse cancer types including breast, colorectal, gastric, kidney, and lung, prostate, pancreatic, and oral cancer [24]. The circadian clock plus the cell cycle contribute to a few universal features in molecular pathways and theoretical stages. It has been hypothesized that clock genes have a crucial role in the cell cycle and with this role they are highly involved in tumorigenesis [22].

2. CIRCADIAN CLOCK

2.1 Structure of the Circadian System

Living systems possess an exquisite internal biological clock, and the major function of which is to regulate the daily sleep–wake cycle [25]. The circadian clock follows a rhythm of approximately 24 h and ensures accurate adaptation to external daily rhythms through a powerful endogenous timing system [26]. The circadian clock also drives numerous molecular and cellular processes by generating oscillations. Virtually, all body cells have an autonomous circadian clock [27,28], which is composed of a central clock existing in the suprachiasmatic nucleus (SCN) neuron and peripheral clocks. Clock, Bmal1 (brain and muscle ARNT-like protein-1), Pers, and Crys constitute a set of circadian oscillation genes in mammals [29].

2.1.1 Suprachiasmatic nucleus

The central circadian clock, located in the SCN of the anterior hypothalamus, is the primary circadian pacemaker [30]. The SCN comprises a network of approximately 20,000 neurons. Each neuron is considered to have an oscillator of the autonomous circadian clock. As the neurons are joined and oscillated in a consistent manner [31], the SCN neuron can generate an autonomous circadian clock similar to other cells [32,33]. The SCN as the primary circadian pacemaker regulates independent gene expressions through neuronal firing [34].

The retina captures optical signals and transmits signals to the SCN [35]. SCN neurons organize coupling mechanisms that ensure their synchronization even in darkness [36]. SCN neurons change the gene expression levels by converting electrical information into chemical information [34]. Neuronal firing frequency can synchronize the other cells of the body with rhythmic changes [37]. The central clock is controlled by external signals; food and light are the strongest signals affecting the clock. Once synchronized, the central clock consequently mediates the synchronization of the peripheral clocks through signaling [38].

Moreover, lability and plasticity of the phase in the intrinsic period are two critical functions of the central clock [39]. As the phase is labile, the length of the intrinsic period leads to different phases [40]. The waveform of the SCN amplitude is mainly related to the light cycle. The waveform is narrow with high amplitude in short photoperiods, whereas it is broader with a low amplitude in long photoperiods. The circadian waveform in SCN oscillation is strong correlated with the SCN and behavioral rhythms [41].

2.1.2 Peripheral clocks

Peripheral and central clocks have been discovered in various tissues. One study reported the ubiquity of peripheral clock and its mechanism in both SCN and other cells [42]. Another study reported that cultured SCN cells maintained a firm rhythmic pattern through photoreception, also expressed in many organs, such as the liver, lungs, and kidneys [43]. In addition, numerous mammalian peripheral tissues exhibit circadian oscillation; consequently, oscillations are suppressed when the SCN is absent [40,41]. Thus, a delayed feedback loop originally associating the same components is considered to be composed of the rhythm-generating molecular circuitry, which is constructed by both SCN and peripheral cells [34]. Several pivotal physiological functions are influenced by light–dark oscillations in peripheral organs, including the heart, liver, lung, kidney, and skeletal muscles [44].

Local peripheral oscillators can be synchronized by neuronal signals and stimulating hormones. The SCN sends signals to all body systems, coordinating the feeding–fasting cycles [45,46]. Although the SCN functions as the master synchronizer of the entire system, food intake can disrupt the control in peripheral clocks. A change in the feeding schedule alters the phase in the central and peripheral clocks in the liver [47]. Moreover, light information is transmitted to the adrenal gland, liver, and pancreas by the SCN, which distributes a rhythmic signal to all tissues of the peripheral organs [48]. The central neural and peripheral tissues maintain the normal neurological and metabolic homeostasis in the sleep–wake cycle [49]. The endogenous mechanism of oscillation in peripheral cells is a gene regulatory network to generate sustained oscillations. A group of genes forms the core network of the mammalian circadian clock, which can function even in the absence of external inputs in individual cells [50]. Numerous signaling pathways participate in the phase entrainment of peripheral clocks and warrant additional studies.

