Impact of sleep status on lung adenocarcinoma risk: a prospective cohort study

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Abstract. – OBJECTIVE: The association between sleep status and lung adenocarcinoma risk was analyzed using long-term follow-up data from 60,443 patients over the period 2016-2022 to provide a reference for exploring the association between sleep status and lung adenocarcinoma development.

PATIENTS AND METHODS: Based on long-term follow-up data, a total of 60,443 people were included. Sleep data collected for the study included insomnia symptoms, lunch break habits, and sleep duration. A sleep score (0-3) was constructed based on difficulty falling asleep, premature awakening and sleep duration. Proportional risk regression models were used to analyze the association between each sleep factor, sleep score and lung cancer risk.

RESULTS: The study population was followed up for 9.9 ± 4.8 years and a total of 307 cases of lung adenocarcinoma were first recorded during the follow-up period. After controlling for potential confounders, the risk ratios (HR) for lung adenocarcinoma in those with difficulties going asleep or waking up too early were 1.12 (95% CI: 1.02-1.14) and 1.07 (95% CI: 1.01-1.11), respectively, compared to those without symptoms of insomnia. The HR for lung adenocarcinoma in those with less than 7 h of sleep [HR = 1.17 (95% CI: 1.05-1.21)] was compared to those with ≥ 7 h of sleep per day. Compared to those with a sleep score of 3 (highest quality sleep), those with a sleep score of 2, 1 and 0 corresponded to HR of 1.06 (95% CI: 1.01-1.12), 1.11 (95% CI: 1.09-1.18) and 1.15 (95% CI: 1.01-1.32) respectively.

CONCLUSIONS: Patients who suffer from insomnia or have a short sleep schedule are at increased risk of developing lung cell cancer. Sleep has an important impact on health and improving sleep conditions can reduce the incidence of lung cancer.

Key Words:
Sleep quality, Lung adenocarcinoma, Sleep score, Influencing factors, Cohort study.

Introduction

Currently, lung cancer is the biggest cause of cancer-related fatalities worldwide, and its incidence continues to climb[1]. Non-small cell lung cancer accounts for approximately 85% of lung cancer cases, while lung adenocarcinoma accounts for approximately 50% of newly diagnosed non-small cell lung cancer cases. Current 5-year survival rates for lung adenocarcinoma range from 5% to 14%, with developing countries having a significantly lower 5-year survival rate than developed nations[2-4].

The majority of lung adenocarcinoma patients are diagnosed at a late stage, losing the opportunity for radical surgery and ultimately passing away[5-7]. This is primarily due to cancer cells' malignant proliferation, invasion, and metastasis[8-10]. The pathogenesis of lung adenocarcinoma is complex and involves a combination of genetic and environmental factors, and the exact mechanisms remain unclear[11-13]. Goodarzi et al[14] have shown that the Human Development Index can influence the development of various types of cancer, while Soucise and Vaughn[15] found that patients with poor sleep quality were more likely to develop breast cancer. Several studies[16,17] have shown that sleep status is associated with coronary heart disease, stroke, diabetes, chronic kidney disease, malignancy, depression and many other diseases.

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Only one study has reported an association between snoring and lung adenocarcinoma risk, and no other sleep-related factors have been studied[18]. This study analyses the association between sleep status and lung adenocarcinoma risk in Chinese adults based on long-term follow-up data from 60,443 patients during 2016-2022 in China, thus providing a reference for subsequent studies on the effect of sleep status on lung adenocarcinoma development.

Patients and Methods

Study Population

Recruitment of study participants and completion of surveys were performed in 10 urban areas and 10 rural areas selected from three provinces in China (Yunnan, Guizhou and Sichuan) between 2016 and 2022. A total of 60,443 study subjects were available for analysis. Study subjects who reported having lung disease, self-reported extreme sleep duration (≤ 2 h/d or ≥ 13 h/d), and with a history of cancer were eliminated from the study, leaving a total of 60,443 participants.

