Oncology Research and Treatment

Research Article

Oncol Res Treat 2021;44:469–475
DOI: 10.1159/000518108

Received: February 6, 2021
Accepted: June 2, 2021
Published online: July 20, 2021

Why Do Our Cancer Patients Sleep So Badly? Sleep Disorders in Cancer Patients: A Frequent Symptom with Multiple Causes

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Keywords
Sleep disorder · Insomnia · Pain · Depression · Anxiety · Return to work

Abstract
Introduction: On the one hand, sleep disorders in cancer patients are reported in 30–50% of cancer patients. On the other hand, specific causes for these sleep disorders are little known. This study was done to evaluate factors which may affect sleep of cancer patients. To our knowledge, this is the first study which includes return to work as one factor of sleep disturbance. ***Methods:*** 107 patients with various types of cancer treated in 2 hospitals were interviewed with a battery of questionnaires after having given informed consent. The questionnaires intended to detect abnormalities of sleep and related pain, breathing disorders, restless legs syndrome, depression, rumination, medication, and psychosocial distress. The study was approved by the ethics committee of the University of Marburg. ***Results:*** The analysis of the 6 sleep-related questionnaires indicated a sleep disorder of any kind in 68% of all patients. Insomnia symptoms were present in 48 patients (44.9%). Pain, depression, anxiety, and worries about the workplace were significantly related to sleep disorders. ***Conclusion:*** Sleep disorders are common in cancer patients. The causes are manifold and should be considered by caregivers during diagnosis, therapy, and aftercare of cancer patients. Tumour patients should actively be asked about sleep disorders. If these are present, they should be addressed, and as they have a large impact on quality of life, treatment options should be offered in cooperation with sleep specialists.

Introduction

Regenerative night sleep is an important prerequisite for our personal well-being. Sleep disturbances can be caused by various factors. Somatic symptoms like pain or breathing disorders, hormonal dysregulation, or external influences like medical treatment or alcohol may disturb physiological sleep. Psychiatric disorders, especially depressive symptoms, and psychosocial factors can negatively influence our night sleep as well. This can lead to daytime sleepiness and exhaustion and affection of fitness and general well-being [1].

Cancer patients are possibly affected by numerous of the aforementioned factors. In the literature, sleep disorders in cancer patients are reported in 30–50% of cancer patients [2–4]. Surprisingly, the perception of sleep disorders in this group of patients is relatively low [1]. This

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Table 1. Questionnaires and rating scales used in the study

1. BDI
2. Berlin Questionnaire (sleep-related dyspnoea risk detection)
3. EQ5D (health questionnaire)
4. ESS
5. ISI
6. ISQ
7. PSQI
8. RLS screening (RLS Questionnaire)
9. Pain detection questionnaire
10. Social distress questionnaire
11. Numeric rating scales for sleep, anxiety, rumination, and pain

RLS, restless legs syndrome; PSQI, Pittsburgh Sleep Quality Index; ISQ, Insomnia Symptom Questionnaire; ISI, Insomnia Severity Index; ESS, Epworth Sleepiness Scale; BDI, Beck's Depression Inventory.

Table 2. Patient characteristics

Age, years	58.6 (±11.0)
Seize, cm	172.1 (±9.4)
Weight, kg	78.3 (±15.9)
Body mass index	26.5 (±5.2)

may be due to the fact that usually, patients do not report spontaneously about their bad quality of sleep because they seem to consider bad sleep normal, given the eminent threat to health and life that comes with a cancer diagnosis. Furthermore when asked for specifically, though, sleep disorders that severely affect the general quality of life are reported frequently. The evaluation of symptoms directly associated with the tumour disease like pain or shortness of breath is a part of daily oncological practice. This is usually not the case for specific questions about sleep disorders. One reason why doctors do not ask about sleep disorders may also be because the causes of sleep disorders are little known.

Therefore, this study was done to evaluate different factors which may affect sleep of cancer patients. To our knowledge, this is the first study which considers such a variety of influencing factors, including psychosocial aspects like return to work, which is a common problem in cancer patients [5], as one factor of sleep disturbance.

