BMJ Open

Association of occupational physical activity and sedentary behaviour with the risk of hepatocellular carcinoma: a case-control study based on the Inpatient Clinico-Occupational Database of Rosai Hospital Group

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To cite: Nakazawa S, Fukai K, Sano K, *et al*. Association of occupational physical activity and sedentary behaviour with the risk of hepatocellular carcinoma: a case-control study based on the Inpatient Clinico-Occupational Database of Rosai Hospital Group. *BMJ Open* 2025;**15**:e092020. doi:10.1136/bmjopen-2024-092020

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-092020).

Presentations of preliminary data at the 60th annual meeting of the Japan Society of Hepatology, which was held on 16 June 2024.[45]

Received 14 August 2024
Accepted 25 February 2025

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ABSTRACT

Objectives While there is growing evidence that physical activity reduces the risk of hepatocellular carcinoma (HCC), the impact of occupational physical activity and sedentary behaviour remains unclear. This study aimed to investigate the associations between occupational physical activity and sedentary behaviour and HCC risk.

Design Matched case-control study.

Setting Nationwide multicentre, hospital-inpatient data set in Japan, from 2005 to 2021.

Participants The study included 5625 inpatients diagnosed with HCC and 27 792 matched controls without liver disease or neoplasms. Participants were matched based on sex, age, admission date, and hospital.

Primary measures The association between levels of occupational physical activity (low, medium, high) and sedentary time (short, medium, long) with the risk of HCC.

Secondary measures Stratification of HCC risk by viral infection status (hepatitis B/C virus), alcohol consumption levels and the presence of metabolic diseases (hypertension, diabetes, dyslipidaemia, obesity).

Results High occupational physical activity was not associated with HCC caused by hepatitis B/C virus infection in men. In women, high occupational physical activity was associated with a reduced risk of non-viral HCC, with ORs (95% CIs) of 0.65 (0.45–0.93). Among patients with non-viral HCC, medium occupational physical activity combined with medium alcohol intake further decreased the HCC risk in men with an OR of 0.70 (0.50–0.97), while high occupational physical activity combined with lowest alcohol intake decreased the HCC risk in women with an OR of 0.69 (0.48–0.99). Men and women with medium sedentary time had a lower HCC risk compared with those with long sedentary time, with ORs of 0.88 (0.79–0.98) in men and 0.77 (0.62–0.97) in women, respectively. In patients without viral infection or alcohol use, medium sedentary time reduced the HCC risk associated with fatty liver disease without comorbid metabolic diseases in women.

Conclusions High levels of occupational physical activity and/or medium periods of sedentary time are associated with a reduced risk of HCC, particularly non-alcoholic steatohepatitis.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The database contained detailed occupational histories, which were collected by trained surveyors, ensuring high accuracy and reliability of the data.
⇒ This was a large, nationwide multicentre inpatient data set in Japan, and their occupational distributions are similar to Japan's representative values.
⇒ Diagnosis of hepatocellular carcinoma was registered by physicians, which were reliable.
⇒ Participants were all inpatients, and selection bias may have occurred.
⇒ The availability of clinical data such as blood tests and liver biopsy results was limited.

INTRODUCTION

Three factors primarily cause hepatocellular carcinoma (HCC): viral infection, heavy alcohol consumption and non-alcoholic steatohepatitis (NASH). In Japan, hepatitis B virus (HBV)/hepatitis C virus (HCV) infection causes approximately 80% of liver cancer-related deaths.[1] However, mortality due to HCC caused by viral infection is decreasing, and mortality due to HCC caused by non-alcoholic fatty liver disease (NAFLD)/NASH is increasing.[2]

In 2023, the DELPHI consensus announced that the terms NAFLD/NASH would be replaced with steatotic liver disease (SLD).[3] The term metabolic dysfunction-associated SLD (MASLD) was selected as a replacement

for NAFLD because the terms NASH and NAFLD are potentially stigmatising. Moreover, Met alcoholic liver disease (MetALD) was defined as MASLD with a higher alcohol intake. Therefore, more focus should be placed on metabolic syndromes and moderate alcohol consumption in patients wth SLD at risk of HCC.[3] Estes *et al* predicted that the prevalence of NASH will increase by 15–56% worldwide, and liver-related mortality will more than double in some populations by 2030.[4] Therefore, this issue is important for public health, and action should be taken not only to eradicate HBV/HCV infection and alcohol abuse but also to prevent HCC progression through MetALD and MASLD.

