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Original article

Daytime napping and risk of liver cancer: A large population-based prospective cohort study

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ABSTRACT

Introduction and Objectives: Liver cancer is a major cause of morbidity and mortality in Japan and worldwide. Daytime napping is a common behavior, especially among older adults, that was related in previous research to unfavorable health conditions. Herein, we investigated the association between daytime napping and liver cancer risk.

Materials and Methods: In this prospective cohort study, data from 51,185 participants aged 40–79 years and registered in the Japan Collaborative Cohort Study (JACC Study) were analyzed. Incident cases of liver cancer were diagnosed using cancer registries, hospital records, and death certificates. Daytime napping was assessed using the JACC baseline self-administered questionnaire. We used the Cox regression to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) of incident liver cancer among participants in the age categories of the 40s, 50s, 60s, and 70s who reported daytime napping compared with their counterparts who did not.

Results: Within 669,734 person-years of follow-up, 341 participants developed liver cancer. Daytime napping was associated with a higher risk of liver cancer among participants who were in their 60s and 70s of age after adjusting for sex: HRs (95% CIs) 1.88 (1.35–2.61) and 1.96 (1.18–3.26), lifestyle and medical history: 1.76 (1.27–2.47) and 1.82 (1.07–3.09), and history of liver diseases: 1.66 (1.18–2.34) and 1.72 (1.01–2.94), respectively. No associations were detected among participants from the 40s and 50s age groups.

Conclusions: Daytime napping was associated with a higher risk of liver cancer among older adults.

1. Introduction

With 905,677 new cases and 830,180 deaths in 2020, liver cancer contributed to 4.7% of all-cause cancers and 8.3% of all cancer deaths worldwide. In the same year in Japan, liver cancer was the seventh most diagnosed cancer, with 45,663 new cases and the fifth leading cause of cancer death, with 28,155 deaths [1]. Most major risk factors for liver cancer, including chronic viral hepatitis, excessive alcohol drinking, obesity, and smoking, are modifiable, suggesting that liver cancer is potentially preventable [2].

On the other hand, a growing body of evidence has shown that some sleep behaviors could contribute to the increased risk of cancers, including liver cancer [3]. Of these behaviors, daytime napping, a common practice among community-dwelling older adults [4], was shown to be associated with all-cause, cardiovascular, and cancer mortality [5–11]. However, epidemiological evidence of the relationship between daytime napping and liver cancer risk is scarce and inconsistent; two studies showed a positive association in the minimally adjusted regression models only [12,13], while one study showed no association at all [9]. In addition, the previous studies were limited by the lack of adjustment for important confounders such as chronic hepatitis [9,13] and alcohol consumption [13], confining analysis to women [9,12] who have a lower risk of liver cancer than men [2], and not studying the impact of age [9,12,13] despite previous literature suggested varying effects of daytime napping on health outcomes by participants' age [14,15].

Abbreviations: CI, Confidence interval; HR, Hazard ratio; JACC Study, Japan Collaborative Cohort Study

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Herein, we used data from the Japan Collaborative Cohort Study (JACC Study) to study the prospective association between daytime napping and the risk of liver cancer among Japanese middle-aged and older adults. We avoided the limitations of the previous studies by adjusting the results for most potential confounders and measuring the impact of sex and age on the association.

2. Materials and Methods

2.1. Study population and baseline questionnaire

The JACC Study is a prospective cohort study that aims to investigate the risk factors for cancer and cardiovascular diseases among middle-aged and older adults in Japan. The JACC baseline self-administered questionnaire was collected from 110,585 people aged 40−79 years between 1988 and 1990 from 45 areas. Of them, 65,042 participants in 24 areas were followed up for cancer incidence to the end of 1994 in one area, 1997 in four areas, 1999 in one area, 2000 in one area, 2002 in eight areas, 2003 in one area, 2006 in two areas, 2008 in two areas, and 2009 in four areas [16,17].

In the current study, we excluded 1,604 participants for having a positive history of cancer before the baseline, 6,806 participants for working night or rotational shifts, and 5,447 participants for having no data about daytime napping to leave a total of 51,185 participants for analysis.