Methods

107 patients with various types of cancer treated in the University Hospital and in the rehabilitation centre "Sonnenblick" in Marburg were interviewed with a battery of questionnaires (Table 1) after having given informed consent. The questionnaires intended to detect abnormalities of sleep and related pain, breathing disorders, restless legs syndrome (RLS), depression, rumination, medication, and psychosocial distress. Patients aged at least 18 years with histologically proven malignant tumour disease were enrolled. The time from diagnosis had to be >4 weeks, and the patient should not be in the terminal stage of the disease in order to avoid acute distress effects.

Results

Over a period of 2 months, a total of 107 patients with various types of malignant neoplasms were interviewed in the outpatient and inpatient departments of both clinics. Among these were 58 (54%) females and 49 (46%) males with a median age of 60 years. Patient characteristics are listed in Table 2.

Ninety patients (84%) had active disease; 43 patients (40%) were treated with curative intention; 79% of the patients suffered from solid and 21% from haematological neoplasms. Due to the focus of the interdisciplinary outpatient chemotherapy unit and to the specialization of the first author, a relatively high proportion of breast cancer and that of neuro-oncological patients were included (Table 3).

The analysis of the 6 sleep-related questionnaires indicated a sleep disorder of any kind in 73 patients (68%). Bad quality of sleep was indicated in 51 patients (47.7%) by pathological Pittsburgh Sleep Quality Index (PSQI) scores. Signs of insomnia were found in 48 patients (44.9%) with the Insomnia Severity Index (ISI) questionnaire and 23 patients (21.5%) with the Insomnia Symptom Questionnaire (ISQ). Sleep-related apnoea was probable in 19 patients (17.8%) and increased daytime sleepiness in 16 (14.9%). Signs of RLS were found in 12 patients (11.2%) (Fig. 1).

Insomnia was further divided into 3 groups of severity (Fig. 2). While more than half of the patients had low scores (0–7 points, ISI 0, 55%), 29% of patients suffered from latent insomnia (8–14 points, ISI 1), 14% from moderate (15–21 points, ISI 2), and 2% from severe insomnia (>22 points, ISI 3).

Aspects of Tumour Disease

Of the 107 patients, 40% were treated with curative and 60% with palliative intention. At the time of the interview, 76% received active tumour therapy, 90% had received at least one line of treatment.

Regarding the treatment groups, 73% of patients with active tumour therapy suffered from disturbed sleep, but only 54% of patients without specific treatment (ns). Among the patients with any kind of sleep disorder, 81% received tumour treatment, as opposed to 19% without specific therapy (p = 0.072, ns). Patients with curative treatment intention accounted for only one-third (33%) of the 73 patients with disturbed sleep, as opposed to two-thirds (67%) with palliative intention (p = 0.09).

Table 3. Types of neoplasms

Type of neoplasm	Histology	*N* (%)
Solid tumours		84 (79 of total group)
	Breast cancer	18 (17.8)
	Primary brain tumour	18 (16.8)
	Colorectal carcinoma	10 (9.3)
	Pancreatic carcinoma	9 (8.4)
	Gynaecological cancer and other	8 (7.5)
	Lung cancer	6 (5.6)
	Oesophageal carcinoma	5 (4.7)
	Urothelial carcinoma	4 (3.7)
	Neuroendocrine tumour	2 (1.9)
	Prostate cancer	2 (1.9)
	Gastrointestinal cancer and other	2 (1.8)
	Head and neck cancer	1 (0.9)
	Ewing sarcoma	1 (0.9)
Haematological neoplasms	Total	23 (21 of total group)
	Non-Hodgkin lymphoma	9 (8.4)
	Hodgkin lymphoma	4 (3.7)
	Multiple myeloma	5 (4.7)
	Leukaemia	2 (1.9)
	Aplastic anaemia	1 (0.9)

