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REVIEW ARTICLE

Emerging Relation between Chrononutrition and Cancer

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ABSTRACT

Circadian rhythms, driven by the suprachiasmatic nucleus and orchestrated by clock genes, regulate vital cellular and systemic processes including DNA repair, apoptosis, metabolism, and immune surveillance. Disruption of these rhythms, through shift work, artificial light at night, or irregular eating, is strongly associated with increased cancer risk and progression. Chronotype the individual preference for morning or evening activity modifies susceptibility, with evening types consistently showing higher incidence of breast, lung, prostate, and endometrial cancers. Nutrition timing, or chrononutrition, further influences circadian alignment; early time-restricted eating (TRE) and prolonged overnight fasting improve metabolic balance and appear protective against tumorigenesis. Fasting and ketogenic diets enhance cancer therapy responsiveness by lowering insulin/IGF-1 signaling, inducing autophagy, and reducing inflammation. Chronotherapy, synchronizing drug delivery with circadian rhythms, improves tolerability and therapeutic efficacy. Integration of chrononutrition and chronotherapy offers a promising framework for precision oncology, although large-scale clinical validation remains a critical need.

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INTRODUCTION

It is common knowledge that Earth has a cycle of rotation around its axis with a periodicity of approximately twenty-four hours, which in turn has led to the development of intrinsic biological time-dependent processes in most organisms that allow them to adapt and anticipate environmental fluctuations daily. This highly specific mechanism has come to be known as the Circadian rhythm and finds a central role in the alignment of behavioral and physiological processes with the daily dark and light cycle, governing the sleep-wake cycle in animals and, similarly, the rhythmic closing and opening of flowers in plants, augmenting homeostatic functions by synchronizing with environmental cues.[1]

The mammalian hypothalamic Suprachiasmatic nucleus has been identified to serve as the Master Clock, synchronizing the internal biological rhythmic functions with the external Dark-Light cycle, with subsequent downstream regulation of the Autonomic and Neuroendocrine pathways.[2–4]

Circadian rhythms govern a wide array of fundamental physiological processes, including anabolic and catabolic metabolism, cell proliferation and the cell cycle, immune surveillance, programmed cell death (apoptosis), and the repair of DNA damage.[5] Disruption of these tightly regulated rhythms, due to environmental factors such as shift work or travel across time zones, has shown to have strong associations with the contributory processes in development of different pathological conditions, starting from sleep-related disorders, cardiovascular dysfunction, neurodegenerative diseases to the development of various malignancies.[6–8]

Disruption of the circadian clock has been linked to dysregulated cell growth, genomic instability, and impaired apoptotic mechanisms hallmarks that are central to cancer development.[9,10] Both epidemiological data and experimental research have demonstrated a significant correlation between circadian misalignment and an elevated risk of malignancies. In recognition of this evidence, the World Health Organization (WHO) has categorized circadian disruption as a probable carcinogenic factor.[11,12] This designation has spurred increasing scientific interest in elucidating the underlying molecular pathways by which circadian dysfunction contributes to tumor initiation and progression.

Chronotype and Chrononutrition

The term "Chronotype" points towards the inherent preferences of an individual with respect to the timing of sleep, wakefulness, and related physiological and behavioral patterns within a 24-hour cycle.[13] The Chronotypes have been classically categorized into three broad groups as "M-types" or "Morning types", "E-types" or "Evening types", who have shown their predilection for activities towards Morning or Evening hours respectively. The third type is the "N-type" or "Neither type" that includes those who have not demonstrated any specific preference and operate with variability between the spectrum of morning and evening.[14] Approximately 60% of adults are identified as N-types, while the remaining 40% are distributed between morning and evening types. Understanding chronotype variability is crucial, as it has significant implications for health, cognitive performance, and disease susceptibility.

