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ESSAY

Hypothesis: ubiquitous circadian disruption can cause cancer

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Abstract
Circadian disruption (CD) was implicated in chains of cancer causation when the International Agency for Research on Cancer classified shift-work involving circadian disruption as probably carcinogenic in 2007. In the following decade, epidemiological studies into causal concepts associated with circadian disruption were inconclusive. Unappreciated complexity with an exclusive focus on shift-work, light-at-night, sleep, and melatonin in regard to circadian disruption may be accountable. With compelling non-epidemiological evidence, we posit that ubiquitous circadian disruption causes cancer and, moreover, that this is unexplored epidemiologically. This hypothesis offers a novel explanation why numerous studies in shift-workers evince inconsistent results: If circadian disruption is a ubiquitous causal phenomenon, confining assessments to the workplace, ignoring circadian disruption at play, and potential misclassification of 'who' is 'when' and 'how much' exposed to circadian disruption may disallow detecting the existence and magnitude of cancer risks. The rationale herein provides plausible explanations for previous observations and makes falsifiable predictions.

Keywords Chronodisruption · Shift-work · Cancer · Circadian disruption · Melatonin · Light · LAN · Sleep · Chronotype · IARC

Introduction

Remarkable work by Nobel laureates Hall, Rosbash, and Young contributed to explaining how plants and animals adapt their diurnal rhythms in synchrony with the Earth's revolutions of light and dark [1]. As an evolutionary legacy, circadian systems organise determinants of health and survival in humans as rhythmic expression of physiology over 24 h. Due to circadian rhythm alignment, we can achieve peak performances during active periods (e.g. increased body temperature, energy allocation, etc.) and facilitate sleep and sleep-associated processes during inactive periods (e.g. growth and repair, memory consolidation, information processing, etc.). The temporal expression of these periods can vary per individual chronotypes. Empirically, contributors to health such as hormones, metabolism, detoxification, body temperature, blood pressure, cell growth and repair processes, sleep, and even immune system function are all regulated by the circadian system.

Shift-work that disrupts circadian rhythms [circadian disruption (CD)] can be expected to be detrimental to health and performance. In this vein, already in 2007, the International Agency for Research on Cancer (IARC) classified shift-work with CD as a probable human carcinogen citing shift-work, light-at-night (LAN), altered melatonin rhythms, and deficient sleep as potential co-causal mechanisms [2]. Importantly, the panel judged the evidence derived from studies in experimental animals and from mechanistic and other relevant data to be so persuasive that a Group 1 classification (carcinogenic to humans) of shift work involving CD was discussed. It was the limited epidemiological evidence in humans which deterred the experts from the group 1 verdict. Now, given compelling non-epidemiological evidence, why then has extensive epidemiological research into probable links between shift-work and cancer during the past decade yielded inconsistent results [3]?

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Hypothesis

Empirically, research has likely detected a signal about CD effects in shift-workers who are, in some cases, exposed to higher doses of CD. We hypothesize that ubiquitous CD can cause cancer and put forward that, to-date, ubiquitous CD has not been comprehensively assessed in epidemiological studies, and that several causal concept caveats have been overlooked.

Causal concept caveats

Only two of the laboratory studies synthesized by IARC demonstrated increased incidence of tumours in an experimental group compared to controls wherein no initiation-promotion protocols were used (Jöchle 1963, 1964; Anisimov et al. 2004) [2]. The vast majority of "sufficient evidence in experimental animals" pertains to circadian timing of carcinogen exposure affecting tumour development, circadian system defects at structural or genetic levels, or paradigms of unusual light exposures (some modelling shift-work) accelerating tumour development post-initiation [2]. Thus, potential causal concepts put forward in the IARC monograph have perhaps over-focussed the field on these concepts as sufficient causal phenomena. A closer look at these causal concepts and how they were explored epidemiologically reveals numerous caveats.