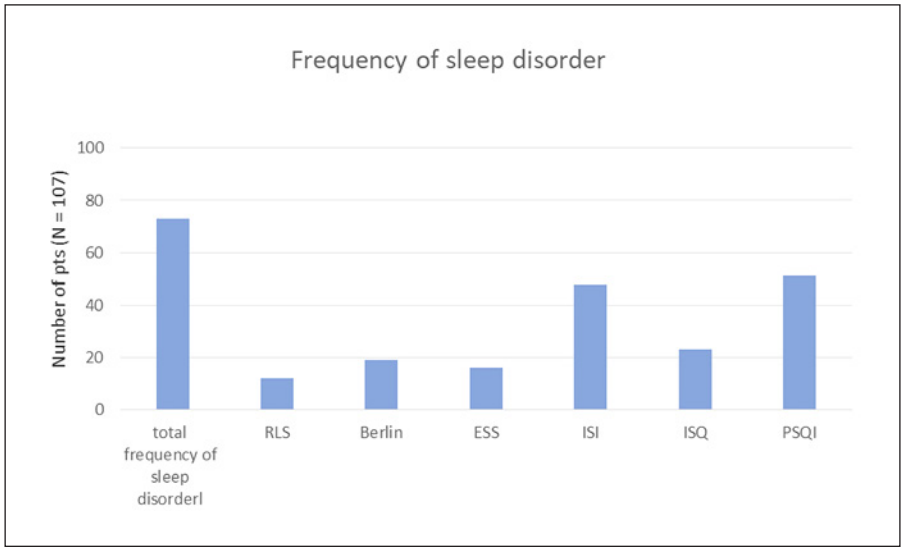

Fig. 1. Frequency of sleep disorder. Berlin, Berlin Questionnaire (sleep-related dyspnoea risk detection); ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index; ISQ, Insomnia Symptom Questionnaire; PSQI, Pittsburgh Sleep Quality Index; RLS, Restless Legs Syndrome Questionnaire.

Medication

Since insomnia is a common side effect of medication, we analysed this aspect separately. A total of 10 substance groups were actually taken by the patients. Table 4 gives an overview of drug use. No significant differences regarding sleep disturbance or insomnia were observed.

Pain

The burden of pain was recorded by the pain questionnaire and a numerical rating scale (0 = no pain, 10 = extreme pain). The mean value of the numerical rating scale for pain was 2.6 (±2.7) in patients with signs of sleep disturbance and was thus significantly increased ($p = 0.004$) as compared to the group without sleep disturbances, which had a value of 1.3 (±2.09).

Depressive Symptoms

In order to assess the influence of depression on night sleep, those 54 patients with <10 points at the Beck Depression Inventory (BDI, minor or no depression) were compared with the 53 patients with >10 points (severe depression). While only 50% of patients without depressive symptoms had signs of sleep disorder, indicated by pathological scores in 1 of the 6 questionnaires, 87% of the depressive patients had signs of disturbed sleep ($p < 0.0001$). With minor depressive symptoms, 84% of pa-

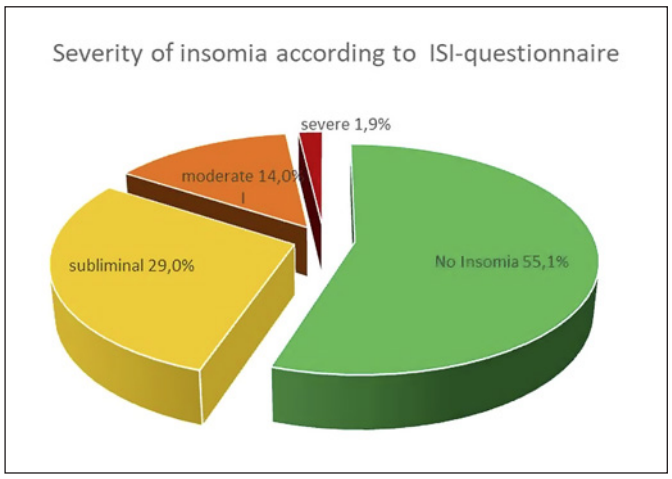

Fig. 2. Severity of Insomnia according to ISI questionnaire. ISI, Insomnia Severity Index.

