Sleep Medicine 58 (2019) 107–113

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

The course of cancer-related insomnia: don't expect it to disappear after cancer treatment

Katharina Schieber [a, *, 1], Alexander Niecke [b, 1], Franziska Geiser [c, 1], Yesim Erim [a], Corinna Bergelt [d], Antje Büttner-Teleaga [e], Imad Maatouk [f], Barbara Stein [g], Martin Teufel [h], Martin Wickert [i], Alexander Wuensch [j], Joachim Weis [k]

[a] University Hospital of Erlangen, Department of Psychosomatic Medicine and Psychotherapy, Friedrich-Alexander-University Erlangen-Nürnberg, Schwabachanlage 6, D-91054, Erlangen, Germany
[b] University Hospital Cologne, Department of Psychosomatics and Psychotherapy & Centre Psychooncology (CePO), Kerpener Str. 62, D-50937, Cologne, Germany
[c] University of Bonn, Clinic for Psychosomatic Medicine and Psychotherapy, Sigmund-Freud-Str.25, D-53127, Bonn, Germany
[d] Department of Medical Psychology, University Medical Center Hamburg-Eppendorf, Center for Psychosocial Medicine, Martinistrasse 52, D-20246, Hamburg, Germany
[e] Institute of Cognitive Science, Woosuk University, 565-701, Samrye-up, Wanju-gun, Jeonbuk, Republic of Korea
[f] Medical University Hospital Heidelberg, Department of General Internal Medicine and Psychosomatics, Im Neuenheimer Feld 410, D-69120, Heidelberg, Germany
[g] Department of Psychosomatic Medicine and Psychotherapy, Paracelsus Medical University, Nuremberg General Hospital, Prof.-Ernst-Nathan-Straße 1, D-90419, Nuremberg, Germany
[h] University of Duisburg-Essen, Department of Psychosomatic Medicine and Psychotherapy, Comprehensive Cancer Center Essen (WTZ) and LVR Hospital, Virchowstr. 174, D-45147, Essen, Germany
[i] Medical University Hospital Tuebingen, Universitätsklinikum Tübingen, Comprehensive Cancer Center Tübingen-Stuttgart, Herrenberger Str. 23, D-72070, Tübingen, Germany
[j] Clinic for Psychosomatic Medicine and Psychotherapy, Medical Center Freiburg, Faculty of Medicine, University Freiburg in Cooperation with Outpatient Support for Cancer Patients, Comprehensive Cancer Center Freiburg, Hauptstr. 5a, D-79104, Freiburg, Germany
[k] Comprehensive Cancer Center, Department Self-help Research, Medical Center Freiburg, Faculty of Medicine, University of Freiburg, Hugstetter Str. 49, D-79106, Freiburg, Germany

ARTICLE INFO

Article history:
Received 7 November 2018
Received in revised form
8 February 2019
Accepted 10 February 2019
Available online 11 March 2019

Keywords:
Insomnia
Cancer
Sleep disorder
Prevalence
Psychological distress
Gender-specific predictors

ABSTRACT

Objective: The study aimed to examine the 12-month course of cancer-related insomnia (CRI) and to identify possible predictors for the prevalence and persistence of CRI.
Methods: This longitudinal multicenter study included N = 405 patients with cancer (56% females, mean age: 58.6 years). CRI was measured by the Insomnia Severity Index (ISI). Socio-demographic and clinical data, as well as psychological parameters (Distress Thermometer, PHQ-9, GAD-7, and EORTC-Fatigue), were assessed at baseline (T1) and 12 months later (T2).
Results: In our sample, a high prevalence of relevant insomnia symptoms (49.4%, ISI > 7) was found, while a clinical insomnia diagnosis was verified in 12.8% (ISI > 14). When insomnia was present at T1, this problem was persistent after one year in 64%. At T2, however, significantly more women suffered from insomnia symptoms (53.3% women vs. 39.3% men; $p = 0.003$). Insomnia was associated with many clinical and psychological parameters, especially with fatigue ($r = 0.5$). Multiple regression analysis revealed that, in women, only insomnia at T1 was a significant predictor for insomnia at T2 ($R^2 = 0.40$; $F(5) = 12.5$; $p < 0.001$), whereas in men insomnia, depressive symptoms and the use of psychotropic drugs at T1 predicted the extent of insomnia at T2 ($R^2 = 0.28$; $F(7) = 9.5$; $p < 0.001$). In all participants, levels of distress, depression, and anxiety decreased from T1 to T2 (p's < 0.016).
Conclusion: Insomnia is a common disorder in cancer patients. Although medical and psychological parameters improved during the 12-month course of cancer treatment, our results show that insomnia is highly persistent, especially in women. This indicates that adequate support for those affected is needed. Clinical Trial Registration Number: DRKS00004860.

* Corresponding author. University Hospital Erlangen, Department of Psychosomatic Medicine and Psychotherapy, Friedrich-Alexander University Erlangen-Nürnberg, Schwabachanlage 6, D-91054, Erlangen, Germany. Fax: +49 9131 8535952.
E-mail address: katharina.schieber@gmail.com (K. Schieber).
[1] Authors contributed equally to this manuscript.

https://doi.org/10.1016/j.sleep.2019.02.018
1389-9457/

1. Background

Humans spend on average about one-third of their lives asleep [1]. Sleep is essential for survival and plays a key role in biological and mental regeneration processes. Lack of sleep is associated with an increased risk for many disorders of mental and physical health, increased mortality, as well as substantial disease costs [2–7].

