

Clinical Psychopharmacology and Neuroscience - Manuscript

Submission

- **Manuscript ID:** CPN-21-865
- **Title:** Assessing the Sleep-wake Pattern in Cancer Patients for Predicting a Short Sleep Onset Latency
- **Running Title:** Short Sleep Onset Latency in Cancer Patients
- **Article Type:** Original Article
- **KeyWords:** insomnia, sleep parameters, cancer, sleep onset latency

Conclusion: Cancer patients who fell asleep quickly ~~spent~~showed less time in bed during the day. ~~Thus, before cancer patients with insomnia are prescribed~~Before prescribing sleeping pills, ~~to cancer patients with insomnia, we should explore~~ their sleep parameters should be examined to improve their ~~sleep-onset latency~~SL.

Keywords: insomnia, sleep parameters, cancer, sleep onset latency

INTRODUCTION

The sleep ~~disturbances experienced by disturbance in cancer~~ patients ~~with cancer~~ are increasingly being recognized and examined ~~increasing~~ [1]. ~~Although studies. Studies~~ on the prevalence of insomnia ~~in cancer patients~~ vary ~~in with factors such as study~~ design, type of cancer ~~assessed~~, type of treatment, and phase of treatment, ~~it is clear that. About 20–60%~~ of ~~cancer~~ patients ~~with cancer~~ suffer from insomnia and sleep disturbances, ~~especially women and the elderly. This is particularly true for female and elderly patients~~ [2-4]. ~~This is particularly true for female and elderly patients.~~ In the past, insomnia was regarded as a natural reaction to cancer and its related treatments. However, as cancer patients' survival rates ~~have increased~~, ~~improving~~ their quality of life ~~gains has become~~ important ~~ee~~. Insomnia is directly and indirectly related to the quality of life. Additionally, persistent insomnia is a risk factor for subsequent psychiatric disorders, such as depression, which ~~can~~ lead to noncompliance with ~~cancer the~~ treatment [5, 6]. Recently, both doctors and patients have expressed their interest in the awareness and treatment of insomnia.

In clinical settings, pharmacologic treatment of insomnia is preferred owing to its efficacy and simplicity. However, cancer patients with insomnia may experience maladaptive sleep behaviors or ~~have~~ faulty beliefs and attitudes regarding sleep, and these factors ~~further exacerbate maintain~~ insomnia [3, 4]. Unfortunately, pharmacologic agents do not affect the perpetuating factors of insomnia. Cognitive-behavioral therapy for insomnia (CBT-I) improves insomnia by targeting perpetuating factors, such as dysfunctional beliefs [7], ~~and CBT-I~~ is an effective treatment for insomnia secondary to cancer [8]. CBT-I is ~~particularly~~ useful for ~~cancer~~ patients ~~with cancer~~ as it has no associated drug-interactions or side effects

[3], ~~and. With CBT-I,~~ patients can regain control over their sleep ~~—~~and effectively deal ~~with~~reduce the emotional stress caused by insomnia [9].

Approximately 60—70% of cancer patients with insomnia face difficulties in both, initiating and maintaining sleep [10]. It is, therefore, important to record details~~detail surveys~~ of night sleep characteristics ~~of night sleep~~ and insomnia ~~type~~ in patients suffering from sleep disturbances. of insomnia patients.— If we understand sleep parameters (e.g. sleep onset time, wake-up time, and time in bed), ~~and so on~~), we can provide individualized cognitive-behavioral therapy properly in a busy clinical setting. An earlier study revealed that insomnia patients who were able to fall~~fell~~ asleep faster usually went to bed later and had longer durations between their wake-up times and bedtimes [11]. ~~However, We need to ascertain~~ whether these findings also~~results~~ apply to ~~cancer~~ patients with cancer remains to be determined. Indeed,—as cancer patients with insomnia tend to adopt compensatory behaviors such as napping and going to bed earlier. They also ~~have decreased~~participate in less daytime activities and spend more~~increased~~ time in bed because of fatigue regardless of treatments [12]. ~~Moreover, Cancer~~ patients with cancer can ~~—~~experience sleep/wake disturbances. In other words, their ability to maintain sleep and waking states is affected, which—~~It~~ may result from~~be due to~~ the dysregulation of ~~the~~ homeostatic and circadian processes [13]. Therefore, insomnia in ~~cancer~~ patients with cancer may present differently than ~~have aspects different from~~ general insomnia does. To this end, we investigated the association between sleep parameters and short sleep ~~onset~~-latency ($SL_{\leq 30 \text{ min}}$ ~~30 minutes~~) [14]; and studied the differences in sleep parameters, especially time in bed during daytime (TIB/d), ~~and the~~ duration from wake-up time to bedtime (WTB), between cancer patients who were taking sleeping pills and those who were not.