The M-types and E-types display distinct patterns in their sleep-wake cycles and daily fluctuations in mental and physical alertness. M-types tend to retire and awaken earlier, with their cognitive and physical performance peaking in the morning hours.[15] In contrast, E-types prefer later sleep and wake times, often reaching their optimal functioning in the latter part of the day.[13,14]

Chronotype has far-reaching implications beyond sleep patterns, influencing an individual's lifestyle choices, cognitive abilities, athletic capabilities, and personality traits.[16–19] The body of existing evidence points out typical character traits for the M-types being goal-oriented and agreeable with an active element of conscience while the E-types

are typically prone to neurotic traits with increased susceptibility for psychological deviations presenting as disorders of mood or subtle behavioral alterations like eating disorders.[20–26]

Chronotype expression is regulated by a complex interaction between genetic and environmental factors with the involvement of critical genetic elements such as the variable expression of genes *CRY1, PER3* and *CLOCK* at its core. Additional modulation is exerted by environmental factors, especially the quantified exposure to light. To put into perspective, prolonged exposure to particularly artificial BLUE light emission from infotainment screens along with seasonal geographic changes in terms of altitude or latitudes may affect melatonin secretion and consequently promote a shift in the chronotype from M-type to E-type.[27]

Among the various environmental cues that influence circadian rhythms, the interplay between light-dark cycles and nutrition particularly the timing of food intake rather than its composition has emerged as a critical modulator of how caloric restriction (CR) impacts physiological systems.[28] In parallel, internal biological clocks are entrained not only by light exposure but also by recurring daily patterns of metabolic and physiological activity, which are tightly linked to the timing, frequency, and composition of meals.

This temporal pattern of nutrient consumption across the 24-hour day is referred to as the circadian distribution of food intake, forming the conceptual foundation of chrono-nutrition.[29,30] In chrono-nutrition, the emphasis is chiefly on the alignment of food intake with the circadian rhythms of the body aimed towards optimization of metabolic health, enhancing the effects of dietary interventions such as CR and potentially mitigating the risk of various chronic diseases.

Molecular Basis of Circadian Rhythms in Cancer

A distinct class of genes, known as clock genes, encodes proteins that constitute the core components of the molecular architecture underlying circadian rhythms endogenous biological clocks that regulate a wide range of physiological processes based on an approximate 24-hour cycle. These genes play a crucial role in orchestrating the rhythmic expression of numerous downstream targets involved in hormone secretion, energy metabolism, and other time-dependent cellular functions.[31–33]

The circadian rhythm is postulated to be regulated through complex biological mechanisms, of which, "Transcriptional Translational Feedback Loops (TTFLs)" hold a central regulatory role, that facilitates the interaction between the core genes and their protein products precisely regulating their own expression maintaining a self-sustained cycle. Key regulators within this system include Clock, Bmal1, Per (Period), and Cry (Cryptochrome), which dynamically coordinate to maintain circadian rhythmicity.[33,34]

A growing body of epidemiological evidence indicates that circadian rhythm disruption (CRD) triggered by factors including shift work, jet lag, inadequate sleep, irregular eating patterns, and altered physical activity can exacerbate the risk and progression of various health conditions.[35]

One of the most critical concerns related to circadian rhythm disruption is its strong association with increased risk of cancer. Emerging evidence suggests that circadian misalignment, often resulting from irregular sleep patterns or lifestyle factors, is linked to a heightened incidence of various cancers, including colorectal, breast, and prostate malignancies. This association is thought to arise from the involvement of circadian system in the regulation of fundamental processes such as hormonal balance, DNA repair, and cell cycle progression.[12]

Circadian rhythms play a quintessential role in coordinating the timing of cell division and genomic maintenance. When these rhythms are disrupted, the temporal control of DNA repair and cell proliferation may become desynchronized, leading to accumulation of genetic mutations a hallmark of tumorigenesis. Additionally, circadian clocks modulate the secretion of crucial hormones such as melatonin, cortisol, and growth factors, all of which influence cellular growth, programmed cell death (apoptosis), and oncogenic potential.[36] Disruption of these hormonal rhythms may disturb the delicate balance between cell survival and apoptosis, thereby facilitating cancer development.

