

Sleep Disorders in Cancer

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Sleep disorders, especially insomnia, are very common in different kinds of cancers, but their prevalence and incidence are not well-known. Disturbed sleep in cancer is caused by different reasons and usually appears as a comorbid disorder to different somatic and psychiatric diagnoses, psychological disturbances and treatment methods. There can be many different predictors for sleep disturbances in these vulnerable groups, such as pre-existing sleep disorders, caused by the mental status in cancer or as side effect of the cancer treatment.

Keywords: sleep ; sleep disorders ; sleep disturbances ; insomnia ; sleep-related breathing disorder (SRBD)/obstructive sleep apnea syndrome (OSAS)

1. Introduction

Sleep disturbances and different sleep disorders (e.g., insomnia and sleep-related breathing disorder (SRBD)/obstructive sleep apnea syndrome (OSAS)) are common and considerable complaints of cancer patients. Narcolepsy, restless legs syndrome (RLS) and REM-sleep behavior disorder (REM-SBD) are rarely found. Up to 95% of cancer patients complain of sleep disturbances/disorders during diagnosis, treatment and after 10 years of survivorship. Sleep disturbances/disorders and excessive daytime sleepiness (EDS) have been reported to influence fatigue [1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27] and its perceptions. Savard et al. studied cancer survivors and showed that 52% of them reported sleeping difficulties, and 58% reported that cancer either caused or aggravated their sleeping problems [28][29][30][31][32][33][34][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49][50][51][52][53][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68][69][70][71][72][73][74][75][76][77][78][79][80][81][82][83][84][85][86][87][88], especially [58].

Disturbed sleep appears before, while and after cancer diseases. The personalized treatment of the most frequent sleep disorders, e.g., insomnia or sleep-related breathing disorder, could improve both their mental and physical health, specifically for diseases such as cancer.

2. Sleep Disorders in Cancer

2.1. Sleep Disturbances in the Case of Cancer-Related Fatigue (CrF)

In spite of severe cancer-related fatigue (CrF) [1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27] and its perceptions [43][54][58][63][64][67] in cancer patients, there is often also a high prevalence of sleep disturbances (30–50%) in which the proportion of poor sleep or bad sleep quality is significantly higher than in the general population [6][21][23][58][64] (Table 2). Due to frequent “naps” during the day caused by CrF, an additional increase in nocturnal problems can be observed [1].

For the research of sleep and quality of sleep, the easy-to-use actigraphy is commonly used [89][90]. Actigraphy data from various studies have shown that there is a strong correlation between the changes in subjectively experienced CrF and sleep quality [2][10][16]. Therefore, CrF-induced sleep disorders can be used as a well-quantifiable CrF-induced event to diagnose and control the course of CrF. **Table 1** shows the four sleep-specific phenotypes according to which patients with chronic fatigue syndrome can be classified by means of the more elaborate, but more informative, polysomnography [11].

Table 1. Sleep-specific phenotypes of fatigue (according to Reference [11]).

First Phenotype	• longer Sleep*Onset*Latency • longer REM latencies • lower percentage of stage 2 and REM
Second Phenotype	• more frequent arousals per hour
Third Phenotype	• longer Total Sleep Time (TST) • shorter REM latencies • higher percentage of REM and lower percentage of waking time
Fourth Phenotype	• shortest Total Sleep Time (TST) • highest percentage of waking time

