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Are sleep continuity disturbance and fatigue prodromal symptoms of cancer development?

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ABSTRACT

Sleep continuity disturbance (also known as insomnia) and fatigue are common complaints of individuals diagnosed with cancer. Traditionally, many have believed that sleep continuity disturbance and fatigue are caused, in large measure, by the impact of the cancer diagnosis and treatment. Recent prospective research suggests however, that sleep continuity disturbance and fatigue may actually precede a cancer diagnosis. We suggest that sleep continuity disturbance and fatigue may in fact represent prodromal symptoms of cancer. We review the current perspectives of this sequence of events and present a revised schematic that accounts for the role of biological, behavioural, and cognitive factors that contribute to the development and maintenance of sleep continuity disturbances in cancer patients. Monitoring emergent and unexplained patient-reported fatigue, sleepiness, and insomnia may serve as early warning signs of new onset cancer, providing opportunity for early detection and early intervention.

Relative to the general population, sleep continuity disturbance (i.e., insomnia) occurs disproportionality in individuals diagnosed with cancer. Prevalence rates for insomnia (problems falling and staying sleep) in individuals with cancer range from 30 to 60%, depending on the definition, time of assessment and measurement tool used [1,2]. The common belief is that the sleep continuity disturbance and daytime fatigue experienced in individuals diagnosed with cancer are iatrogenic, caused in part by the psychological impact of the diagnosis and the physiological consequences of the treatments used to slow or halt the disease [2]. With respect to treatment, the therapies most likely to precipitate insomnia and fatigue appear to be chemotherapy and endocrine treatments [3,4]. This original perspective is represented schematically (Fig. 1).

As face valid as the above perspective may be, there is emerging evidence to suggest that sleep and circadian abnormalities occur prior to the initiation of cancer treatment [5,6]. For example, in one study, patients reported an average insomnia duration of 6.8 years and an average cancer duration of 3.2 years [7]. Sleep and circadian disruption, attributed to shift work, insomnia, or other sleep disruption, has been implicated in breast, prostate, colorectal, and thyroid cancers [8–10]. The strength of the evidence for the impact of sleep and circadian disruption and inappropriately timed light exposure on tumor growth in animal models led the World Health Organization to classify shift work it as a "probable carcinogen" [11]. Collectively, these findings suggest that sleep continuity disturbance may not only be a consequence of the cancer diagnosis and treatment but may also represent a risk factor for the development of the disease or be the activating trigger for tumorigenesis [12,13].

In contrast, a number of other prospective cohort studies, have not found an association between sleep and circadian disturbance, sleep duration, sleep quality, or insomnia and incident cancer; [14] however, the research has been heavily criticized for variable definition and measurement of sleep. In an attempt to understand these conflicting results, Erren and colleagues conducted *meta*-analyses of sleep and cancer incidence among more than 1,500,000 study individuals across 13 countries [15]. While they failed to find a clear answer to the question of "*How are sleep and cancer linked in humans?*" they did conclude that a relationship is chronobiologically plausible, complex, and presumably multidirectional.

We suggest that one possible reason for the conflicting results is that the research to date has largely overlooked the possibility that sleep continuity disturbance is associated with, or a consequence of, a disease

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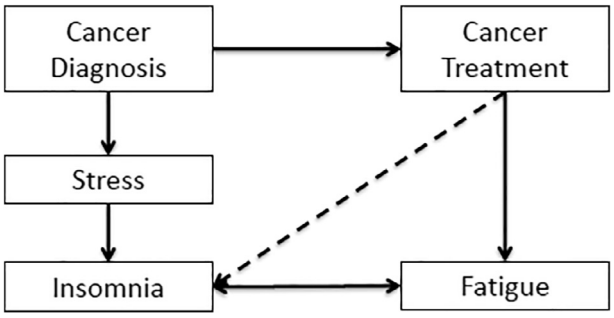

Fig. 1. Original Perspective. *Note*: The dotted line represents an additional pathway by which insomnia can present after a cancer diagnosis.

process that is already underway, and as such may represent a prodromal sign of cancers that are yet to be diagnosed. There is a growing body of literature demonstrating that sleep and circadian disruption is reciprocally associated with inflammation [16], with evidence that sleep disturbance can activate inflammatory signaling. These inflammatory cytokines have countervailing influences and are associated with disruption of sleep maintenance and loss of sleep depth, which together induces vicious feedforward and feedback cycles [17].

How might activation of inflammation be initiated to lead to disturbances of sleep? Activation of innate immunity as a result of solid tumorigenesis is one likely pathway [18]. As the growing tumor damages normal tissue, inflammatory repair systems are activated and further exacerbate tumor progression, which together lead to the expression of certain inflammatory cytokines such as interleukin-6, that in turn induces C-reactive protein (CRP). These cytokines recruit neutrophils and macrophages to the disease site, which release additional inflammatory molecules, amplifying the immune response. As long as there is no anti-tumor immunity, this inflammatory process becomes exaggerated, further instigating cancer invasion. Additionally, such release of inflammatory cytokines and increases in systemic inflammation (i.e., CRP) in response to invading tumor cells, is known to induce sleep disturbance as well as a number of other behavioral symptoms, one of the most noticeable being profound fatigue [19].

