EDITORIAL

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The Metastatic Spread of Breast Cancer Accelerates during Sleep: How the Study Design can Affect the Results

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Abstract

Metastasis is the most common event that determines survival in patients with breast cancer. The benefits of appropriate sleep in enhancing cancer patients' prognosis have been demonstrated. Likewise, emerging evidence has noted the positive impacts of regular circadian rhythm on cancer survival. Proper sleep and regular circadian rhythm can help to improve the cancer prognosis by enhancing the immune system. Besides, circadian rhythm disruption can assist cancer progression by promoting systemic inflammation. However, a recent study by Diamantopoulou et al. titled "The Metastatic Spread of Breast Cancer Accelerates during Sleep" demonstrated that sleep can aggravate breast cancer metastasis. This article outlines how the study design can affect this controversy.

Keywords: Cancer- Immune system- Metastasis- Mitochondria- Sleep

Dear Editor

Metastasis is a crucial step in breast cancer progression. Patients with metastasis are considered incurable (Valachis et al., 2022). About one-third of patients with early breast cancer will develop distant metastases (Lobbezoo et al., 2015). Numerous studies have been conducted to explore the determining factors affecting cancer metastasis (Min et al., 2021). Emerging evidence has found the impact of sleep pattern, duration, and quality on cancer metastasis. The benefits of appropriate sleep in enhancing cancer prognosis have been demonstrated. Trudel-Fitzgerald et al. showed that regular sleep difficulty was associated with an elevated risk of all-cause mortality in patients with breast cancer (Trudel-Fitzgerald et al., 2017). Likewise, emerging evidence has noted the positive impacts of regular circadian rhythm on cancer survival (Lee, 2021). Proper sleep and regular circadian rhythm can help to improve the cancer prognosis by enhancing the immune system (Z. Zhang et al., 2021). Besides, circadian rhythm disruption can assist cancer progression by promoting systemic inflammation (Lawther et al., 2022).

In mid-2022, Diamantopoulou et al. found that the intravasation of cancer cells mainly occurs during sleep in patients with breast cancer (Diamantopoulou et al., 2022). This study also demonstrated that jet-lagged mice (placed in altered light-cycle conditions) had significantly fewer circulating tumor cells (CTCs) in their bloodstream than the control group with a normal light-dark schedule. After that, the investigators examined the effect of melatonin supplementation on cancer intravasation and found that the melatonin group had significantly more CTCs than the control mice. The authors concluded that (a) the greatest release of CTCs occurs during sleep, (b) circadian rhythm disruption (CRD) decreases CTCs, and (c) melatonin administration can enhance the rate of CTCs. At first glance, the results are surprising and in contrast to the literature. However, they can be justified by the applied methodology, as follows:

(a) In the human study, investigators collected the peripheral blood samples at two timepoints (04:00 am and 10:00 am representing the rest and active times, respectively) and found significantly more CTCs in the former group. The details of blood sampling were not presented. Supposedly, the conventional blood sampling (using needle and tourniquet) was applied. In that case, it might subject the findings to design bias due to the following two reasons: (1) in the tumor microenvironment (TME), regulatory T cells (Tregs) can promote metastasis (Kos & de Visser, 2021). It has been demonstrated that Tregs in the TME are suppressed at high serum melatonin levels (Mu & Najafi, 2021). In the Diamantopoulou et al. study, turning on the lights at 4:00 am for sampling can interfere with the normal circadian rhythm, which results in a decline in the serum melatonin level. This condition can remove the inhibitory effect of melatonin on Tregs and increases the likelihood of cancer metastasis. (2) Tumor-targeting immune cells prevent the tumor cells'

