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The Impact of Circadian Rhythm Disruption on Breast Cancer: Mechanistic Insights into Hormonal Dysregulation, Gene Expression Alterations, and Potential Therapeutic Strategies

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Abstract. Disruption of the circadian rhythm, frequently due to shift work and nighttime light exposure, is increasingly being associated with a greater risk of breast cancer. This disruption affects melatonin secretion, a hormone known for its tumor-suppressing properties, and alters circadian gene expression, particularly in genes like PER and CRY, which are crucial for regulating the cell cycle and apoptosis. The imbalance in melatonin can lead to increased estrogen activity and promote tumor development. Additionally, circadian misalignment affects metabolic processes, contributing to an environment conducive to cancer growth. Specifically, shift work is linked to a heightened risk of breast cancer because of such hormonal and genetic disruptions. This review highlights the potential of therapies such as melatonin supplementation and light therapy in minimizing the negative impacts of circadian disruption. By investigating the molecular pathways that connect circadian rhythms and cancer, this review underscores the need for further research and public awareness of the impact of circadian misalignment on breast cancer risk, offering insights for potential preventative and therapeutic strategies.

Keywords: Circadian rhythm, breast cancer, melatonin, circadian genes, shift work

1. Introduction

Circadian rhythms are internal cycles of about 24 hours that govern a wide range of physiological functions, including sleep-wake patterns and hormone secretion. These rhythms are coordinated by the suprachiasmatic nucleus (SCN), which functions as the primary pacemaker to synchronize the body's internal clocks [1]. The SCN is located in the hypothalamus, which receives cues from environmental light via the retina, aligning internal timekeeping mechanisms with the external day-night cycle [1]. The circadian system is inextricably linked to physiological processes. Disruptions to circadian rhythms, such as those experienced by shift workers or individuals with jet lag, can lead to health problems, including metabolic disorders and an increased risk of cancer. It is essential to understand the relationship between circadian rhythms and health outcomes to develop strategies that can reduce the negative impacts of circadian misalignment. Given the essential role of circadian rhythms in preserving homeostasis, studying their influence on various diseases, particularly breast cancer, is of paramount importance [2].

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Globally, breast cancer is the most prevalent form of cancer, leading to approximately 670,000 fatalities in 2022 [3]. Furthermore, among women, it was the most frequently diagnosed cancer in 157 of 185 countries in 2022 [3]. Despite progress in early detection methods and treatment approaches, its morbidity and mortality rates continue to rise, and it is now the biggest threat to women's health. The significantly higher prevalence in industrialized nations compared to developing ones indicates that environmental factors in modern societies might play a crucial role in the development of breast cancer [4]. The risk factors for breast cancer are varied and include gender, age, estrogen levels, genetic mutations and family history [5]. However, the human understanding of breast cancer and the development of prevention methods have made great progress in the past decade, and in certain developed countries, early intervention strategies have dramatically improved the 5-year outlook for individuals with breast cancer, with survival rates climbing well above 80%. [5]. Despite some achievements, there are still many unknowns to be explored, for example regarding its relationship to circadian rhythms.

Comprehending the link between breast cancer and circadian patterns is imperative given the increasing recognition of the role that disrupted circadian patterns play in health and disease. Disruptions to these rhythms, like those from night shift work, have been associated with a heightened risk of breast cancer. The mechanism behind this association is thought to involve the suppression of melatonin—a hormone that normally peaks at night and is known for its anti-cancer properties—due to the retina receiving excessive light at night [6,7]. Additionally, circadian genes such as clock genes Cryptochrome 2 (CRY2) and period 2 (PER2), have been shown to influence breast cancer risk and the development of tumors [8]. Given the widespread occurrence of breast cancer and the potential modifiability of circadian rhythm disruptions, elucidating the connection could lead to novel preventative and therapeutic strategies. Consequently, delving into the intricate connection between circadian rhythms and breast cancer is imperative for advancing our comprehension of oncological mechanisms and devising sophisticated strategies to diminish cancer risk.

The objective of this review is to elucidate the complex interrelationship between circadian rhythms and breast cancer, recognizing the burgeoning insights into how circadian disruptions may potentiate breast cancer risk. This comprehensive analysis seeks to offer novel viewpoints on the dynamic interplay between circadian rhythms and breast cancer, thereby establishing a foundation for the formulation of cutting-edge strategies in cancer prevention and therapy.