Insomnia is listed in the International Classification of Sleep Disorders – Third Edition (ICSD-3) as one of six categories of sleeping disorders. A distinction between acute and chronic insomnia is described; the earlier etiological distinction was between primary and secondary forms of insomnia [8]. Insomnia disorders are defined as sleep onset and/or sleep maintenance disorders and/or early-morning awakening, which are associated with impaired performance and daytime wellbeing. The modern operationalized classification systems, ICD-10 (1992) and DSM-5 (2015), also require that the symptoms persist for a minimum of one month before a diagnosis of insomnia is established.

Insomnia is one of the most common disorders worldwide, affecting at least 6–10% of the adults in industrialized countries in its chronic form [1,9]. Results of a longitudinal study in a representative population-based sample showed that women persistently scored higher in insomnia than men over the course of five years [10]. In general, women seem to report more insomnia than men in healthy populations as well as in cancer patients. In cancer patients, studies show that the reported prevalence figures vary between 17% and 70% for sleep problems [11] and between 19% and 63% for cancer-related insomnia disorders [12–14]. On average, 40% of cancer patients are affected by discrete insomnia symptoms, and almost 20% meet the diagnostic criteria for a clinically relevant insomnia syndrome. The prevalence for cancer-related insomnia is thus substantially greater than in the general population [15,16,11,17,12,18]. At the level of individual tumor entities, insomnia disorders appear to occur most frequently in lung and breast cancers [12]. Although insomnia in tumor patients is frequent, there is still a dearth of studies on predisposing and perpetuating factors in the course of cancer-related insomnia.

Insomnia disorders are comorbid with a physical ailment and rarely occur in isolation. The hyperarousal model of insomnia postulates that increased levels in cognitive, emotional and physiological domains represent both predisposing and perpetuating factors in the pathogenesis of insomnia [19]. Insomnia tends rather to be associated in a cluster of symptoms with fatigue and pain, as well as mental disorders such as anxiety and depression, and to be in bidirectional correlation with these symptoms [17,12,18,20–26]. In a large sample of cancer patients, it was found that anxiety predicted insomnia after controlling for fatigue, depression, and pain [27]. Furthermore, depression and anxiety were identified as risk factors for insomnia in prostate cancer survivors [28], whereas female gender (as well as anxiety, together with dyspnea and pain) was a risk factor for insomnia in a sample of patients with lung cancer [29]. Treatment of depression has been shown to improve insomnia in breast cancer survivors [30]. However, more research is needed to understand the associations between cancer-related insomnia and socio-demographic, clinical and psychological parameters of cancer patients.

Therefore, we conducted a prospective, observational study in national Comprehensive Cancer Centers (CCC) in Germany examining the nature and extent of cancer-related insomnia. The present study especially aimed at:

- reporting prevalence rates of cancer-related insomnia throughout one year
- analyzing associations of cancer-related insomnia with socio-demographic, clinical and psychological parameters
- identifying gender-specific predictors of cancer-related insomnia.

2. Methods

2.1. Design and subjects

This analysis is part of a Germany-wide longitudinal survey among patients in national CCCs evaluating self-reported use of psychological support [31]. The study was funded by German Cancer Aid, and it was registered in the German Clinical Trials Registry (registration no. DRKS00004860). Data collection was carried out in 2013/2014 in a survey of patients aged ≥18 years with cancer in 13 German CCCs. After consenting to participate in the study, the patients were asked to complete questionnaires at baseline (T1) and 12 months later (T2). All participants gave their informed consent in writing. The survey was approved by the ethics committee of the Medical Centre Freiburg (No. 139/13) in accordance with the Declaration of Helsinki. Furthermore, the approval was confirmed by the respective ethics committees of all CCCs. Details on the study design, recruitment procedure, participants, and the primary outcome were published by Weis and colleagues [31].

Of the many validated assessment tools used to evaluate insomnia, only two questionnaires have been validated specifically in cancer patients: the Pittsburgh Sleep Quality Index (PSQI) and the Insomnia Severity Index (ISI). The ISI is reliable, sensitive to changes over time and able to quantify the severity of insomnia [32,33,16] and was therefore chosen for the study. According to the aim of this secondary analysis, we included only patients who completed the ISI twice. At T1, a total of n = 796 patients filled in the questionnaire, whereas at T2 the questionnaire was completed by n = 469 participants. For data analysis, we selected patients with no more than one missing item in the ISI at T1 and T2. This resulted in a final sample of N = 405 patients.

2.2. Measurements

All participants completed a form to assess socio-demographic parameters (eg, gender, age, relationship status, educational level) and clinical data (eg, use of psychotropic drugs, psychotherapy in the past). Medical information of the disease (eg, tumor and status) was taken from medical records.

Insomnia Severity Index (ISI): The ISI measures the severity of insomnia, evaluating sleep onset, sleep maintenance, early morning awakening, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by disturbed sleep [34]. It consists of seven items rated on a five-point Likert scale. The total score ranges from 0 to 28, higher values indicating a greater degree of severity of insomnia. The standard cut-offs are >7 for sub-threshold insomnia and >14 for clinical insomnia. The reliability and validity of the questionnaire have been confirmed, and it is sensitive to insomnia in cancer patients [16].

