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"Time" for obesity-related cancer: The role of the circadian rhythm in cancer pathogenesis and treatment

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ABSTRACT

The circadian rhythm is regulated by an intrinsic time-tracking system, composed both of a central and a peripheral clock, which influences the cycles of activities and sleep of an individual over 24 h. At the molecular level, the circadian rhythm begins when two basic helix-loop-helix/Per-ARNT-SIM (bHLH-PAS) proteins, BMAL-1 and CLOCK, interact with each other to produce BMAL-1/CLOCK heterodimers in the cytoplasm. The BMAL-1/CLOCK target genes encode for the repressor components of the clock, cryptochrome (Cry1 and Cry2) and the Period proteins (Per1, Per2 and Per3). It has been recently demonstrated that the disruption of circadian rhythm is associated with an increased risk of developing obesity and obesity-related diseases. In addition, it has been demonstrated that the disruption of the circadian rhythm plays a key role in tumorigenesis. Further, an association between the circadian rhythm disruptions and an increased incidence and progression of several types of cancer (e.g., breast, prostate, colorectal and thyroid cancer) has been found. As the perturbation of circadian rhythm has adverse metabolic consequences (e.g., obesity) and at the same time tumor promoter functions, this manuscript has the aim to report how the aberrant circadian rhythms affect the development and prognosis of different types of obesity-related cancers (breast, prostate, colon rectal and thyroid cancer) focusing on both human studies and on molecular aspects.

1. Introduction

The prevalence of overweight and obesity is increasing worldwide, and the evidence supporting the link between obesity and cancer is growing [1]. Indeed, numerous cohort studies, summarized in systematic reviews, have shown an association between obesity and cancer incidence overall and for selected cancer types (eg, postmenopausal breast, thyroid, prostate and colorectal). Several mechanisms have been hypothesized to explain the association between cancer and obesity, involving elevated lipid levels and blunted lipid signaling, inflammatory responses, insulin resistance, and adipokines. However, recent literature highlights a shared mechanism between cancer and obesity, i.e., disruption of circadian rhythm [2]. Indeed, an impairment of the biological clock has been detected in obesity, causing an increased expression of inflammatory cytokines, which is worsened by the disease itself [3]. In addition, the circadian rhythm disruption could contribute to the metabolic dysfunction of the adipose tissue, thus increasing the risk of developing obesity-related cardiometabolic diseases, as detected in the night shift workers [4].

The disruption of the circadian rhythm is also associated with an

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increased susceptibility to tumors and to a worse response to anticancer treatment and prognosis [5]. Indeed, the circadian clock is an endogenous timekeeper system that regulates biological processes, which are consistent with a master circadian clock and peripheral clocks and are controlled by various genes. Existing evidence indicates that the circadian clock functions are a gate governing many aspects of the cancer-immunity cycle that is composed of seven major steps, namely cancer cell antigen release and presentation, priming and activation of effector immunity cells, trafficking, and infiltration of immunity to tumors, and elimination of cancer cells [6]. The circadian clock is an endogenous timekeeper system that controls and optimizes biological processes, which are consistent with a master circadian clock and peripheral clocks and are controlled by various genes. Notably, the disruption of circadian clock genes has been identified to affect a wide range of ailments, including cancers. The cancer-immunity cycle is composed of seven major steps, namely cancer cell antigen release and presentation, priming and activation of effector immunity cells, trafficking, and infiltration of immunity to tumors, and elimination of cancer cells. Existing evidence indicates that the circadian clock functions as a gate that govern many aspects of the cancer-immunity cycle. Nocturnal shifts workers have a mildly augmented risk of developing breast cancer (BC) as well as prostate cancer (PCa), instead is less common in individuals which are usually more active during the morning and less active in the evening, thus living according to the circadian rhythm [7,8]. Also there is evidence of a higher prevalence of colorectal cancer (CRC) in shift workers, as demonstrated by a population-based case-control study carried out in Spain investigating the risk for CRC in relation to shift work history [8]. This analysis included 1626 incident CRC cases and 3378 randomly selected population controls of both sexes, enrolled in 11 regions of Spain. Rotating shift work (morning, evening and/or night) was associated with an increased risk for CRC, as compared to day workers and OR increased with increasing lifetime cumulative duration of rotating shift work (P-value for trend 0.005) [8]. Further, it has been demonstrated on rats that forced alterations of the biological clock produce effects on the intestinal microbiota, causing a low-grade inflammation at the intestinal level potentially involved in carcinogenesis [9]. The disruption of the circadian rhythm, evidenced in the human CRC, has been reported also to have a role in accelerating the progression of this tumor [10].

A reciprocal link between circadian clock and thyroid disorders has been reported in both in vitro and in vivo studies [11,12]. Chronic sleep deprivation has been linked with derangements of rhythmic TSH secretion, which, in turn, is linked to an increased incidence of human thyroid cancer (TC) [11,12] (Fig. 1). Thus, the aim of our manuscript is to review the current evidence on the association of the disruption of circadian rhythm and obesity related cancer reporting both human and basic studies.

2. Human studies on circadian rhythm disruption

2.1. Breast cancer

For some time now, "shift work involving circadian disruption" is classified as being probably carcinogenic in humans [13]. In the last 15 years, the number of human studies investigating the connection between night work and BC has increased more than threefold [14].