2.2 Circadian Clock Mechanism, Clock Genes, and Cancer

The circadian clock regulates both physiology and behavior according to the daily cycle of light

and dark. In mammals, it is hierarchically organized and integrates the master clock, which is located in the suprachiasmatic nucleus (SCN) within the hypothalamus, and the peripheral clocks as well, ubiquitously found virtually in all peripheral tissues and cells [51]. SCN clock is constantly coupled to environmental cues, mainly photoperiod, through the photic signals from the retina [52], daily rhythms in temperature, diet and social phenomena through complex downstream neurohumoral pathways. Oscillators located in brain nuclei and peripheral tissues are also connected by SCN clock [53].

Circadian rhythms are controlled by circadian pathway genes. The molecular circadian clock is originated by a transcriptional/translational loop of circadian clock genes with auto regulatory feedback. The primary loop involves the genes *CLOCK, BMAL1* (also known as *ARNTL1), PER1–3*, and *CRY1-2*. During the day, the complex integrated by CLOCK and BMAL1 stimulates the expression of negative regulators period genes (*PER1–3*) and cryptochrome genes (*CRY1-2*). Heterodimers constituted by PER and CRY operate as co-repressors, binding to the CLOCK-BMAL1 complex and inhibiting *CRY* and *PER* gene transcription induced by CLOCK-BMAL1. Furthermore, in the dark phase, *CRY* and *PER* expression decrease to the CRY-PER repressor complex. This leads to a new cycle of the transcription activation of the *CLOCK-BMAL1* complex, which completes the basic auto regulatory loop [54]. Otherwise, different modulators display fine tuning of output signals in molecular clock.

Currently, several core circadian genes, also known as circadian clock genes, have been identified in humans [55] *ARNTL* (aryl hydrocarbon receptor nuclear translocator like, also identify in brain and muscle as Arnt-like protein-1, BMAL1) [56-57], *CLOCK* (clock circadian regulator) [58], *CRY1* (cryptochrome circadian clock 1), *CRY2* (cryptochrome circadian clock 2) [59], *PER1* (period circadian clock 1), *PER2* (period circadian clock 2), *PER3* (period circadian clock 3) [60-62], *CSNK1E* (casein kinase I epsilon) [63], *NPAS2* (neuronal PAS domain protein 2) [64-65], *NR1D1* (nuclear receptor subfamily 1 group D member 1 also called Rev-Erb alpha) [66-67], *NR1D2* (nuclear receptor subfamily 1 group D member 2 also referred to Rev-Erb beta) [68], *RORA* (RAR related orphan receptor A)[69] and *TIMELESS* (timeless circadian clock) [70].

3. CIRCADIAN RHYTHM DISRUPTION AND CANCER DEVELOPMENT

Circadian clocks influence the cell division cycle through a complex regulatory pathway. It is likely that a number of additional pathways contribute to the regulation of circadian rhythms, carcinogenesis, and progression of cancer, as e.g. the NONO (non-POU domain containing, octamer-binding) protein is involved in both transcriptional and post-transcriptional gene regulatory functions and DNA repair [71-73]. Thus, it is likely that there are several intersections of the cancer-related and circadian pathways. However, it is disruption of the circadian rhythms and the subsequent loss of synchronization in the regulation that is in common here. Therefore, the disruption is the key we think that can predispose individuals to the development of cancer. The mechanism by which the circadian clock is disrupted may make a difference: in particular, there is a common light-induced signaling pathway that regulates both the circadian rhythms and the cell division cycle [74]. The molecule of key importance may be different from tissue to tissue, e.g. ARNTL (BMAL1) in the skin [75] and, hypothetically, PER2 or CRY2 in some of the remaining, and their disruption may then lead to a specific mode of cancer.