Distress Thermometer: The Distress Thermometer is a short screening tool designed to measure cancer patients' levels of distress [35]. It is a self-rating scale of 0–10, where 0 = "no distress" and 10 = "extreme distress".

Patient Health Questionnaire (PHQ-9): The PHQ-9 is a self-rating measurement assessing depressive symptoms present during the

last two weeks [36]. Nine items can be rated on a four-point Likert scale resulting in a total score ranging from 0 to 27. Higher values indicate a greater degree of severity of depression.

Generalized Anxiety Disorder Scale (GAD-7): The GAD-7 assesses symptoms of generalized anxiety disorder over the past two weeks [37]. It is a seven-item self-report instrument that uses a four-point Likert scale to rate each item. The total score ranges from 0 to 21 with higher values indicating a greater degree of anxiety.

EORTC QLQ-FA13: The EORTC QLQ-FA13 is a multidimensional questionnaire assessing cancer-related fatigue [38]. Its 13 items are rated on a four-point Likert scale. Higher values indicate higher levels of fatigue.

2.3. Data analysis

For data analysis, we used the software IBM SPSS statistics 21. We accepted one missing value in the questionnaires, which was substituted by the mean of the completed items. If the number of missing values was $n \geq 2$, the case was excluded from the analysis. Student's t-test and χ^2-test were used to assess the differences in socio-demographic and clinical features. The prevalence of insomnia was based on individuals with an ISI cut-off of 7 for sub-threshold insomnia ("screening positive") and an ISI cut-off of 14 for moderate to severe insomnia ("clinical insomnia"). Furthermore, we calculated 95% confidence intervals to indicate the precision of the estimation. For repeated-measure analyses, dependent sample *t*-tests were conducted as well as McNemar tests. To analyze gender-specific associations of socio-demographic and clinical characteristics, we first computed Pearson correlations, followed by a multiple linear regression analysis to explore to what extent insomnia can be predicted by socio-demographic and clinical parameters. A significance level of $p < 0.05$ was predefined for all analyses.

3. Results

3.1. Sample characteristics

The whole sample included n = 178 (44%) male and n = 227 female participants (56%). The mean age of the sample was 58.6 years (SD = 10.9) with men being on average two years older than women. The majority of the participants reported being in a relationship (78%). The most frequent tumor diagnoses were breast cancer, prostate/testicular cancer, and colorectal cancer. One-third of the men had prostate or testicular cancer, whereas more than half of the women in the sample had breast cancer (54.8%). In most of the patients, the disease was a primary tumor (82.9%), while 17.1% had a relapse or secondary tumor. At T1, 45.7% of the patients were tumor-free but still receiving oncological treatment, whereas the percentage of tumor-free patients at T2 increased to 81.3%. For details, see Tables 1 and 2. Ten percent of the sample reported current use of psychotropic drugs, and 16.8% had undergone psychotherapy in the past, significantly more of these patients being women than men. Women also reported higher values in all questionnaires concerning psychological parameters (distress, depression, anxiety, and fatigue) than men. However, in women as well as in men distress, depression, and anxiety improved from T1 to T2 (p's < 0.016, see Table 3). Only with regard to levels of fatigue were gender differences found: whereas men showed decreased levels of fatigue at T2 ($t(81) = 2.6$; $p = 0.012$), women did not show any differences in fatigue from T1 to T2 ($t(99) = 1.9$; $p = 0.068$). For details see Table 3.

3.2. Prevalence and course of cancer-related insomnia

A total of 49.4% of the participants (n = 200) exceeded the cut-off of 7 in the ISI at baseline and therefore screened positive for insomnia (95% CI [44.5–54.3]). Men and women did not differ significantly from each other (men: 47.2%, 95% CI [39.9–54.5] vs. women 51.1%, 95% CI [44.6–57.6]). Clinically relevant insomnia (ISI > 14) was found in 12.8% of patients (n = 52) of the present sample (95% CI [9.5–16.1]). There were no statistically significant differences regarding gender (men: 10.1%, 95% CI [5.7–14.5] vs. women 15.0%, 95% CI [10.3–19.7]).

After one year, 47.2% (n = 191; 95% CI [42.3–52.1]) of the participants were still suffering from insomnia symptoms (ISI > 7); significantly more women than men (men: 39.3%; 95% CI [32.2–46.4] vs. women 53.3%; 95% CI [50.0–56.6]). Although the overall prevalence rate did not differ significantly from T1 to T2 ($Chi^2(1) = 0.47$; $p = 0.494$), the group exceeding the cut-off was not identical from T1 to T2 ($Chi^2(1) = 42.3$; $p < 0.001$). Furthermore, clinical insomnia (ISI > 14) at follow-up was reported significantly more often in women (total: 13.6%; 95% CI [10.3–16.9]; men: 8.4%; 95% CI [4.3–12.5] vs. women: 17.6%; 95% CI [12.6–22.6]).

A total of n = 64 participants (15.8% of the whole sample) developed insomnia during the one year, not exceeding the cut-off (ISI > 7) at T1 but exceeding it at T2, whereas n = 73 participants (18%) reported an improvement in insomnia, falling below the cut-off at T2. N = 127 patients screened positive for insomnia both at T1 and T2 (31.4% of the whole sample, or 63.5% of patients reporting insomnia at T1). Of 116 women who screened positive (cut-off > 7) at T1, 70% (n = 81) also had insomnia symptoms at T2 (persistent or recurrent insomnia). In men, this proportion was only 55% (gender difference: $p = 0.021$). This gender difference was also found when using the cut-off of 14, although it did not reach significance due to the small sample sizes (persistence/recurrence of insomnia in 53% (n = 18) of affected women, in contrast to 28% (n = 5) of affected men, $p = 0.073$).