Moreover, the circadian system tightly regulates immune function, including natural

killer (NK) cell and cytotoxic T cell activity, which are instrumental in tumor surveillance. Circadian rhythm disturbances may impair immune cell function, weakening the body's ability to recognize and neutralize emerging cancer cells.[37,38]

A particularly modifiable risk factor in this context is exposure to artificial light at night (ALAN) from screens, street lighting, or indoor lighting which can suppress melatonin synthesis. Melatonin, along with its well-documented influence on the sleep wake cycle, also possesses antiproliferative and antioxidant properties, contributing to its role in cancer prevention. Lower melatonin levels, often observed in individuals with disrupted circadian rhythms, have been associated with increased susceptibility to hormone-related cancers such as breast and prostate cancer.[39]

Recent studies have unmasked a significant link associating the core circadian clock with the regulation of apoptosis. Depending on the cellular environment and the functional state of the circadian system, circadian components can either facilitate or inhibit programmed cell death mirroring their dual role in cell cycle control. Key clock proteins such as Cryptochrome (CRY1/2) and Period 1 (PER1) have been implicated in modulating distinct apoptotic pathways. Specifically, CRY1/2 influences the intrinsic (mitochondria-mediated) apoptotic pathway, while PER1 plays a role in the extrinsic pathway triggered by tumor necrosis factor-alpha (TNF-α), both contributing to the regulation of cell death in a time dependent manner.[40]

An expanding body of evidence also highlights a strong association between circadian gene disruption and increased cancer susceptibility. Alterations such as single nucleotide polymorphisms (SNPs), gene deletions, epigenetic modifications, and transcriptional dysregulation of clock genes have been linked to tumor initiation and progression.[41] These molecular disturbances interfere with the normal functioning of circadian regulators, thereby affecting pathways involved in DNA repair, apoptosis, immune surveillance, and cell proliferation all of which are central to oncogenesis and metastasis.

In mammals, the Period gene family encodes three homologous proteins PER1, PER2, and PER3 which are integral components of the circadian clock. Among these, Period Circadian Regulator 2 (PER2) has a pivotal role in suppressing abnormal cell-proliferation by modulating the activity of several downstream genetic regulatory mechanisms of cell cycle and tumor suppression. Key targets influenced by PER2 include Cyclin B1 (CCNB1), a critical regulator of mitosis; Cyclin D1 (CCND1), which promotes G1/S phase progression; and the TP53 gene, which encodes the tumor suppressor protein p53.

The TP53 gene is a central node in the cellular defense against oncogenesis, particularly in tissues frequently exposed to carcinogens or oncogenic stress. PER2-mediated regulation of TP53 supports cell cycle arrest and survival under stress, making p53 a common target for selective pressures during early tumor development. As cancer progresses, this selection may favor clonal expansion of cells with TP53 mutations, contributing to tumor heterogeneity and aggressiveness.[42]

Functionally, p53 plays a key role in genomic stability by retarding the progress of the cell cycle to allow adequate time to the DNA repair mechanisms to correct genetic damage.[43] Beyond its role in cell cycle control and apoptosis, p53 also influences cellular metabolism. In most cell types, evidence supports the notion that p53 promotes oxidative phosphorylation (OXPHOS) over glycolysis, favoring energy efficient pathways. However, in certain specialized cells, such as pancreatic β-cells and hepatocytes, p53 activity may shift toward enhancing glycolysis while simultaneously repressing mitochondrial respiration.[44]

The intricate interplay between the circadian clock and cellular metabolism is increasingly recognized as a critical factor in cancer biology, with oncogenic signals mediating the disruption of circadian and metabolic homeostasis in tumor cells. A key player in this process is the oncogene MYC, a potent metabolic regulator and transcription factor that drives tumorigenesis. MYC exerts its effects by binding to E-box elements in the genome binding sites that are also recognized by the core circadian transcriptional complex CLOCK-BMAL1.[41]

Multiple studies have established that the circadian clock regulates key cell cycle checkpoints, particularly those governing the G1/S and G2/M transitions. In cancer,

this regulatory alignment is often disrupted, resulting in uncoordinated cell cycle progression alongside circadian dysregulation. Such disturbances contribute to unchecked cellular proliferation and genomic instability hallmarks of malignancy.

