Chronotype and Cancer Risk: A Literature Review of Genetic, Behavioral, and Physiological Pathways

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August 11, 2025

Abstract

Chronotype is a person's natural tendency to be productive early in the morning or late at night. Evening chronotypes, those who prefer the night, are found at a higher risk for several different types of cancers: digestive tract, lung, breast, and esophageal. Evidence suggests that this might be due to circadian misalignment leading to unhealthy lifestyle behaviors which has altered sleep quality and hormonal quality. However, some studies suggest that chronotype is insignificant or a U-type curve, which states that both morning and evening extremes are at a higher risk, are more applicable. The contradictory findings, as well as the conflated biological and behavioral role of chronotype, call for more research. Several key limitations such as small sample sizes, self-reported data, chronotype measured only once, and uncontrolled lifestyle variables contribute to the inconsistency of results. Thus, it is imperative to conduct more longitudinal studies with a diverse population to determine chronotypes' connection to cancer. This literature review synthesizes findings from several studies to provide an outlook on chronotype and its risk to cancer.

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Chronotype, determined by the circadian clock in the body, determines a person's preference to wake up early in the morning or stay up late at night. People who tend to be more active during the day are referred to as morning types, or early birds. People productive during later hours are evening types or night owls. This genetically influenced trait, which is seemingly benign, has sparked interest amongst researchers about its correlation with cancer. Chronotype influences many physiological and behavioral systems relevant to cancer development. Circadian misalignment caused by chronotypes and societal schedule due has been linked to poor sleep, increased stress hormone levels, unhealthy dietary habits, reduced physical activity, and disrupted melatonin secretion.

All these factors can contribute to an increased risk of cancer. Several studies have analyzed chronotype connection to cancer, but the evidence is mixed. Many studies state that certain types of cancers have shown a clear indication of increased risk, while others have dismissed chronotype as a significant factor. Some research even proposes a U-shaped curve, where both extreme early and late types may face elevated risk compared to moderate chronotypes. Recognizing chronotype as a potential risk factor could lead to more personalized approaches to cancer prevention. By focusing on genetic, behavioural and physiological evidence, this literature review compiles data from several studies to analyze overarching patterns and key findings regarding chronotypes' effect on cancer.

Chronotype and Cancer Risk

A growing number of researches have shown that chronotype might be independently increasing cancer risk where morning chronotypes have shown a reduced risk for cancer. A

genetic study, conducted using data from UK Biobank and FinnGen, used a method called Mendelian Randomization to analyze the participants' DNA for 317 genetic markers that determine chronotype. That analysis showed a general trend that people with the morning chronotype have a lower risk of stomach, colorectal, and biliary tract cancer (Yuan et al., 2023). Some reasons that might explain this trend are gut microbiota and healthier diet differences: morning people have a healthier gut due to dietary choices such as fruits and whole grains. This presented a limitation on the study, as the analysis of interactions between chronotype and diet was unexplored, especially since diet might modify the relationship between chronotype and cancer risk. For biliary tract cancers, moreover, the number of cases was small, impacting the statistical power of the association negatively. Although the study didn't confirm evidence of a biological cause of chronotype affecting cancer, it demonstrated how morning types tend to have a lower cancer risk.

Furthermore, through a prospective study, the large UK Biobank cohort suggests that poor sleep is associated with cardiovascular disease, coronary heart disease, in addition to an increased lung cancer risk (Huang et al., 2021). The participants in this study were adults aged between the years 37–73 that were asked to complete questionnaires, interviews, physical measurements and give consent to access their national health-related hospital and death records to the researchers. The results of this study demonstrated that poor sleep, which can be attributed to evening chronotype due to inadequate duration and insomnia symptoms, has a higher mortality risk particularly in combination with physical inactivity. This study conducted using the UK Biobank had participants of European ancestry which presents a limitation of its findings for other racial groups. The self reported data also provides room for speculation about measurement errors and bias despite efforts to minimize confounders.

Another prospective cohort study in UK Biobank suggested the link between chronotype and cancer. When comparing risks between morning and evening types, evening types were at a 25% higher risk of lung cancer (Xie et al., 2021). This increased risk may be attributed to circadian misalignment, which is more common in evening types and has been linked to disruptions in biological processes that regulate cell growth and repair. All said, the main limitation of this study was the self reporting for sleep-related traits, which can be subjective and susceptible to recall bias or inaccurate reporting.

In addition to digestive tract and lung cancers, similar trends have been observed for breast and esophageal cancers. In a study with 180,216 women of European ancestry in the UK Biobank, it was found that morning preference is protective of breast cancer (Richmond et al., 2019). It suggests that evening preference may increase risk, possibly because of more exposure to artificial light at night and hormonal disruption. However, some limitations of the causal connections of this study are it being a prospective cohort study, and the baseline data was used and assumed to be consistent over the time. Self reporting of sleep data in the study may also prevent total accuracy even though adjustments were in place. The prospective cohort study regarding esophageal cancers also supported similar results. Evening types had a higher risk of esophageal squamous cell carcinoma. MTRNR2L9, a gene associated with evening chronotype, was also associated with increased risk of esophageal adenocarcinoma (Wang et al., 2023). Given that, there were a low number of cases with ESCC, the chronotype was self-reported, and the participants were white individuals pressing limitations on the findings of the study.