2.2. Outcome, exposure, and covariates

Data about cancer incidence were collected using a systematic review of population-based cancer registries, hospital records, and death certificates. Incident cases of liver cancer were given a code of (C22) that included malignant neoplasm of the liver and intrahepatic bile ducts according to the ICD-10 [16,17]. Daytime napping was assessed during the preceding year using a question in the baseline questionnaire, *"Do you take daytime napping?"* with *"yes"* and *"no"* as possible responses [8]. Regarding covariates, data about participants' age, sex, weight and height, education, employment, sleep duration, perceived stress, smoking habits, alcohol consumption, walking and leisure physical activities, medical histories of diabetes, liver diseases including hepatitis, and gallbladder diseases including stones or inflammation, blood transfusion, and family history of cancer were retrieved from the baseline questionnaire.

2.3. Statistical analysis

The differences in the age-and sex-adjusted mean values and proportions of sociodemographic characteristics between participants with and without daytime napping were calculated using the linear and logistic regression analyses, respectively. The Cox proportional hazards models were used to calculate the age-stratified hazard ratios (HRs) with their 95% confidence intervals (CIs) of liver cancer incidence for daytime napping among all participants and participants in their 40s, 50s, 60s, and 70s of age compared to their counterparts who did not report daytime napping. In a further analysis, we stratified participants by their age group and daytime napping behavior into the following groups: 40s−50s/no daytime napping, 40s−50s/daytime napping, 60s−70s/no daytime napping, and 60s−70s/daytime napping before computing the HRs (95% CIs) of liver cancer for the last three groups compared to the first group.

Person-years of follow-up were calculated from the date of baseline to the date of liver cancer diagnosis, death, moving out, or end of the study. The HRs were adjusted for the following variables: sex, age (years), body mass index (<18.5, 18.5−24.9, or ≥25 kg/m^2), education (<16, 16−17, or ≥18 years), employment (employed, part−time, self−employed, housemaker, unemployed, or others), sleep duration (<six, six to eight, or >eight hours/day), perceived stress (no, mild, moderate, or high), smoking (never, ex <20 cigarettes/day, ex ≥20 cigarettes/day, current <20 cigarettes/day, or current ≥20 cigarettes/day), alcohol intake (never, ex, current <180 ml/day, or current ≥180 ml/day), leisure physical activity (never, one to two, three to four, or ≥five hours/week), walking (never, <30, 30−60, or >60 minutes/day), history of diabetes (yes or no), history of gallbladder diseases (yes or no), previous blood transfusion (yes or no), history of liver diseases (yes or no), and family history of cancer (yes or no). Dummy categories were made for missing data. We conducted four sensitivity analyses that included removing participants with a follow-up period ≤three years (n= 2,164), with a positive history of liver diseases (n= 3,525), who reported short (<six hours/day) or long (>eight hours/day) sleep duration (n= 8,588), and who reported being unemployed or housemaker (n= 17,361). SAS version 9.4 software (SAS Institute Inc, Cary, NC) was used for statistical analyses.

2.4. Ethical statement

The research ethics committees of Nagoya University School of Medicine and Osaka University approved the protocol of the JACC study (number/ID 14285-6). Informed consent was obtained not only from participants but, in some areas, from community leaders.

3. Results

Among the 51,185 participants, 16,863 (32.9%) reported daytime napping. Compared with non-daytime nappers, the group of daytime nappers included higher proportions of older adults and men but lower proportions of highly educated and employed individuals (p-value< 0.001). The proportion of participants with a positive history of liver diseases did not differ significantly between both groups: 7.7% in daytime nappers versus 6.5% in non-daytime nappers (p-value= 0.250) (Table 1).

Within 669,734 person-years (median= 13.7 years) of follow-up, 341 participants developed liver cancer. In the overall sample, daytime napping was associated with the increased risk of liver cancer in the models adjusted for sex and age: 1.58 (1.27−1.97), lifestyle and medical history: 1.40 (1.12−1.75), and history of liver diseases: 1.31 (1.04−1.64). The results were consistent across the sexes. In the age-stratified analyses, daytime napping was associated with an increased risk of liver cancer among participants in their 60s and 70s

Table 1
Age-and sex-adjusted sociodemographic characteristics of participants distributed by their daytime napping