In recent epidemiological studies, circadian rhythm disruption has been indicated as a risk factor for breast cancer. Long-term night shift work seems to associate with an increased risk for breast cancer [76]. However, studies in which the duration of shift work has been quantified demonstrate that robust elevations in risk are seen only after about 20 years of working night shifts, and it is unclear whether there is a risk after shorter durations. Heterogeneity of the exposure metrics and the study outcomes has been problematic in these studies and limited the usefulness of a meta-analysis as a conclusive tool.

Serum or saliva melatonin concentrations can be used as a reliable biomarker of the phase position of the circadian rhythms [77]. However, the current data concerning the actions of melatonin as a bioactive protein, the nocturnal synthesis of which is inhibited by exposure to light, in the pathogenesis of cancer are still conflicting [78], albeit that melatonin induces CRY1 expression [79-80] and that melatonin levels, if reduced, are likely to affect the metabolic cascades of the cell, at least those in

the liver, through the compromised actions of CRY1 and CRY2 [81]. It has been suggested that circadian rhythm disruption influences the regulation of estrogen levels, thereby increasing the risk for developing breast cancer. Few epidemiological studies indicate a link between shift work and prostate cancer [70-71]. Here, circadian rhythm disruption may also influence the levels of androgens and thereby increase the risk for prostate cancer.

Another line of evidence for the links between the circadian clock and cancer is based on findings which demonstrate that the long-term circadian misalignment, similar to that which occurs in circadian rhythm sleep disorders, reduces leptin levels throughout the day and night and thereby predisposes to weight gain [82], known to be a risk factor for both breast and prostate cancers. However, further research is needed in order to elucidate whether these hypotheses are correct and, if correct, what the detailed mechanisms of action are.

On the other hand, circadian rhythm disruption that affects the immune response pathways might predispose to non-Hodgkin lymphoma [83-84]. Here, the circadian clock gene PER2 in specific may be a key, because mice deficient in the mPer2 gene are prone to malignant lymphoma, having not only a substantial increase in tumor development and a reduced apoptosis in thymocytes after gamma irradiation but also spontaneously malignant lymphoma at younger age [85]. So far, only one study has investigated the association of night shift work with non-Hodgkin lymphoma, suggesting an increased risk for non-Hodgkin lymphoma as a result of shift work that involves night work and is therefore likely to cause circadian disruption [81]. Moreover, the leptin-guided signals may play a role, since leptin triggers an inflammatory response in tumor tissue by stimulating, e.g. in colorectal cancer, colonocytes to recruit T lymphocytes with a role in antitumor response in the tumor microenvironment [86-87]. Currently, it is not known whether leptin has a similar role, if any, in other modes of cancer in humans.

4. MELATONIN AND CANCER

In 2007, the International Agency for Research on Cancer categorized “shift-work that involves circadian disruption [as] *probably carcinogenic to humans*” (Group 2A in the IARC classification system of carcinogenic potency of an agent) [88]. Light during the night can suppress melatonin, disrupting circadian rhythms [89]. Melatonin (5-methoxy-N-acetyltryptamine) is a hormone of the circadian system, synthesized in the pineal gland and retina (reviewed in [90-91]. In patients with untreated non–small-cell lung cancer (NSCLC) melatonin/cortisol mean nocturnal level ratio and melatonin nocturnal levels are decreased [92-93]. These results may indicate a neuro-immune-endocrine system dysfunction. Melatonin concentrations progressively decrease after standard chemotherapy in NSCLC patients [93]. Melatonin can resynchronize a rhythmic pattern of gene expression, correcting defects in expression patterns of various circadian rhythm genes responsible for cancer development [67]. Melatonin inhibits myeloperoxidase catalytic activity [94], which is important in the pathogenesis of cancer [95-96]. Melatonin has a protective effect against the DNA-damaging action of hydrogen peroxide, by chemical inactivation of this DNA-damaging agent and stimulation of DNA repair [97]. Melatonin inhibits tumor signal transduction and metabolic activity of cancer cells, leading to suppression of growth of human breast cancer via activation of melatonin receptor MT1 [98]. Disruption of nocturnal circadian melatonin signal by light at night up regulates tumor metabolism, stimulating its growth [99]. Women with total visual blindness have a lower risk of breast cancer than blind women with light perception [100]. The antiproliferative ability of melatonin is associated with its uptake into human androgen-dependent LNCaP and androgen-independent PC-3 prostate cancer cells, mainly mediated by an active transport [101].