A very recent systematic review and meta-analysis by Manouchehri et al. including 26 eligible studies with over one million participants has shown an increased risk for BC in both short-term and long-term night shift workers adjusted for family history and reproductive factors, while

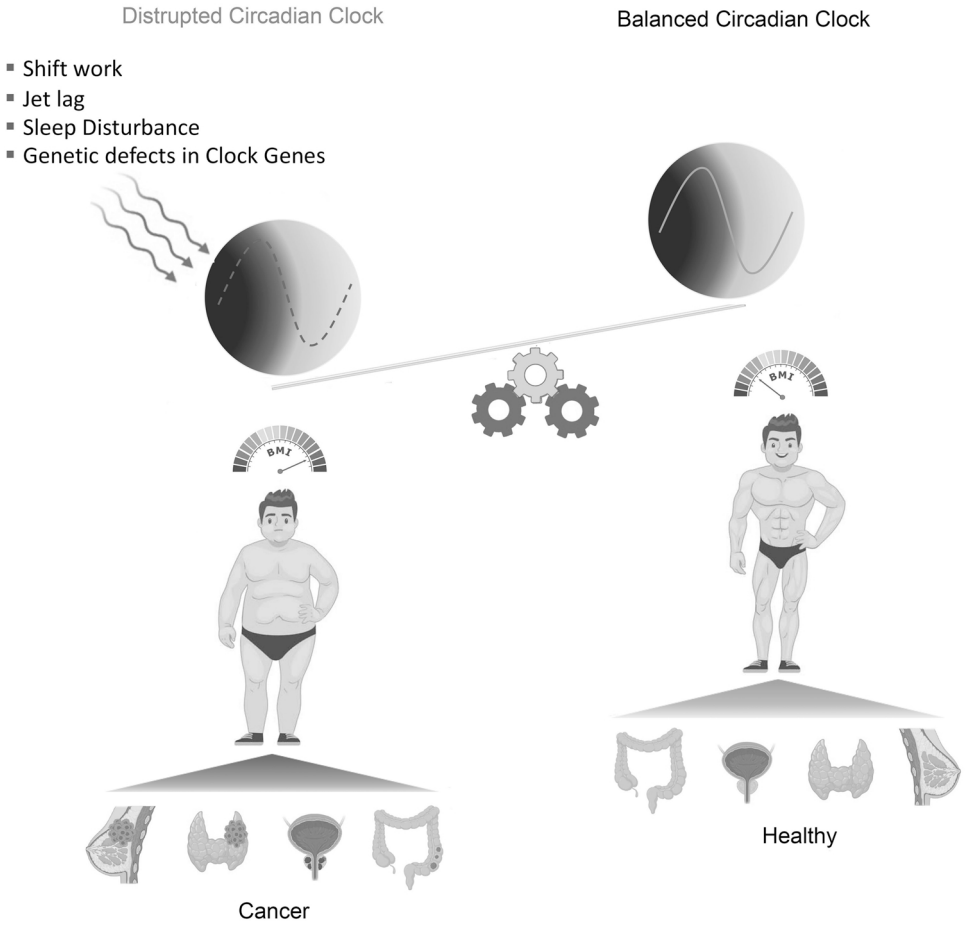

Fig. 1. Differences between disrupted and balanced Circadian Clock.

highlighting that flight attendants with long overnight flights are an especially vulnerable subgroup [15]. Prior to this research, conflicting results were reported [16]. A prospective sister study, following a cohort of BC-free women with a sister who was diagnosed with BC, investigated female work patterns, rotating shifts, and irregular work patterns, involving nighttime work. In the results, little evidence was observed in favor of night-time work as a major risk factor, however, compared to women who never worked at night, those who reported short-term night work (under 5 years) had a greater risk of BC [16]. In a consequent paper from the International Agency for Research on Cancer (IARC) group, it was highlighted that it is necessary to perform more research in relation to the impact of different shift schedules on circadian rhythm in real-world environments with a clearer definition of shift intensity, cumulative exposure and shift systems [17]. A number of studies with different designs investigated sleep duration, quality and disturbance in relation to BC, showing that the beneficial effect of sleep increases with adequate alignment to circadian rhythms and exogenous light-dark cycle [18]. Data also showed that a decreased nighttime melatonin could promote tumor proliferation through elevated blood glucose levels [19]. This condition correlates with tumor size while also being lower in estrogen receptor positive (ER+) patients [20]. Chrono pharmaceutical agents, timed lighting, and the use of biomarkers of circadian phase could help in proper circadian rhythm timing with scheduled radiation therapy [21]. Despite various factors contributing to discrepant results such as the healthy worker effect [22], and a vast coverage of non-modifiable risk factors for BC, research also tends to cover the role of modifiable factors such as diet and physical activity [23,24], smoking [25], alcohol consumption and folate intake [26] and many more with a considerable bidirectional link to sleep quality and circadian rhythm impairment. By modifying simple lifestyle and emphasizing the importance of primary prevention along with further studies in the field of chronobiology and BC, we can get closer to the goal of reducing the incidence of BC and timely management.