Recent epidemiological studies show that physical activity (PA) plays an important role in decreasing HCC risk and liver-related death. Large-scale cohort studies conducted in the USA by Simon *et al* and Luo *et al* showed that participants with a higher PA had a lower risk of HCC or liver-related death compared with those with a lower PA.[5 6] Matthews *et al* showed that PA, such as activities with 7.5–15.0 metabolic equivalent task (MET) hours/week, can lead to an 18–27% reduction in HCC risk.[7] According to Pang *et al*, total PA decreased HCC risk in a Chinese population.[8] In Japan, Inoue *et al* showed that a higher PA decreased HCC risk in men compared with a lower PA.[9]

Total PA consists of daily PA (OPA + commuting to work) and leisure-time PA (LTPA). To date, most studies have focused on LTPA and walking for total PA.[5–7 9] OPA and sedentary time (ST) have been highlighted as independent factors. For instance, blue-collar workers with medium or high OPA may tend to engage in less PA during leisure time, whereas workers in sedentary jobs tend to have higher levels of LTPA.[10] Prince *et al* demonstrated in their systematic review that LTPA requirements differ depending on workers' OPA levels, even though LTPA is beneficial for all workers.[11] In particular, the undesirable impacts of sitting time on individual health have been clarified, with studies reporting that long ST could independently increase the risks of various metabolic diseases, cardiovascular disease (CVD) and cancers.[12 13] However, to date, only a few studies have reported the relationship between OPA, ST and HCC.[8]

Therefore, we aimed to investigate the impact of OPA and work-related ST on HCC risk caused by each pathological background—including major factors such as (1) viral (HBV/HCV) infection, (2) alcohol consumption and (3) others, mainly NASH—using data from the Inpatient Clinico-Occupational Database of Rosai Hospital Group (ICOD-R), which contained information on longest-held occupation, medical summary and lifestyle, including alcohol consumption.

METHODS

Study design and setting

This nationwide, multicentre hospital-based matched case-control study included patient data obtained between 2005 and 2021 from the ICOD-R study conducted by the Japan Organization of Occupational Health and Safety. Details of the study have been described previously.[14–16] The ICOD-R has concomitantly investigated both clinical and occupational histories of all inpatients admitted to nationwide facilities belonging to the Rosai Hospital Group (250 000 admissions per year from 34 hospitals). The hospitalisation summary for each admission contained basic and medical information (including a definitive diagnosis and surgical procedure name). The physicians registered up to seven definitive diagnoses, including the primary one, which were eventually coded using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10).

The occupational history survey was conducted by trained occupational history surveyors who interviewed inpatients or their families based on a questionnaire that contained questions regarding inpatients' current and past three job types and industries, including age at the start and end of each job, coded in accordance with the Japan Standard Industrial Classification (JSIC) and the Japan Standard Occupational Classification (JSOC) published by the Japanese Ministry of Internal Affairs and Communications.[17 18] Additionally, the questionnaire addressed habits, such as smoking or alcohol use, as well as existing diagnoses of hypertension, diabetes, dyslipidaemia and obesity.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of our research. The data used in this study were obtained from a retrospective analysis of an existing inpatient database, and thus, direct patient involvement was not feasible. However, the results of this study are intended to inform public health strategies and occupational health policies, ultimately benefiting patients and the general public.

Patients and controls

The study participants were patients aged ≥20 years at initial hospitalisation with available information on occupational history and a questionnaire of habits. The cases were defined as patients whose primary diagnosis was HCC (ICD-10, C22.0) at the time of first admission. Regarding controls, we excluded those with a primary diagnosis possibly related to liver disease (ICD-10, K, I and N) at the time of first admission. Additionally, we excluded patients with diagnoses of any neoplasms (ICD-10, C00-C97 and D00-D48), HBV (ICD-10, B16.0, B16.1, B16.2, B16.9, B17.0, B18.0 and B18.1) and HCV (ICD-10, B17.1 and B18.2) across all admissions. The primary diagnoses of control included spinal canal stenosis of the lumbar, senile cataract, explicit disc herniation, pneumonia and insulin-independent diabetes mellitus (details provided in online supplemental table 2). For each case, five control participants were randomly selected from the eligible source and matched for sex (male or female), age (5-year strata), admission date (1-year strata) and

admitting hospital (34 hospitals). Moreover, for sensitivity analysis, we alternatively selected controls with liver disease (ICD-10, C70-77) but without HCC or any other neoplasms. For each case, one control participant was randomly selected as the number of participants with liver disease was limited.