2.2. Insomnia in Cancer

Insomnia is a very common and frequent comorbidity in cancer patients. The cancer-related insomnia rate is nearly three times higher than that in the general population. Different analyses have shown that 30–50% (up to 95%) of cancer patients have severe sleep difficulties, such as insomnia symptoms or insomnia syndromes (Tables 3–5). Cancer-related insomnia is characterized by a delayed sleep onset, sleep maintenance disorders, reduced total sleep time and/or early-morning awakenings and is associated with excessive daytime sleepiness, fatigue, impaired performance and daytime wellbeing. Furthermore, we established a connection between insomnia and pain, depression, anxiety and/or a reduced quality of life [27][43][53][54][58][63][64][65]. Various types of treatments for insomnia include pharmacological therapies (e.g., hypnotics, sedatives, antidepressants, neuroleptics, antihistamines, hormones (melatonin) and herbal extracts) [28][30][42][44][48][57] and nonpharmacological therapies (like Psychoeducational intervention, Cognitive Behavior Therapy (CBT), Professionally administered CBT (PCBT), Video-based CBT (VCBT), Behavioral Therapy (BT), Individualized Sleep Promotion Plan (ISPP), Mindfulness-Based Stress Reduction (MBSR), Valencia model of Waking hypnosis, Internet intervention/Sleep Healthy Using The internet (SHUTi), Progressive Muscle Relaxation (PMR), Autogenic Training (AT), (Electro)Acupuncture (EA), Tai Chi Chih (TCC), Cool Pad Pillow Topper (CPPT), Combined multimodal-aerobic Treatment (CT), Multimodal Treatment (MT) and Aerobic Treatment (AeT)) [29][31][32][33][34][35][36][37][38][39][40][41][44][46][47][49][50][51][52][55][56][57][59][61][62][66][67][68][69][70][71]. Most of the patients with comorbid cancer-related insomnia (that means around 25–50%) are treated pharmacologically [31]. Especially, cancer patients have many side effects and several physical problems from this kind of treatment, so there are numerous limitations that emerge from these pharmacological treatments. Such side effects generally include headaches, dizziness, fatigue, excessive daytime sleepiness and residual daytime sedation and could be potentiated in cancer patients [31]. There is a need and use of complementary and alternative medical methods in cancer patients with cancer-related insomnia. Recent research has shown that complementary and alternative treatments may provide a clinically relevant benefit in cancer-related insomnia [29][31][32][33][34][35][36][37][38][39][40][41][44][46][47][49][50][51][52][55][56][57][59][61][62][66][67][68][69][70][71].

2.3. Sleep-Related Breathing Disorder (SRBD)/Obstructive Sleep Apnea Syndrome (OSAS) in Cancer

Sleep-related breathing disorders (SRBD), especially obstructive sleep apnea syndrome, (OSAS) are common disorders that are characterised by repetitive interruptions of ventilation during sleep. They are caused by recurrent (upper) airway collapses and followed by sleep fragmentation, intermittent hypoxia and oxidative stress. Systemic and vascular inflammations with endothelial dysfunctions cause diverse multiorgan chronic morbidities and mortalities that affect the cerebrovascular, cardiovascular and metabolic systems in the progress to cancer. Sleep-related breathing disorders are an independent risk factor for cerebrovascular diseases, cardiovascular diseases, metabolic diseases and cognitive decline and are associated with high rates of morbidity and mortality [72][73][74][75][76][77][78][79][80][81][82].

Chronic and intermittent hypoxias seem to play a key role in the regulation of various stages of tumor formation and their progressions. In recent years, some important studies have shown that OSAS patients tend to have a higher prevalence and incidence of cancer and even a higher prevalence of cancer-related mortality [72][73][74][75][76][77][78][79][80][81][82].

2.4. Narcolepsy in Cancer

The cancer risk as a comorbidity profile of narcoleptic patients has been rarely analyzed ^{[83][84][85]} (Tables 3 and 7). There exist only two case studies, and one evaluated the Taiwan nationwide database. Tseng et al. researched the risk of cancer (incidence) among adult narcoleptics ^[85]. They found that adult narcoleptic patients have a higher risk for developing cancer, but the study was not able to describe the underlying mechanisms for this ^{[83][84][85]}. Further research is needed to understand the association between narcolepsy and the development of cancer.

2.5. Restless Legs Syndrome (RLS) in Cancer

Decreased sleep quality, sleep disturbances and/or sleep disruption are very common in cancer patients, especially when they receive chemotherapy ^{[1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26]} (Tables 3 and 7). Until now the processes and their pathophysiology have not been completely understood, but most likely, they are multifactorial ^[86]. Additionally, disturbed sleep and sleep disorders like insomnia and OSAS as disorders and/or diseases with pain, fatigue and mood disturbances often occur in clusters. These clusters can negatively impact the quality of life and the outcome of diseases ^{[1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26]}. Sleep disturbance, fatigue and mood disorders (like depression and anxiety) can be based on distinct biologic processes. These processes could be the trigger for inflammatory signaling as a contributing factor of restless legs syndrome (RLS) ^[86].