	Daytime napping	No daytime napping	P-value
Study population	16,863	34,322	–
Age (years)*	60.6 (10.2)	56.5 (9.9)	<0.001
Men %	43.9	35.4	<0.001
BMI (kg/m^2)*	22.9 (3.1)	22.7 (2.9)	<0.001
Education ≥18 years %	30.5	41.7	<0.001
Sleeping hours/day*	7.5 (1.2)	7.1 (1.0)	<0.001
Sleep <6 hours/day %	8.4	9.0	<0.001
Sleep 6−8 hours/day %	78.8	85.4	
Sleep >8 hours/day %	12.8	5.6	
Employed %	11.4	27.1	<0.001
High perceived stress %	19.6	15.3	<0.001
Current smoking %	23.2	21.2	<0.001
Current alcohol intake %	41.4	40.9	0.027
No leisure sport %	67.3	69.8	0.650
No walking %	8.9	9.7	<0.001
History of diabetes %	6.3	4.5	0.242
History of gallbladder disease %	5.0	4.9	0.018
History of liver disease %	7.7	6.5	0.250
History of blood transfusion %	10.2	8.4	0.329
Family history of cancer %	3.3	3.9	0.001

* Mean (standard deviation) for all such variables.

of age in the models adjusted for sex: 1.88 (1.35−2.61) and 1.96 (1.18 −3.26), lifestyle and medical history: 1.76 (1.26−2.47) and 1.82 (1.07 −3.09), and history of liver diseases: 1.66 (1.18−2.34) and 1.72 (1.01 −2.94), respectively. Daytime napping was not related to liver cancer risk among participants from the age groups 40s and 50s in all regression models (Table 2).

Compared to participants in their 40s or 50s of age who reported no daytime napping, their peers of the same age but who reported daytime napping showed no excess risk of liver cancer in the most adjusted model: 1.02 (0.70−1.49). Older non-daytime nappers showed increased liver cancer risk: 1.62 (1.16−2.27), and the risk was much higher among older daytime nappers: 2.57 (1.86−3.55). The results did not materially change across the sexes (Table 3).

The association among participants in their 60s and 70s of age remained significant after excluding participants with a follow-up period ≤ three years: 1.77 (1.20−2.62) and 1.95 (1.00−3.85), respectively (Supplementary Table 1). Excluding participants with a positive history of liver diseases did not affect the association between daytime napping and liver cancer risk in the 60s age group 1.73 (1.07 −2.81) and even strengthened the association in the 70s age group 2.53 (1.25−5.14) (Supplementary Table 2). Alike, excluding participants with a short or long sleep duration did not affect the association between daytime napping and liver cancer risk in the 60s age group 1.65 (1.13−2.40) and the 70s age group 2.05 (1.06−3.98) (Supplementary Table 3). On the other hand, excluding the unemployed and housemakers attenuated the association among participants in the 60s and 70s age groups to become statistically insignificant (Supplementary Table 4).

Table 2
Association between daytime napping and risk of liver cancer

	Daytime napping	No daytime napping
Overall (n= 51,185)		
Person-years	218,658	451,076
Incident cases	173	168
Model I	1.58 (1.27−1.97)	1
Model II	1.40 (1.12−1.75)	1
Model III	1.31 (1.04−1.64)	1
Men (n= 19,566)		
Person-years	94,727	161,894
Incident cases	107	94
Model I	1.55 (1.17−2.06)	1
Model II	1.35 (1.01−1.81)	1
Model III	1.25 (0.93−1.68)	1
Women (n= 31,619)		
Person-years	123,931	289,182
Incident cases	66	74
Model I	1.63 (1.16−2.28)	1
Model II	1.45 (1.03−2.04)	1
Model III	1.37 (0.97−1.94)	1
40s (n= 12,417)		
Person-years	42,296	145,478
Incident cases	7	18
Model I	1.31 (0.55−3.14)	1
Model II	1.03 (0.41−2.57)	1
Model III	0.95 (0.38−2.39)	1
50s (n= 15,751)		
Person-years	67,353	155,045
Incident cases	37	64
Model I	1.22 (0.81−1.83)	1
Model II	0.98 (0.64−1.49)	1
Model III	0.93 (0.61−1.43)	1
60s (n= 15,467)		
Person-years	72,642	114,450
Incident cases	83	64
Model I	1.88 (1.35−2.61)	1
Model II	1.76 (1.26−2.47)	1
Model III	1.66 (1.18−2.34)	1
70s (n= 7,550)		
Person-years	36,367	36,103
Incident cases	46	22
Model I	1.96 (1.18−3.26)	1
Model II	1.82 (1.07−3.09)	1
Model III	1.72 (1.01−2.94)	1