Total and longest OPA and ST

The database included the age at the start and end of each job for each study participant. We calculated the length of the longest-held occupation and industry from the participants' current and three previous most recent occupational histories and classified them for each patient using the 12 JSOC categories and 19 JSIC categories. The JSOC categories were as follows: (A) managers; (B) professionals; (C) clerical workers; (D) sales workers; (E) service workers; (F) security workers; (G) agricultural, forestry and fishery workers; (H) manufacturing workers; (I) transportation workers; (J) construction and mining workers; (K) carrying, cleaning and packing workers; and (L) students, homemakers, unemployed individuals and those unclassifiable.[18] If the participants' longest jobs were in the JSOC L category (student, homemaker, unemployed and unclassifiable), we calculated the second longest job and categorised the OPA group (online supplemental methods).

In this study, we classified OPA and ST using a Job Exposure Matrix (JEM) to evaluate workers' industries and occupations.[19 20] We classified occupational categories into three OPA levels, as in previous studies.[15 21] Specifically, we created the OPA categories by applying the OPA data obtained in the study conducted by Steeves *et al*, which used accelerometer measurements.[22] A comparison table of the JSOC classifications used in this study is provided in online supplemental table 1. The high OPA group was divided into the JSOC categories G, J and K. The low OPA group included the A, B and C categories. Other occupational categories, including categories D, E, F, H and I, were in the intermediate OPA group. The JSOC L category was categorised as an unclassified group. For ST, as the questionnaire from 2020 included questions regarding ST, we first created a JEM to estimate the specific duration of ST and sorted them into long, medium and short groups for each JSOC and JSIC category. Second, we adjusted sedentary categories based on JSOC and JSIC status in the data for admissions prior to 2020 (online supplemental methods, online supplemental figure 2).

Covariates

Parameters such as sex, age, admission date and admitting hospital were controlled by an exact matching procedure. Smoking (never, former, or current), hypertension (ICD-10, I10-13 and I15 or participants who presented with hypertension in annual check-ups), type 2 diabetes (ICD-10, E11), dyslipidaemia (ICD-10, E78.0–78.5 or participants who presented with dyslipidaemia in annual check-ups) and obesity (participants who presented with obesity in annual check-ups) were included in the regression models as confounding variables. HBV (ICD-10, B16.0, B16.1, B16.2, B16.9, B17.0, B18.0 and B18.1) and HCV (ICD-10, B17.1 and B18.2) infections were used in the stratified analysis. Moreover, we calculated the amounts of alcohol intake per day and per week separately and categorised ALD and MetALD amounts of alcohol consumption by calculating the pure ethanol amount in grams. The ALD amount was defined as alcohol consumption >60 g per day or >420 g per week in men, and >50 g per day or >350 g per week in women. The MetALD quantity was defined as alcohol consumption of 30–60 g per day or 210–420 g per week in men and 20–50 g per day or 140–350 g per week in women (online supplemental methods).

Statistical analysis

We estimated the ORs and 95% CIs for HCC risk using conditional logistic regression, with the low OPA or long ST groups as references in accordance with a previous study.[15] Stratified by sex (male or female), ORs adjusted for age, admission date and admitting hospital were calculated in Model 1. Smoking was additionally adjusted for in Model 2, and hypertension, type 2 diabetes, hyperlipidaemia and obesity were additionally adjusted for in Model 3. Furthermore, we stratified the analysis based on the prevalence of HBV/HCV infection and alcohol consumption. Additionally, we stratified the analysis according to the detailed alcohol amounts of ALD, MetALD and under that of MetALD (low MetALD; <30 g/day or <210 g/week in men and <20 g/day or <140 g/week in women). As a sensitivity analysis, we performed stratified analysis according to hypertension, type 2 diabetes, dyslipidaemia and obesity because MASLD includes these metabolic factors.[23] We also conducted a Cochran-Armitage test to examine the distribution of alcohol consumption across occupations using clerical workers (low OPA and relatively long ST) as the reference group.