Evaluation of Sleep Status

The following 4 areas were obtained through face-to-face questioning by the investigator:

1) Insomnia symptoms: ask if the following have occurred in the past month: 1. difficulty falling asleep: ≥ 3 d per week requiring more than half an hour to fall asleep (including after waking up in the middle of the night); 2. waking up too early: ≥ 3 d per week waking up very early in the morning and having difficulty falling back to sleep.
2) Lunch break: ask if you take a lunch break.
3) Snoring: ask if you have a habit of snoring when you sleep.
4) Sleep duration: asking how many hours of sleep (including lunch breaks) on average per day, usually. Approximately 4.9% of the study population was randomly selected within 1-2 weeks after the baseline survey for a quality control survey of some of the core questions in the questionnaire. A total of 2,962 people were surveyed and the Spearman's correlation coefficient for self-reported sleep duration between the two surveys was 0.93 ($p < 0.01$).

In this study, sleep scores were constructed based on 3 sleep factors: difficulty in falling asleep, waking up too early, and sleep duration. The sleep score was assigned a value of 1 for no difficulty falling asleep, no premature awakening, and sleep duration ≥ 7 h/d, and a value of 0 for not satisfying each of the 3 sleep factors. The range of the sleep score was 0-3, with higher scores indicating better sleep quality.

Covariate Evaluation

The baseline survey was conducted by uniformly trained enumerators who asked to obtain: (i) socio-demographic information – sex, age, occupation, education level, annual household income; (ii) lifestyle – smoking status, physical activity, tea and alcohol consumption, intake of dairy products, fresh vegetables and fresh fruit; (iii) height (cm) and weight (kg) were measured using a uniformly calibrated instrument.

Outcome Evaluation

Information on morbidity and mortality during follow-up was obtained from multiple sources, including the Universal Health Coverage database, routine disease and mortality surveillance systems and active targeted surveillance. For disease coding, the 10th Revision (ICD-10) was utilized. Outcome events in this study included the first recorded incidence of lung cell carcinoma during follow-up

Statistical Analysis

Using general linear regression models for continuous variables and logistic regression models for categorical variables, describe the baseline characteristics of the population in different sleep score groups, reporting means or composition ratios after adjusting for age, gender, and region.

Follow-up of patients was recorded from the completion of the baseline survey until patients presented with a confirmed lung adenocarcinoma, died, were lost to follow-up or the date reached the survey cut-off on 31 December 2017. Proportional risk regression models were used to analyze the association between sleep status and lung adenocarcinoma risk, using age as the time scale, stratified by age (5-year age group) and region (10 regions) jointly, with estimated risk ratios HR and 95% CI models adjusted stepwise for known or possible confounders. Model 1 was analyzed primarily as a gender factor. Model 2 was further analyzed by adding factors such as education, occupation, annual household income, smoking, physical activity level, alcohol consumption, and intake of various foods and fruits. Model 3 further analyses the patient's BMI.

In this study, subgroup analyses were conducted according to different baseline characteristics and interaction tests were used to compare whether the differences between models with and without interaction terms were statistically significant using likelihood ratio tests. Stata 20.0 software (StataCorp LLC, College Station, TX, USA) was used for data analysis and all tests were two-sided, with differences deemed statistically significant if $p < 0.05$.

Results

Baseline Characterization

As shown in Table I, the baseline age of the 60,443 study participants included in the analysis was 47.0 ± 17.3 years, 58.84% were female and 44.34% were urban dwellers. The higher the sleep score, the younger the age, the higher the proportion of males and the higher the BMI compared to those with lower sleep quality (those with a sleep score of 0-1).

Analysis of the Association Between Sleep Status and Lung Cancer Risk

As shown in Table II, the study subjects included in the analysis were followed up for 9.9 ± 4.8 years. A total of 307 cases of lung adenocarcinoma were first recorded during the follow-up period. After adjusting for potential confounders, those with insomnia symptoms had a 73% increased risk of lung adenocarcinoma compared to those without insomnia symptoms (HR=1.12, 95% CI: 1.02-1.14). The HR (95% CI) corresponding to difficulty falling asleep and waking up too early was 1.13 (95% CI: 1.02-1.19) and 1.07 (95% CI: 1.01-1.11). There was no statistically significant association between daytime sleepiness, lunch break, snoring and risk of lung adenocarcinoma.