Shift-work concept

Shift-work causes CD when it interferes with circadian rhythm alignment, e.g. individuals working at times when their bodies are primed for sleep. Some 40 individual epidemiological studies into links between shift-work and diverse cancers after the IARC 2007 classification are inconsistent, often conveying cancer risks slightly above or at the null. One caveat to assessing shift-work as the independent variable is that it may not always interfere with circadian alignment. The circadian system has the ability to phase-shift (a certain amount per day), thus facilitating different timing of activities. Additionally, diurnal preferences that may be in part genetically determined can affect the shape and timing of circadian rhythms [2]. Thus, certain shifts may not be as disruptive to a given individual as others. Moreover, the difference between chronotype-associated time propensities of sleep and activity as imposed by the social life on non-work days and the professional life on work days can be considered a form of circadian disruption. Such misalignment of internal and external times has been referred to as chrono-disruption [4] and misalignment between work days and days off as social jet lag [5]. Arguably, the most important caveat of assessing shift-work per se is that misalignments of internal time (individual circadian phase) and external time, as determinants of CD, can be experienced both at work and play [3]. Thus, CD is not limited to work status—shift-worker or otherwise [1]. Clearly, shift-work on its own serves only to potentially, but not necessarily, increase doses of CD to an individual.

LAN concept

Light is a key zeitgeber which "affects our circadian rhythms more powerfully than any drug" [6]. Outdoor LAN has been studied in ten epidemiological studies which, overall, yielded inconsistent results [7]. Research into effects of indoor LAN and cancer risks is even scarcer and capturing exposure appropriately can be difficult. The caveat is that LAN is only disruptive to the circadian system if it 'pushes' or 'pulls' circadian phase to such an extent that it causes transition period misalignment between rhythms. This is not always the case in shift-work as genetics, circadian phase, and previous light history affect the magnitude of the response to LAN [2, 8]. Clearly, no one knows yet how ambient light factually contributes to CD [8].

Melatonin concept

One biological node often linked to the LAN concept due to light being powerfully able to phase delay its rhythm is melatonin [9]. It may be conceptualized as a potential oncostatic agent [2]. Pinealectomy can increase tumour acceleration and metastasis in laboratory animals and low melatonin levels have been associated with cancer progression in humans [2]. Yet, melatonin differences between groups are not necessarily indicative of higher CD in one group over another or even amongst individuals. For instance, while chronotype-melatonin associations have been made, melatonin phase can manifest as hours apart for individuals of the same chronotype [10, 11]. Furthermore, we lack evidence that differences in melatonin affect risk of cancer in humans. This does not mean that melatonin is not ensnared in CD and possible links with cancer as it may offer oncostatic protection against all cancer hallmarks [2]. However, how melatonin can act in individuals who engage in shift-work or not is very complex—individuals vary in melatonin production and circadian changes of receptor density or sensitivity, some melatonin actions depend on receptors while others do not, and there may be oncostatic mechanisms that vary with the cancer type. Clearly, multifaceted relationships between melatonin and CD are a challenge for observational research.

Sleep concept

Epidemiological evidence of cancer incidence in association with sleep duration, napping or "poor sleep" is inconsistent [12]. Moreover, almost all studies into facets of sleep and cancer occurrence relied on a one-time assessment of sleep behaviour which is likely to vary over decades. One explanation for, if at all, marginally elevated cancer risks in regard to impaired sleep is that studies did not capture significant sleep-effect complexity in study individuals over time. The IARC suggests that the most prevalent health problem for shift-workers is the quantity and quality of sleep. Indeed, individuals sleeping at different times on work days and free days must be exposed to CD [5, 6, 13, 14]. Clearly, a major caveat of studies targeting "sleep" is that timing and duration of sleep, presumably associated with CD, have not been taken into account over prolonged periods [1, 13].