Preventing low-wavelength light from reaching the retina, for example, by using optical filter goggles may protect shift workers from bright-light suppression of melatonin [102]. If epidemiologic and basic science evidence leads to a “proof of causality” of adverse effects from light at night, then lighting standards and building designs should be developed with consideration of the circadian system both at night and during the day, to minimize or eliminate adverse consequences for human health [103-105].

5. PROSTATE CANCER

Prostate cancer exhibits the highest cancer prevalence in men, being the second cause of cancer-related deaths [106]. Normal prostate cancer development is dependent on androgens levels. Circadian clock genes regulate androgen production [107], affecting prostate cancer

evolution [108]. On the other hand, a balanced regulation of the circadian clock genes might modulate and even suppress tumor growth by controlling DNA replication, repair mechanisms and cell proliferation [109]. Although a limited number of epidemiologic studies have been realized, several circadian genes have been implicated in prostate cancer regulation: *ARNTL, CLOCK, CRY1-2, CSNK1e, MTNR1A* and *MTNR1B, NPAS2, NR1D1, PER1*-3, *RORA, RORB*, and *TIMELESS* [110-111].

One of the first epidemiologic studies performed on prostate cancer and their associated SNPs, Chu et al. identified five polymorphisms in five circadian genes. This case-control study was conducted in a Chinese population with 187 cases and 242 control subjects [112]. These polymorphisms encompassed *CRY2* rs1401417, *CSNK1E* rs100 5473, *NPAS2* rs2305160, and *PER1* rs2585405. The C allele from *CRY2* presented an elevated prostate cancer risk compared to GG genotype carriers. Higher risk was found in men whom also sustained elevated insulin resistance (IR) compared to these with the GG genotype and lower IR. Moreover, the allele from *NPAS2* polymorphism was associated with a reduced risk of developing prostate cancer in men with reduced IR when compared to the GG genotype carriers.

Zhu and colleagues also investigated the link between circadian genes with prostate tumors. The case-control study in a Caucasian men population included 1,308 cases and 1,266 control subjects. In this study was genotyped 41 variants in ten genes related with circadian clock [113]. At least one polymorphism in nine clock circadian genes was significantly associated with prostate cancer risk. Specifically, it was found the variants rs7950226 in *ARNTL*, rs11133373 in *CLOCK*, rs12315175 in *CRY1*, rs2292912 in *CRY2*, rs1534891 in *CSNK1E*, rs1369481, rs895521, and rs17024926 in *NPAS2*, rs885747 and rs2289591 in *PER1*, rs7602358 in *PER2* and rs1012477 in *PER3*. They observed that the estimate risk for variants rs885747 and rs2289591 in *PER1*, rs1012477 in *PER3*, and rs11133373 in *CLOCK* significantly changed depending on disease aggressiveness.

Lin et al. carried out studies in prostate cancer using two populations, from Seattle and Sweden, respectively) [114]. They genotyped 937 polymorphisms corresponding to 156 genes in 1,309 men with prostate cancer in a Seattle cohort. They identified 22 variants associated to prostate cancer-specific mortality (PCSM), and validated them afterward in a Swedish cohort (2,875 patients. In the Swedish cohort, five polymorphisms out of the 22 SNPs identified in the Seattle cohort, were found to be significantly associated with PCSM, with a statistical significance variant in the CRY1 gene (rs10778534). The study also identified another variant in the Seattle cohort, rs228697 in *PER3*, associated with PCSM, which was not further tested in the Swedish cohort due to genotyping drawbacks.