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access to the bloodstream. To this end, immune cells require enough mitochondrial biogenesis to supply energy (Herbel et al., 2016; Houshyari & Taghizadeh-Hesary, 2022; L. Zhang et al., 2022). It has been demonstrated that sleep deprivation can negatively affect mitochondrial biogenesis. A study on drosophila showed that short-term sleep deprivation promoted mitochondrial dysfunction in oxidative phosphorylation and electron transport change (Rodrigues et al., 2018). Rapid eye movement (REM) sleep deprivation can largely impair mitochondrial function (Kim, Kim, & Park, 2022). Since REM sleep duration increases overnight and is the longest in the last one-third of the sleep episode, sampling at 4 am can largely affect the REM sleep, hence the mitochondrial biogenesis (Institute of Medicine Committee on Sleep & Research, 2006). Mitochondria are the primary sources of cellular adenosine triphosphate (ATP), and an adequate ATP level is required for the proper immune reaction. Hence, mitochondrial dysfunction can increase the likelihood of immune escape of tumor cells and increases the chance of cancer cell intravasation (Herbel et al., 2016; Taghizadeh-Hesary, Akbari, Bahadori, & Behnam, 2022). In the Diamantopoulou et al. study, the 4 am-group had (seemingly) disrupted sleep to obtain the blood sample that impairs the immune cells' mitochondrial recovery; however, this event did not happen for the 10 am-group. This condition makes a difference in the mitochondrial biogenesis of immune cells and can justify the difference in CTCs. To validate the results, it is suggested to sample during the afternoon nap instead of 4 am sleep. This change can minimize the impacts of melatonin suppression on Tregs as well as interference with mitochondrial recovery. The latter effect can further be minimized if blood sampling is done gently via a peripheral intravenous cannula without awakening the patients.

Next, Diamantopoulou et al. demonstrated that CRD reduced the rate of CTCs. This finding contrasts Hadadi et al.'s study on a breast cancer mouse model, in which CRD promoted cancer cell dissemination and lung metastasis (Hadadi et al., 2020). These two studies are similar in general design but differ regarding CRD duration (Diamantopoulou's study: 32 days, Hadadi's study: 10 weeks). A study on a breast cancer mouse model demonstrated that short-term CRD decreases intra-tumoral inflammation. Lawther et al. found that 26 days of CRD reduced the expression of inflammation-related genes in tumor tissue, especially interleukin 1b (IL1b) (Lawther et al., 2022). On the other hand, in Hadadi et al.'s study, long-term CRD (10 weeks) led to IL1b overexpression in tumor (Hadadi et al., 2020). It has been demonstrated that enhanced IL-1b expression in tumor tissue can increase the probability of bone and lung metastasis (Tulotta et al., 2019). The contradiction between Diamantopoulou's and Hadadi's findings seems to be due to different CRD duration. Further studies can reveal this notion.

Diamantopoulou et al. found that tumor-bearing mice developed more CTCs and lung metastasis when treated with melatonin (Diamantopoulou et al., 2022). This finding is in contrast to the previous literature. In a breast cancer mouse model, Agbaria et al. demonstrated that melatonin administration diminished the rate of metastasis (Agbaria, Haim, Fares, & Zubidat, 2019). The oncostatic, antimetastatic, and anti-angiogenic effects of melatonin have been established (Borin et al., 2016). It was expected that the authors discuss the reasons for this discrepancy. Considering these limitations, cautious interpreting the results of Diamantopoulou et al.'s study is suggested.

Notably, sleep can improve prognosis only if in moderate ranges (i.e. not too long or too short). The study by Collins et al. demonstrated that both short and long sleep durations are associated with an increased risk of cancer mortality. The authors found that 6.5 hours of sleep per day was associated with minimal cancer-associated mortality (Collins et al., 2017). Another study found that sleep duration does not matter, but instant changes in sleep duration can impact cancer-specific survival (Marinac et al., 2017). These issues illustrate that the impacts of sleep pattern on cancer progression and prognosis is complex and requires well-designed studies. To this end, studies must consider different aspects of sleep patterns by considering duration, timing, or structure and its impacts on cellular substructures and immune health.

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Conflicts of Interest

The author declare that they have no competing interests.

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