Furthermore, environmental circadian disruption such as that caused by irregular light exposure or shift work has been shown to facilitate tumor metastasis, particularly by promoting systemic changes that create a pro-tumorigenic microenvironment. These include the release of inflammatory cytokines and neurotransmitters, activation of tumor-associated macrophages, suppression of anti-tumor immune responses, and stimulation of angiogenesis, all of which support cancer progression and the spread of malignant cells to distant organs.[45]

Impact of Chronotype on Cancer Risk and Progression

Chronotype is typically assessed using self-reported measures based on perceived preferences for activity timing or through standardized, validated questionnaires.[46] These instruments help classify individuals into chronotype categories morning, evening, or intermediate based on behavioral and physiological patterns.

Women's chronotype has emerged as an important area of investigation in relation to cancer risk. Findings from the California Teachers Study suggested that women with a pronounced evening preference experienced a higher likelihood of developing endometrial cancer compared to those identifying as morning types.[47] In contrast, evidence from a hospital-based case–control study reported less consistent patterns, underscoring possible variability in the association between chronotype and cancer across different study designs and populations.[48]

Analyses from the California Teachers Study, which examined thousands of participants, indicated that women with an evening chronotype were more likely to develop breast cancer compared to those identifying as morning types.[49] Consistent with this, a large-scale longitudinal study conducted between 2012 and 2019, following women who were initially cancer free, also observed an elevated risk of breast cancer among evening-oriented individuals.[50] Together, these findings point toward a reproducible association between evening preference and heightened breast cancer susceptibility across different prospective cohorts.

An increasing number of studies indicate that evening chronotype may be linked to greater cancer susceptibility. Evidence from the UK Biobank, a large prospective cohort including nearly half a million participants without lung cancer at baseline, demonstrated that individuals identifying as evening types exhibited a higher likelihood of developing lung cancer compared to those with a morning orientation.[51]

An updated investigation within the same large-scale cohort, after removing individuals who reported engaging in shift work at baseline, revealed that participants with an evening-oriented chronotype had a higher likelihood of developing lung cancer compared with those identified as clear morning types. The elevated risk was evident for both individuals with a mild evening preference and those with a strong evening preference.[52]

Research on chronotype has shown comparable patterns in relation to prostate cancer. Evidence from the Older Finnish Twin Cohort, which tracked over eleven thousand twins and documented several hundred incident cases and deaths, indicated that men with an evening-oriented preference had a significantly greater risk of developing prostate cancer compared to those strongly aligned with a morning preference.[53] Consistent with this, findings from a case control study involving newly diagnosed patients and matched controls suggested nearly a twofold higher likelihood of prostate cancer among individuals exhibiting an evening chronotype.[54]

Further evidence highlights the intricate interplay between chronotype, shift work, and cancer susceptibility. In a population-based study including over a thousand prostate cancer cases and comparable controls, prolonged exposure to shift work was linked to an increased incidence of prostate tumors. The risk was especially pronounced among individuals with an evening preference, although men with a morning preference also showed heightened vulnerability after long-term night work, underscoring the cumulative detrimental impact of circadian disruption irrespective of chronotype.[55]

In contrast, findings from a population-based case–control study involving women with epithelial ovarian cancer and matched controls did not show a significant overall link between shift work and ovarian cancer risk. Nonetheless, subgroup analyses indicated a stronger association among women classified as morning types, suggesting that a mismatch between inherent circadian preference and imposed work schedules may contribute to heightened cancer vulnerability in specific groups.[56]

Recent evidence further refines understanding of chronotype-related cancer susceptibility. Analysis of data from nearly half a million participants within the UK Biobank showed no meaningful association between an evening chronotype and the risk of pancreatic cancer, when comparing individuals who identified as "definitely an evening person" to those identifying as "definitely a morning person".[57]

Analyses from the UK Biobank encompassing several cancer types demonstrated that individuals with a definite evening chronotype showed an elevated risk of developing cancer overall, including breast, lung, endometrial, and ovarian malignancies. Complementary Mendelian randomization analyses supported a likely causal role, indicating that a stronger inclination toward a morning chronotype was linked with reduced susceptibility across multiple cancers. These findings underscore evening preference as a risk-enhancing factor, while morning orientation appears to confer a protective effect against cancer development.[58]