For sleep duration, compared to those sleeping 9 h per day, those sleeping ≤ 4, 5, 6, 7, 8 and ≥ 10 h/d corresponded to HR of 1.36 (95% CI: 1.23-1.51), 1.15 (95% CI: 1.06-1.27), 1.12 (95% CI: 1.06-1.20), 1.05 (95% CI: 0.98-1.14), 1.09 (95% CI: 0.97-1.12), 1.08 (95% CI: 0.95-1.18) (p<0.001). Those who slept < 7 h/d had a 13% increased risk of lung adenocarcinoma compared to those who slept ≥ 7 h/d (HR=1.17, 95% CI: 1.05-1.21). After adjusting for potential confounding variables, those with a sleep score of 2, 1 and 0 had corresponding HR of 1.06 (95% CI: 1.01-1.12), 1.11 (95% CI: 1.09-1.18) and 1.15 (95% CI: 1.01-1.32), respectively, compared to those with a sleep score of 3 (highest quality sleep) (Table III). The HR for lung adenocarcinoma risk increased by 7% for each 1-point decrease in sleep score (HR=1.05, 95% CI: 1.03-1.12).

Subgroup Analysis

As shown in Table IV, the association between sleep score and lung adenocarcinoma risk was not completely consistent across people with different drinking statuses, smoking statuses, and physical

Table I. Baseline characteristics of the study population.

Baseline characteristics	Sleep score			
	0-1	2	3	*p*-value
Number of people (%)	6,907 (11.42%)	14,072 (23.28%)	39,464 (65.19%)	
Average age (years)	58.6	55.2	53.6	<0.001
Female (%)	65.4	61.9	56.6	<0.001
Urban residents (%)	41.7	49.4	43.0	<0.001
Alcohol consumption ≥ 50 g/d ethanol (%)				
Male	19.8	12.8	11.6	<0.001
Female	0.2	0.6	0.1	0.737
Intake ≥ 4 d per week (%)				
Red meat	47.2	49.8	51.9	<0.001
Dairy products	12.1	12.4	12.2	0.012
Vegetable	98.8	99.1	98.9	0.793
Fruit	22.4	26.2	30.4	<0.001
Smoking (%)				
Male	62.2	61.9	62.1	0.322
Female	2.6	2.1	2.3	0.021
Physical activity level ≥ 6 h/d (%)	21.2	22.9	23.1	<0.001
Average BMI (kg/m^2)				
Male	21.1	22.9	23.8	<0.001
Female	22.2	23.9	24.6	<0.001

Table II. Comparison of the association between sleep-related factors and lung adenocarcinoma.

Sleep status	Number of cases	Incidence of adenocarcinoma of the lung	Model 1	Model 2	Model 3
Insomnia symptoms					
No	51,245	0.46%	1.00	1.00	1.00
Yes	9,198	0.76%	1.14 (1.03-1.17)	1.12 (1.02-1.17)	1.12 (1.02-1.14)
Difficulty falling asleep					
No	49,072	0.49%	1.00	1.00	1.00
Yes	11,371	0.60%	1.13 (1.02-1.18)	1.12 (1.04-1.15)	1.13 (1.02-1.19)
Waking up too early					
No	50,241	0.46%	1.00	1.00	1.00
Yes	10,202	0.73%	1.04 (0.99-1.11)	1.07 (0.98-1.09)	1.07 (1.01-1.11)
Snoring					
Never	23,014	0.09%	1.00	1.00	1.00
Sometimes	19,201	0.12%	1.05 (1.02-1.09)	1.06 (1.01-1.13)	1.03 (0.95-1.09)
Always	18,228	0.14%	1.14 (1.02-1.18)	1.13 (1.04-1.16)	1.05 (0.92-1.11)
Sleep time (h/d)					
≤ 4	857	1.1%	1.41 (1.24-1.51)	1.34 (1.23-1.50)	1.36 (1.23-1.51)
5	5,039	0.71%	1.17 (1.07-1.28)	1.12 (1.05-1.27)	1.15 (1.06-1.27)
6	10,124	0.56%	1.13 (1.08-1.22)	1.11 (1.06-1.20)	1.12 (1.06-1.20)
7	13,727	0.51%	1.11 (0.99-1.15)	1.07 (0.98-1.14)	1.05 (0.98-1.14)
8	24,016	0.50%	1.06 (0.97-1.13)	1.05 (0.97-1.12)	1.09 (0.97-1.12)
9	5,658	0.47%	1.00	1.00	1.00
≥ 10	1,022	0.42%	1.09 (0.94-1.16)	1.02 (0.95-1.18)	1.08 (0.95-1.18)
Sleep time (h/d)					
≥7	44,423	0.49%	1.00	1.00	1.00
< 7	16,020	0.61%	1.17 (1.06-1.20)	1.16 (1.05-1.20)	1.17 (1.05-1.21)

Table III. Association between sleep score and lung cancer risk.