Table 4. Overview of the drug use of the whole collective

Drug	Patients taking the drug (proportion of the total group), *n* (%)
Beta-blocker	26 (24.3)
Statins	10 (9.3)
Thyroid hormone replacement	13 (12.1)
Glucocorticoids	12 (11.2)
Pain or migraine drugs	28 (26.2)
Antibiotics	12 (11.2)
NSAIDs	10 (9.3)
Asthma medications	2 (1.9)
Drugs for other lung diseases	5 (4.7)
Psychopharmaceuticals	15 (14.0)

NSAID, non-steroidal anti-inflammatory drug.

tients had sleep disturbances, as compared with 93% with major depression.

Of the 53 patients with a BDI score >10, significantly more patients (26%) suffered from daytime sleepiness than patients with BDI < 10 ($p < 0.001$). Approximately two-thirds of patients (66%) with depressive symptoms had a clinical insomnia according to the ISI-questionnaire ($p < 0.0001$). The ISQ questionnaire indicated in 38% of patients a clinically relevant insomnia ($p < 0.0001$). Sixty-four percent of patients with depressive symptoms suffered from bad sleep quality according to the PSQI questionnaire ($p < 0.002$).

Anxiety

Anxiety was measured with 2 instruments: an 11-step numeric rating scale and the EQ5D questionnaire where patients indicate on a 3-step scale whether they feel less, moderate, or severely anxious/depressed. The 11-scale rating scale showed an average level of 3.8 (±2.8) in the whole group. Patients with sleep disturbances indicated a higher average level of anxiety (4.4 ± 2.7) than patients with normal sleep (2.5 ± 2.6; $p < 0.001$). With the EQ5D, 48% of patients indicated moderate and 2% extreme anxiety and depressiveness. Of those, 85% suffered from disturbed sleep, as opposed to 51% of patients with few or no anxiety ($p < 0.0001$).

Social Distress

With a questionnaire established in a previous study [5] and used by the German pension fund as a standard instrument since >10 years, patients were asked for their working history; professional skills; change of work life caused by the tumour disease; shift work; conflicts and satisfaction at work; disease-related times off work within the last 12 months; rehabilitation; worries about financial situation, workplace, and family; and sports activity since tumour diagnosis.

A change of job was indicated by 32 patients (30%), 78% of which suffered from any kind of sleep disorder, as opposed to 66% in patients who could stay in their job ($p = 0.153$). Insomnia, as measured by the ISQ, was found in 50% of patients with a change of their job situation, but only in 34% without a change of profession ($p = 0.035$).

Worries about Family, Workplace, and Financial Situation

Worries about their family were reported by one-third of patients (33%). Of those, 80% of patients suffered from sleep disorders, but only 63% of patients without those worries ($p = 0.069$). When worried about the financial situation, 85% of patients suffered from disturbed sleep, as opposed to 63% of patients without financial problems ($p = 0.04$). Only 8% of patients were anxious about their workplace. All of them however had sleep disorders, significantly more than patients without worries about their job ($p = 0.033$). Results and data are available in the study centre regarding this investigation.

Discussion

The frequent occurrence of sleep disorders in cancer patients has been described in a number of previous studies. Possible causes are numerous, starting from organic factors like pain, medication, or breathing disorders like cough, until psychosocial distress such as anxiety, depression, and worries about family or financial situation. To our knowledge, this is the first study that investigates not only the frequency of sleep disorders in cancer patients but also all possible related factors that can be analysed

with questionnaires. The results of our analysis indicate a high incidence of sleep disorders not only during active tumour therapy, but also in phases of remission. Associated factors span from somatic symptoms to depression and psychosocial distress. Since many of these related factors are amenable by symptomatic treatment, it is worth asking cancer patients for sleep disorders and searching for underlying causes in order to improve the patient's quality of life.