Fig. 1 shows the prevalence rates according to the tumor diagnoses at T1 and T2. In 16%, breast cancer showed the highest prevalence rate of insomnia among all tumor diagnoses. In most entities, the prevalence rate did not differ from T1 to T2; only in patients with prostate/testicular cancer was a significant ($p = 0.021$) decrease found. When patients with breast cancer and prostate/testicular cancer were excluded, the gender difference regarding the prevalence of insomnia symptoms at T2 disappeared for ISI > 7 (71% of persistence/recurrence in affected women vs. 61% in men, $p = 0.191$) and for ISI > 14 (36% of persistence/recurrence in affected women vs. 39% in men, $p = 0.598$).

When using the mean scores instead of dichotomous cut-off categories, the picture remains the same (see Table 4). At T1 the whole sample showed on average an ISI sum score of M = 8.7 (SD = 4.6) and at T2 a sum score of M = 8.6 (SD = 4.8). Thus, the sum score of insomnia did not change over the course of one year in the whole sample ($T(404) = 0.635$, $p = 0.526$). The score for men decreased somewhat towards T2 ($T(177) = 1.6$, $p = 0.111$), while it increased very slightly in women ($T(226) = -0.49$, $p = 0.625$), but these differences were not significant. However, a repeated-measure ANOVA revealed a significant main effect for gender differences in insomnia ($F(1) = 9.4$, $p = 0.002$), with a higher rate for persistent/recurrent insomnia for women at T2.

3.3. Gender-specific predictors of cancer-related insomnia

As differences between men and women were found in insomnia at T2, we conducted correlation analyses of socio-demographic and clinical parameters at T1 with insomnia at T2 according to gender. In men, significant moderate correlations were found between insomnia at T2 and both depression and insomnia at T1. In women, insomnia at T2 correlated significantly with depression, anxiety, fatigue, and insomnia at T1. For details, see Table 5.

Table 1
Socio-demographic parameters.

		Whole sample (N = 405)	Men (n = 178)	Women (n = 227)	Statistics	*p*
Age	M (SD)	58.6 (10.9)	60.9 (11.1)	56.7 (10.5)	t(403) = −3.9	0.000
	Range	20–90	20–90	30–89		
Classification by age						
20–39 years	n (%)	22 (5.4)	8 (4.5)	14 (6.2)	$Chi^2(2) = 20.1$	0.000
40–59 years	n (%)	197 (48.6)	66 (37.1)	131 (57.7)		
60–90 years	n (%)	186 (45.9)	104 (58.4)	82 (36.1)		
In a relationship						
Yes	n (%)	302 (78.0)	138 (82.6)	164 (74.5)	$Chi^2(1) = 3.6$	0.063
No	n (%)	85 (22.0)	29 (17.4)	56 (25.5)		
Educational level						
Secondary school	n (%)	128 (32.0)	66 (37.9)	62 (27.4)	$Chi^2(2) = 11.7$	0.003
Intermediate school	n (%)	117 (29.2)	36 (20.7)	81 (35.8)		
High School	n (%)	155 (38.8)	72 (41.4)	83 (36.7)		

Note: sample sizes may vary due to missing data.

Table 2
Cancer-related parameters.

		Whole sample (N = 405)	Men (n = 178)	Women (n = 227)	Statistics	*p*
Tumor diagnosis						
Breast cancer	n (%)	121 (30.6%)	–	121 (54.8)	$Chi^2(5) = 189.4$	0.000
Prostate/testicular cancer	n (%)	58 (14.7%)	58 (33.3)	–		
Colon/rectal cancer	n (%)	54 (13.7%)	36 (20.7)	18 (8.1)		
Lung cancer	n (%)	33 (8.4%)	10 (5.7)	23 (10.4)		
Skin cancer	n (%)	30 (7.6%)	19 (10.9)	11 (5.0)		
Other tumors	n (%)	99 (25.1%)	51 (29.3)	48 (21.7)		
Classification by cancer manifestation						
Primary cancer manifestation	n (%)	305 (82.9)	140 (86.4)	165 (80.1)	$Chi^2(1) = 2.6$	0.126
Secondary tumor/relapse	n (%)	63 (17.1)	22 (13.6)	41 (19.9)		
Time since diagnosis	M (SD)	2.0 (3.0)	1.8 (2.9)	2.1 (3.1)	t(397) = 1.1	0.278
	range	0–22	0–22	0–18		
Status of the disease at T1						
With tumor	n (%)	158 (54.3)	64 (47.4)	94 (60.3)	$Chi^2(1) = 4.8$	0.034
Tumor-free	n (%)	133 (45.7)	71 (52.6)	62 (39.7)		
Status of the disease at T2						
With tumor	n (%)	54 (18.7)	19 (16.5)	35 (20.1)	$Chi^2(1) = 0.6$	0.538
Tumor-free	n (%)	235 (81.3)	96 (83.5)	139 (79.9)		

Note: sample sizes may vary due to missing data.

Table 3
Psychological parameters.