All statistical analyses were performed using SAS Software V.9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Patient characteristics

Overall, 5625 patients with HCC were included (online supplemental figure 1). Table 1 shows the characteristics of the patients and controls. Online supplemental table 2 shows the primary diagnoses of controls who were admitted for non-HCC-related diseases (such as senile cataract, spinal canal stenosis of the lumbar spine and pneumonia). Online supplemental tables 3 and 4 show the characteristics stratified by sex. The mean ages (±SD) of the whole survey population, patients and controls were 70.5 (±10.0), 70.5 (±9.9) and 70.5 (±10.0) years, respectively. Herein, 4085 (72.6%) patients and 20 114 (72.4%) controls were male. We also calculated the ORs (95% CIs) of factors using univariate analysis. Hypertension or type 2 diabetes increased HCC risk, while

Table 1 Background characteristics of participants

	Patients	Controls	OR (95% CI)
Population, no.	5625	27 792	
Male sex	4085	20 114	–
Age, years	70.5±9.9	70.5±10	–
Smoking status			
Never	2056 (36.6%)	11 907 (42.8%)	1 (reference)
Former	2106 (37.4%)	10 307 (37.1%)	**1.34 (1.24–1.45)**
Current	1463 (26%)	5578 (20.1%)	**1.77 (1.62–1.93)**
Alcohol use			
ALD (weeks)*	170 (3%)	409 (1.5%)	**2.22 (1.84–2.67)**
MetALD (weeks)†	1008 (17.9%)	4530 (16.3%)	**1.17 (1.08–1.26)**
Low MetALD (weeks)‡	4447 (79.1%)	22 853 (82.2%)	1 (reference)
ALD (days)*	266 (4.7%)	599 (2.2%)	**2.53 (2.17–2.94)**
MetALD (days)†	1593 (28.3%)	6780 (24.4%)	**1.32 (1.23–1.41)**
Low MetALD (days)‡	3766 (67%)	20 413 (73.4%)	1 (reference)
Diagnosis of hypertension, yes	2233 (39.7%)	10 664 (38.4%)	**1.06 (1–1.13)**
Diagnosis of type 2 diabetes, yes	725 (12.9%)	2854 (10.3%)	**1.32 (1.21–1.44)**
Diagnosis of dyslipidaemia, yes	282 (5%)	3348 (12%)	**0.38 (0.34–0.43)**
Obesity, yes	499 (8.9%)	2923 (10.5%)	**0.82 (0.74–0.91)**
Occupational physical activity of the longest job			
Low OPA	1479 (26.3%)	7689 (27.7%)	1 (reference)
Medium OPA	2331 (41.4%)	10 986 (39.5%)	**1.11 (1.03–1.19)**
High OPA	909 (16.2%)	4485 (16.1%)	1.05 (0.96–1.16)
Uncategorised	906 (16.1%)	4632 (16.7%)	1.01 (0.91–1.12)
Sedentary time			
Long	1307 (23.2%)	6313 (22.7%)	1 (reference)
Medium	898 (16%)	5035 (18.1%)	**0.86 (0.78–0.94)**
Short	2511 (44.6%)	11 805 (42.5%)	1.03 (0.96–1.11)
Uncategorised	909 (16.2%)	4639 (16.7%)	0.94 (0.85–1.05)
HBV	662 (11.8%)	0 (0%)	–
HCV	2389 (42.5%)	0 (0%)	–
Region			
Hokkaido	304 (5.4%)	1517 (5.5%)	–
Tohoku	848 (15.1%)	4075 (14.7%)	–
Kanto	786 (14%)	3923 (14.1%)	–
Chubu	414 (7.4%)	2064 (7.4%)	–
Kansai	1476 (26.2%)	7275 (26.2%)	–
Chugoku-shikoku	1055 (18.8%)	5240 (18.9%)	–
Kyushu	742 (13.2%)	3698 (13.3%)	–

Values in bold represent statistically significant results (two-sided $p < 0.05$)
Percentage may not add up to 100 because of rounding.
*ALD amount is defined as alcohol consumption over 60 g per day and over 420 g per week in men and over 50 g per day and over 350 g per week in women.
†MetALD amount is defined as alcohol consumption 30–60 g per day and 210–420 g per week in men and 20–50 g per day and 140–350 g per week in women.
‡Low MetALD amount is defined as alcohol consumption below 30 g per day and below 210 g per week in men and below 20 g per day and below 140 g per week in women.
ALD, alcohol-related liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, MASLD with a higher alcohol intake; OPA, occupational physical activity.