METHODS

Subjects

This was a retrospective review of existing medical records. Patients who visited the Sleep Clinic for Cancer Patients in the Asan Medical Center between January 2017 and February 2020 were enrolled in this study. At this clinic, all patients were routinely assessed by a psychiatrist and a sleep specialist (S. Chung) for their psychiatric or sleep problems. Patients who had severe disabilities that could limit activities of daily living, organic brain diseases, cognitive dysfunction, or other primary sleep disorders including obstructive sleep apnea (snoring or repetitive apneic events during sleep) and restless legs syndrome or those who had undergone CBT-I before they visited our clinic were excluded from the final analysis. This study was approved by the Institutional Review Board of Asan Medical center (S2020-1238-0001) and Yongin Mental Hospital (2020-16), and the requirement of written informed consent was waived for this retrospective medical records review study.

Rating scales

Patient Health Questionnaire-9

Patient Health Questionnaire-9 (PHQ-9) is a self-rated scale used to assess the severity of depression. It consists of nine criteria, each of which can be scored from 0 to 3 for a maximum score of 27 [15].

State subcategory of State and Trait Anxiety Inventory

The State and Trait Anxiety Inventory (STAI) is a self-rated scale for measuring the traits and state of a patients anxiety. Among all 40 scoring criteria on this scale, 20 are designed to

assess state anxiety and 20 to assess trait anxiety [16]. In this study, we used the Korean version of the 20 items of state anxiety, each of which can be rated from 1 to 4 [17].

Insomnia Severity Index

The Insomnia Severity Index (ISI) is a self-rated scale used to assess the severity of insomnia symptoms. It consists of seven items rated 0–4 on a Likert scale and is represented as a sum of the scores ranging from 0–28, categorized into mild (8–14), moderate (15–21), and severe insomnia (22–28) [18]. In this study, we used the Korean version of this scale [19].

Cancer-related Dysfunctional Beliefs about Sleep

The Cancer-related Dysfunctional Beliefs about Sleep (C-DBS) scale is a 2-item rating scale for assessing dysfunctional beliefs concerning sleep in patients with cancer [20]. It consists of two items: “My immune system will have serious problems if I do not go to sleep at a certain time” (question 1, immune dysfunction) and “If I do not sleep well at night, my cancer may recur or metastasize” (question 2, cancer recurrence). Each item can be rated on a scale of 0–10.

Fear of Progression-short form.

The original Fear of Progression (FoP) is a 43-item rating scale that evaluates concerns related to disease progression. In this study, we used the Korean version [21] of a 12-item short form of the original scale [22]. Each item on the FoP-short form is rated on a scale of 1–5.

Assessment of sleep-wake pattern, time and duration variables, and hypnotics usage

On their first visit, patients were routinely asked the following questions: 1) “How many tablets of sleeping pills per day are you taking now?”; 2) “Are you satisfied with your sleeping pills’ ability to induce sleep?”; 3) “What is the usual time at which you take sleeping pills?”; 4) “What is your usual bedtime?”; 5) “What is the usual time you fall asleep?”; 6) “What is the usual time you take to finally get out of bed in the morning?”; and 7) “What is the total number of hours you spend lying down within 24 h, including sleeping time?” [22]. Their answers were recorded in the electronic medical records system.

Based on ~~patient~~^{their} responses, we calculated the time and duration variables. The time variables, including sleeping pills ingestion time, bedtime, sleep onset time, and wake-up time, were calculated by averaging the times reported in our previous study [23]. Using the calculated time variables ~~calculated~~, duration variables, including sleep onset latency, time in bed, time in bed in 24 h (TIB/d), durations from the ingestion of pills to bedtime (PTB), to sleep onset time (PTS), and to wake-up time (PTW), and durations from wake-up time to bedtime (WTB) and to sleep onset time (WTS) were calculated.