			Whole sample (N = 405)	Men (n = 178)	Women (n = 227)	Statistics	*p*
Current use of psychotropic drugs							
	Yes	n (%)	40 (10.0)	7 (4.0)	33 (14.8)	$Chi^2(1) = 12.9$	0.005
	No	n (%)	360 (90.0)	170 (96.0)	190 (85.2)		
Psychotherapy in the past							
	Yes	n (%)	67 (16.8)	19 (10.8)	48 (21.4)	$Chi^2(1) = 8.0$	0.005
	No	n (%)	333 (83.3)	157 (89.2)	176 (78.6)		
Distress T1		M (SD)	5.0 (2.5)	4.7 (2.7)	5.3 (2.3)	t(341.4) = 2.4	0.017
		Range	0–10	0–10	0–10		
Distress T2		M (SD)	3.9 (2.6)	3.5 (2.6)	4.2 (2.6)	t(355) = 2.5	0.014
		Range	0–10	0–10	0–10		
Depression T1		M (SD)	6.1 (4.7)	4.9 (4.2)	7.1 (4.8)	t(398.3) = 5.0	0.000
		Range	0–23	0–20	0–23		
Depression T2		M (SD)	5.3 (4.9)	4.1 (4.1)	6.3 (5.2)	t(397) = 4.6	0.000
		Range	0–24	0–21	0–24		
Anxiety T1		M (SD)	4.6 (4.3)	3.7 (3.9)	5.3 (4.5)	t(397.4) = 3.7	0.000
		Range	0–21	0–21	0–20		
Anxiety T2		M (SD)	3.7 (4.2)	2.5 (3.3)	4.5 (4.6)	t(396) = 5.1	0.000
		Range	0–21	0–18	0–21		
Fatigue T1		M (SD)	5.4 (2.0)	5.0 (1.7)	6.0 (2.1)	t(193) = 3.5	0.001
		Range	3–12	3–9	3–12		
Fatigue T2		M (SD)	5.1 (1.8)	4.5 (1.4)	5.5 (2.0)	t(177.6) = 4.0	0.000
		Range	3–11	3–8	3–11		

Note: sample sizes may vary due to missing data.

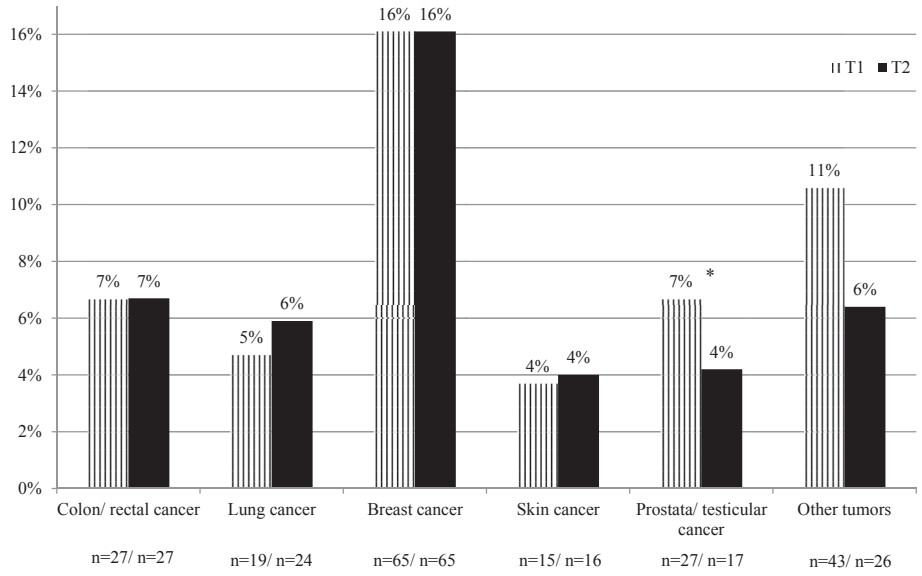

Fig. 1. Prevalence of insomnia (ISI > 7) according to cancer diagnosis comparing T1 and T2.

In the next step, gender-specific multiple linear regression analyses were performed to reveal possible predictors of insomnia at T2. Significantly correlated socio-demographic, clinical and psychological parameters at T1 were included in the regression model as predictors, whereas insomnia at T2 represented the dependent variable. In men, the use of psychotropic drugs, depression, and insomnia at T1 were found to be reliable predictors for the extent of insomnia at T2. The predictors explained 28% of the variance in insomnia scores at T2 in men. The results of the regression analysis in woman indicated that only insomnia at T1 was a reliable predictor for insomnia at T2, explaining 40% of the variance. In both women and men, insomnia at T1 was found to be the strongest predictor. For details, see Table 6.

4. Discussion

Insomnia is a frequent, but underestimated problem in cancer patients [15]. There is a dearth of studies on the course of insomnia during and especially after cancer treatment. In our longitudinal study with heterogeneous cancer entities, we found a prevalence of almost 50% for symptoms of insomnia (ISI > 7), and a prevalence of 13% for severe (clinical) insomnia (ISI > 14). This is higher than the prevalence in the normal population in Germany [39] and lies within the margins of prevalence rates for CRI reported in the literature, although severe forms of insomnia were somewhat scarcer in our sample [12,13]. Age, social status and cancer status were not correlated with insomnia. The strong correlation in our study with fatigue, depression and the use of psychotropic drugs is not surprising, given that sleep disorders may cause fatigue, that insomnia can be a symptom of depression and that psychotropic drugs may be prescribed for mental disorders or psychological distress, which are often associated with insomnia. Other studies likewise reported no correlation of CRI with age, but a high correlation with psychological distress [15].