2. Melatonin and Metabolic Changes in Circadian Disruption on Breast Cancer Development

Circadian rhythms are essential in controlling various biological processes, such as hormone production, metabolism, and cellular repair mechanisms. Disruptions to the circadian rhythm, often resulting from night shift work or too much exposure to artificial light at night, can lead to decreased melatonin secretion. Melatonin, a hormone predominantly synthesized by the pineal gland, is not only essential for regulating sleep-wake cycles but also exhibits protective effects against cancer, particularly breast cancer. In this section, we will explore how melatonin contributes to breast cancer prevention and the impact of circadian disruption on its secretion.

2.1. Melatonin and Its Role in Circadian Rhythm Regulation and Breast Cancer Suppression

Typically, melatonin levels rise in the evening as darkness falls, peak at night, and fall in the morning because of SCN regulation [9]. This nocturnal surge serves multiple functions, including the synchronization of the sleep-wake cycle, regulation of body temperature, and modulation of other hormonal activities. Melatonin's antioxidant properties also protect cells from oxidative stress and damage [11]. Furthermore, melatonin may also possess anti-invasive and anti-metastatic properties [11]. Extensive research has illustrated that melatonin is implicated several anticancer mechanisms, such as inhibiting cell growth, promoting cell apoptosis, and reducing tumor growth and metastasis, making it a key player in maintaining cellular health and preventing tumorigenesis [10]. Disruptions to the circadian rhythm, such as those experienced by individuals working night shifts or those suffering from

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jet lag, can lead to reduced melatonin production, thereby potentially increasing the risk of cancer, including breast cancer.

2.2. Hormonal and Metabolic Changes in Circadian Disruption

Circadian rhythm disruption alters hormone production and metabolic processes, allowing bodily functions to be compromised and potentially further affecting the development of cancers, including breast cancer. The next section discusses melatonin secretion and some of the metabolic pathways in response to circadian rhythm disruption and how they may impact breast cancer development.

2.2.1. Abnormal Melatonin Secretion and Its Consequences

When the circadian rhythm is disrupted, melatonin secretion is adversely affected, leading to a series of hormonal and metabolic changes that can promote cancer development. Exposure to light at night, a common occurrence for shift workers and individuals using electronic devices before bedtime, can significantly suppress melatonin synthesis [2]. This suppression is mediated through the retinal-hypothalamic tract, which transmits light signals to the SCN, leading to a diminished stimulus for melatonin production by the pineal gland [4]. Chronic melatonin deficiency can have far-reaching consequences for the body.

2.2.2. Melatonin's Role in Estrogen Regulation and Breast Cancer

In addition to melatonin's direct anti-cancer effects, it also influences the production and activity of other hormones, such as estrogen. Estrogen exerts a proliferative effect on specific subtypes of breast cancer cells. However, melatonin can function similarly to a selective estrogen receptor modulator (SERM) by interacting with estrogen receptor alpha (ERα), thereby altering estrogen binding, DNA interaction, and transcriptional activity [11]. Additionally, the production of estrogens from cholesterol or other steroid precursors can be inhibited by melatonin through reducing the activity of enzymes like aromatase, sulfatase, and aldo-keto reductases (AKRs) [11]. Therefore, with reduced melatonin levels, estrogen's proliferative effects may go unchecked, contributing to the progression of breast cancer. Furthermore, melatonin's regulation of the menstrual cycle suggests that it might play a protective role against breast cancer by modulating the timing and duration of estrogen exposure [12].

2.2.3. Metabolic Disturbances Linked to Circadian Disruption

Disrupted circadian rhythms also impact metabolic processes, which can indirectly contribute to cancer risk. For instance, circadian misalignment has been linked to compromised glucose tolerance and insulin resistance, conditions that serve as significant risk factors for the development of cancer. These metabolic disturbances can lead to chronic inflammation and insulin-like growth factor (IGF) overexpression, creating an environment that supports tumor growth [13]. Thus, the abnormal secretion of melatonin due to circadian disruption not only directly affects cancer prevention mechanisms but also indirectly influences other hormonal and metabolic pathways that are critical for maintaining cellular health.

In summary, the importance of melatonin in the circadian rhythm cannot be overstated, particularly in relation to its potential protective effects against breast cancer. Disruptions to circadian rhythms can precipitate hormonal and metabolic alterations, including diminished melatonin secretion, which may elevate the risk of carcinogenesis.