Another study evaluating the association between mortality in prostate cancer and circadian clock-related genes was carried out by Markt et al. [115]. Authors tested 96 variants in 12 circadian-related genes using 3 patient cohorts (24, 40, and 105 cases/respectively). It was also analyzed the association with lower levels of melatonin (measured by 6-sulfatoxymelatonin). This study showed no variants significantly associated with overall risk of prostate cancer, however in all cohorts was observed that variation in the *CRY1* gene was associated with mortality in prostate cancer This study of individual cohorts revealed that two polymorphisms from *CRY1*, rs7297614, and rs1921126 were associated to increased mortality in 2 out 3 prostate cancer cohorts, and a similar association was proved for rs12315175 in the *CRY1* gene in a single cohort. Finally, their analysis of the 6-sulfatoxymelatonin levels showed that patients with metabolite levels lower than the median had an increased risk of advanced disease, where polymorphisms in *CSNK1E, NPAS2, PER3*, and *TIMELESS* were associated to changes in these 6-sulfatoxymelatonin production. Future investigations should be designed including a large population compared to the one used in this study, and similar clinico-pathological factors as well to ensure statistical power and allow for results comparisons.

Recently, Mocellin et al. performed an analysis using adaptive rank truncated product (ARTP)-based gene and pathway analysis to discern the relevance of the variation in circadian clock genes and cancer susceptibility [116]. In this analysis using previously published dataset of prostate cancer [117], they found a highly significant association between genetic variation of circadian pathway and susceptibility to prostate cancer. This result was founded on data regarding 17 SNPs located in seven genes, with

the most significant SNP rs142435152 from *ARNTL* gene. Their analysis of subgroups revealed that the risk of suffering aggressive prostate cancer was also highly associated with circadian pathway variation. This finding was based on 28 SNPs located in seven genes, where the most significant gene was *RORA* with the rs17191414 SNP.

6. CONCLUSION

A major consequence of modern lifestyle is disruption of circadian rhythms. Circadian disruptions induced by light at night, genetic or epigenetic variations in circadian genes and interactions between genes and environment form a set of data that propose that some cancer cases could be explained by these mechanisms. Elucidation of molecular mechanisms that form a link between disruption of circadian rhythm and cancer and determination of how a disrupted circadian peripheral clock contributes to neoplastic transformation is fundamental to provide essential leads developing future novel circadian clock–based strategies for cancer prevention, control and therapeutic intervention.

Implications of the circadian systems biology in oncology are about to be introduced into clinical practice. They include clinically feasible methods for the assessment of the individual's circadian time that are based on the analysis of levels of time-indicating molecules. Such molecules include metabolites derived from a single sample of venous blood and messenger RNAs captured directly from a tissue of interest through biopsy. In the former the assessment can be based on a range of methods, e.g. enzyme-linked immune sorbent assay or mass spectrometry using the approximate 20 time-indicating metabolites, whereas in the latter it is based on DNA microarray using the approximate 60 time-indicating genes.

To understand the pathogenesis of cancer in more detail, it is important to identify the details of those mechanisms that contribute to the loss of control of the cell division cycle in particular. All cancers where circadian rhythms are disrupted need to be identified, as some of the circadian-based options available for the treatment may prove to be clinically feasible. However, this step ahead needs to be based on experimental evidence and clinical trials. New potential preventive measures of these circadian-type cancers should then be targeted at large in order to avoid the long-term or recurrent circadian rhythm disruptions. Such actions can be achieved by making living and working circumstances more compatible with the circadian preference of an individual, which is driven by the timing of innate physiology.

The current findings suggest that some genes must be involved in the predisposition to cancer development of reproductive tissues, other genes must be specific to a type of cancer, and other genes should affect tissues modulated by endocrine hormones. The effect of these genes is probably showed up at the hormone pathways level, as in the *CLOCK* gene. The activity of the *CLOCK* gen product regulates estrogenic and androgenic hormonal pathways. This could be related to the fact that polymorphisms of this gene alter the regulation of these pathways and produce an uncontrolled proliferation of prostate tissue cells.

We reckon that a screening of polymorphisms related with the circadian clock could provide valuable information regarding predisposition of suffering a particular type of cancer, thus facilitating its prognosis. When cancer is already present, malignancy intervention strategies could be immediately applied due to earlier detection.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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