2.2. Prostate cancer

A large population-based case-control study estimating the association between circadian gene single nucleotide polymorphisms in 31 clock genes with PCa found that circadian genes may also play a role in PCa, with statistical significance for genes NPAS2 and PER1 at the gene level in the whole cohort and retinoic acid-related orphan receptor alpha (RORA) in aggressive tumor variants [27]. A variety of study designs and different methodologies in patient selection (subjects taking a range of therapies, various stages of cancer), as well as insufficient circadian gene variations are present in human circadian gene studies related to PCa [28]. The relationship between the circadian rhythm and rhythm shifts and PCa has also been explored, but to a lesser extent than BC or example. Due to emergence of new data in this field, there are vast efforts to identify factors that are targetable by public health measures and could aid in reducing incidence of PCa. The results of these studies are somewhat conflicting but promise novel therapeutic directions in treatment. In a study performed by Barul et al., data concerning detailed work schedules taken from patients with PCa did not show any association between PCa and nightshift work metrics such as work exposure, cumulative exposure, intensity, early morning shits and shift rotations, nor was the data significant for high or low-grade cancers [28]. This has been also reported in several other cohort studies, including a large prospective follow-up study on male twins [29]. In this study, despite not finding an association between sleep features (quality, duration), shift work and PCa, the chronotype of a worker has been shown to significantly modify their shift-work association to PCa [29]. On the contrary, in a meta-analysis with a large sample size, overall meta-relative risk of 1.24 has been demonstrated in night-shift workers for PCa [30]. Similar supportive findings were reported in several other studies [31–33]. Nevertheless, such as in BC, they must be taken in account the possibility of recall bias and the difficulty of defining the exposure and the confounding factors [34,35]. In addition, different ethnicity and cohort selection could contribute to the variation and significance of the results [34,35]. African American men (AA) are diagnosed with PCa 1.6 times more often than Caucasian men and are at 2.6 times higher risk of PCa-related mortality [34,35]. They are also more likely to be exposed to various negative environmental factors (pollution, low daytime light levels, worse food choices, poverty and access to healthcare) as well as chronic conditions and diseases contributing to PCa [36–38]. An occupational component to PCa related to night shifts has also been established in healthcare workers, firefighters, policeman and other professions requiring a degree of night-shift work [39,40]. Furthermore, exposure to other factors such as artificial light at night (ALAN) can alter melatonin levels, contributing to one of the supposed mechanisms of PCa development [41]. The prolonged exposure to ALAN increased the risk of PCa in long-term night-shift workers irrespective of chronotype and especially in those with worse prognosis [42]. Melatonin supplementation and chronotherapy could be proposed as a significant addition to chemotherapeutic drugs in order to reduce adverse effects and enhance survival [43]. Stress, circadian rhythm disruption and metabolic components act in synergy trough androgen receptor signaling pathway resulting in disruption of the PCa tumor microenvironment [41]. For this reason, targeting these mechanisms could also aid in tumor growth reduction and a better therapeutic response [41]. Controlling all the aforementioned factors and maintaining a healthier lifestyle with regular screening is one of the best ways for primary prevention in both BC and PCa, but further randomized prospective studies will help elucidate the crucial factors and targets for novel therapy.

2.3. Colorectal cancer

Abnormal eating time (during or around physiologic rest time) caused circadian rhythm disruption in mice by shifting the phase of the colon rhythm, and interacted with alcohol exposure in promoting colon carcinogenesis, by inducing a proinflammatory profile, and by changing the colon microbiota and butyrate signaling [44]. Disrupting the circadian clock of cells thought shift work may increase the risk of CRC, and several studies have evaluated this risk [8,45]. Two German and a Spanish population-based cohort studies have not found an association between exposure to night shift work and risk of CRC (incidence rate ratios: 1.03 [95% CI: 0.62; 1.71], and OR=0.79 [95% CI: 0.62–1.00], respectively), but the rotating shift work significantly increased the CRC risk (IRR=1.45 [95% CI: 0.72; 2.92], and OR=1.22 [95% CI: 1.04–1.43]) compared with day work [8,45]. In contrast, two prospective female cohort studies did not find and association between the rotating night shift work and CRC risk [46]. However, this correlation was seen for the rectal cancer. The risk increased with the shift work duration, implying a role of long-term circadian disruption in rectal cancer [46]. Another case-control study from Australia found no evidence of an increased risk of CRC with long-term exposure (>7.5 years) to shiftwork [47]. Nevertheless, a meta-analysis (n = 6 studies) that quantitatively evaluated the correlation between the risk of CRC and night shift work not only confirmed this association (OR=1.318 [95% CI: 1.121–1.551], although with heterogeneity), but it also reported a dose-response relationship, as for every 5 years increase in night shift work the rate of CRC raised by 11% (OR=1.11 [95% CI: 1.03–1.20]) [48]. The association has been found for both for colon and rectal cancer, both in female and male subjects [48].

Moreover, the circadian disruption, as evidenced by both extreme long (≥ 9 h) and short (≤5 h) sleep duration, was shown to be associated with a higher risk of CRC in postmenopausal women (HR: 1.47 [95% CI: 1.10–1.96] and 1.36 [95% CI: 1.06–1.74], respectively, versus 7 h sleep duration) [49]. In addition, the exposure to ALAN, particularly the blue light spectrum, was shown in a Spanish case-control study to be positively associated with CRC risk (OR=1.6 [95% CI: 1.2–2.2] for highest vs. lowest tertile), even after adjustment for various other risk factors

[50].