The association between the activation of innate immunity and fatigue has been documented in other chronic diseases, such as chronic fatigue syndrome [20,21] but has not been fully explored in the context of early tumorigenesis, although extensive evidence had demonstrated that inflammation is associated with fatigue in cancer survivors [19,22,23]. Anemia, associated with internal bleeding, may also contribute to the experience of fatigue, and such anemia can lead to the development of occult restless legs syndrome and periodic leg movements of sleep (PLMS) [24]. In this case, unexplained fatigue and/or sleepiness are thought to result from the sleep fragmenting effects of PLMS. In either case (activation of innate immunity or anemia related PLMs or both), the experience of disabling fatigue may serve as a false cue to the individual that they require more sleep.

Although there are many different conceptualizations of fatigue that depend on the patient group affected, in general fatigue can be defined as a subjective sensation (perceived fatigue) and as an objective and quantifiable change in performance (fatigability) [25–27]. Fatigue also has a temporal component which can be used to distinguish "normal" transient acute fatigue and persistent fatigue [28]. Transient acute fatigue tends to be time limited and of mild to moderate severity. While transient fatigue makes daily functioning harder, it can be managed and worked through, and it is typically responsive to increased sleep and/or caffeine or stimulants [28]. In contrast, fatigue associated with cancer development is not time limited, is of extreme severity (daily functioning is impaired, cannot be managed with sleep, and/or caffeine or stimulants), is persistent throughout the day, and cannot be tied to health behaviors.

Despite having different pathophysiological origins, both transient and persistent fatigue is often confused with sleepiness in patients, clinicians, and researchers [29]. Without awareness of the disease processes underway, this lack of attributional clarity may prompt the individual to think, "I am tired (aka, fatigued). I must, therefore, need more sleep". Thus, a likely and understandable behavioral response to the experience of profound fatigue is for the individual to attempt to increase sleep opportunity (i.e., sleep expansion). These efforts may take the form of napping during the day, going to bed earlier at night, and staying in bed later in the morning. Such sleep extension may result in increased total sleep time, if it is within the individual's ability to achieve more sleep.

In the case of new onset cancer, the fatigue may not be related to sleep loss and thus no amount of increased sleep time (even if it is within the individual's ability to substantially increase their total sleep time) will diminish the experience of fatigue. This all but ensures that the patient with new onset cancer will continue to expand sleep opportunity (as a counter fatigue strategy) until there is a mismatch between sleep opportunity and sleep ability, thus increasing the likelihood that insomnia occurs (including decreased sleep efficiency, potentially diminished slow wave sleep, and dysregulation of the homeostatic mechanisms which control sleep) [30,31].

Finally, as the insomnia becomes more frequent and/or severe, it is likely that other standard perpetuating factors may also come into play and serve to transition insomnia that occurs with new onset cancer into Insomnia Disorder, including (but not to limited to) insomnia attention-related bias [32], increased sleep effort [33], and brain physiology changes that are posited to occur with conditioned activation [34]. This revised perspective of the sequence of events is represented schematically (Fig. 2).

The implication of this revised perspective is that fatigue and insomnia occur early on in the development of cancer and likely long prior to the diagnosis and treatment of the disease. Our hypothesis that unexplained fatigue and sleep disturbance may be a marker of ongoing cancer onset, which is temporally distinct from the one posited in prior epidemiologic studies, namely, that sleep disruption a risk factor of future cancer onset [35]. Although the are no clear-cut points available yet [36], one could postulate that sleep disturbances that occur 10–15+ years before cancer detection, are more likely to represent a risk factor than a marker of underlying disease development, whereas sleep disturbances that occur 2–5 years before tumor detection may hint more toward an underlying disease. Further, there is accumulating and compelling evidence that health behaviors such as smoking, exercise, and alcohol consumption can impact cancer onset [37], hence acting as confounders of the association between sleep/fatigue and cancer initiation. For example, fatigue and sleep continuity disturbance may limit the energy one has to be physically active which may increase cancer risk, hence acting as mediators of the hypothesized associations.

If it can be shown in prospective studies that the hypothesized sequence of events occurs as stipulated, this suggests that monitoring emergent and unexplained patient-reported fatigue, sleepiness, and insomnia may serve as early warning signs of tumorigenesis and new onset cancer, which in turn provide a critical opportunity for early detection and treatment.

Once fatigue and sleep disturbance are identified, what strategies might be used to interrogate the possibility of an underlying cancer? One non-specific strategy could include the evaluation of inflammation [38], with measurement of circulating levels of CRP, a widely available marker of systemic inflammation. If inflammation is elevated, possibly into the high risk category of > 3.0 pg/ml [39], then this would point to a biologically plausible pathway underlying or associated with sleep disturbance and/or fatigue. Following this non-specific strategy, a more specific approach could be used, namely, the use of "liquid biopsies" [40]. Such liquid biopsies provide an analysis of the presence of circulating tumor cells, circulating tumor DNA, or tumor-derived extracellular vesicles, which have been shed from tumors and their metastatic sites into the blood [41]. These techniques have been applied