Model I: Adjusted for sex and age in the overall analysis, age only in the sex-specified analysis, and sex only in the age−specified analysis.
Model II: Adjusted further for body mass index, education, sleep duration, employment, stress, smoking, alcohol, physical activity, walking, histories of diabetes, gallbladder diseases, and blood transfusion, and family history of cancer.
Model III: Adjusted further for liver disease history.
P-values for sex interaction= 0.775 and for age-group interaction= 0.116

4. Discussion

Our study indicated that within a median follow-up period of 13.7 years, daytime napping was associated with an increased risk of liver cancer in older Japanese participants in their 60s and 70s of age by 66% and 72%, respectively. On the other hand, daytime napping was not related to liver cancer risk among younger age categories.

An early report using data from the JACC Study revealed that the age-adjusted association between daytime napping (yes versus no) and mortality from liver cancer was significant in women: HR (95% CI): 1.62 (1.17−2.24) and tended to be significant in men 1.23 (0.97 −1.55) [13]. Unlike our study, the former JACC Study examined the risk of cancer mortality as a proxy for incidence, had a relatively short follow-up period, included nightshift and rotational shift workers who might show disturbed sleep and high risk of cancer [18,19], did not adjust their results for most confounders including the history of liver diseases and alcohol intake, and did not examine the impact of age on the association.

Later, the Million Women Study showed that daytime napping was not associated with liver cancer risk among women aged 50−64 years; relative risks (95% CIs) of liver cancer for daytime napping (sometimes/usually versus rarely/never) were 1.19 (0.84−1.69) during the first four years and 1.09 (0.82−1.46) in longer follow-up years [9]. Though, the Women's Health Initiative Study that included women aged 50−79 years, relatively older than the Million Women Study, showed that daytime nappers were at higher risk of liver cancer: HR (95 CI%) of liver cancer for daytime napping (≥one to two times/day versus <one time/day) were 1.40 (1.02−1.90). However, additional adjustments for sociodemographic and clinical characteristics attenuated the association 1.12 (0.80−1.57) [12]. Unfortunately, both studies did not stratify their results by age group.

The mechanisms underlying the association between daytime napping and liver cancer are unknown; however, some explanations could be suggested. First, daytime napping may reflect a disturbed circadian clock [15]. Peripheral clock genes that regulate the absorption of xenobiotics are predominantly expressed in the liver [20], and their mutation can lead to liver cancer [21]. Second, daytime napping might be a consequence of obstructive sleep apnea [22], a common sleep disorder characterized by episodes of partial or complete upper airway collapse that result in fragmented sleep and daytime somnolence [23]. Human and animal studies showed that intermittent hypoxia attributed to obstructive sleep apnea was independently associated with non-alcoholic fatty liver disease via inducing hepatic steatosis, inflammation, and cirrhosis [24,25]. Patients with non-alcoholic fatty liver are at high risk of developing liver cancer [26,27]. Interestingly, the Multi-Ethnic Study of Atherosclerosis showed that Asians had significantly more obstructive sleep apnea than Caucasians [28], which could partly explain the positive results in the JACC Study and the negative results in the Western studies. Unfortunately, we could not test this assumption because we had no data about obstructive sleep apnea and we did not know exactly how many participants developed liver cancer related to non-alcoholic fatty liver.

Table 3
The combined effect of age and daytime napping on the risk of liver cancer