In the patient population analysed here, we found a frequency of sleep disorders in 68%. Sharma et al. [6] described in >2,000 outpatients sleep problems in 30.2% (865/2,862, 95% CI = 28.5–31.9) of the patients. They were common in both patients with active cancer (34.5%) and in cancer survivors (28.0%). There was only a modest association with the cancer site and treatment status, but there was a strong association with pain (odds ratio = 2.7, 95% CI = 2.2–3.4) and emotional distress (odds ratio = 4.5, 95% CI = 3.7–5.6). In our study, we find a higher incidence, which is probably caused by the structure of the patient population. In our study, we did see inpatients and no representative distribution of tumour diagnoses.

Another explanation could lie in the different survey instruments. Sharma et al. [6] used the sleep item from the Patient Health Questionnaire-9. Our analysis is based on 6 sleep-related questionnaires. Pathological values of any of the questionnaires were considered indicating a sleep disturbance. Therefore, a higher sensitivity can be expected in our study than the analysis of Sharma et al. [6].

Another investigation done by Akman et al. [7] found in 40.4% out of 314 cancer patients sleep disturbance measured by the PSQI. Even in this study, there was no statistically significant relationship between PSQI scores and sexuality, marital status, cancer stage, and chemotherapy type ($p > 0.05$), while the patients with bone and visceral metastasis had much lower PSQI scores ($p = 0.006$). Patients with Eastern Cooperative Oncology Group performance scores of 3 or more had also significantly lower PSQI scores ($p = 0.02$).

Except the higher incidence of sleep disturbance, our data are supported by these findings. The higher incidence may be explained by the structure of our patient population. Therefore, the population and the results in this study may not be representative for all tumour patients.

Insomniac complaints are generally considered the most significant sleep disorder in the context of cancer, occurring in 30–50% of patients [1–3]. In this project, the frequency was 44.9%, which also agrees well with the published data.

The results clearly show that sleep disorders are common in patients with cancer. Since the patients themselves usually do not spontaneously report disturbed sleep and the diagnosis and treatment focuses on the cancer disease itself [8], sleep disorders are often not recognized by the treating physician. A study by Engstrom et al. [9] showed that in a group of cancer patients, 44% suffered from a sleep disorder, but of these, again only a third had reported it to the medical staff. Other authors describe that 80% of the sleep disturbed patients think that the symptoms are caused by the cancer itself, or about 60% assume that the doctors cannot help them [10, 11]. The S3 guideline "Non- Restorative Sleep/Sleep Disorders" of the German Society for Sleep Research and Sleep Medicine (DGSM) reports that a medical history of sleep disorders in patients with organic diseases is currently not yet a standard, and it must be assumed that the diagnostic and therapeutic potential has not been used to its full extend [12].

In our experience, doctors are more likely to address problems if they know the causes that could be treated. That is the reason why we tried to identify causes for the sleep disorders in our study. Apart from depression and anxiety disorders, pain is one of the most common comorbidities, which directly affects sleep duration, sleep quality, and daytime tiredness or is associated with problems falling asleep and sleeping through the night [13–15].

These results were confirmed in our study. In the group of patients with sleep disorders, a significantly increased pain level was observed. At the same time, only 35.5% of the patients took analgetics. Thus, undertreatment of pain might be one important cause of sleep disorders because management of the pain is the primary method to improve sleep, and medications directed towards sleep should be reserved until maximal pain control is established. Physicians should actively ask for pain information from tumour patients with sleep disorders and, if necessary, aim for optimal pain therapy. However, as sleeplessness most likely increases pain intensity and frequency, insomnia treatment is an important goal in optimal pain relief.

In this study collective, 45.8% of the 107 patients study reported pain at the time of the survey, which correlates well with the reports in the literature. The comparison between the mean values of the numerical rating scale (1.3 vs. 2.6) for pain without and with a sleep disorder shows that patients with pain are not only more likely to have sleep disorders but also classify them as more severe.

