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The Function of Circadian Rhythm in Breast Carcinoma and Lung Carcinoma

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Abstract:

With the advent of electricity, people's nightlife is gradually enriched. The prevalence of late nights which disturbance circadian rhythm has raised concerns about the potential risk of cancer. A low quality of sleep decreases immunity, distracts people's attention, and weakens people's memory. This paper is going to review the previous research and discuss scientist's attitudes on circadian rhythm in cancer. By targeting the clock gene, scientists have found that both the mammary gland and lung are affected by circadian rhythm. Scientists execute research on the working times of shift workers and their health, the sleep duration of people, and the effect of clock genes on tumor cells. After analyzing the result, this study believes that in the long term, the disturbance of circadian rhythm can be one of the cancer risk factors. To address possible cancer risk factors, this paper examines the influence of circadian rhythm on lung and breast cancer.

Keywords: Circadian rhythm; breast cancer; lung cancer; clock gene.

1. Introduction

Circadian rhythm is a periodical rule for animals in metabolism, endocrine, and immune functions to adapt to the periodic alters every day in the surroundings [1]. Therefore, the rhythm of organisms following and adjusting to the 24-hour cycle of the sun. The sleep-wake cycle is the most conspicuous circadian rhythm that affects human mechanisms. Sleep deprivation and disruption of cell activity can be harmful to the regulation of the organ system [2]. Circadian rhythms are affected by various aspects like light exposure, stress, and social influence.

The clock system is located on the suprachiasmatic nucleus (SCN), including central and peripheral clock systems. The central clock system works independently directly by light and peripheral clock systems are regulated by signaling molecules. Cycles Kaput (CLOCK), Brain and muscle Arnt-like protein-1 (BMAL1), Period2 (Per2), and Timeless (TIM) are among the common clock genes [3]. Scientists believe disturbance of circadian rhythm is one of the risk factors for mental health including Major Depressive Disorder (MDD), bipolar disorder, and schizophrenia [4]. Research showed that 3% of adults suffer from circadian rhythm disorder [5].

A type of abnormal cell caused by a mutation that propagates in an uncontrol and fast way may converge benign or malignant tumor [6]. The cancer cell, which is also called a malignant tumor cell, increases rapidly in an uncontrolled way. Meanwhile, cancer cells are able to hide from the immune system which means they can survive in the human body [6]. Cancer cells can spread to the whole body and cause compression of nerves resulting in pain or bodily dysfunction.

2. Role of Circadian Rhythm on Breast Cancer

There were 61% of breast cancer patients have problems sleeping [7]. One type of cancer that begins in the tissue of the breast and extends to the other regions of the body via the blood or lymph system is called breast cancer [8]. It is the second most common cancer in women. About 30% of cancer diagnosed in females accounts for breast cancer. Breast cancer not only attack women but also men, mainly in middle and old-aged women. Breast cancer is predicted to kill more than 40000 women in 2024 [9].

The clock gene is essential to breast cancer. The usage of PERIOD2::LUCIFERASE protein in mice let scientists discover the clock genes in breast epithelium, leading to the further discovery of BMAL1 and Per 2 in the clock have rhythm [10]. This means genes in the mammary gland follow a circadian rhythm and imbalanced Per 2 gene will affect breast cancer [2]. Besides, mice that have deficient master transcription factors CLOCK and BMAL1, had a problem with self-generating on mammary progenitor cells [10]. Mammary stem cells additionally regulate mammary cell renewal and mammary gland regression [11]. The disorder stem cells and progenitor cells

would terminally become a tumor [12].

Numerous clinical studies have shown that long hours of work involving a work shift will cause a wrong-hour exposure to light which causes a disturbance in circadian rhythm. A case study aimed at shift workers demonstrates a favorable association exists between the disturbance of circadian rhythm and being diagnosed with breast cancer [13]. Female nurses in Denmark were analyzed for cancer, and the scientists returned the calls to collect information about shift time, age, and menstruation. The result shows people who have a longer duration of shift work have a higher risk of breast cancer [13]. However, according to the research in Finland, there was no strong correlation between long sleep deprivation and breast cancer (Table 1). Not only should we consider the effect of short (smaller than 6 hours) sleep on the risk of breast cancer but also long (longer than 10 hours) hours expose people to danger. Long sleep duration was found to be strongly correlated with cancer mortality in certain studies [14]. Long sleep will cause a higher risk of diabetes and obesity [15]. Obesity certainly will increase the probability of getting breast cancer after menopause [16]. This means long sleep may be one of the future targets for the risk factors for breast cancer after menopause, but it still needs further research to confirm that.