Sleep status	Number of cases	Incidence of adenocarcinoma of the lung	Model 1	Model 2	Model 3
0	2,042	0.78%	1.16 (1.05-1.34)	1.14 (1.07-1.32)	1.15 (1.01-1.32)
1	4,865	0.76%	1.12 (1.09-1.19)	1.10 (1.07-1.19)	1.11 (1.09-1.18)
2	14,072	0.54%	1.06 (1.01-1.12)	1.07 (1.02-1.14)	1.06 (1.01-1.12)
3	39,464	0.45%	1.00	1.00	1.00
Linear trend (1 point per reduction)			1.05 (1.03-1.12)	1.05 (1.02-1.10)	1.04 (1.02-1.19)

activity levels (p=0.0013, 0.014, <0.001). Effect values for the association between low sleep score (0-1) and lung adenocarcinoma risk were higher in those with smoking, alcohol consumption, and high physical activity levels. No statistically significant interactions were found when subgroup analyses were performed by other baseline characteristics.

Discussion

Using data from a large cohort, this study analyzed the association between sleep status and lung adenocarcinoma risk. The results showed that lung adenocarcinoma risk was increased in study subjects with symptoms of insomnia or short sleep duration[19]. Those with the lowest sleep quality (sleep score of 0) had a 73.3% increased risk of lung adenocarcinoma compared to those with the highest sleep quality (sleep score of 3).

Park and Bhandari[20] shows that insomnia and daytime sleepiness are related to the risk of several diseases, including cardiovascular disease, diabetes, and cancer. Before this study, no research has found a correlation between sleeplessness and lung cancer risk. However, this study has shown that two insomnia symptoms – trouble falling asleep and early awakening – were related to an increased risk of lung cancer, and Ravenel[21] noted that either too little or too much sleep can have adverse health effects, such as increased risk of

Table IV. Subgroup analysis of the association between sleep score and lung adenocarcinoma.

	0-1		2		3		
Subgroup	Incidence of adenocarcinoma of the lung	HR value (95%CI)	Incidence of adenocarcinoma of the lung	HR value (95%CI)	Incidence of adenocarcinoma of the lung	HR value (95%CI)	Interaction *p*-value
Age							0.29
< 60	0.56%	1.14 (1.07-1.22)	0.53%	1.08 (1.02-1.14)	131	0.54%	
≥ 60	0.64%	1.12 (1.00-1.25)	0.61%	0.99 (0.89-1.10)	1,305	0.59%	
Area							0.119
Rural	0.71%	1.40 (1.32-1.48)	0.62%	1.14 (1.08-1.20)	6,960	0.57%	
City	0.68%	1.15 (1.01-1.32)	0.63%	1.10 (1.00-1.22)	1,535	0.61%	
Sex							0.214
Male	0.65%	1.22 (1.12-1.33)	0.59%	1.04 (0.97-1.11)	4,068	0.52%	
Female	0.63%	1.12 (1.04-1.20)	0.58%	1.10 (1.03-1.18)	4,427	0.58%	
Tea consumption (cups/d)							0.113
< 3	0.64%	1.14 (1.07-1.21)	0.62%	1.08 (1.02-1.14)	6,330	0.58%	
≥3	0.63%	1.29 (1.15-1.45)	0.63%	1.08 (0.98-1.19)	2,165	0.57%	
Drinking							0.0013
< 30 mg/d	0.58%	1.16 (1.10-1.23)	0.56%	1.07 (1.02-1.12)	0.53%	1	
≥ 30 mg/d	0.64%	1.23 (1.01-1.49)	0.61%	1.15 (0.98-1.35)	0.60%	1	
Fruit intake (d/week)							0.164
< 4	0.62%	1.15 (1.09-1.22)	0.60%	1.09 (1.04-1.15)	6,873	0.55%	
≥ 4	0.66%	1.25 (1.10-1.42)	0.57%	1.00 (0.90-1.12)	1,622	0.54%	
Smoking							0.014
No	0.60%	1.14 (1.07-1.22)	0.57%	1.12 (1.06-1.19)	5,421	0.56%	
Yes	0.67%	1.21 (1.10-1.33)	0.64%	0.99 (0.91-1.07)	3,074	0.61%	
Physical activity level							<0.001
Low	0.65%	1.14 (1.03-1.25)	0.63%	0.95 (0.87-1.04)	2,398	0.59%	
High	0.51%	1.25 (1.14-1.38)	0.49%	1.09 (1.01-1.19)	2,929	0.48%	
BMI (kg/m²)							0.413
< 24.0	0.64%	1.13 (1.05-1.22)	0.62%	1.08 (1.02-1.16)	4,825	0.58%	
≥ 24.0	0.59%	1.23 (1.13-1.33)	0.54%	1.06 (0.99-1.14)	3,670	0.53%	