2.4. Thyroid cancer

Several studies evaluated the association between sleep disorders and the risk of TC, but the results are controversial. In a study including about 6000 female flight attendants no consistent evidence was found regarding the correlation between the risk of TC and circadian disruption/ time zones crossed [51]. Similar results have been shown by a systematic review and meta-analysis (n = 3334,114 person-years of follow-up), indicating a similar standardized incidence ratio of TR for cockpit crew (1.21 [95% CI: 0.75–1.95]; p = 0.383) and for cabin crew (1.00 [95% CI: 0.60–1.66]; p = 0.646) compared to the general population [52]. On contrary, data from the Women's Health Initiative that enrolled 142,933 postmenopausal women (n = 295 TC) suggested that those with sleep disturbance (insomnia) had higher risk of TC (HR=1.44 [95% CI: 1.01, 2.05]), and this association was rather seen in women not affected by obesity ($p_{interaction}$=0.07) [53]. A large US cohort study (n = 464,371 participants) has also found a positive association between LAN, which may cause circadian disruption, and the risk of TC (HR=1.55 [95% CI: 1.18–2.02] for the lowest versus highest quintile), and the association was stronger in women [54]. Thus, more clinical data is needed in order to clarify the association between the circadian clock alterations and the TC risk.

3. Molecular bases of the links between genetic changes in circadian clock machinery and cancer

The 24-hour rotation of the Earth has been a driving force in developing intrinsic circadian clocks in all living organisms as an adaptation to the light/darkness pattern [55]. The rhythmicity of the circadian cycle is a consequence of a transcriptional/post-translational positive and negative feedback loop triggered by the brain in response to light cues [55]. The circadian clock is an intrinsic time-tracking system, composed both of a central and a peripheral clock [56–58]. In detail, there is a central clock pacemaker in the suprachiasmatic nucleus (SCN) of the hypothalamus [59], composed of a gene set named "clock genes" which controls the cycling expression of downstream genes, called "clock-controlled genes" (CCGs), resulting in daily oscillations of proteins synthesis [60]. At the molecular level, the circadian rhythm begins when the BMAL-1 (Brain and Muscle ARNT-Like 1) and CLOCK (Circadian Locomotor Output Cycles Kaput), two bHLH-PAS (basic helix–loop–helix/Per-ARNT-SIM) proteins, interact with each other to produce BMAL-1/CLOCK heterodimers in the cytoplasm [61–64]. These heterodimers translocate to the nucleus, where they act as transcription factors and bind the E-box regions on the promoters of their target genes. The BMAL-1/CLOCK target genes encode for the repressor components of the clock, cryptochrome (Cry1 and Cry2) and the Period proteins (Per1, Per2 and Per3) [61–64]. Next, the protein products of these genes dimerize and form complexes between themselves, which allows them to translocate into the nucleus, where they inhibit the BMAL1-CLOCK complex activity, thereby repressing their own expression. This gives rise to a new cycle of transcription by BMAL-1/CLOCK, closing the cycle [61–64]. Thus, at the start of the circadian day, the BMAL1-CLOCK complex begins the circadian system, causing the accumulation of CRY and PER transcripts and proteins during the second part of the day. During the nighttime, PER and CRY enter the nucleus to inhibit BMAL-1/CLOCK activity, while post-translational modifications of CRY and PER allow their own degradation by the proteasome, thus creating the first negative feedback loop to control the clock genes expression [61–64]. This auto-regulatory feedback loop is also sustained by the orphan nuclear receptors, REV-ERBs and RORs (retinoid-related orphan receptors) [65,66]. Both receptors are activated by BMAL-1/CLOCK but, while REV-ERBs repress BMAL-1 expression, RORs induce BMAL-1 transcription, promoting the restarting of the clock [65,66].

Remarkably, this molecular oscillator not only regulates the expression of the core clock genes, but it also drives the rhythmic expression of many genes in the peripheral tissues (e.i., liver, kidney, skin, intestine, lung, pancreas, ovary, and heart), that have their own intrinsic circadian oscillations, but are dependent on the central clock and tissue-specific factors for synchronization [67–69].

In recent years, the impact of circadian disruption on human health has attracted increasing attention [70,71]. Several pieces of evidence highlighted that the environment changes, the mutation in clock genes or alteration of their expression leads to a disruption of circadian clocks and this condition has been associated with the increased risk of developing several diseases or be the leading cause of the worsening of pre-existing pathologies: cardiovascular diseases, cognitive impairment, premature aging, obesity and metabolic syndrome (Fig. 1) [70,71]. Furthermore, in humans, a strong relationship has been observed between the alteration of the circadian timekeeping system and the increased incidence and progression of certain types of cancer [72–75]. Indeed, the deregulation of circadian rhythms is a common condition identified in different cancer cell lines [76,77] and advanced-stage tumors [78]. It is interesting to note that in some types of cancer, the rhythm recovery is linked to a better quality of life, better response to chemotherapy and longer survival [79].

Although different evidence supports this observation, the molecular connections between rhythm disruptions and oncogenesis are still not well understood.

3.1. Disruption of circadian rhythm in cancer

The healthy cells normally proliferate with a division rate of ~24 h, due to the direct control of cell cycle checkpoints by the intracellular circadian clock machinery [80,81]. In contrast, tumor cells are characterized by uncontrolled cell proliferation resulting in abnormal and accelerated tissue growth [78,81]. The increase in the proliferation rate of cancer cells is due to circadian rhythm disruption, since tumor suppressors and key cell cycle genes are under the control of the clock genes [78,81]. Several studies have demonstrated that many factors, such as drugs and radiation, can disrupt the circadian clock [82]. Moreover, the deregulated expression of the clock-related genes is a common feature of tumor cells and mutations of single clock genes, such as PER2 or BMAL-1, accelerate tumor growth [76,83] or even the whole carcinogenesis process [84–86]. Keeping the synchronicity of the circadian clock is important for the coordination of various physiological and behavioral activities [87]. The circadian desynchrony affects all aspects of human health, and increases the risk of different human diseases, including obesity, depression, metabolic diseases and cancer [88–90]. Circadian clocks can be disturbed by irregular shift work, and repeated periods of jet lag; these conditions can promote the susceptibility to certain diseases and directly drive others [91–93].