The number of tablets of equivalent hypnotic drugs (TEQ) was calculated using the equivalent dosage of each medication: alprazolam (0.25 mg), bromazepam (3 mg), clonazepam (0.25 mg), diazepam (5 mg), lorazepam (0.5 mg), triazolam (0.25 mg), and zolpidem (10 mg for the immediate release and 12.5 mg for the extended-release forms [24].

Statistical analysis

Statistical analyses were performed using the SPSS ver. 21.0 for Windows (IBM Corp., Armonk, NY, USA). The clinical characteristics were summarized as mean \pm standard deviation values. The level of significance for all analyses was defined as two-tailed $p < 0.05$.

Student's t-test for continuous variables and a chi-square test for categorical variables were performed for between group analyses. A Spearman correlation analysis was performed to explore the association between the patients' clinical characteristics. A logistic regression analysis was used to explore the factors that may predict short SL (≤ 30 min) in patients with cancer.

RESULTS

Among the 255 patients, 20 were excluded owing to inadequate medical records of sleep parameters. Table 1 shows the clinical characteristics of the study subjects (N = 235). About 75% of the patients were women, with a mean age of 56.1 ± 11.2 years. The types of cancer included breast (n = 103, 43.8%), lung (n = 20, 8.5%), gastro-esophageal (n = 19, 8.1%), pancreas and biliary tract (n = 17, 7.2%), colorectal (n = 15, 6.4%), head and neck (n = 14, 6.0%), gynecologic (n = 12, 5.1%), hematologic (n = 11, 4.7%), kidney (n = 7, 3.0%), urinary tract (n = 6, 2.6%), liver (n = 5, 2.1%), thyroid (n = 3, 1.3%), and ~~other~~ (n = 3, 1.3%). The most common psychiatric diagnosis in these patients at the first visit was insomnia (153, 65.1%), followed by major depressive disorder (55, 23.4%), and anxiety disorder/somatic symptom disorder (12, 5.1%).

All 145 cancer patients were taking sleeping pills when they visited the sleep clinic for the first time. Among them, 84 showed $SL \leq 30$ min, and 61 showed $SL > 30$ min (Table 2). There was no significant difference in sex, age, depression, anxiety, fear of disease progression, and dysfunctional beliefs about sleep. The group in which SL was > 30 min reported more severe insomnia symptoms, earlier bedtimes ($10:30 \pm 1:09$ pm), and later sleep onset times ($12:07 \pm 1:24$ pm). There was a significant difference in duration variables such as SL, time in bed, TIB/d, PTS, PTW, WTB, and WTS.

Among the 90 ~~cancer~~ patients with cancer who were not taking sleeping pills at the first visit, patients with short SL (≤ 30 min) showed earlier sleep onset ($11:00 \pm 1:15$ pm) and wake-up times ($6:06 \pm 1:30$ am) (Table 3). Additionally, they showed a shorter time in bed, shorter TIB/d, and longer WTB. SL of the group that did not take sleeping pills showed significant

correlations with depressive symptoms ($r = 0.23$, $p < 0.05$), sleep onset time ($r = 0.60$, $p < 0.01$), wake-up time ($r = 0.34$, $p < 0.01$), TIB/d ($r = 0.28$, $p < 0.01$), and WTB ($r = -0.38$, $p < 0.01$) (Table 4). TIB/d was correlated with clinical symptoms, including FoP score ($r = 0.23$, $p < 0.05$), depressive symptoms ($r = 0.34$, $p < 0.01$), and anxiety ($r = 0.24$, $p < 0.05$). Longer TIB/d showed significant correlations with later wake-up time ($r = 0.43$, $p < 0.01$) and earlier bedtime ($r = -0.28$, $p < 0.01$). SL of sleeping pill users showed correlations with earlier bedtime ($r = -0.22$, $p < 0.01$) and later sleep onset ($r = 0.35$, $p < 0.01$) and wake-up times ($r = 0.22$, $p < 0.01$). Among the duration variables, longer time in bed at night ($r = 0.35$, $p < 0.01$) and all day ($r = 0.37$, $p < 0.01$) showed a correlation with longer SL. Longer TIB/d showed a positive correlation with PTS ($r = 0.34$, $p < 0.01$), PTW ($r = 0.50$, $p < 0.01$), and TEQ ($r = 0.26$, $p < 0.01$).