death, cardiovascular disease, type 2 diabetes, cognitive impairment and falls. In this study, the increased risk of lung adenocarcinoma was mainly found in those who slept < 7 h/d.

Maldonado and Chassagnon[22] found that inflammatory mediators, including C-reactive protein, interleukin-6 and tumor necrosis factor-alpha, were increased in the peripheral circulation of patients with sleep disorders. In addition, higher inflammatory proteins and decreased antioxidants were found in the urine and serum of lung cancer patients[23-25]. These results suggest that the inflammatory response may play an important role in the development of lung adenocarcinoma caused by sleep disturbances[26].

This study found that the effect values for the association between low sleep score and lung cancer risk were higher in people with adequate fruit intake or high physical activity levels[27-29]. Those with a higher fruit intake have a lower risk of developing lung cancer, according to previous research[30-32]. Increased physical activity led to increased fluid intake, and those who exercised regularly had a lower risk of lung cancer. In contrast, the baseline risk of lung adenocarcinoma was higher in individuals with inadequate fluid intake or low levels of physical activity, and the additional increase in risk due to low sleep quality was therefore less pronounced[33-35]. The results of this study show that the effect values for the association between low sleep scores and lung adenocarcinoma were higher among smokers; in addition to the carcinogenic nicotine ingested by smokers, tobacco contains high levels of unstable oxidants and free radicals, which cause the smoker's organism to be chronically over-oxygenated and increase lung damage, thus acting synergistically with low sleep quality[36].

Strengths and Limitations

The large sample size, long mean follow-up time and high cumulative number of cases in this study allowed for detailed grouping of sleep duration to explore trends in associations; the baseline survey provided multiple perspectives on sleep status and the opportunity to analyze the impact of multiple sleep factors on lung cancer risk. When possible, known or potential confounders were accounted for in the model, and suitable subgroup analysis was conducted based on baseline characteristics[37].

At the same time, there are some limitations to this study. Information on sleep scores of the subjects included in this study was only collected at the baseline survey and did not take into account changes in respondents' sleep status over time. Follow-up studies will continue to investigate the impact of sleep status over time on health status and further investigate the impact of changes in sleep status on the development and progression of lung adenocarcinoma. Further research will be conducted to investigate the mechanisms by which sleep status affects the development of lung adenocarcinoma.

Conclusions

Based on long-term follow-up data from 60,443 patients in China between 2016 and 2022, this study analyzed the association between sleep status and lung adenocarcinoma risk in Chinese adults and found that individuals with symptoms of insomnia or short sleep duration had an increased risk of developing lung adenocarcinoma. Improving sleep quality was effective in reducing the incidence of lung adenocarcinoma, and therefore the incidence of lung adenocarcinoma could be reduced by improving the quality of sleep in the population. Follow-up studies will further investigate the mechanisms by which sleep status regulates the development of lung adenocarcinoma and extend them to reduce the incidence of lung adenocarcinoma.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Informed Consent

Informed consent was obtained from all patients included in this study prior to submission of data.

Ethics Approval

The patient in our research has signed the informed consent. This study was designed in accordance with the Declaration of Helsinki and approved by the ethics committee of Kunming University of Science and Technology. Approval number: KUST2023032128.

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Data Availability

The data used to support the findings of this study are included within the article.

Authors' Contributions

Conceptualization: Qiang Cao and Qi Zhang, Methodology: Qiang Cao and Yi Qiang, Validation: Xiaochen Li, Formal analysis:Chunfang Ren ,Investigation: Qiang Cao and Qi Zhang, Resources: Chunfang Ren and Xiaochen Li, Data Curation: Yi Qiang, Writing - Original Draft: Qiang Cao, Writing - Review & Editing: Yi Qiang, Supervision: Yi Qiang, Project administration: Yi Qiang and Qiang Cao.

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