	40s–50s/ No napping	40s–50s/ Napping	60s–70s/ No napping	60s–70s/ Napping
Overall (n= 51,185)				
Person-years	300,524	109,650	150,552	109,008
Incident cases	82	44	86	129
Model I	1	1.39 (0.96–2.01)	2.22 (1.64–3.01)	4.23 (3.20–5.58)
Model II	1	1.14 (0.78–1.65)	1.65 (1.18–2.31)	2.72 (1.97–3.77)
Model III	1	1.02 (0.70–1.49)	1.62 (1.16–2.27)	2.57 (1.86–3.55)
Men (n= 19,566)				
Person-years	111,650	47,903	50,244	46,823
Incident cases	47	31	47	76
Model II	1	1.25 (0.78–1.99)	1.58 (1.01–2.49)	2.35 (1.53–3.62)
Model III	1	1.13 (0.71–1.81)	1.62 (1.03–2.54)	2.25 (1.46–3.46)
Women (n= 31,619)				
Person-years	188,874	61,747	100,308	62,185
Incident cases	35	13	39	53
Model II	1	0.89 (0.46–1.70)	1.50 (0.91–2.49)	2.86 (1.75–4.68)
Model III	1	0.76 (0.40–1.46)	1.39 (0.83–2.31)	2.66 (1.64–4.33)

Model I: Adjusted for sex in the overall analysis.
Model II: Adjusted further for body mass index, education, sleep duration, employment, stress, smoking, alcohol, physical activity, walking, histories of diabetes, gallbladder diseases, and blood transfusion, and family history of cancer.
Model III: Adjusted further for liver disease history.

The positive association between daytime napping and liver cancer risk among older but not younger participants came in line with previous reports that showed a higher risk of all-cause, cardiovascular, and cancer mortality among older daytime nappers than younger ones [10, 29–31]. One explanation is that younger adults take short daytime naps because they have to go back to work, while older adults, who are typically retired, have more free time to take longer daytime naps. Unlike long daytime napping, short daytime napping was shown to have no pathogenic impacts [31,32]. People who take short daytime naps do not enter deep slow-wave sleep, while those who take long daytime naps enter deep slow-wave sleep before disrupting the sleep cycle by awakening [33,34]. Such disruption is strictly associated with a disturbed circadian clock [35]. This explanation is supported by our sensitivity analysis that showed attenuation in the association between daytime napping and liver cancer risk after excluding participants who reported being unemployed or housemakers from the analysis. Besides, the increased prevalence of daytime napping among older adults could be related to chronic diseases such as cardiovascular disease that share common risk factors with liver cancer [36,37]. Still, this finding might reflect the increased risk of liver cancer among older adults or the limited number of liver cancer cases in the age groups 40s and 50s.

This study included several strengths, such as investigating a large cohort with no history of cancer, having a prospective cohort design with a long follow-up period, using standardized methods to diagnose liver cancer, measuring the impact of age on the association between daytime napping and the risk of liver cancer, and adjusting the results for most potential confounders.

However, some limitations should be addressed. First, daytime napping was evaluated using a simple yes/no question making misclassification possible. Second, the daytime napping question did not assess the duration and frequency of daytime napping; thus, a dose-response relationship could not be attained. Two meta-analyses of prospective cohort studies showed that the risk of all-cause mortality was more evident among participants with daytime napping ≥60 min than participants with daytime napping <60 min [11,31]. Third, daytime napping was assessed at a one-time point; we do not know whether participants changed their daytime napping behavior during follow-up. Fourth, it could be speculated that the lifestyle and health conditions of daytime nappers were the reason behind the increased risk of liver cancer rather than daytime napping itself. This possibility cannot be entirely excluded, yet excluding participants with liver diseases, including hepatitis, which is considered the chief risk factor for liver cancer among Japanese [38], did not affect the results. It could also be speculated that daytime napping could refer to a short or long sleep duration, which is considered a risk factor for liver diseases [39] and cancer [12]. However, excluding participants with short or long sleep duration from the analysis did not affect the results. Besides, the positive association between daytime napping and liver cancer risk remained significant after excluding participants with a follow-up period of ≤three years, suggesting that preclinical conditions cannot explain this association. Finally, because of the observational nature of this study, the presence of undetected confounders was likely.

5. Conclusions

In conclusion, daytime napping could be associated with a higher risk of liver cancer among older adults. More studies to elucidate biological explanations are warranted. Future studies should assess the frequency and duration of daytime napping and stratify their results by participants' age.

Author contributions

AA (conceptualization, review literature, draft writing, and data analysis), EE and HI (supervision), EE, KS, IM, AT, and HI (visualization, critical revision, and editing), and AT and HI (resources and funding acquisition). All authors approve the final version of the manuscript, including the authorship list, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data availability statement

Data cannot be shared for privacy and ethical reasons.

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Declaration of interest

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.aohep.2022.100877.

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