Associations of daily walking and television viewing time with liver cancer mortality: findings from the Japan Collaborative Cohort Study

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The members of the JACC Study Group are provided in the appendix.

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Abstract

Background and purpose: Several studies have suggested that daily vigorous physical activity reduces the risk of liver cancer, whereas sedentary behavior increases the risk of several cancers. However, the link between liver cancer and low-intensity physical activity (walking) and sedentary behavior is unclear. Therefore, we explored the links between liver cancer mortality and daily walking time/television (TV) viewing time in Japanese adults aged 40 to 79 years in a large-scale nationwide cohort study.

Methods: We excluded participants with a history of liver disease, cancer, stroke, or myocardial infarction at baseline (1988–1990) and those who died within the first 5 years of follow-up. A total of 69,752 adults (28,642 men and 41,110 women) were enrolled and followed for a median of 19.4 years. The Cox proportional hazards model was used to calculate hazard ratios (HRs) and 95% confidence intervals (CI) for liver cancer mortality adjusted for age, sex, and other possible confounding factors.

Results: During the study period, 267 participants died of liver cancer. The HRs of participants who walked for >0.5 hours/day and watched TV for 2 to 4 hours/day versus <2 hours/day were 0.58 (95% CI, 0.39–0.89) and 0.58 (95% CI, 0.35–0.98),

respectively, compared with those who walked for <0.5 hours/day and watched TV for >4 hours/day.

Conclusions: Our findings suggest that longer walking times and shorter TV viewing times may reduce the risk of liver cancer.

Abbreviations

BMI = body mass index

CI = confidence interval

HBV = hepatitis B virus

HCV = hepatitis C virus

HR = hazard ratio

ICD = International Classification of Disease

JACC Study = Japan Collaborative Cohort Study

TV = television

Introduction

Liver cancer is the third most common cause of cancer-related death worldwide [1]. Several reviews have suggested that hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, cirrhosis, obesity, heavy alcohol intake, and cigarette smoking are associated with increased risks of liver cancer, whereas coffee intake is associated with a decreased risk of liver cancer [2-7]. Chronic HBV and/or HCV infection is the strongest contributor to the development of liver cancer in Japan [8].

Two previous reports suggested that daily vigorous physical activity [9,10] and leisure time physical activity [11] reduce the risk of liver cancer. On the other hand, sedentary behavior, including watching television (TV), is reportedly associated with obesity, diabetes, and the risk of several cancers [12,13]. However, the impact of low-intensity physical activities (e.g., walking) and sedentary behavior on liver cancer has not been reported. Therefore, the aim of this study was to determine whether a prolonged daily walking time and TV viewing time is associated with liver cancer mortality in Japanese participants aged 40 to 79 years.

Material and Methods

Study population and data collection

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study) was established in 1988-90 and has been described in detail elsewhere [14]. Briefly, 110,585 (46,395 men and 64,190 women) apparently healthy inhabitants aged 40 to 79 years from 45 areas throughout Japan were enrolled. Participants were mostly recruited at the time of their health check-up using a self-administered questionnaire, and a response rate of 86% to 91% was obtained.

Information on the average daily number of hours spent walking and watching TV and other lifestyle factors was obtained in the baseline questionnaire. Two categories of walking time (≤0.5 and >0.5 hours/day) were created. TV viewing time was categorized into three groups (<2, 2 to <4, and ≥4 hours/day) because the average amount of time Japanese adults spend watching TV has been reported to be about 3 to 4 hours/day [15] and because several previous studies reported associations between TV watching and the incidence of lung cancer [16] and cardiovascular disease [17].

Of the 110,585 original cohort members, 11,093 participants were excluded because they had a medical history of liver disease, cancer, stroke, or myocardial infarction at baseline. An additional 17,782 participants in 5 areas were also excluded because the questionnaire used there did not include items on the average number of daily hours of walking and TV viewing. A further 3,670 participants were excluded because they died within the first 5 years of follow-up. Finally, 8,297 participants with missing data for the average daily hours of walking and/or TV viewing were excluded. Consequently, 69,752 (28,642 men and 41,110 women) participants were analyzed in the present study.

Follow-up

The date and cause of death were confirmed by death certificates and coded according to the 10th revision of the International Classification of Disease (ICD-10). The primary outcome for the present study was death of primary liver cancer (C22). Participants who moved away from the study area during the study period were treated as censored cases. The overall study design was approved by the Ethical Board of Nagoya University

School of Medicine.