Our main finding is that, after one year, although 80% of patients were tumor-free and all psychological parameters (distress, anxiety, depression) had improved, the overall rate of insomnia had only marginally decreased; 64% of those who had previously reported insomnia symptoms continued to suffer from these complaints. We found no significant gender difference in insomnia at baseline, but, while the rate of insomnia decreased in men from baseline to follow-up one year later, it persisted in women. As the predominant cancer entity was prostate cancer in men and breast cancer in women, this result may have been affected by differences not only in treatment strategies and recovery rates but also in the impact on bodily self-concept. When these two entities were excluded, the rates for persistent/recurrent insomnia for men matched those for women more closely. In both sexes, the strongest predictor for insomnia at follow-up was insomnia at baseline. Insomnia was closely related to actual psychological distress, anxiety, and depression. As neither time since diagnosis nor cancer status (primary or relapse, with tumor or tumor-free) was associated with insomnia at baseline or predicted insomnia prospectively at follow-up, we assume that insomnia was less related to physical conditions than to worries and psychological distress both during cancer treatment and after remission. Unlike in men, psychological

Table 4
Prevalence (ISI > 7) and course of insomnia.

		Whole sample (N = 405)	Men (n = 178)	Women (n = 227)	Statistics	*p*
T1 insomnia						
Sum score	M (SD)	8.7 (4.6)	8.2 (4.4)	9.1 (4.8)	t(403) = 1.9	0.053
	Range	1–24	1–22	3–24		
Cut-off > 7	n (%)	200 (49.4)	84 (47.2)	116 (51.1)	$Chi^2(1) = 0.61$	0.248
T2 insomnia						
Sum score	M (SD)	8.6 (4.8)	7.7 (4.3)	9.3 (5.1)	t(401.6) = 3.4	0.001
	Range	2–24	2–24	2–24		
Cut-off > 7	n (%)	191 (47.2)	70 (39.3)	121 (53.3)	$Chi^2(1) = 7.8$	0.003

Table 5
Gender-specific correlations of socio-demographic, clinical and psychological parameters at T1 with insomnia at T2.

		Insomnia at T2			
		Men (n = 178)		Women (n = 227)	
		r	*p*	r	*p*
Socio-demographic parameters	Age	0.2	0.007	−0.1	0.234
	Relationship	−0.1	0.338	0.1	0.042
Clinical parameters	Classification of cancer manifestation	−0.1	0.650	0.1	0.893
	Time since diagnosis	−0.1	0.658	0.1	0.390
	Status of the disease	−0.1	0.935	−0.1	0.529
	Actual use of psychotropic drugs	0.2	0.008	0.1	0.563
	Psychotherapy in the past	0.1	0.145	0.1	0.460
Psychological parameters	Distress	0.2	0.001	0.3	0.000
	Depression	0.4	0.000	0.4	0.000
	Anxiety	0.3	0.000	0.4	0.000
	Fatigue	0.3	0.011	0.5	0.000
	Insomnia	0.5	0.000	0.5	0.000

Table 6
Gender-specific models of regression.

Dependent variable	Predictors (at T1)	B	SE	Beta	t	*p*
Insomnia at T2	Men					
$R^2 = 0.28$;	Psychotropic drugs	3.8	1.5	0.2	2.6	0.009
$F(7) = 9.5$; $p = 0.000$	Depression	0.2	0.1	0.2	2.1	0.034
	Insomnia	0.4	0.1	0.4	4.3	0.000
Insomnia at T2	Women					
$R^2 = 0.40$;	Insomnia	0.3	0.1	0.3	2.5	0.014
$F(5) = 12.5$; $p = 0.000$						

Note: the table shows only variables that reached significance in the regression analysis; thus, distress and anxiety in men as well as relationship, distress, and anxiety in women were excluded.

variables did not predict insomnia one year later in women. This may be due to the variability of psychological distress over time but could also result from the close correlation of these variables with the main predictor, insomnia at baseline. Overall, we found that even when anxiety and depression improve, sleep disturbances may be intractable and persistent far beyond remission.

The results of our study have to be interpreted in light of the following limitations. The main weakness of our study is that we used a self-report measurement, while a clinical diagnostic interview would have been the gold standard. We used the standard cut-offs of the ISI, but other instruments and cut-offs were applied in previous studies, which may render the comparison of prevalence rates difficult. Unfortunately, there are a few parameters that should have been assessed to strengthen the results of the present analysis. Eg, in our sample there was no data available on the existence or extent either of insomnia in the past or other sleep disorders. Likewise, it was overlooked to measure pain and its influence on insomnia in cancer patients. Furthermore, it would have been important to consider drug therapy or cancer treatment in the analysis. As the present study is based on a naturalistic design, though, drug therapy and cancer treatment differed too much within the sample. Future research may examine this effect in a randomized controlled trial. Moreover, with only two assessment points, we cannot distinguish between chronic and recurrent sleep disturbances. The sample was based on many different cancer entities but included a high proportion of breast cancers. Therefore, some conclusions may be most appropriate for this patient group.