Logistic regression analysis was conducted after adjusting for age, sex, cancer types, TNM staging, psychiatric disorder and, ISI, PHQ-9, STAI, C-DBS, and FoP scorescales score to explore the predictingidentify predictive variables forof the short sleep latencySL. Among cancer-patients with cancer who were not taking sleeping pills, early wake-up time (adjusted OR: 0.39, 95% CI 0.19–0.78) and early sleep onset time (adjusted OR: 0.50, 95% CI 0.27–0.93) from the time variables and low ISI score (adjusted OR: 0.82, 95% CI 0.71–0.93) were identified as the predictive factors for $SL \leq 30$ min (Table 5). Longer duration of WTB (adjusted OR: 2.49, 95% CI 1.48–4.18) from the duration variables and low ISI score (adjusted OR: 0.78, 95% CI [0.68–0.89]) predicted ed $SL \leq 30$ min. Among cancer-patients with cancer who were taking sleeping pills, early sleep onset time (adjusted OR: 0.54, 95% CI 0.39–0.76) from the time variables and short duration from ingestion of pills to sleep onset

time (adjusted OR: 0.05, 95% CI 0.02–0.16) from the duration variables were predictive of $SL \leq 30$ min.

DISCUSSION

In this study, we observed that early wake-up time and early sleep onset time from the time variables and longer WTB from the duration variables were predictive of short ~~sleep-onset-latency-SL~~ among ~~cancer~~ patients with cancer who were not taking sleeping pills. In addition, among ~~cancer~~ patients who were taking sleeping pills, early sleep onset time from the time variables and short PTS from the duration variables were predictive of short SL.

Patients with cancer~~Cancer patients~~ who did not take sleeping pills with $SL \leq 30$ min showed a low ISI scores, which is score, suggestive of subthreshold insomnia. In contrast, ~~cancer~~ patients with $SL > 30$ min showed moderate insomnia severity. ~~SL~~ Sleep-onset latency has been identified as an important factor in defining insomnia [25] in all ages [26]. This suggests that recording asking for SL is essential for evaluating to evaluate the severity of insomnia in ~~cancer~~ patients with cancer. ~~Subjects~~ Patients in the ~~groups of~~ $SL > 30$ min, group who did not take sleeping pills, reported greater delays in sleep onset and wake-up time. They also spent more of their day and night time in bed than did the ~~patients~~subjects from ~~the groups of~~ $SL \leq 30$ min group. Cancer patients had a longer daytime total nap time than cancer-free people [27]. In our study, TIB/d showed a positive correlation with FoP score, depressive symptoms, and anxiety symptoms. Thus, it would mean some of the untreated psychiatric symptoms were related to reduced awakening and probably also to reduced daytime activity. However, we found~~there is~~ no significant differences~~difference~~ in PHQ-9, state subcategory of STAI, FoP, and C-DBS scales~~scales~~ scores between the $SL \leq 30$ min~~minutes~~ and $SL > 30$ min~~minutes~~ groups in this study. Accordingly, these scale~~And also, those scales~~ scores were excluded from~~in~~ the final model of logistic regression analysis.

~~No~~In this study, there is no significant ~~differences~~difference in the PTB ~~or~~, duration from ~~ingestion of~~ pills to bedtime ~~were observed~~, between the $SL \leq 30$ ~~min~~minutes and $SL > 30$ ~~min~~minutes groups (Table 2). ~~The~~BTP was not significantly correlated with ~~sleep latency~~SL ~~and~~ TIB/d (Table 4), and ~~as such~~, this index was not included as a predicti~~ve~~ng variable in the logistic regression analysis. ~~Clinically, m~~Most patients reported~~ed~~ that they ~~are~~~~were~~ taking sleeping pills 30 minutes before bedtime, since ~~this~~~~it is~~~~was~~ what was typically assumed to be ~~correct~~ generally known and ~~guided~~recommended by clinicians.~~.~~ Previously, we reported that the PTB index was not significantly different between patients ~~who~~satisfied with their sleeping pills and ~~those who were~~ not [23]. ~~It is plausible to consider~~We ~~considered~~ that this result ~~also~~came ~~about~~ because~~from that~~ most patients think they should take sleeping pills 30 minutes before bedtime,~~.~~ ~~and it seems to be~~ ~~expectable~~