Adding to this evidence, a large-scale genetic analysis conducted by a consortium incorporating over 79,148 prostate cancer cases found that men with a genetic predisposition toward morningness had a substantially lower risk of developing prostate cancer compared with those inclined toward eveningness.[59]

Time-Restricted Eating and Cancer

A nutritional approach known as time-restricted eating (TRE) also called time-restricted feeding (TRF) involves confining daily food consumption to a consistent, limited time window, typically between 4 to 12 hours within a 24-hour cycle.[60] This approach emphasizes the timing of eating as a critical factor in metabolic health, independent of calorie restriction.

Optimal health benefits are observed when TRE is practiced during the early part of the day, commonly known as early TRE, which aligns food intake with the body's endogenous circadian rhythms. This alignment enhances metabolic efficiency and supports physiological processes regulated by the biological clock. In contrast, late TRE, characterized by food consumption in the evening or night, can disrupt circadian synchronization, potentially attenuating the positive effects of this dietary intervention.

Meal timing represents a critical but often underappreciated component of circadian disruption and its association with carcinogenesis. While much attention has been given to light exposure at night, dietary patterns particularly the timing of food intake also appear to influence cancer risk by affecting circadian alignment.

Evidence from a large French cohort study demonstrated a significant association between late-night eating and an increased risk of breast and prostate cancers, suggesting that delaying the last meal of the day may interfere with biological clock function and elevate cancer susceptibility.[61]

The Spanish multicase control (MCC) study conducted between 2008 and 2013, including prostate cancer cases and population controls without any history of night shift work, suggested that a longer duration of overnight fasting was linked to a lower risk of prostate cancer compared to shorter fasting periods. Furthermore, individuals who combined extended nighttime fasting with an early breakfast showed a reduced likelihood of developing prostate cancer relative to those with shorter fasting times and later morning meals.[62]

A study employing a case–control design with participants drawn from the same population in which an earlier analysis reported a beneficial association between nighttime fasting duration and breast cancer risk found no significant overall relationship between fasting duration and breast cancer occurrence. Notably, for individuals who had not yet reached menopause, delaying the time of eating the first meal of the day was linked with a measurable elevation in breast cancer risk, even after accounting for other known risk factors.[63]

Further supporting the concept that eating later in the evening could impact cancer risk, research comparing breast cancer survivors with a representative sample of Australian women found that those who had experienced breast cancer tended to report consuming food later at night, having shorter periods without food overnight, and spending more time sleeping compared to the general population.[64]

Analysis from the NutriNet-Santé cohort, a large-scale prospective study of French adults, has shown that consuming food later in the evening is associated with an increased risk of developing both breast and prostate cancers. Specifically, this elevated risk was observed when the last meal occurred later at night, while no meaningful association was found between cancer risk and how often participants ate, the length of the overnight fasting interval, or when the first daily meal was consumed.[61]

Role of Chrononutrition in Cancer Prevention and Therapy

In recent years, the timing of dietary intake has garnered increasing attention in nutrition science, leading to the development of the field known as chrononutrition. Chrononutrition focuses on not just what and how much is eaten, but also when food is consumed, advocating for meal timing that is in harmony with the body's natural circadian rhythms.[65] By aligning eating patterns with the biological clock, this approach aims to support optimal metabolic functioning and may contribute to the prevention of various diseases.

Among dietary interventions aligned with circadian biology, fasting and ketogenic diets (KDs) have gained attention for their potential role in obesity-related cancers. These strategies influence both metabolic and circadian pathways, offering dual benefits in weight regulation and tumor suppression (66,67) Specifically, they impact critical molecular mechanisms associated with cancer development, including insulin signaling, inflammatory responses, and oxidative stress.[68]

The findings revealed a 20% reduction in combined and individual risks of breast and prostate cancers among participants who waited at least two hours between their evening meal and sleep onset. Similarly, individuals who had supper before 9:00 PM demonstrated lower cancer risk compared to those eating after 10:00 PM. The protective effect of maintaining a longer interval between supper and sleep was particularly pronounced among individuals who adhered to established cancer prevention guidelines and those identified as morning chronotypes. In contrast, this benefit was less evident in evening-type individuals.[69]