The neoplastic formation and progression is a very intricate and complex process since, besides inducing profound cell cycle changes, it requires the occurrence of several steps including the blockage of apoptotic events caused by the tumoral cell contact, the initiation of tumor vascularization, which is fundamental in the transition of tumors from a benign state to a malignant one, and the acquisition of the migration and invasion ability [91–93]. These processes are all regulated by different crucial genes that appear to function as CCGs [94]. Indeed, clock genes can participate in tumor development, directly or indirectly, by altering the expression of downstream CCGs involved in cell cycle regulation, DNA damage repair, cell proliferation and apoptosis, and tumor immunity [94]. Concerning tumor immunity, many studies have underlined an important regulation of the immune system CGs-mediated, that allows an ordinary function of various populations of immune cells [95]. With a disturbance of the circadian clockwork, an alteration of immune system functioning ensues that involves all the immune cells, leading to immune suppression that impacts tumor onset and progression. The central mediator of the circadian control of the immune system is BMAL-1, able to also promote an

anti-inflammatory state [95]. Indeed, in hematologic diseases such as large B-cell lymphoma, chronic lymphocytic leukemia, and acute myeloid leukemia the expression of BMAL-1 is strongly downregulated compared to healthy patients, reinforcing the concept of crosstalk between the circadian clock and cancer-immunity [96,97].

Several studies have demonstrated the existence of links between altered circadian clocks and high incidence of cancers, such as lung, BC, ovarian, PCa, pancreatic, CRC, endometrial cancers, hepatocellular carcinoma, osteosarcoma, acute myeloid leukemia, non-Hodgkin's lymphoma, and head and neck squamous cell carcinoma (HNSCC) [75,90,98,99]. Moreover, the microenvironmental changes caused by growing tumors may disrupt the circadian rhythms in surrounding cells, inducing the acquisition of different clock phenotypes among cells in the same tumor [100]. Circadian disruption not only correlates with the onset of neoplastic disease, but it also affects the cancer progression, prognosis, and the treatment outcomes of cancer patients [5]. Thus, restoration of circadian rhythms could potentially improve patients' prognosis.

Dissecting the link between disruption of circadian rhythm and cancer, and understanding the influence of circadian rhythms on neoplastic transformation, would provide an insight for developing novel circadian clock–based strategies for cancer prevention and for the development of more efficacious therapies or novel adjuvant strategies to improve patient outcomes.

Considering that the perturbation of circadian rhythm has adverse metabolic consequences (e.g., obesity) and that the core clock genes exert tumor promotive functions, here we describe how the aberrant circadian rhythms affect the development and prognosis of different types of obesity-related cancers.

4. Clock genes in obesity-related cancers

4.1. Breast cancer

BC is the most frequent cancer in females worldwide [101,102] with a high incidence in the developed world. Indeed, the onset frequency of BC is much higher in Western Europe than in Middle Africa and Eastern Asia, suggesting that the modern western lifestyle may contribute to the occurrence and progression of BC [103]. Women affected by overweight and obesity have a higher risk of developing BC than women who maintain a healthy weight [103]. Moreover, growing evidence has demonstrated a strong connection between circadian clock interruption and BC [104]. Manipulating circadian patterns could be a prominent approach to preventing or treating this type of cancer [105].

Clock genes are expressed in normal breast tissue and their levels are finely regulated by the cellular microenvironment and the developmental stage of the tissue. Since circadian genes have central roles in normal breast biology, disrupting the normal light/dark cycle can increase BC risk. Several data confirm the importance of clock genes in BC etiology: indeed, PER1 and PER2 mutations have been demonstrated to be common in both sporadic and familial BC [105]. PER2-deficient mice showed a higher incidence of BC and exhibited reduced p53 expression with an elevated level of c-Myc and its target cell-cycle genes Cyclin D1, thus boosting cancer cell proliferation [84,106,107]. Both PER1 and PER2 also promote apoptosis, therefore the loss of PER leads to a decrease in the apoptotic rate and to the accumulation of damaged cells as a result of p53 alterations [91,108]. Moreover, the inhibition of PER1 alters the expression of checkpoint proteins ATM and Chk2 (checkpoint kinase 2), necessary to control the G1 checkpoint during DDR [109].

Also, Cry affects tumorigenesis via the cell cycle, since is a key regulator of the cell cycle [110]. Indeed, the loss of Cry leads to disrupted cell cycle regulation as a consequence of the alteration of Wee-1 and Cyclin D1 [110]. The clock genes in BC can also influence the epithelial-mesenchymal transition (EMT), driving the formation of lethal metastases [106]. In normal breast tissue, PER2 recruits a corepressor complex to the promoters of the EMT genes Twist1, Slug and Snail, through the interaction with OCT1; thereby the lack of PER2 facilitates invasion and metastasis [106]. Lastly, a recent work has reported that the expression of BMAL-1 in BC is also altered by tumor hypoxia-induced acidosis and the authors demonstrated that targeting the microenvironment acidosis (i.e., by using a buffering solution as NaHCO3 or inhibiting anaerobic glycolytic enzymes) might help to treat BC through restoring the expression of the circadian gene BMAL-1 [59]. Therefore, clock genes defects in mammary epithelium cause a down-regulation of growth control genes, enhanced susceptibility to BC onset, and lead to the appearance of more aggressive tumors.