~~Through~~During anticancer ~~treatments~~,~~treatment~~,~~cancer~~ patients ~~with cancer~~ experience increased fatigue and ~~spend~~ more time in bed [28]. ~~They~~Cancer patients frequently ~~show~~~~participate in~~ less activity~~ies~~ during the day and ~~take~~ frequent naps [13, 29]. Additionally, cancer-related fatigue ~~would be~~has been reciprocally associated with sleep disturbance. As mentioned above, many factors may change ~~the~~their sleep-wake pattern ~~of patients~~ during the day and night. ~~Patients with cancer~~ Cancer patients who were taking sleeping pills ~~with and~~ ~~had~~ $SL \leq 30$ min had later bedtimes and fell asleep faster. ~~Similar~~In primary insomnia ~~patients, similar~~ results ~~have been~~were observed ~~in patients with primary insomnia~~ [11]. Patients ~~typically report~~reported dissatisfaction with their hypnotic medications if they ~~observe~~observed long intervals between the time of ~~administration of~~sleeping pill ~~ingestion~~pills and sleep onset time [23]. Reduced sleep efficiency and dissatisfaction with sleeping pills may worsen dysfunctional beliefs of sleep and maladaptive behaviors. As sleep

efficiency is likely a prognostic factor ~~for~~ cancer [30], it is important to find a way to improve it by reducing SL.

Moreover, patients with prior experience of using sleep aids ~~were~~ are more likely to use hypnotic medicine during cancer treatment [31]. Taking sleeping pills during cancer treatment may ~~raise~~ raises the risk of ~~adding~~ starting or increasing hypnotic medications use, than they usually taken. Clinicians should be concerned with the ~~if~~ change of hypnotic medication usage pattern and periodically evaluate ~~the cancer~~ patient's quality of life [32].

Sleep quality can be improved by increased walking at home [33]. ~~Longer times spent~~ The longer time outside of bed helps to reduce the initial insomnia, and it is important to pay attention to the respiratory depression induced by sleeping pills, especially when patients have already taken sleeping pills.

Homeostatic processes interact with circadian processes and both regulate sleep patterns [34]. Homeostatic processes are determined by sleep-wake history. A longer duration of wakefulness induces increased sleep propensity [35]. As shown in our study, especially in patients with cancer, increased homeostatic drive for sleep is accompanied by decreased ~~sleep onset latency~~ SL. ~~Previous~~ There are some studies have shown that changes in which the change in circadian processes in ~~cancer~~ patients with cancer are is associated with dysfunctions in ~~deviated~~ cortisol and melatonin secretion [36, 37]. However, the role of the homeostatic process is still important because the two processes are compensatory. An uncontrollable biological change due to cancer actively changes cognition and behavior ~~for~~ by increasing the homeostatic drive to sleep.

This study had some limitations. First, numerous clinical factors related to cancer itself might influence the ~~insomnia~~ severity ~~of insomnia as precipitating factors~~ [3]. Insomnia is a persistent problem ~~into~~ all ~~cancer~~ patients with cancer [38][39], and their maladaptive behaviors or dysfunctional beliefs about sleep might ~~exacerbate their~~ ~~run the risk of~~ ~~maintaining~~ insomnia [3]. ~~in many cases~~. However, the clinical characteristics of insomnia can vary according to ~~be different in each~~ cancer type, stage, or stages, treatment modality. ~~Whilst we did not focus on a specific modalities, or patients' states in the cancer trajectories~~. ~~Ideally, this~~ type of cancer, future studies should study needs to be conducted to assess insomnia in each type of cancer. ~~type separately, but in this study we could not explore it in each cancer types~~. Second, there ~~were~~ is no significant ~~differences~~ difference in psychiatric symptoms such as depression, anxiety, fear of progression, or dysfunctional beliefs about sleep between the two SL groups. ~~Many~~ It may come from many cancer patients in this study suffer ~~ed~~ from ~~these~~ those symptoms regardless of sleep latency SL, and this should ~~It needs to~~ be investigated ~~elucidated~~ in the future. ~~further study~~. Third, other factors affecting insomnia, such as hot flushes and flush, pain, ~~and so on~~, were not evaluated because this was a retrospective review of medical records. Fourth, sleep parameters were acquired through clinician's questions instead of objective methods of actigraphy or polysomnography. Fifth, the history of cancer treatment was assessed based on answering yes or no questions; hence, concurrent medical treatments were not evaluated alongside with psychiatric evaluation ~~evaluation~~. Finally, TIB/d cannot be considered as having ~~would not have~~ the same significance as daily activity during the day, and we did not evaluate the amount. ~~Amount~~ of daily activity and resting state in this study ~~were not evaluated~~.