Statistical analysis

Age- and sex-adjusted and multivariate hazard ratios (HR) and confidence intervals (CI) for liver cancer mortality were calculated using a Cox proportional hazards model. Demographic information such as age (as a continuous variable), sex, smoking status (never, former, current smokers or unknown), alcohol consumption (never, former, current alcohol drinker of 0.1–22.9, 23.0–45.9, or 46 g ethanol/day or unknown), daily consumption of coffee (0, <1, or ≥1 cups/day or unknown), body mass index (BMI; <18.5, 18.5–24.9, or ≥25.0 kg/m^2 or unknown), educational level (school up to age 15, 15–18, or ≥19 years or unknown), marital status (single, married, divorced/widowed, or unknown), and a self-reported medical history of diabetes mellitus, gallbladder diseases, and blood transfusion were included in the multivariate models. Tests for linear trends were conducted to assess associations between the original continuous variables of the number of daily hours spent watching TV and the risk of liver cancer mortality. We also conducted additional analyses stratified by sex. An alpha level of 0.05 was considered to

be statistically significant. All statistical analyses were performed using JMP Pro version 10.0.2 for Mac (SAS Institute Inc., Cary, NC, USA).

Results

The median follow-up period was 19.4 years. During 1,190,482 (men, 486,080; women, 704,402) person-years of follow-up, 267 (163 men and 104 women) participants died of liver cancer, 2,822 left the study area, and 13,446 died of causes other than liver cancer. The mean age ± standard deviation of participants at baseline was 56.8 ± 10.0 years (men, 56.4 ± 10.0 years; women, 57.0 ± 10.0 years).

Baseline characteristics of the study participants according to walking and TV viewing time are shown in Table 1. Compared with the participants in the shortest walking category (≤0.5 hours/day), participants in the longest walking category (>0.5 hour/day) tended to be older; were more likely to be female, have a normal BMI, and be unmarried; and were less likely to be a smoker, consume coffee, be educated, and have a history of diabetes mellitus, gallbladder disease, and blood transfusion. Participants

who spent a longer time watching TV tended to be older; were more likely to be female, a smoker, and single; were more likely to have a history of diabetes mellitus, gallbladder disease, and blood transfusion; and were less likely to have a healthy BMI. (Table 1 here)

The HRs for liver cancer mortality associated with walking time are shown in Table 2. Compared with participants in the shorter walking category (≤0.5 hours/day), participants in the longer walking category (>0.5 hours/day) were 23% less likely to die of liver cancer after adjusting for variables such as age, sex, smoking status, alcohol drinking, coffee intake, BMI, education, marital status, and history of diabetes mellitus, gallbladder diseases, and blood transfusion (HR, 0.77; 95% CI, 0.59–0.99). (Table 2 here)

The HRs for liver cancer mortality associated with TV viewing time are shown in Table 3. Although the HRs were >1.0, statistically significant associations between the number of daily hours spent watching TV and a risk of liver cancer were not found. (Table 3 here)

Multivariate HRs for liver cancer mortality according to walking and TV

watching times are shown in Table 4. Compared with participants in the shorter walking category (≤0.5 hours/day) and longest TV watching category (≥4 hours/day), those in the longer walking category (>0.5 hours/day) and middle and shortest TV watching categories (2 to <4 and <2 hours/day) had a significantly reduced risk of liver cancer mortality (HR, 0.58; 95% CI, 0.39–0.89 and HR, 0.58; 95% CI, 0.35–0.98, respectively) after adjusting for potential confounders. (Table 4 here)

Discussion

In this large cohort study, we found that walking more than 30 minutes per day reduced the risk of liver cancer mortality. This association was greater among participants who watched TV for <4 hours per day.

The present findings are consistent with those of two previous reports that suggested that daily vigorous physical activity [9,10] and leisure physical activity [11] are associated with a reduced risk of liver cancer. Potential mechanisms involved in the prevention of liver cancer by low-intensity physical activities (e.g., walking) are not

clear. Several studies have suggested that physical activity helps to treat and/or prevent obesity [18] and increase insulin sensitivity [19], which could decrease hyperinsulinemia and in turn regulate carcinogenesis [20] as well as reduce liver fat stores [21]. Additionally, physical activities enhance immune function by increasing macrophages, natural killer cells, and neutrophils; regulating cytokines [22]; and altering prostaglandin synthesis [23]. A further possibility is that physical activities increase oxidative liver metabolism [24], which may slow or stop the loss of antioxidants [25]. All of these factors may reduce the influence of chronic inflammation on the liver.