4.2. Prostate cancer

PCa is the most diagnosed cancer in men and the second most common cause of cancer-related death [111]. The main leading cause of PCa is the up-regulation of the androgen receptor (AR), which contributes to the development, growth, and progression of PCa [112]. Accordingly, the current therapy for PCa is the androgen deprivation (ADT), however, a large proportion of treated tumors become independent from the AR signaling axis, resulting in the so-called "castration-resistant prostate cancer (CRPC)" [113,114]. This reduces dramatically the therapeutic possibilities, and about 19.5% of patients die of metastatic-CRPC [115]. Furthermore, obesity further increases the risk of relapse after therapy, progression to advanced cancer, and mortality for PCa [116–118], but, in the last years, epidemiological studies have also reported an interesting association between altered circadian rhythmicity and increased risk of PCa [119]. To date, different clock genes have been associated with prostate tumorigenesis; a recent study has demonstrated that PER2 and Clock are downregulated in PCa, whereas BMAL-1 is significantly up-regulated compared with normal prostate tissue. *In vitro* studies using three different prostate cancer cell (PCa cells) lines, have shown that the PER2 overexpression reduces the cellular viability driving apoptotic events. Furthermore, the same study has demonstrated that the treatment of PCa cells with melatonin, a pineal gland hormone able to affect the modulation of sleep patterns in the circadian rhythm, increased PER2 and Clock. Also, melatonin treatment reduced BMAL-1 levels, promoting a resynchronization of oscillatory circadian rhythm genes, thus operating as a tumor suppressor in PCa cells [119].

Besides, CRY1, a known regulator of cell proliferation and DNA repair, has an increased expression in PCa tissue and this up-regulation is associated with a poor outcome for metastatic-CRPC [120].

Other studies found that PER1 levels are significantly down-regulated in PCa samples compared with normal samples and the overexpression of PER1 in PCa cells induces strong growth inhibition and apoptosis [99]. Briefly, Cao and colleagues demonstrated that PER1 interacts with the promoter of the AR and appears to be a negative regulator of AR in PCa cells. Also, AR may stimulate PER1 transcription as a feedback pathway. Indeed, the authors reported that the expression of PER1 inhibits the AR transcription, thereby reducing the expression of known androgen-sensitive genes. This research has underlined that in the normal prostate tissue, PER1 is regulated by the AR signal and in turn, PER1 attenuates AR activity contributing to the maintenance of the hormonal homeostasis, while the disruption of circadian-AR connections may contribute to the onset of prostate tumorigenesis [99].

4.3. Colorectal cancer

CRC accounts for almost 1.4 million new cancer cases diagnosed each year and is the third most frequent cancer in humans, with a high mortality rate worldwide [121]. Different risk factors underlie the CRC etiology, such as smoking, alcohol consumption, unhealthy dietary habits and increased body mass index (BMI) [122].

During the past decades, several studies suggested that the circadian clock genes are important regulators of different molecules involved in the DNA damage response (DDR), such as ATM, CHK2 [109] and BRCA1

[123], in the cell cycle progressions, such as c-Myc and p21 [83,124] and Wnt/β-catenin pathway [125]. Considering that mutations of these pathways lead to CRC, it is not surprising that, among the well-known factors associated with higher CRC risk, some studies have revealed a strong relationship between the dysregulation of the circadian system and, not only the pathogenesis of CRC, but also the development of resistance to cancer chemotherapeutic treatment [126–128]. Indeed, clock genes play an essential role in the gastrointestinal physiology, so they are often altered in CRC and affect the phenotype of colon neoplastic cells, cancer progression, survival rate, and chemotherapy responses. Interestingly, multiple studies have demonstrated that PER1, PER2, PER3 and CRY2 act as tumor suppressors in the intestinal mucosa [126–128]. In detail, PER proteins regulate β-catenin activation and are involved in maintaining genomic integrity by controlling cell cycle progression. In the CRC tissue, a marked downregulation of these clock genes compared to adjacent normal tissue was found, as well as the association between the downregulation of PER1 and PER3 and poorer survival rates and metastatic disease [126–128]. Furthermore, another important study has shown that Clock and BMAL-1 are upregulated in the CRC tissue and this was strongly associated with poor clinical outcomes [129].

4.4. Thyroid cancer

TC is the most common endocrine cancer, but only in 5% of cases it is malignant [130]. The incidence of TC is increasing rapidly, but mortality has remained stable [131]. Thyroid tumors are divided into well-differentiated papillary (PTCs) and follicular thyroid carcinomas (FTCs), poorly differentiated (PDTCs) and undifferentiated thyroid cancers (ATCs), with the latter two representing the less common subtypes [131].

Over the past decade, several studies have suggested that environmental drivers and lifestyle changes are responsible for the increase in TC impact [132,133]. Among these, the analyses of some anthropometric evaluations suggested a correlation between excessive weight and thyroid malignancies. Indeed, studies on euthyroid subjects have demonstrated that regional obesity and the tendency to be overweight are associated with slight variations in thyroid function [132,133] until a higher risk of developing TC in patients affected by severe obesity [134].