Despite the limitations of this study, our ~~we hope that the~~ results may ~~in this study could~~ be applied in clinical practice for improving the ~~taking~~ care of patients with ~~cancer patient~~ who

suffer from insomnia. First, the TIB/d index in this study was calculated to estimate the time spent ~~laying~~lying in~~down on~~ bed during the daytime. Classically, ~~we can estimate~~ the TIB index ~~is estimated~~TIB from bedtime to wake-up time. However, many ~~cancer~~ patients with cancer spend their time laying down on their bed during the daytime because of ~~their~~ fatigue-symptoms. Therefore, we propose ~~that to use~~ the TIB/d index be used in clinical practice for estimating the daytime activity of ~~cancer~~ patients with cancer in clinical settings. Second, the WTB index, ~~duration from wake-up time to bedtime~~, was ~~finally~~ included as an expecting variable for ~~the~~ short sleep latencySL among in patients ~~who are~~ not taking sleeping pills. Thus, an~~It means that it will take so long time from wake-up in the morning until falling asleep. And we need to advice cancer patients that~~ early bedtime cannot guarantee that patients with cancer will fall asleep quickly. Our~~the early falling asleep. We hope that the~~ results ~~in this study~~ may help~~be helpful~~ to improve the sleep latencySL and decrease the use of sleeping pills ~~in of cancer~~ patients with cancer.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

Author Contribution

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Table 1. Clinical characteristics of the study subjects (N = 235)

Variable	Subjects
Female, n (%)	175 (74.5%)
Age (years)	56.1 ± 11.2
Cancer type	
Breast	103 (43.8%)
Lung	20 (8.5%)
Gastro-esophageal	19 (8.1%)
Pancreatic and biliary tract	17 (7.2%)
Colorectal	15 (6.4%)
Head and neck	14 (6.0%)
Gynecologic	12 (5.1%)
Hematologic	11 (4.7%)
Kidney	7 (3.0%)
Urinary tract	6 (2.6%)
Liver	5 (2.1%)
Thyroid	3 (1.3%)
Others	3 (1.3%)
Cancer stages *	
Stage 0	3 (1.4%)
Stage I	52 (24.4%)

Stage II	60 (28.2%)
Stage III	23 (10.8%)
Stage IV	66 (31.0%)
Not yet confirmed	9 (4.2%)
Psychiatric diagnosis	
Insomnia	153 (65.1%)
Major depressive disorder	55 (23.4%)
Anxiety disorder/somatic symptom disorder	12 (5.1%)
Mixed anxiety and depression	5 (2.1%)
Acute stress reaction/adjustment disorder	5 (2.1%)
No diagnosis	3 (1.3%)
Others	2 (0.9%)

*Patients with cancer can be graded using the TNM staging system (n = 213)

Table 2. Clinical characteristics of cancer patients who were taking sleeping pills (N = 145)

	SL ^a ≤ 30 (N = 84)	SL ^a > 30 (N = 61)	<i>p</i> - value
Male, N (%)	23 (27.4%)	25 (41.0%)	0.06
Age (years)	57.5 ± 11.1	57.8 ± 10.6	0.86
Rating scales scores			
Insomnia Severity Index	17.9 ± 4.9	20.2 ± 4.9	0.006
Cancer-related Dysfunctional Beliefs about Sleep	12.6 ± 5.4	12.1 ± 5.0	0.59
Fear of Progression	35.0 ± 12.3	33.9 ± 11.8	0.58
Patient Health Questionnaire-9	11.6 ± 7.2	12.5 ± 6.6	0.42
State Subcategory of State and Trait Anxiety Inventory	42.3 ± 10.9	41.8 ± 10.6	0.81
Time variables			
Sleeping pills ingestion time	10:42 ± 1:10 pm	10:22 ± 1:21 pm	0.13
Bedtime	10:54 ± 1:10 pm	10:30 ± 1:09 pm	0.037
Sleep onset time	11:18 ± 1:09 pm	12:07 ± 1:24 pm	<0.01
Wake-up time	6:33 ± 1:25 am	6:59 ± 1:30 am	0.10
Duration variables			
Sleep latency (min)	22.8 ± 10.0	96.0 ± 54.0	<0.01
Time in bed (h)	7.6 ± 1.5	8.5 ± 1.6	<0.01
Time in bed during 24 h, TIB/d (h)	9.9 ± 3.1	11.8 ± 3.7	<0.01
Duration from pills to bedtime, PTB (min)	12.6 ± 24.6	7.2 ± 48.6	0.41
Duration from pills to sleep onset time, PTS (min)	36.0 ± 25.8	103.8 ± 61.2	<0.01
Duration from pills to wake-up time, PTW (h)	7.9 ± 1.5	8.6 ± 1.7	<0.01
Duration from wake-up time to bedtime, WTB (h)	16.4 ± 1.5	15.5 ± 1.6	<0.01