Cyclic eating and fasting regimens, including strategies such as intermittent fasting (IF) and ketogenic diets (KDs), have emerged as powerful modulators of cancer therapy responsiveness. These strategies appear to have a dual impact by increasing the ability of normal cells to withstand stress, while at the same time making cancer cells more vulnerable to chemotherapy and other cancer treatments. By leveraging the distinct metabolic vulnerabilities of cancer cells, these dietary patterns promote a therapeutic window that improves treatment efficacy and reduces harm to healthy tissues.

Fasting and ketogenic diets induce significant metabolic changes in critical tissues such as adipose tissue and skeletal muscle, which enhance the effectiveness of cancer treatments and reduce the side effects associated with these therapies. These interventions lower circulating levels of key growth-fueling nutrients and hormones, including glucose, insulin, and insulin-like growth factor 1 (IGF-1). The resulting decrease in glucose availability, coupled with the inhibition of glucose uptake through glucose transporters, suppresses the Warburg effect—where cancer cells preferentially use aerobic glycolysis—and promotes a metabolic shift towards oxidative phosphorylation.

This metabolic transition results in increased reactive oxygen species (ROS) production specifically within cancer cells, leading to oxidative damage to DNA and heightened apoptosis when exposed to chemotherapy. Additionally, both fasting and ketogenic diets modulate critical signaling pathways, notably the IGF1R–mTOR–AMPK axis, which promotes autophagy and enhances the immune system's anticancer activity.[68]