Several authors have recently reported a relationship between the misalignment of the circadian clock and malignant transformation of the thyroid nodules [135–140]. The mechanisms linking circadian clock disruption and TC could be represented in part by insulin resistance [141]. Indeed, insulin resistance might influence TC development and progression, and often insulin resistance is a consequence of both the circadian clock interruption and increased levels of TSH, which in turn are partly controlled by the central circadian pacemaker in the SCN [141]. The daily rhythmicity of TSH levels is mediated by an intrinsic timekeeping machinery, which includes the central circadian pacemaker as well as a peripheral clock [141,142]. The peripheral clock, in turn, via the rhythmic TSH secretion, also defines the daily rhythm of thyroid hormone release from the thyroid gland [141,142]. In detail, TSH plasma concentration reaches a peak during the nighttime and, afterwards, the secretion of TSH declines during the rest of the sleep period, maintaining low daytime levels [143,144]. Therefore, the daily rhythmicity of TSH and of circulating thyroid hormones are influenced by sleep-wake homeostasis [144] and the thyroid hormone deficiency or excess might affect the clock genes expression and metabolic CCGs in several peripheral tissues [145–150].

Various studies found a possible relationship between the circadian clock and thyroid tumorigenesis [145–150]. Changes in the BMAL-1 and CRY2 levels have been detected in TC, with a significant upregulation of BMAL-1 in PTC and FTC samples and a decrease of CRY2 expression, compared to healthy thyroid tissue and radically modified circadian oscillations have been reported in PDTCs [138], linking the TC transformation and changes in the circadian clock machinery [149]. Considering that the alteration of circadian rhythm contributes to thyroid transformation, the study of clock gene expression could improve thyroid nodules diagnosis and therapy.

4.5. To date: role of circadian rhythms in other obesity-related cancer types

Genetic and epigenetic alterations of clock genes can also drive carcinogenesis of other obesity-related cancer types, but clear evidence of their biological role is still needed [150–152]. The expression of PER2, CRY1 and CRY2 appears to be critical for hepatic carcinogenesis and potentially involved in its development. A detailed analysis has revealed that the expression of PER and CRY is significantly altered in HCC samples compared to corresponding adjacent normal tissue [150–152]. Therefore, the alteration of CLOCK function can predispose to liver cancer development [153]. Indeed, analysis of miRNA profiles in CLOCK mutant mice has demonstrated that CLOCK-regulated miRNAs can also promote the initiation or progression of hepatic cancer by regulating genes related to cell proliferation, invasion or metabolism in the mouse liver [153]. Moreover, in HCC, the expression of the neuronal PAS domain protein 2 (NPAS2), a core circadian molecule analogue of CLOCK, is strongly upregulated and promotes cancer cell survival [154]. The increase of NPAS2 levels in tumoral samples is associated with HCC a poor prognosis and may constitute a potential therapeutic target in HCC patients [155].

In epithelial ovarian cancer the expression levels of PER1, PER2, CRY2 and CLOCK are lower than in normal tissue, while CRY1 is higher, except for mucinous adenocarcinomas (a rare subtype of ovarian cancer), in which it is reduced. Also, the BMAL-1 expression is low in mucinous adenocarcinomas [155]. The methylation of the promoters' CpG-island in PER1, PER2 or CRY1 circadian genes, is possibly involved in the development of endometrial cancers [156]. Furthermore, a recent study has demonstrated a strong association between the expression of CLOCK in ovarian cancer and cisplatin resistance: in particular, this study has revealed that CLOCK mRNA and protein expression is lower in cisplatin-sensitive ovarian cancer cells compared with cisplatin-resistant cells [157]. Thus, the increase in the expression of circadian gene CLOCK may reduce the sensitivity to cisplatin treatment in ovarian cancer cells [157].

D. Relles et al. have shown the influence of circadian clock genes on the biology of pancreatic cancer (PC) development [158]. Patients with pancreatic adenocarcinoma revealed a lower expression of the different circadian genes in cancer tissue compared to adjacent normal tissue. Furthermore, the results revealed that the low expression levels of the clock genes are also correlated with poor overall survival of patients with PC [158]. Moreover, an in vitro study has demonstrated that the overexpression of BMAL-1 reduced cell growth and induce cell-cycle arrest, whereas the silencing of BMAL-1 promoted cell proliferation [159]. Thus, the authors suggested that BMAL-1 may act as an anti-oncogene in PC through the binding to the p53 gene promoter, thereby promoting the activation of the tumor suppressor pathway [159].

Regarding the renal carcinoma (RC), some studies highlighted an association between the clock system imbalance with the alteration of the cell cycle, apoptosis, and DDR pathway [160]. In agreement with these, an earlier study suggested that the dysregulation of clock genes might mediate an increase in cancer susceptibility through the variation of several biological behaviors, including DNA damage, repair mechanisms and apoptosis [140]. Moreover, Mazzoccoli G. and co-authors [161], have demonstrated a down-regulation of the clock gene PER2 in renal cancer by comparing tumor tissue with nontumorous tissue [84,162]. This dysregulation led to dysfunction of cell cycle checkpoints and susceptibility to DNA damage, while in vitro experiments evidenced that the overexpression of PER2 reduced cell growth and promoted apoptotic events [84,162].