Duration from wake-up time to sleep onset time, WTS (h)	16.7 ± 1.5	17.1 ± 1.5	<0.01
Number of tablets of equivalent hypnotic drugs, TEQ (tablets)	0.87 ± 0.38	1.00 ± 0.54	0.07

^aSL, sleep latency

Table 3. Clinical characteristics of cancer patients who were not taking sleeping pills (N = 90)

	SL ^a ≤ 30 (N = 28)	SL ^a > 30 (N = 62)	<i>p</i> -value
Male, N (%)	6 (21.4)	6 (9.7)	0.12
Age (years)	54.4 ± 9.8	53.3 ± 12.0	0.67
Rating scales scores			
Insomnia Severity Index	12.2 ± 6.3	17.2 ± 5.0	< 0.01
Cancer-related Dysfunctional Beliefs about Sleep	11.3 ± 4.8	11.6 ± 5.3	0.82
Fear of Progression	33.3 ± 12.4	35.8 ± 13.3	0.41
Patient Health Questionnaire-9	9.1 ± 6.3	11.7 ± 7.1	0.10
State subcategory of State and Trait Anxiety Inventory	41.6 ± 15.3	42.8 ± 11.5	0.69
Time variables			
Bedtime	10:45 ± 1:16 pm	10:38 ± 1:02 pm	0.62
Sleep onset time	11:00 ± 1:15 pm	12:34 ± 1:18 pm	<0.01
Wake-up time	6:06 ± 1:30 am	7:05 ± 1:08 am	<0.01
Duration variables			
Sleep latency (min)	14.4 ± 14.4	115.8 ± 67.2	<0.01
Time in bed (h)	7.3 ± 1.7	8.5 ± 1.3	<0.01
Time in bed during 24 h, TIB/d (h)	9.7 ± 3.5	11.0 ± 3.8	<0.01
Duration from wake-up time to bedtime, WTB (h)	16.7 ± 1.6	15.5 ± 1.4	<0.01
Duration from wake-up time to sleep onset time, WTS (h)	16.9 ± 1.7	17.5 ± 1.2	0.08

^aSL, sleep latency

Table 4. Spearman's correlation (rho) analysis of sleep latency with the clinical characteristics of insomnia patients

	Sleeping pill Non-users (N = 90)		Sleeping pill users (N = 145)	
	SL ^a	TIB/d ^b	SL ^a	TIB/d ^b
Age	-0.07	-0.03	0.01	-0.01
Rating scale scores				
Insomnia Severity Scale	0.33**	0.15	0.25**	0.11
Cancer-related Dysfunctional Beliefs about Sleep	0.01	0.03	-0.05	-0.05
Fear of Progression	0.16	0.23*	-0.09	0.12
Patient Health Questionnaire-9	0.23*	0.34**	0.05	0.17*
State subcategory of State and Trait Anxiety Inventory	0.12	0.24*	-0.05	0.10
Time variables				
Sleeping pills ingestion time	-	-	-0.15	-0.19*
Bedtime	-0.17	-0.28**	-0.22**	-0.11
Sleep onset time	0.60**	0.002	0.35**	0.09
Wake-up time	0.34**	0.43**	0.22**	0.44**
Duration variables				
Sleep latency (SL)	-	0.28**	-	0.37**
Time in bed	0.38**	0.60**	0.35**	0.51**
Time in bed during 24 h (TIB/d)	0.28**	-	0.37**	-
Duration from pills to bedtime (PTB)	-	-	-0.16	-0.001
Duration from pills to sleep onset time (PTS)	-	-	0.76**	0.34**
Duration from pills to wake-up time (PTW)	-	-	0.28**	0.50**