5. Conclusion

In conclusion, our results strongly indicate that, although sleeping problems have been shown to be associated with cancer treatments [40], insomnia in cancer patients cannot be regarded as a transient problem restricted to treatment phases but tends to become a chronic condition also in the post-treatment period, particularly in women. The period after treatment completion is often described by survivors as more difficult than the treatment itself [41]. Sleep disorders impair the quality of life and are a risk factor for further physical and psychological disorders. In a review for the EORTC quality of life group, insomnia and fatigue were the most prevalent symptoms; they were also the issues rated as most relevant in cancer survivors two and more years after diagnosis [42]. Routinely screening cancer patients for sleeping problems should be not only part of standard diagnostics in cancer care during the treatment course but also an integral part of survivorship care. Sleep disturbances are highly treatable; however, although physicians tend to prescribe hypnotics, patients are often reluctant to take psychotropic medication [43]. Therefore, psychoeducation about sleep hygiene, relaxation methods, and psychological interventions should be offered more often [44]. With our study, we hope to draw more attention to the risk of chronic or recurrent insomnia in cancer, especially in female cancer survivors.

Financial support

The study was funded by a grant from the German Cancer Aid (Deutsche Krebshilfe, Grant No. 109977). However, this funding source had no role in the design of this study, during its execution, analyses, interpretation of the data, or decision to submit results.

Conflict of interest

All authors had nothing to disclose.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.02.018.

References

[1] Ohayon MM. Epidemiological overview of sleep disorders in the general population. Sleep Med Rev 2011;2:1–9.
[2] Anothaisintawee T, Reutrakul S, Van Cauter E, et al. Sleep disturbances compared to traditional risk factors for diabetes development: systematic review and meta-analysis. Sleep Med Rev 2016;30:11–24. https://doi.org/10.1016/j.smrv.2015.10.002.
[3] Baglioni C, Battagliese G, Feige B, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. J Affect Disord 2011;135(1–3):10–9. https://doi.org/10.1016/j.jad.2011.01.011.
[4] Gustavsson A, Svensson M, Jacobi F, et al. Cost of disorders of the brain in Europe 2010. Eur Neuropsychopharmacol 2011;21(10):718–79. https://doi.org/10.1016/j.euroneuro.2011.08.008.
[5] Liu TZ, Xu C, Rota M, et al. Sleep duration and risk of all-cause mortality: a flexible, non-linear, meta-regression of 40 prospective cohort studies. Sleep Med Rev 2017;32:28–36. https://doi.org/10.1016/j.smrv.2016.02.005.