This result is statistically significant and clinically relevant. For this reason, pain patients should always have a sleep history.

Mood swings and depressive moods are a normal reaction to cancer [16]. The depressive symptoms of cancer patients are most likely to manifest themselves in sleep disorders [17], and sleep disorders can aggravate depression.

In this study, almost half of the patients (49.5%) had mild or moderate depressive mood. This is slightly above the average of previous studies, which indicate frequencies of 15–40% [17, 18].

As expected patients suffering from depressive symptoms showed significantly more insomnia and sleep disturbance. For this reason, we recommend that physicians actively ask their cancer patients who complain about sleep disorders about depression and, vice versa, patients who suffer from a known depression about sleep disorders.

The occurrence of anxiety disorders in cancer patients has not yet been well investigated. Frequencies of 15–40% are reported [18]. Anxiety also affects sleep architecture and has been shown to be associated with reduced sleep duration, daytime tiredness, and insomnia [19, 20].

Among our study participants with a moderate or extreme feeling of anxiety, only 8 of 53 respondents (15.1%) found no evidence of a sleep disorder; in the remaining patients, at least one of the 6 questionnaires (RLS, Berlin questionnaire, ESS, ISI, ISQ, and PSQI) showed pathological results. Patients with a sleep disorder gave an average value on the numerical rating scale for anxiety that was twice as high as those without evidence of a disturbed sleep.

These results are statistically highly significant. To our knowledge, the present study is the first to describe this phenomenon in cancer patients. We also deduce from this observation that physicians, especially if they are looking for anxious patients, should actively ask about sleep disorders, since these patients probably do not discuss this topic during consultation hours.

In this study, approximately one-third of all patients experienced a change in their employment status as a result of the cancer diagnosis, in most cases even losing their job. There was a statistically significant difference in frequency between the change in the work situation and insomnia according to the ISQ questionnaire. All 9 patients who had job worries also reported sleep disturbances. Eight patients reported poor sleep quality. While current and past research focuses mainly on sleep in relation to the job situation, comparable data on job loss or job change cannot be found in the literature.

Financial distress is a well-known side effect in cancer patients. In our study, a total of 24.3% of the respondents stated that they were financially affected by the tumour disease. Of these 26 patients, 22 (84.6%) showed signs of sleep disturbance, 69.2% had poor sleep quality, and 65.4% had signs of insomnia. All of these results were not statistically significant but indicate a strong negative influence of financial worries on night sleep. Slopen and Williams were able to demonstrate a statistically significant influence of financial distress on sleep duration [20]. The study by Delgado-Guay et al. [21] also showed an association between disturbed sleep and financial worries and further for anxiety, depression, and poor quality of life. Furthermore, this study showed that 30% of cancer patients considered financial problems to be more burdensome than physical, family, or emotional stress [21].

Conclusion

The present study shows that sleep disorders are common in cancer patients. The causes are manifold but should be considered by professional helpers during and after therapy in cancer patients.

These are especially pain, depression, anxiety, and also worry about the workplace. The authors recommend that physicians who treat tumour patients actively ask them about sleep disorders and, if these are present, to record and care about the aforementioned causes.

Statement of Ethics

The study was approved by the Ethics Committee of the University of Marburg (AZ 08/15). All participants of the study have given their written informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There was no source of funding.

Author Contributions

Herwig Strik: idea, contributed to the study, and wrote the manuscript. Michael Teepker: did the neurological analyses, recruited patients, and wrote and edited the manuscript. Thomas Schulte: recruited patients and wrote and edited the manuscript. Jorge Riera-Knorrenschild: responsible for questions in oncology, recruited patients, and wrote and edited the manuscript. Ulrich Koehler: did the sleep analyses and wrote and edited the manuscript. Werner Cassel: idea, did the sleep analyses, and wrote and edited the manuscript. Ulf Seifart: idea, did the social analyses, recruited patients, and wrote and edited the manuscript as the main author.

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