3. The Role of Circadian Genes in Breast Cancer

Circadian rhythm genes form a series of negative feedback pathways, which can respond to external environmental signals and harmonize physiological processes in the body with external circadian rhythms. CLOCK (Circadian Locomotor Output Cycles Kaput) and BMAL1 (Muscle ARNT-Like Protein 1) stimulate expression of PER and CRY, which then inhibit their own production, creating a rhythmic oscillation [14]. This regulation influences various functions such as sleep, metabolism, hormone secretion, and body temperature. Disruptions in these genes can lead to circadian rhythm

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disorders, affecting mental and physical health, emphasizing their critical role in maintaining homeostasis. Moreover, these circadian genes can also significantly contribute to cancer prevention and suppression when circadian rhythms are normal. The anticancer effects of selected circadian genes are discussed in this section.

3.1. Impacts on Cell Cycle Regulation and Apoptosis Due to Circadian Disturbances

Circadian rhythm genes are essential in regulating various physiological processes, including the cell cycle and apoptosis. Alterations in these genes can perturb the critical processes essential for genomic stability and cancer prevention, resulting in dysregulation. Two principal components of the circadian clock mechanism are the PER and CRY genes, with their aberrant function being implicated in the etiology of breast cancer [8].

3.1.1. PER Genes

The PER gene family, comprising PER1, PER2, and PER3, is involved in the negative feedback loop of the circadian clock [14]. PER proteins accumulate in the cytoplasm during the day and then translocate into the nucleus at night, where they inhibit their own transcription by forming complexes with CRY proteins. Mutations or polymorphisms in PER genes can disrupt this feedback loop, leading to altered circadian rhythms [8]. For instance, the PER3 variable number of tandem repeats (VNTR) polymorphism, which results in different protein isoforms, has been linked to a heightened risk of breast cancer [15]. Patients carrying the shorter allele of PER3 VNTR, which leads to a reduced number of repeats and a less stable PER3 protein, experience impaired circadian regulation, resulting in aberrant cell cycle control and decreased apoptotic signaling, which can facilitate the accumulation of genetic mutations and the subsequent development of cancerous cells [15].

3.1.2. CRY Genes

Similarly, the CRY genes, including CRY1 and CRY2, are essential components of the circadian clock that act as negative regulators by forming heterodimers with PER proteins[14]. Mutations in CRY genes can compromise the ability of CRY proteins to interact effectively with PER proteins, thus weakening the negative feedback loop that controls circadian rhythm. This suggests that CRY2 plays a critical role in maintaining the integrity of the circadian clock and, consequently, in suppressing tumorigenesis. When CRY2 function is impaired, cells may experience deregulated cell division and reduced apoptosis, contributing to the onset and progression of breast cancer.

Studies using the MCF-7 cell line, an ERα-positive human breast tumor cell line, have shown that the PER2 gene is minimally expressed. [8]. Additionally, in MCF-7 cells transfected to express PER2, and in those transfected to express both PER2 and CRY2, cell proliferation was significantly inhibited, and the latter was more inhibited than the former. However, in MCF-7 cells transfected with and expressing CRY2, cell proliferation was not inhibited[8]. This further suggests that PER2 itself can prevent breast cancer from developing by inhibiting its proliferation, and CRY2 can promote this inhibitory effect, but CRY2 itself does not have this inhibitory effect.

3.2. Impact on Cellular Metabolism in Circadian Disturbances

Beyond their roles in regulating cell cycle regulation and apoptosis, circadian rhythm also significantly influences cellular metabolism, another critical aspect of cancer biology. Disruptions in the circadian clock result in metabolic reprogramming, a key characteristic of cancer cells that enables them to support rapid proliferation. Circadian rhythm disruption has been linked to dysregulated glucose metabolism, marked by enhanced glycolysis even when oxygen is plentiful, a phenomenon known as the Warburg effect [16]. This metabolic shift not only fuels cancer cells with energy but also supplies building blocks for nucleotide, lipid, and amino acid biosynthesis, essential for tumor growth [16]. Moreover, circadian rhythm genes are pivotal in regulating the expression of enzymes that participate in diverse metabolic pathways. For instance, the circadian clock directs the time-dependent expression of genes involved in fatty acid metabolism, such as those that encode acetyl-CoA carboxylase (ACC) and fatty acid synthase

(FASN) [17]. When the circadian clock is disrupted, this rhythmicity is lost, leading to uncontrolled lipid synthesis, which can fuel tumor growth [17].