Null Findings

Some studies have eliminated chronotype as a factor for cancer risk demonstrating that correlations do not exist or are inconsequential. A large prospective cohort study of Black

women demonstrated that chronotype was not associated with colorectal cancer risk as there was a null association (Barber et al., 2023). This study suggests that chronotype may not independently influence colorectal cancer risk, unlike other cancers and more research is required to clarify the role of chronotype. This study included several limitations, such as chronotype measured only once in 2015. There was also a survival bias while collecting the chronotype as only people alive in the year 2015 were surveyed for chronotype. Moreover, the small number of colorectal cancer cases, 264 cases among 33,698 women, could also have masked the correlation between cancer and chronotype.

A clinical trial studied the association between the genetic variation in 9 circadian rhythm genes and the 1,092 prostate cancer patients. The participants took either a drug called finasteride, a drug that lowers dihydrotestosterone levels which ensure normal prostate growth, or a placebo and had their DNA tested for small genetic changes called SNPs. One gene, NPAS2, had a variation that seemed linked to a higher risk of cancer, but only in men taking finasteride. This SNP change wasn’t linked to cancer in men who took the placebo. Most of the other gene changes had no connection to cancer, ruling out circadian rhythms' role in prostate cancer (Chu et al., 2018). Furthermore, their finding of the interaction with finasteride suggests that drug exposure may modify genetic risk, but replication is required to solidify evidence as this is a preliminary study. That said, this study did not directly look at chronotype but circadian rhythm, limiting its direct relevance to chronotype linkage to cancer. Additionally, all the men in this study were caucasian to keep results consistent but this limits the generalizability to different populations.

A historical clinical cohort study presented a very different finding from prior research that reported a higher cancer risk among evening chronotypes and null studies: moderate

chronotypes have the lowest risk for cancer. Using the Morningness-Eveningness Questionnaire, it found that both extreme morning and evening types may face higher risk as shown by the U-curve (Kendzerska et al., 2024). Some reasons proposed for this finding is light exposure at unusual hours. Artificial lighting during early hours in the morning or late hours at night can suppress melatonin, a sleep regulating hormone, and affects cortisol, a stress hormone, which may be responsible for increased cancer risk because of increased inflammation (Liu et al., 2022). However, this study presented several limitations such as using pre-collected data making it a retrospective design study with a small sample size. The participants in this study also either had or were suspected of having a sleeping disorder, limiting the application of the findings on the healthy population.

Physiological and Behavioral Changes Associated with Chronotype and Cancer Risk

Chronotype induces many physiological changes to a person's body influencing habits and lifestyle. A person waking up early in the morning tends to follow a different life pattern than someone who stays up at night. Some of these habits have indirectly contributed to cancer risk. For example, some habits which are often seen in evening people are skipping breakfast, eating late, and drinking more alcohol. Moreover, evening types are more prone to insulin resistance, higher LDL cholesterol, and poorer metabolic health, all of which have been linked to an increased risk of colorectal cancer (Yuan et al., 2023). Altered hormones, metabolism, inflammation, melatonin were also often seen in evening types due to poor diet and low activity (Xie et al., 2021). So chronotype might not be biologically linked to cancer but rather a factor that makes an individual more susceptible to an increased risk by engendering behavioural changes.

A study assessed 119 obese, short-sleeping adults to find a correlation of chronotype with eating, sleeping and hormonal patterns. Using the Horne and Ostberg Morningness-Eveningness questionnaire, a dietary intake diary, sleep diary, actigraphy, and measurements of sleep apnea were used to compare results. Although this study had the limitation of a small sample and self-reported data, the findings showed that evening chronotypes had lower HDL-C levels and higher BMI (Lucassen et al., 2013). This was because evening chronotypes had fewer but larger meals at late times in the day. And according to a prospective cohort study, obese individuals, people with a high BMI, are at a much higher risk for cancer than people of normal weight. The death rates from cancer in these individuals was 52% higher than normal people in men and 62% higher in women (Calle et al., 2003). This suggests that changes in behaviors in evening chronotypes can induce changes such as high BMI which put people at a higher risk for cancer. Along with higher BMI, evening type individuals also had elevated levels of ACTH, stress hormone and high resting heart rate (Lucassen et al., 2013). In a study with breast cancer patients, it was found that the patients have significantly higher levels of basal cortisol, a stress hormone (van der Pompe et al., 1996). Higher levels of cortisol increase inflammation and inhibit the body's natural defense in the form of T-cells against tumors (Liu et al., 2022). However, the sample size for the study with breast cancer patients was very small, serving as a limitation. But nevertheless, these findings suggest that behavioral and hormonal disruptions in evening chronotypes may together elevate cancer risk, particularly for breast cancer.

Conclusion

Overall, the mixed evidence for the relationship between chronotype and cancer still puts the connection in question. Some studies suggest that due to circadian misalignment, behavioral habits, and hormonal disruptions, evening chronotypes may be more vulnerable to cancer,

specifically in breast, lung, and digestive tract cancers. But other studies find no significant associations. So, whether chronotype biologically affects cancer or influences changes that lead to cancer needs to be examined more thoroughly. Although chronotypes' role in cancer remains unclear, it would be imprudent to dismiss a potential connection. These findings discern the need for further research with more diverse populations to validate results which use more than self-reported data to control confounding variables. Moreover, factors such as diet and lifestyle should be controlled to provide an accurate reflection of the findings. In essence, understanding the potential long-term health consequences of misaligned sleep patterns is very important, especially in a society where going to bed late is increasingly normalized. Clarifying chronotypes' role as biological or behavioral can be essential for lifestyle interventions in the future of public health.

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