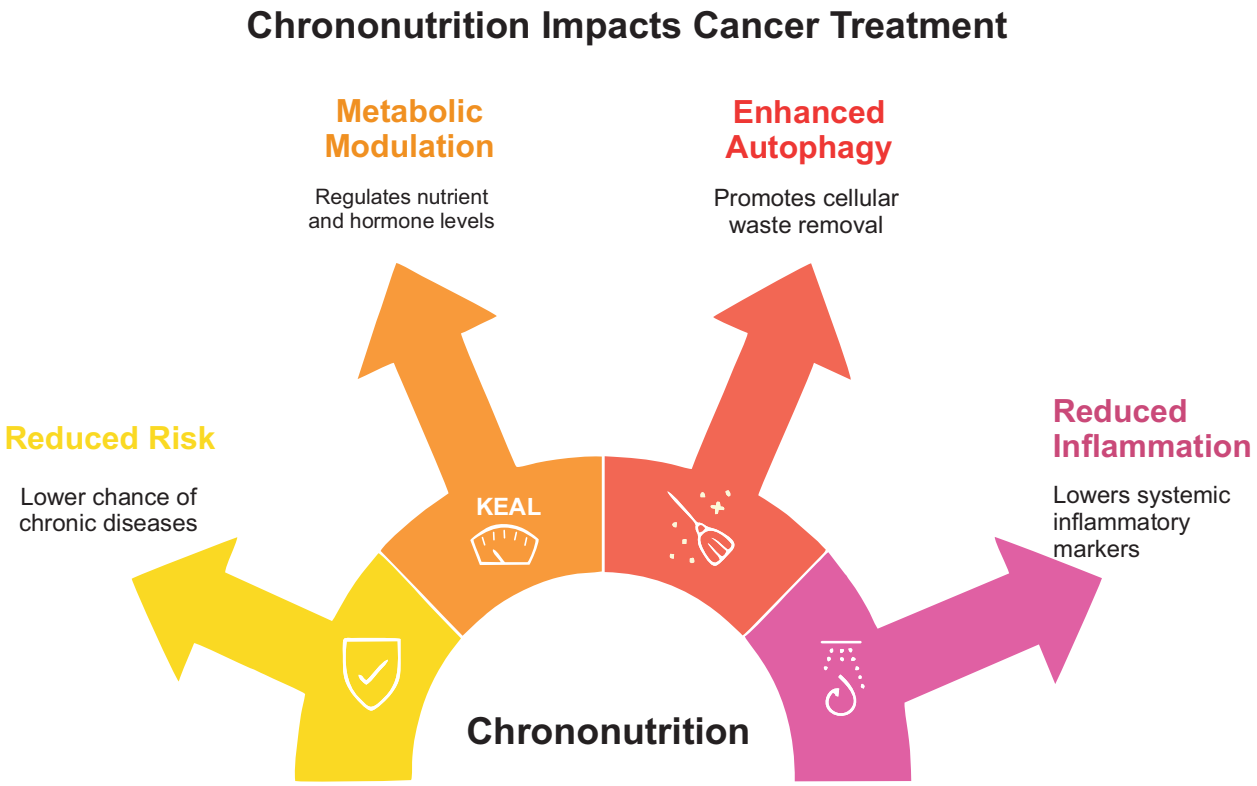

Figure 1: Chrononutrition impacts cancer treatment by reducing risk, modulating metabolism, enhancing autophagy, and reducing inflammation

Emerging clinical evidence supports these mechanisms. For example, time-restricted eating (TRE) has shown promising results in cancer patients. A randomized study involving patients with HER2-negative breast cancer demonstrated that time-restricted eating (TRE) prior to chemotherapy reduced gastrointestinal side effects and helped stabilize glucose and insulin levels compared to a group consuming an unrestricted diet. The participants in this study had an elevated average BMI.[70] Similarly, research on colorectal cancer patients observed that fasting during the month of Ramadan improved chemotherapy tolerance, including in individuals with a high prevalence of overweight or obesity.[71]

Prolonged fasting interventions, as examined in studies by Zorn *et al.* and Bauersfeld *et al.*, were linked to a reduction in chemotherapy-related side effects and improvements in quality of life among patients with gynecologic2 cancers. In breast cancer cohorts, Harvie *et al.* further investigated intermittent compared with continuous energy restriction implemented prior to chemotherapy and observed that intermittent fasting promoted greater reductions in body fat while not exacerbating treatment-associated toxicities.[72]

The therapeutic benefits of fasting observed across various clinical and experimental studies are underpinned by well-characterized biological mechanisms that impact both metabolic and cellular functions.

Fasting triggers a broad metabolic reprogramming that lowers circulating concentrations of glucose, leptin, insulin, and insulin-like growth factor 1 (IGF-1).[71,72] These hormonal changes contribute to the suppression of oncogenic signaling, most notably the PI3K/AKT/mTOR pathway, which is frequently activated in cancer. At the same time, fasting elevates insulin-like growth factor-binding protein 1 (IGFBP-1), thereby reducing the bioavailability of IGF-1. This reduction is associated with diminished cellular motility and metastatic capacity, ultimately exerting a protective influence against tumor progression.[73,74]

Another key mechanism is the stimulation of autophagy, a fundamental cellular process that facilitates the breakdown and recycling of dysfunctional organelles and misfolded proteins, thereby supporting cellular homeostasis and resilience under stress conditions. Through this mechanism, fasting promotes the clearance of toxic cellular

debris, contributing to tumor suppression and improving the sensitivity of cancer cells to chemotherapy, while simultaneously mitigating treatment-related toxicity in healthy tissues.[75]

In addition to its metabolic and cellular benefits, fasting also exhibits anti-inflammatory properties. It markedly reduces circulating concentrations of critical pro-inflammatory mediators, such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), contributing to a less inflammatory tumor microenvironment, which is often associated with better therapeutic outcomes.[76]

Chronotherapy, which synchronizes the administration of anticancer drugs with endogenous circadian rhythms, has emerged as a promising strategy to enhance both the efficacy and tolerability of cancer treatments. Circadian rhythms significantly influence the pharmacokinetics (absorption, distribution, metabolism, and excretion) and pharmacodynamics (drug–target interaction and therapeutic effect) of chemotherapeutic agents, thereby affecting their overall clinical performance.[77]