Watching TV is a major form of sedentary behavior in many industrialized countries [26-28]. In this study, a longer time spent watching TV was associated with an increased risk of liver cancer mortality, although these results did not reach statistical significance. Several previous studies have reported that prolonged sedentary behavior is a risk factor for lung [16], endometrial [29], ovarian [30], and colon [31] cancer. Prolonged sedentary behavior has been shown to increase levels of inflammatory factors [32,33] and cause metabolic dysfunction [34]. For this reason, participants in the longer

walking category and middle and shortest TV watching categories might have had a lower risk of liver cancer mortality than those in the shorter walking and longest TV watching categories.

A previous study reported that physical activity was much more strongly associated with the incidence of hepatocellular carcinoma (HCC) than with other types of liver cancer [10]. In this study, 219 of 267 participants (82%) died of HCC. The HRs for HCC mortality associated with walking time were almost identical to those of all-cause liver cancer mortality, although this did not reach statistical significance because of the reduced number of deaths (HR, 0.74; 95% CI, 0.57–1.00). Accordingly, because the longer walking time reduced the risk of both HCC and other types of liver cancer mortality, we considered the presence of an association between daily walking time and primary all-cause liver cancer.

We excluded participants with a medical history of liver disease because they exhibited significantly higher rates of death of liver cancer and spent less time walking and more time watching TV per day. In the analysis that included participants with a medical history of liver disease, the associations among daily walking time, TV viewing

time, and liver cancer mortality were stronger than in the analysis that excluded these participants (data not shown). Thus, we attempted to reduce the potential for reverse causation as much as possible, and we believe that reverse causation did not occur.

Strengths of this study include its prospective cohort design, long follow-up period, and inclusion of participants from all over Japan. Additionally, information on potential confounders for liver cancer was collected at baseline and adjusted for in the analysis as much as possible.

This study has several limitations that warrant discussion. First, we had no information on HBV or HCV infection, which is a major risk factor for liver cancer [35]. Such viral infection may be associated with the gradual development of liver cancer over 20 to 30 years [36] and might have been related to the decreased walking times and increased TV viewing times at baseline in this study and thus to the increased liver cancer mortality. However, we excluded participants who died within the first 5 years of follow-up to reduce the influence of latent cancer that already existed at baseline but was infrequently detected because the cumulative survival rate within 5 years for all-cause liver cancer was poor (19.9%) [8] and adjusted for variables such as a history

of diabetes mellitus, gallbladder diseases, and blood transfusion. Accordingly, our results should represent true associations. Second, we could not completely exclude the effects of residual confounding factors. We collected data only at baseline, and that information was not updated; therefore, subsequent lifestyle changes could not be taken into account. If lifestyle changes occurred, misclassification might have been included in the results. However, such error would have occurred at random, which might have diminished the estimated HR toward null.

In conclusion, this large-scale cohort study demonstrated that a longer walking time reduced the risk of liver cancer mortality among Japanese individuals aged 40 to 79 years. This association was greater among participants who watched TV for <4 hours per day. Our findings suggest that prolonging the walking time and reducing the TV viewing time may be of benefit in the prevention of liver cancer.

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on Priority Area of Cancer Epidemiology.

Conflict of interest

The authors have no conflict of interest to disclose.

Appendix: Members of Japan Collaborative Cohort Study Group

The present members of the JACC Study Group who coauthored this paper are: Dr. Akiko Tamakoshi (present chairperson of the study group), Hokkaido University Graduate School of Medicine; Drs. Mitsuru Mori and Fumio Sakauchi, Sapporo Medical University School of Medicine; Dr. Yutaka Motohashi, Akita University School of Medicine; Dr. Ichiro Tsuji, Tohoku University Graduate School of Medicine; Dr. Yosikazu Nakamura, Jichi Medical School; Dr. Hiroyasu Iso, Osaka University School of Medicine; Dr. Haruo Mikami, Chiba Cancer Center; Dr. Michiko Kurosawa, Juntendo University School of Medicine; Dr. Yoshiharu Hoshiyama, Yokohama Soei University; Dr. Naohito Tanabe, University of Niigata Prefecture; Dr. Koji Tamakoshi, Nagoya University Graduate School of Health Science; Dr. Kenji Wakai, Nagoya

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Table 1. Baseline characteristics of study participants according to walking time and television viewing time.