'Zeitgebers not specifically studied' concept

There are other zeitgebers that may compound or provide relief from the CD caused by shift-work such as meal times [15, 16] and exercise [17]. Indeed, first studies have been conducted into the potential direct effects of circadian nutritional behaviours and links to cancer [15, 16]. We appreciate this information was not available to IARC in 2007 but we would implore its inclusion in future consideration of the carcinogenicity of shift-work that causes circadian disruption.

Predictions for CD epidemiology

We operationalize CD as misalignments of internal and external times and this can be explored. Meal timing and exercise will either aid or hinder circadian alignment with internal and external time. Equally so, internal time will play a role in governing meal timing and exercise behaviours. Thus, focussing on the misalignment of internal and external times should capture CD including the impact of meal timing and exercise, at least in part. Questionnaires offer necessary tools for predicting individual circadian phase in prolonged longitudinal studies. Questionnaires used to obtain information on external times must include information on sleep and/or activity times. From either time window we can infer the other as the complement. This, in turn, allows calculation of CD doses—which are fundamental to CD and shift-work epidemiology studies—as time asleep during the circadian system-timed active phase or time engaged in activities during the circadian system-timed sleep phase. Following our hypothesis, we can make predictions with regard to CD doses:

- $\mathbf{P_1 \mid H}$ Increased doses of CD over years and decades—quantified by the number of hours wherein sleep overlaps with the circadian system-timed active phase—are associated with increased risk and progression of cancer.
- $\mathbf{P_2 \mid H}$ Increased doses of CD over years and decades—quantified by the number of hours wherein activities overlap with the circadian system-timed sleep phase—are associated with risk and progression of cancer.
- $\mathbf{P_3 \mid H}$ P1 and P2 are additive.
- $\mathbf{P_4 \mid H}$ P_1 and P_2 are synergistic.

Exploring the hypothesis and predictions

Preferably, we would explore our rationale in sufficiently powered prospective cohort studies. The German National Cohort (GNC) provides such a study option [18]. The GNC will prospectively follow a random sample of 100,000 women and 100,000 men aged 20–69 years from the general population (25–30 years planned follow-up). Regularly administered questionnaires with questions pertaining to sleep combined with information on work schedules, work activity intensities compared to off-work, and meal timing may allow determining doses of CD. Case–control studies will be more difficult as they require information on study individuals' circadian phases plus detailed reconstructions of sleep or activity time windows in past years or decades. Nonetheless, despite difficulties associated with memory bias impacting the precision of exposure measurements, they can give information about exposure over long periods. The dilemma for assessing individuals' circadian phases presents for retrospective industry-based cohort studies, too. However, detailed documentation of work times in industrial settings may be used to infer activity and sleep times over 24 h. Prospective studies will be powerful tools in assessing ubiquitous CD-cancer relationships going forward, but long follow-up times will be needed.

Perspectives

To the best of our knowledge, one experimental study since IARC 2007 demonstrates CD as carcinogenic [19]. In this study, a mouse model was forced to re-entrain to new light–dark cycles weekly—lending to regular transition period internal misalignment and periods where internal time would not match external time, i.e. CD is caused. The outcome was increased tumorigenesis compared to controls [19]. As is the case for humans, CD can be expected when internal time does not match the external time. To assess doses of total CD, epidemiological studies must therefore

compare internal and external times for each study individual at work and play.

Our rationale provides plausible explanations for previous observations and makes falsifiable predictions. Assessment of this broadened hypothesis will, clearly, constitute a challenge. Equally clearly, epidemiological research targeting some but not necessarily all CD and/or by inferring exposures to CD may remain uninterpretable.

Finally, if the hypothesis that CD is a ubiquitous causal phenomenon for cancer is not falsified, shift-work policies and other modern lifestyle factors wherein CD may be manifest may require reassessment. Furthermore, studies into endpoints beyond cancer would be stimulated. From the perspective of public health, ubiquitous CD could be a strong risk factor for cancer and other chronobiology-associated diseases [1].

Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest.

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