For example, chrono-modulated delivery of chemotherapeutics such as continuous infusion of 5-fluorouracil (5-FU) as part of chronotherapy has demonstrated improved therapeutic outcomes, with peak plasma concentrations typically occurring around early morning hours, which coincides with improved drug tolerability and effectiveness.[78] Similarly, time-of-day–adjusted administration of agents like oxaliplatin and 5-FU in patients with metastatic colorectal cancer has been shown to reduce treatment-related toxicity without compromising efficacy.[79]

Notably, irinotecan, another widely used chemotherapeutic agent, exhibited fewer adverse effects and better quality of life outcomes when administered during the early morning hours (2:00 a.m. to 8:00 a.m.), further supporting the importance of circadian timing in oncologic treatment.[80]

Building on this concept, the integration of personalized chrononutrition tailoring meal timing and dietary patterns to individual circadian profiles may provide synergistic benefits alongside chronotherapy. By improving metabolic health, synchronizing internal clocks, and potentially enhancing drug metabolism, such approaches could significantly augment cancer treatment outcomes, paving the way for precision chronomedicine in oncology.

Challenges and Future Directions

While preclinical evidence strongly supports the potential of chrononutrition as a complementary strategy in cancer care, its translation into routine clinical practice remains fraught with challenges. One of the primary obstacles is the inter-individual variability in circadian rhythms, encompassing differences in chronotype, sleep–wake patterns, and metabolic responses. These variations complicate the development of standardized protocols, making it difficult to implement one-size-fits-all dietary interventions across diverse patient populations.

In addition, adherence to structured regimens such as time-restricted eating (TRE), prolonged fasting, or ketogenic diets (KDs) poses significant practical barriers, particularly during extended treatment periods. Maintaining consistency in meal timing, macronutrient composition, and alignment with circadian cycles requires high levels of patient commitment and support, which may not be feasible in all clinical settings.

Despite these limitations, chrononutrition holds considerable promise especially in cancers characterized by metabolic dysregulation, where aligning nutrient intake with circadian biology may enhance therapeutic outcomes. However, there is a critical need for well-powered, large-scale clinical trials to rigorously assess the safety, efficacy, and long-term advantages of such interventions. These studies should be designed with stratification by chronotype, allowing for personalized nutritional and therapeutic timing strategies that optimize patient-specific outcomes.

Furthermore, while fasting and KDs have shown favorable effects in pilot studies, the methodological heterogeneity across trials presents a barrier to reproducibility. Inconsistencies in diet definitions, protocol duration, and monitoring methodologies hinder the ability to compare findings or establish best practices. Long-term adherence remains a pressing issue, often exacerbated by the lack of standardized guidelines, behavioral support systems, and clinical infrastructure to

monitor real-time compliance and metabolic impact.

To advance the clinical applicability of chrononutrition and chronotherapy, future research must focus on:

- Developing harmonized protocols with standardized definitions of feeding/fasting windows.
- Utilizing validated biomarkers of dietary adherence and metabolic response.
- Implementing digital tools for real-time dietary and circadian tracking.
- Designing adaptive, personalized frameworks that consider chronotype variability, metabolic flexibility, and comorbid conditions.

By addressing these scientific gaps, it will become possible to effectively integrate chrononutrition into precision oncology, ultimately enhancing treatment responsiveness, reducing toxicity, and improvements in their overall well-being for cancer patients.

CONCLUSION

Circadian rhythms play a pivotal role in regulating cellular, metabolic, and immune functions, and their disruption is strongly implicated in cancer initiation and progression. Chronotype significantly influences cancer risk, with evening types being more vulnerable across multiple malignancies. Chrononutrition, especially early time-restricted eating and prolonged nightly fasting, emerges as a promising preventive and therapeutic strategy. Fasting and ketogenic diets enhance responsiveness to cancer therapies through metabolic reprogramming, autophagy induction, and reduced inflammation. Chronotherapy further aligns drug delivery with circadian biology, improving efficacy and reducing toxicity. However, interindividual variability in circadian preferences necessitates personalized approaches. Large-scale, well-designed clinical trials stratified by chronotype are essential for translation into oncology practice. Integrating chrononutrition and chronotherapy promises to advance precision cancer care while improving patient outcomes and quality of life.

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