The prevalence and/or incidence of restless legs syndrome in cancer is insufficiently researched. A recent study of Saini et al. showed that RLS is frequent in patients with cancer during chemotherapy. They demonstrated that the prevalence is approximately double compared to the normal population (around 18%). In most cases, restless legs syndrome was correlated with depression, anxiety and a decreased quality of life ^[86].

2.6. REM Sleep Behavior Disorder in Cancer

Rapid Eye Movement Sleep Behavior Disorders (REM-SBD) and cancer are very seldom reported ^{[83][87][88]} (Tables 3 and 9). REM-SBD are forms of parasomnias. They are characterised by severe dream-related behavior and increased abnormal electromyographic activity during REM sleep. Sometimes, they are associated with nightmares and paravor nocturnus ^{[83][87][88]}. The excessive electromyographic activity during REM sleep reflects the dysfunction of the brainstem structures in REM-SBD patients ^[87]; acutely, they can be caused by different medications, such as antidepressants or anticholinergic drugs ^[88].

3. Summary

Bad sleep quality, the degree of sleep disruption and sleep disorders have a very important impact on cancer and can be used as predictors. Sleep disruptions and disruptions in the circadian rhythms affecting the sleep quality and the circadian rhythm themselves can result in a variety of psychological and physiological mechanisms, which can foster the development and persistence of cancer-related fatigue. The role of naps in fatigued cancer patients is unclear; it could be that naps are not helpful to decrease cancer-related fatigue—they could have the opposite effect ^[17]. In noncancer patients, it is known that daytime naps reduce the nightly sleep quality and total sleep time.

The causes of decreased sleep quality; chronic sleep difficulties and the different sleep disorders (insomnia, OSAS, narcolepsy, RLS and REM-SBD) are multifaceted, and in recent studies, the attention that was paid to this problem was too insufficient. Until now, the pathogenesis of cancer-related sleep disorders and the development such as the progression of cancer based on sleep disorders has been unclear. More research about these topics is needed to understand the nature, duration and severity of the different sleep disorders in cancer or their relationship with it.

The prevention of sleep disorders generally and in cancer patients especially and an early personalized treatment can contribute to reducing cancer-related fatigue and severe mental disorders (like depression and anxiety) and can possibly prevent the development, preservation and/or aggravation of cancer.

4. Recommendations

Sleep disturbances; disruptions of the circadian rhythms and different sleep disorders (e.g., insomnia and sleep-related breathing disorder (SRBD)/obstructive sleep apnea syndrome (OSAS)) could be predictors of cancer development and treatment success (look above). Due to that, cancer patients should be screened by sleep anamnesis and/or by sleep diaries, including the structured exploration of predisposing and precipitating cancer factors, and should be diagnosed—in the case of any kind of sleep-wake difficulties—by polysomnography.

Screening should explore unrefreshing sleep: prolonged sleep latency, frequent awakening and reduced sleep efficiency; daytime sleepiness and fatigue; loud snoring; inadequate nightly behavior and/or nightmares.

Both screening and/or the diagnosis of sleep disturbances; disruptions of the circadian rhythm and/or sleep disorders, as well as adequate sleep health education (including sleep hygiene, rules for good sleep quality and information about the consequences of unhealthy and/or untreated sleep disorders for mental and physical health) should be implemented to minimize the health risks caused by sleep disorders.

Tailored programs are needed and could be helpful to reduce cancer-related fatigue and/or severe mental disorders (like depression and anxiety) to support the outcome of the treatment of patients with cancer and comorbid sleep disorders.

Currently, sleep–wake solutions in cancer are mostly aimed only by responding to emergency reasons and based on isolated and/or fragmented interventions, e.g., the treatment of insomnia: cognitive behavioral therapy for insomnia, nightmares: rehearsal therapy and SRBD: CPAP adherence.

Personalized medical services for cancer patients should include integrated coaching or the early treatment of the most common sleep disorders and web-based telehealth programs ^[91] to reduce the preservation and/or aggravation of cancer and/or serious implications, including increased cerebrovascular, cardiovascular and/or metabolic diseases; excessive daytime sleepiness and/or cancer-related fatigue.

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