The disturbance of the normal circadian rhythm is an important risk factor also for lung cancer [163]. Recently, by using a mouse model of lung adenocarcinoma, the effects of rhythm disruption on lung tumorigenesis have been characterized. Both physiologic perturbation (jet lag) and genetic mutation of the clock genes decreased survival and promoted lung tumor growth and progression [163]. Notably, in line with prior studies, the authors verified that PER2 and BMAL-1, by competing with oncogenic c-Myc, have tumor-suppressive roles in transformation and lung tumor progression [164]. Thus, the downregulation of these central clock components contributes to the occurrence and development of lung cancer following the increase of c-Myc expression. Moreover, TCGA analysis have elucidated that high expression levels of CRY2, BMAL-1 and RORA positively correlated with the lung adenocarcinoma prognosis, whereas the increased levels of Timeless and NPAS2, two lesser-known circadian genes, negatively correlated with lung cancer prognosis [164].

All these data indicate that circadian clock genes are pivotal regulators for the development and progression of various cancers.

5. From circadian rhythms to cancer chronotherapeutic

Two different preventive and/or therapeutic approaches for chronic circadian rhythm-related diseases have been defined: direct targeting of the clock genes or the modulation of their regulators, by using small molecules able to adjust the core components of the circadian clock [165]. Considering that most of the core clock genes are transcriptional factors, such as BMAL-1 and CLOCK, it is laborious to directly target these genes [166,167]. Therefore, in the last years, new strategies have emerged to pharmacologically target proteins responsible for the phosphorylation or degradation of clock components, hence, agonists or antagonists capable to control the circadian network [166,167].

Since many antitumor agents may act against tumoral cells as well as normal cells, it is important to establish a correct balance between the maximization of the antitumor effects against malignant cells and the minimization of the toxicity to host cells [168–170]. Most antineoplastic therapies are focused on reinforcing the cytotoxic activity against cancer cells and avoiding drug resistance, rather than limiting their side effects on healthy host tissues [171–173]. To reach this aim, more attention has been paid to chronotherapy, which is a strategy that exploits the rhythms and cycles of physiological and biochemical processes to treat a disorder [171–173]. Circadian timing of anticancer agents often can induce pharmacokinetic variations of antineoplastic drugs improving the treatment outcomes [78,174]. For example, the administration of 5-fluorouracil (5-FU) at a constant rate for 5 days in cancer patients, has led to the observation that the highest plasma concentration of 5-FU is reached at 4:00 a.m., which is also the best-tolerated moment for chemotherapy [78,174].

Interestingly, several studies underlined that chronotherapy significantly reduced the cytotoxic effects of various anticancer drugs and improved the life quality and survival rate of cancer patients [175–177]. Moreover, many chemotherapeutic agents showed increased cytotoxic effects, especially during a specific cell-cycle phase, so this suggests that the circadian chrono-modulated drug delivery systems might translate into better treatment outcomes [178,179].

In addition, the timed infusion of oxaliplatin, 5-FU, and chronoFLO (chronomodulated 5-fluorouracil-leucovorin-oxaliplatin) in patients with metastatic CRC minimized the rate of severe mucosal toxicity and reduced for about 50% the functional impairment from peripheral neuropathy compared to conventional drug delivery [180]. Besides, in 31 patients treated with irinotecan, an antineoplastic enzyme inhibitor primarily used in the treatment of CRC, the chrono-modulated infusion from 2:00 a.m. to 8:00 a.m. reduced the acute and persistent diarrhea and thus improved patients' quality of life [181].

A recent clinical study has demonstrated that immunotherapy is less efficient when infused in the evening than in the daytime, so the application of chronotherapy for immunotherapy has improved the survival of patients with advanced melanoma [182,183]. Successful developments of chrono-therapeutics have been achieved also in the treatment of hepatic carcinoma [184,185]. Indeed, the chrono-modulated infusion of anticancer drugs directly into the hepatic artery has shown a beneficial impact, contributing to improvements in both toxic tolerability and drug effects [184,185].

Numerous chemotherapic agents show their cytotoxic effects at specific phases of the cell division cycle, for example, cells during DNA synthesis are more susceptible to 5-FU [186] and irinotecan treatment [187]. Therefore, the best-tolerated circadian time is during the light period, that is, when the number of G0/G1 cells predominates [188–191]. Moreover, some in vivo studies using mouse models, have shown that the chrono-modulated infusion of 5-FU, irinotecan, docetaxel and gemcitabine have beneficial effects during the early light period, in which the antiapoptotic BCL2 expression is high, and proapoptotic BAX expression is low [188–191]. For these reasons, is important to know the cancer cells timing, to define when tumor exhibits proliferative targets relevant to cancer cell DNA synthesis or cancer cell division.

Together, these findings support the application of chronotherapy in cancer treatment to improve therapeutic efficiency and prolong the survival of cancer patients. However, further clinical trials are necessary to use chronotherapy as an adjuvant treatment for different types of cancer.

6. Conclusions

Both experimental data and studies in humans show large evidence that the circadian disruption favors the incidence and growth of obesity-related tumors.

It is conceivable that not only the maintenance of a healthy state must include the circadian rhythm homeostatic control, but also that reestablishment of a correct day-night time balance can be view as a novel intervention in combination with cancer therapy. Thus, based on the vast observation reported, these new concepts can have implications for therapeutic approaches, and to set the possible design up of chrono-pharmacological strategies in obesity-related cancers.

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Conflict of interest statement

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Data Availability

No data was used for the research described in the article.

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