Characteristic	Code	Walking time (hours a day)		TV viewing time (hours a day)		
		≤0.5 (n=19,850)	**>0.5 (n=49,902)**	**<2 (n=13,021)**	**2 to <4 (n=40,243)**	**≥4 (n=16,488)**
Age		56.2±10.1	57.0±9.9	54.7±10.1	56.2±9.8	60.0±9.7
Sex	Male	43.2	40.2	40.4	43.8	35.1
Smoking status	Current smoker	24.7	23.6	21.0	25.1	23.4
	Former smoker	11.3	10.1	9.8	10.9	9.7
	Non smoker	56.2	57.6	61.8	56.0	56.6
Alcohol consumption	Current drinker					
	0.1-22.9 g ethanol/day	6.7	7.2	6.9	7.0	7.2
	23.0-45.9 g ethanol/day	15.2	14.4	15.3	15.2	12.8
	≥46.0 g ethanol/day	14.8	14.6	15.2	15.9	11.1
	unknown	6.7	6.6	6.4	6.8	7.0
	Former drinker	2.8	2.6	2.1	2.5	3.6
	Non drinker	48.0	48.6	49.3	47. 1	51.1
Coffee consumption	1 cup a day or more	57.5	52.2	54.3	53.4	54.0
Body mass index (kg/m^2)	<18.5	5.3	5.4	5.8	5.2	5.7
	18.5-24.9	68.6	71.1	72.1	71.2	67.1
	≥25.0	21.7	18.7	17.3	19.3	21.9
College education		13.1	10.9	15.3	12.2	15.0
Married		81.5	80.6	84.3	82.2	74.9
Medical history						
Diabetes mellitus	Yes	4.9	3.6	3.5	3.7	4.9
Gallbladder diseases	Yes	4.2	3.7	3.4	3.5	4.8
Blood transfusion	Yes	8.4	7.7	7.3	7.5	9.3

Values are expressed as mean ± standard deviation or percentage.

Table 2. Hazard ratio (HR) of mortality from liver cancer according to walking time.

	Walking time (hours a day)	
	≤0.5	**>0.5**
Over all		
Person-years	334,244	856,238
No of cases	85	182
Age and sex adjusted HR (95%CI)	ref	0.79(0.61-1.03)
Multivariate HR (95%CI)[a]	ref	0.77(0.59-0.99)*
Male		
Person-years	144,073	342,007
No of cases	51	112
Age-adjusted HR (95%CI)	ref	0.84(0.61-1.19)
Multivariate HR (95%CI)[b]	ref	0.81(0.58-1.14)
Female		
Person-years	190,171	514,231
No of cases	34	70
Age-adjusted HR (95%CI)	ref	0.71(0.47-1.09)
Multivariate HR (95%CI)[b]	ref	0.70(0.47-1.07)

HR, hazard ratio. CI, confidence interval. *P<0.05.

[a]Adjusted for age, sex, study area, smoking status (never, former, current smoker, or unknown), alcohol consumption (never, former, current alcohol drinker of 0.1–22.9, 23.0–45.9, 46 g ethanol/day or unknown), daily consumption of coffee (0, <1, or ≥1 cups/day or unknown), body mass index (BMI; <18.5, 18.5–24.9, or ≥25.0 kg/m^2 or unknown), educational level (school up to age 15, 15–18, or ≥19 years or unknown), marital status (single, married, divorced/widowed, or unknown), and a history of diabetes mellitus, gallbladder diseases, and blood transfusion

[b]Adjusted for age, study area, smoking status (never, former, current smoker, or unknown), alcohol consumption (never, former, current alcohol drinker of 0.1–22.9, 23.0–45.9, 46 g ethanol/day or unknown), daily consumption of coffee (0, <1, or ≥1 cups/day or unknown), body mass index (BMI; <18.5, 18.5–24.9, or ≥25.0 kg/m^2 or unknown), educational level (school up to age 15, 15–18, or ≥19 years or unknown), marital status (single, married, divorced/widowed, or unknown), and a history of diabetes mellitus, gallbladder diseases, and blood transfusion

Table 3. Hazard ratios of liver cancer mortality according to television viewing time