Table 1. Sleep and Breast Cancer Risk [17]

Insufficient Sleep	Hours of Sleep Mean(Median)	No. of Women (n=10,844)	No. of Breast Cancer
No lack of sleep (1<h)	7.8(8.0)	8,532	138
Lack of sleep (≥1h)	7.1(7.0)	2,312	41
Increase in lack of sleep (0-4h)	7.6(7.5)	9,042	144

Disturbance of circadian rhythm will affect breast cancer, but at the same time, breast cancer will also damage the sleep cycle. On the one hand, the study found that the hard extracellular matrix caused by cancer cells will inhibit the rhythm of the core clock gene. While, cancer was largely determined by the partial hardness of breast stroma and breast epithelium [18]. To study whether the disturbance of breast cancer on sleep quality, scientists followed women diagnosed with breast cancer for one year and recorded their sleep quality. The result showed that 60.2% of women had bad sleep quality before the treatment of breast cancer. While, after one year of diagnosis of breast cancer, 47.2% of them believe they were getting worse (mostly people did not have circadian disturbance before) and 39.6% of people sleeping are getting better (majority of them had a sleep disturbance before) [19]. The result is quite unexpected, people who feel that their sleep quality is getting better and worse are divided, but the result still can show the disturbance cancer brings to people's circadian rhythm. Another study used multivariate analysis of variance and chi-square to analyze the difference between breast cancer patients with or without sleep disorders. Sixty-one percent of patients with breast cancer had a PSQI score higher than the experiment's predetermined value of five, which indicates that these patients have poor sleep quality, according to the Pittsburgh Sleep Quality Index Table. More than 36% of people's sleep duration is less than average and 40% have sleep latency [7].

3. Role of Circadian Rhythm on Lung Cancer

Among cancers that affect both men and women most frequently is lung cancer. Lung cancer starts in the lungs. Most lung cancer begins from the cells of the bronchi [19]. Inhalation of cigarettes, secondhand cigarettes, and radon will increase the risk of diagnosed cancer. The lung cancer rate in 2020 was 22.4 among 100,000 people and the death rate was 18.0 people among 100,000 people [20]. Roughly eighty percent of scenarios of lung carcinoma are non-small cell lung cancer (NSCLC) [21].

Damage of clock genes in circadian rhythm will result in an abnormality in gene and protein expression. The non-clock function in the circadian rhythm takes responsibility for regulating the cell cycle, responding to DNA damage, and stable genes [22]. The damage of DNA will result in the formation of tumors, leading to cancer. Period 2 (Per2) is the clock gene, which is crucial to both circadian rhythm and tumor growth. To explore the tole Per 2 gene on NSCLC, scientists collected 31 pairs of NSCLC and corresponding para-carcinoma tissues including both male and female. Scientists transduce Lentivirus on the A549 cells and observe the expression rate of the fluorescent protein. Scientists extracted RNA and used western blot and statistics to analyze the outcomes [11]. The result showed Per2 gene may get involved in NSCLC. In addition, the Per 2 gene inhibits tumor cells by stopping the cell cycle at the resting phase (G0) or Growth 1 phase (G1) via analyzing the effect of Per2 on the cell cycle [11]. Since methylation was considered to be the key factor

in silencing the inhibited gene in lung cancer, scientists hypothesize that methylation may cause the inhibition of the Per gene. But they still need further study to confirm that [5]. As a part of the circadian rhythm, diet has caught the attention of scientists. Therefore, scientists designed an experiment on mice and controlled their feeding in 6 hours. The result shows that restricting having food for 6 hours of work is significant in inhibiting lung cancer [23].

Circadian rhythm disorder could be harmful to lung cancer. A chaotic circadian rhythm has been classified possible risk factor of lung cancer. Scientists describe that disturbance in circadian rhythm will interfere with the homeostasis of heat shock transcriptional factor 1 (HSF1) which has been proven to trigger lung cancer. Scientists use 8 hours of advanced light exposure to make chronic jetlag in mice and estimate the harm to the lungs. The scientists observed that chronic jetlag affected clock gene expression in the lungs [24]. The shift in circadian rhythm destruction natural killer cells so they are not able to discern tumor cells and expose more danger [25]. In addition, to explore the impact of clock genes on the prognostic of NSCLC, scientists found the difference in the signal pathway by correlating circadian clock-related genes and overall survival. They concluded that the oscillation brought by circadian clock-related genes would disturb metabolism, but it would also lead to an increase in the release of immune cells [26].

4. Conclusion

Based on this study, on the one hand, clock genes were found in breast epithelium, and clock genes are essential in maintaining circadian rhythm. The disturbance of circadian rhythm will cause damage to progenitor cells, increasing the risk of breast cancer. Lots of clinical data indicate wrong time exposure to light and long-duration sleep will increase breast cancer rate. Also, breast cancer patients will have a disturbed circadian rhythm and have circadian disorders. On the other hand, by halting the cell cycle in the G0 and G1 stages, the Per2 genes in the circadian rhythm are crucial in preventing lung cancer. HSF1 which can be disturbed by chaos circadian rhythm tested to elicit lung cancer.

None of the studies directly proved that disturbance in circadian rhythm causes breast and lung cancer and we still need more evidence. However, this paper believes that there is a lot of indirect evidence to infer that there is a correlation between the circadian rhythm and cancer. In the future, further study should focus on the connection between circadian rhythm on cancer by targeting the Per2 gene. Additionally, future studies could develop cancer prevention medicine targeting regulating sleep cycles.

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