In conclusion, circadian rhythm genes significantly impact breast cancer through their influence on cell cycle regulation, apoptosis, and cellular metabolism. Understanding the molecular mechanisms and underlying these effects is essential for creating targeted therapies and preventive measures focused on restoring normal circadian function and lowering the risk of breast cancer.

4. Shift Work and Breast Cancer

In 2007, drawing on comprehensive epidemiological data and robust mechanistic evidence from animal studies, the International Agency for Research on Cancer (IARC) designated night shift work, which disrupts circadian rhythms, as potentially carcinogenic to humans [18]. Studies reveal that women with a history of extended periods of rotating night shifts exhibit a markedly elevated incidence of breast cancer compared to the broader population. This risk is notably increased for women who have accumulated 20 or more years of rotating night shift work by the time they reach their mid-30s [2]. Shift work is seriously affecting the health of women around the world and contributing to a higher incidence of breast cancer.

Night shifts work often requires employees to be active during typical breaks and exposed to light at the same time, which can lead to an imbalance between the body's internal biological clock and the external environment. This disruption can have profound implications for various physiological processes, including the regulation of hormones and the expression of circadian genes. A major impact of circadian misalignment is the significant reduction in melatonin levels. Its levels are typically suppressed during exposure to light at night, a common occurrence for those working night shifts [19]. Reduced melatonin levels have been linked to increased estrogen activity [11]. Furthermore, melatonin's antioxidant properties suggest that its deficiency could lead to enhanced oxidative stress, potentially damaging DNA and contributing to carcinogenesis [11]. Additionally, as previously mentioned, night shift work rotations can also negatively affect the expression of circadian genes, such as PER-2 and CRY-2, thus providing less resistance to tumor growth [8]. In conclusion, the detrimental effects of shift work on breast cancer are multifaceted, and the more pressing question is how we can effectively mitigate the adverse effects of shift work.

5. Potential Treatments

Given the strong connection between circadian rhythm disruptions and breast cancer, strategies aimed at restoring and consolidating circadian rhythms may offer promising avenues for both prevention and treatment. Supplemental melatonin has been widely investigated for its potential to alleviate circadian disruption in shift workers. Moreover, the antioxidant effect, anti-metastasis, and anti-invasion effect of melatonin can also contribute to the treatment of breast cancer [6].

Light therapy, also known as phototherapy, is a method that utilizes light of specific wavelengths to regulate physiological rhythms and might be a promising treatment [20]. This therapy is grounded in the understanding of how light affects the circadian system [20]. For example, morning light therapy can assist individuals in feeling sleepy earlier and staying alert during the night, which is beneficial for those needing to adjust to new schedules. Conversely, evening light therapy may help postpone sleep onset, enabling people to remain active for longer periods at night [20].

Beyond pharmacological solutions, implementing lifestyle modifications can significantly improve sleep quality and reduce the harmful influences of shift work on health. Essential approaches encompass establishing consistent sleep schedules, improving the sleep environment, and adhering to proper sleep hygiene practices. Creating a sleep-conducive atmosphere, and regular physical activity, while avoiding vigorous exercise close to bedtime, can aid in promoting restful sleep. Moreover, Tai Chi can be another way to treat insomnia, which illustrates the importance of exercise in maintaining a good circadian rhythm [21]. Dietary adjustments, such as limiting caffeine intake and consuming balanced meals, can also support healthy sleep patterns and help manage the metabolic disturbances associated with shift work.

By addressing circadian dysregulation, these combined approaches may offer effective interventions to improve outcomes for individuals at risk of breast cancer or those already undergoing treatment.

6. Conclusion

Circadian rhythm disruption is closely linked to an increased risk of breast cancer, largely due to the misalignment of the body's internal clock with external factors like shift work. The circadian system, regulated by the SCN, influences physiological processes including hormone secretion and cell cycle regulation. Disruptions can affect melatonin levels and circadian genes, both of which play key roles in suppressing tumor growth. Potential treatments such as melatonin and light therapy, combined with healthy lifestyle habits, may reduce breast cancer risk and improve outcomes. Understanding the precise molecular links between circadian rhythms and cancer could further enhance treatment strategies.

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