[6] Palagini L, Bruno RM, Gemignani A, et al. Sleep loss and hypertension: a systematic review. Curr Pharm Des 2013;19(13):2409–19.
[7] Sofi F, Cesari F, Casini A, et al. Insomnia and risk of cardiovascular disease: a meta-analysis. Eur J Prev Cardiol 2014;21(1):57–64. https://doi.org/10.1177/2047487312460020.
[8] American Academy of Sleep Medicine. International classification of sleep disorders – third edition (ICSD-3). American Academy of Sleep Medicine Chicago; 2014.
[9] Riemann D, Baglioni C, Bassetti C, et al. European guideline for the diagnosis and treatment of insomnia. J Sleep Res 2017;26(6):675–700. https://doi.org/10.1111/jsr.12594.
[10] Geue K, Sender A, Schmidt R, et al. Gender-specific quality of life after cancer in young adulthood: a comparison with the general population. Qual Life Res 2014;23(4):1377–86. https://doi.org/10.1007/s11136-013-0559-6.
[11] Davis MP, Goforth HW. Long-term and short-term effects of insomnia in cancer and effective interventions. Cancer J 2014;20(5):330–44. https://doi.org/10.1097/PPO.0000000000000071.
[12] Induru RR, Walsh D. Cancer-related insomnia. Am J Hosp Palliat Care 2014;31(7):777–85. https://doi.org/10.1177/1049909113508302.
[13] Mehnert A, Hartung TJ, Friedrich M, et al. One in two cancer patients is significantly distressed: prevalence and indicators of distress. Psycho Oncol 2017. https://doi.org/10.1002/pon.4464.
[14] Graci G. Pathogenesis and management of cancer-related insomnia. J Support Oncol 2005;3(5):349–59.
[15] Davis MP, Khoshknabi D, Walsh D, et al. Insomnia in patients with advanced cancer. Am J Hosp Palliat Care 2014;31(4):365–73. https://doi.org/10.1177/1049909113485804.
[16] Savard MH, Savard J, Simard S, et al. Empirical validation of the insomnia severity index in cancer patients. Psycho Oncol 2005;14(6):429–41. https://doi.org/10.1002/pon.860.
[17] Harris B, Ross J, Sanchez-Reilly S. Sleeping in the arms of cancer: a review of sleeping disorders among patients with cancer. Cancer J 2014;20(5):299–305. https://doi.org/10.1097/PPO.0000000000000067.
[18] Irwin MR. Depression and insomnia in cancer: prevalence, risk factors, and effects on cancer outcomes. Curr Psychiatry Rep 2013;15(11):404. https://doi.org/10.1007/s11920-013-0404-1.
[19] Riemann D, Spiegelhalder K, Feige B, et al. The hyperarousal model of insomnia: a review of the concept and its evidence. Sleep Med Rev 2010;14(1):19–31. https://doi.org/10.1016/j.smrv.2009.04.002.
[20] Pachman DR, Barton DL, Swetz KM, et al. Troublesome symptoms in cancer survivors: fatigue, insomnia, neuropathy, and pain. J Clin Oncol 2012;30(30):3687–96. https://doi.org/10.1200/JCO.2012.41.7238.
[21] Price MA, Zachariae R, Butow PN, deFazio A, Chauhan D, Espie CA, Friedlander M, Webb PM, Australian Ovarian Cancer Study G, Australian Ovarian Cancer Study – Quality of Life Study I. Prevalence and predictors of insomnia in women with invasive ovarian cancer: anxiety a major factor. Eur J Cancer 2009;45(18):3262–70. https://doi.org/10.1016/j.ejca.2009.05.030.
[22] Smet S, Potter R, Haie-Meder C, et al. Fatigue, insomnia and hot flashes after definitive radiochemotherapy and image-guided adaptive brachytherapy for locally advanced cervical cancer: an analysis from the EMBRACE study. Radiother Oncol 2018. https://doi.org/10.1016/j.radonc.2018.03.009.
[23] Theobald DE. Cancer pain, fatigue, distress, and insomnia in cancer patients. Clin Cornerstone 2004;6(1D):S15–21.
[24] Fiorentino L, Rissling M, Liu L, et al. The symptom cluster of sleep, fatigue and depressive symptoms in breast cancer patients: severity of the problem and treatment options. Drug Discov Today Dis Model 2011;8(4):167–73. https://doi.org/10.1016/j.ddmod.2011.05.001.
[25] Sivertsen B, Lallukka T, Petrie KJ, et al. Sleep and pain sensitivity in adults. Pain 2015;156(8):1433–9. https://doi.org/10.1097/j.pain.0000000000000131.
[26] Davis MP, Goforth H. Fighting insomnia and battling lethargy: the yin and yang of palliative care. Curr Oncol Rep 2014;16(4):377. https://doi.org/10.1007/s11912-014-0377-1.
[27] Trudel-Fitzgerald C, Savard J, Ivers H. Which symptoms come first? Exploration of temporal relationships between cancer-related symptoms over an 18-month period. Ann Behav Med 2013;45(3):329–37. https://doi.org/10.1007/s12160-012-9459-1.
[28] Maguire R, Drummond FJ, Hanly P, et al. Problems sleeping with prostate cancer: exploring possible risk factors for sleep disturbance in a population-based sample of survivors. Support Care Cancer 2019. https://doi.org/10.1007/s00520-018-4633-z.
[29] Bulbul Y, Ozlu T, Arinc S, et al. Sleep disturbances in patients with lung cancer in Turkey. Tuberk Toraks 2018;66(4):297–303. https://doi.org/10.5578/tt.67689.
[30] Qiu H, Ren W, Yang Y, et al. Effects of cognitive behavioral therapy for depression on improving insomnia and quality of life in Chinese women with breast cancer: results of a randomized, controlled, multicenter trial. Neuropsychiatr Dis Treat 2018;14:2665–73. https://doi.org/10.2147/NDT.S171297.
[31] Weis J, Honig K, Bergelt C, et al. Psychosocial distress and utilization of professional psychological care in cancer patients: an observational study in National Comprehensive Cancer Centers (CCCs) in Germany. Psycho Oncol 2018;27(12):2847–54.
[32] Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001;2(4):297–307.
[33] Buysse DJ, Reynolds 3rd CF, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28(2):193–213.
[34] Morin C. Insomnia: psychological assessment and management. New York: Guilford Press; 1993.
[35] National Comprehensive Cancer Network. Distress management. Clinical practice guidelines. J Natl Compr Cancer Netw 2003;1(3):344–74.
[36] Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16(9):606–13.
[37] Spitzer RL, Kroenke K, Williams JB, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166(10):1092–7. https://doi.org/10.1001/archinte.166.10.1092.
[38] Weis J, Arraras JI, Conroy T, et al. Development of an EORTC quality of life phase III module measuring cancer-related fatigue (EORTC QLQ-FA13). Psycho Oncol 2013;22(5):1002–7. https://doi.org/10.1002/pon.3092.
[39] Schlack R, Hapke U, Maske U, et al. Häufigkeit und Verteilung von Schlafproblemen und Insomnie in der deutschen Erwachsenenbevölkerung. Ergebnisse der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1). Bundesgesundheitsblatt Gesundh Gesundh 2013;56:740–8.
[40] Savard J, Ivers H, Savard MH, et al. Cancer treatments and their side effects are associated with aggravation of insomnia: results of a longitudinal study. Cancer 2015;121(10):1703–11. https://doi.org/10.1002/cncr.29244.
[41] Mayer DK, Nasso SF, Earp JA. Defining cancer survivors, their needs, and perspectives on survivorship health care in the USA. Lancet Oncol 2017;18(1):e11–8. https://doi.org/10.1016/S1470-2045(16)30573-3.
[42] van Leeuwen M, Husson O, Alberti P, et al. Understanding the quality of life (QOL) issues in survivors of cancer: towards the development of an EORTC QOL cancer survivorship questionnaire. Health Qual Life Outcomes 2018;16(1):114. https://doi.org/10.1186/s12955-018-0920-0.
[43] Garland SN, Barg FK, Cakouros B, et al. A qualitative examination of the factors related to the development and maintenance of insomnia in cancer survivors. Palliat Support Care 2018:1–6. https://doi.org/10.1017/S1478951518000135.
[44] Howell D, Oliver TK, Keller-Olaman S, et al. Sleep disturbance in adults with cancer: a systematic review of evidence for best practices in assessment and management for clinical practice. Ann Oncol 2014;25(4):791–800. https://doi.org/10.1093/annonc/mdt506.