Duration from wake-up time to bedtime (WTB)	-0.38**	-0.60**	-0.35**	-0.51**
Duration from wake-up time to sleep onset time (WTS)	0.30**	-0.39**	0.14	-0.33**
Number of tablets of equivalent hypnotic drugs (TEQ)	-	-	0.08	0.26**

^aSL, sleep latency; ^bTIB/d, time in bed during 24 h

* $p < 0.05$

** $p < 0.01$

Table 5. Logistic regression analysis to explore expecting variables for sleep latency ≤ 30 min

A) Among subjects who are not taking sleeping pills (N = 90)*				
Time variables	Crude OR^a	95% CI^b	Adjusted OR^a	95% CI^b
Insomnia severity index score	0.85	0.77–0.94	0.82	0.71–0.93
Wake-up time	0.54	0.35–0.83	0.39	0.19– 0.78
Sleep onset time	0.35	0.21–0.59	0.50	0.27–0.93
Duration variables	Crude OR^a	95% CI^b	Adjusted OR^a	95% CI^b
Insomnia severity index score	0.85	0.77–0.93	0.78	0.68–0.89
Duration from wake-up time to bedtime	1.78	1.23–2.56	2.49	1.48–4.18
B) Among subjects who are taking sleeping pills (N = 145)**				
Time variables	Crude OR^a	95% CI^b	Adjusted OR	95% CI^b
Sleep onset time	0.488	1.61–2.92	0.54	0.39–0.76
Duration variables	Crude OR^a	95% CI^b	Adjusted OR^a	95% CI^b
Duration from pills to sleep onset time	0.04	0.01–0.13	0.05	0.02–0.16

^aOR, odds ratio; ^bCI, confidence interval.

*Adjusted for age, sex, cancer types, TNM staging, psychiatric diagnosis, and insomnia severity index score

**Adjusted with age, sex, cancer types, TNM staging, psychiatric diagnosis, insomnia severity index score, and number of tablets of equivalent hypnotic drugs

Table 1. Clinical characteristics of the study subjects (N = 235)

Variable	Subjects
Female, n (%)	175 (74.5%)
Age (years)	56.1 ± 11.2
Cancer type	
Breast	103 (43.8%)
Lung	20 (8.5%)
Gastro-esophageal	19 (8.1%)
Pancreatic and biliary tract	17 (7.2%)
Colorectal	15 (6.4%)
Head and neck	14 (6.0%)
Gynecologic	12 (5.1%)
Hematologic	11 (4.7%)
Kidney	7 (3.0%)
Urinary tract	6 (2.6%)
Liver	5 (2.1%)
Thyroid	3 (1.3%)
Others	3 (1.3%)
Cancer stages *	
Stage 0	3 (1.4%)
Stage I	52 (24.4%)
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Insomnia	153 (65.1%)
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No diagnosis	3 (1.3%)
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*Patients with cancer can be graded using the TNM staging system (n = 213)

Table 2. Clinical characteristics of cancer patients who were taking sleeping pills (N = 145)

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Sleep latency (min)	22.8 ± 10.0	96.0 ± 54.0	<0.01
Time in bed (h)	7.6 ± 1.5	8.5 ± 1.6	<0.01
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Number of tablets of equivalent hypnotic drugs, TEQ (tablets)	0.87 ± 0.38	1.00 ± 0.54	0.07

^aSL, sleep latency

Table 3. Clinical characteristics of cancer patients who were not taking sleeping pills (N = 90)

	SL ^a ≤ 30 (N = 28)	SL ^a > 30 (N = 62)	<i>p</i> -value
Male, N (%)	6 (21.4)	6 (9.7)	0.12
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Rating scale scores				
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^aOR, odds ratio; ^bCI, confidence interval.

*Adjusted for age, sex, cancer types, TNM staging, psychiatric diagnosis, and insomnia severity index score, [patient health questionnaire-9 items score](#), [fear of progression scale score](#), [cancer-related dysfunctional beliefs about sleep scale](#), and [state subcategory of state and trait anxiety inventory](#)

**Adjusted with age, sex, cancer types, TNM staging, psychiatric diagnosis, insomnia severity index score, [patient health questionnaire-9 items score](#), [fear of progression scale score](#), [cancer-related dysfunctional beliefs about sleep scale](#) and [state subcategory of state and trait anxiety inventory](#), and number of tablets of equivalent hypnotic drugs