	TV viewing time (hours a day)			
	<2	**2 to <4**	**≥4**	**P for trend[c]**
Over all				
Person-years	228,521	694,467	267,497	
No of cases	44	146	77	
Age and sex adjusted HR (95%CI)	ref	0.99(0.71-1.40)	1.27(0.88-1.85)	0.12
Multivariate HR (95%CI)[a]	ref	0.98(0.70-1.38)	1.20(0.82-1.77)	0.27
Male				
Person-years	914,546	302,276	92,349	
No of cases	28	91	44	
Age-adjusted HR (95%CI)	ref	0.93(0.62-1.45)	1.30(0.81-2.12)	0.42
Multivariate HR (95%CI)[b]	ref	0.92(0.61-1.44)	1.23(0.76-2.02)	0.64
Female				
Person-years	137,065	392,191	175,148	
No of cases	16	55	33	
Age-adjusted HR (95%CI)	ref	1.08(0.63-1.95)	1.23(0.68-2.31)	0.18
Multivariate HR (95%CI)[b]	ref	1.06(0.62-1.93)	1.13(0.62-2.13)	0.34

HR, hazard ratio. CI, confidence interval. Tests for linear trends were conducted to assess associations between the original continuous variables of daily hours spent watching TV and risk of liver cancer mortality.

[a]Adjusted for age, sex, study area, smoking status (never, former, current smoker, or unknown), alcohol consumption (never, former, current alcohol drinker of 0.1–22.9, 23.0–45.9, 46 g ethanol/day or unknown), daily consumption of coffee (0, <1, or ≥1 cups/day or unknown), body mass index (BMI; <18.5, 18.5–24.9, or ≥25.0 kg/m^2 or unknown), educational level (school up to age 15, 15–18, or ≥19 years or unknown), marital status (single, married, divorced/widowed, or unknown), and a history of diabetes mellitus, gallbladder diseases, and blood transfusion

[b]Adjusted for age, study area, smoking status (never, former, current smoker, or unknown), alcohol consumption (never, former, current alcohol drinker of 0.1–22.9, 23.0–45.9, 46 g ethanol/day or unknown), daily consumption of coffee (0, <1, or ≥1 cups/day or unknown), body mass index (BMI; <18.5, 18.5–24.9, or ≥25.0 kg/m^2 or unknown), educational level (school up to age 15, 15–18, or ≥19 years or unknown), marital status (single, married, divorced/widowed, or unknown), and a history of diabetes mellitus, gallbladder diseases, and blood transfusion

[c]Tests for linear trends were conducted to assess associations between the original continuous variables of daily hours spent watching TV and risk of liver cancer mortality.

Table 4. Hazard ratios of mortality from liver cancer according to walking time and television viewing time

	Walking time (hours a day)	
	≤0.5	**>0.5**
Time spent watching TV (hours a day)		
<2		
Person-years	64,068	164,453
No of cases	13	31
Age- and sex-adjusted HR (95%CI)	0.66(0.33-1.25)	0.57(0.35-0.95)*
Multivariate HR (95%CI)[a]	0.71(0.36-1.34)	0.58(0.35-0.98)*
2-4		
Person-years	188,896	505,569
No of cases	42	104
Age- and sex-adjusted HR (95%CI)	0.65(0.41-1.05)	0.57(0.38-0.87)*
Multivariate HR (95%CI)[a]	0.68(0.42-1.11)	0.58(0.39-0.89)*
>4		
Person-years	81,260	186,238
No of cases	30	47
Age- and sex-adjusted HR (95%CI)	ref	0.65(0.41-1.04)
Multivariate HR (95%CI)[a]	ref	0.64(0.40-1.02)

HR, hazard ratio. CI, confidential interval. *P < 0.05.

[a]Adjusted for age, sex, study area, smoking status (never, former, current smoker, or unknown), alcohol consumption (never, former, current alcohol drinker of 0.1–22.9, 23.0–45.9, 46 g ethanol/day or unknown), daily consumption of coffee (0, <1, or ≥1 cups/day or unknown), body mass index (BMI; <18.5, 18.5–24.9, or ≥25.0 kg/m^2 or unknown), educational level (school up to age 15, 15–18, or ≥19 years or unknown), marital status (single, married, divorced/widowed, or unknown), and a history of diabetes mellitus, gallbladder diseases, and blood transfusion