Table 2 OPA and the risk of HCC in men and women

	Patients	OR (95% CI)		
		Model 1*	Model 2†	Model 3‡
All men				
Low OPA	1132	1 (reference)	1 (reference)	1 (reference)
Medium OPA	1823	**1.11 (1.02–1.20)**	1.09 (1–1.18)	1.06 (0.97–1.15)
High OPA	791	**1.13 (1.02–1.25)**	1.1 (0.997–1.22)	1.05 (0.95–1.16)
Stratified by HBV/HCV infection without HBV/HCV infection				
Low OPA	603	1 (reference)	1 (reference)	1 (reference)
Medium OPA	820	0.93 (0.82–1.04)	0.91 (0.81–1.02)	0.90 (0.80–1.01)
High OPA	372	0.98 (0.85–1.13)	0.97 (0.84–1.12)	0.96 (0.83–1.11)
All women				
Low OPA	347	1 (reference)	1 (reference)	1 (reference)
Medium OPA	508	1.12 (0.96–1.31)	1.08 (0.93–1.26)	1.04 (0.89–1.22)
High OPA	118	**0.75 (0.60–0.95)**	**0.73 (0.58–0.92)**	**0.69 (0.55–0.87)**
Stratified by HBV/HCV infection without HBV/HCV infection				
Low OPA	158	1 (reference)	1 (reference)	1 (reference)
Medium OPA	228	1.08 (0.87–1.36)	1.03 (0.82–1.30)	1 (0.80–1.26)
High OPA	48	**0.69 (0.48–0.98)**	**0.67 (0.47–0.95)**	**0.65 (0.45–0.93)**

Values in bold represent statistically significant results (two-sided $p < 0.05$)
*Conditional logistic regression matched for sex, age, admission date and admitting hospital.
†Additional adjustment for smoking in Model 1.
‡Additional adjustment for diagnosis of hypertension, type 2 diabetes, dyslipidaemia and obesity in Model 2.
HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; OPA, occupational physical activity.

dyslipidaemia was inversely associated with HCC (OR 0.38, 95% CI 0.34–0.43). In this study, HCC was more common in the Kansai region (26.2%) and the Chugoku-Shikoku (18.8%) regions. Online supplemental table 5 shows the regional prevalence of high alcohol consumption (ALD levels), HBV and HCV among patients. ALD levels were highest in the Chugoku-Shikoku region, while HCV prevalence was highest in the Kansai region. Online supplemental table 6 shows the liver diseases in the cases. Of the 5625 cases, the percentages of those with liver disease, HBV and HCV were 39.4%, 11.8% and 42.5%, respectively. Online supplemental tables 7 and 8 show the amount of alcohol consumed by each occupation in cases and controls. The percentage of participants who consumed more alcohol than the MetALD threshold tended to be higher among cases than controls. Among the cases, managers (low OPA), transportation workers (medium OPA) and construction and mining workers (high OPA) had higher percentages of ALD compared with clerical workers, who served as the reference group.

Viral (HBV or HCV) or non-viral HCC

Table 2 shows the association between OPA and the risk of non-viral HCC. Among men, those with a medium or high OPA showed a further increased risk before adjustment (1.11 (1.02–1.20) for medium OPA and 1.13 (1.02–1.25) for high OPA in Model 1). However, no association was observed in non-viral HCC. Additionally, among women, those with a high OPA showed a decreased risk of all HCC and non-viral HCC (0.69 (0.55–0.87) for all HCC in women and 0.65 (0.45–0.93) for non-viral HCC in Model 3).

Table 3 shows the association between ST and the risk of viral or non-viral HCC. In both men and women, medium ST was associated with a decreased risk of HCC (0.88 (0.79–0.98) for men and 0.77 (0.62–0.97) for women in Model 3). Additionally, in women but not in men, medium ST was associated with a decreased risk of non-viral HCC (0.71 (0.50–0.99) in Model 3).

HCC risk according to alcohol consumption, MetALD or low MetALD

The prevalence of HCC with ALD in men and women and alcohol consumption in women with MetALD was low; thus, the ORs for these factors could not be evaluated.

Figure 1 shows the association between OPA, as well as ST, and HCC risk stratified by sex and the amount of daily alcohol consumption. In men with MetALD-level alcohol consumption, medium OPA was associated with a decreased risk of HCC (0.70 (0.50–0.97)), whereas ST was not associated with alcohol consumption or HCC risk. In women, high OPA and short ST were associated with a decreased HCC risk (0.69 (0.48–0.99) and 0.62 (0.42–0.93), respectively). Online supplemental file provides detailed data in online supplemental tables 9–12.

Table 3 ST and the risk of HCC in men and women

	Patients	OR (95% CI)		
		Model 1*	Model 2†	Model 3‡
All men				
Long ST	1934	1 (reference)	1 (reference)	1(reference)
Medium ST	756	**0.88 (0.79–0.97)**	**0.88 (0.79–0.97)**	**0.88 (0.79–0.98)**
Short ST	1054	1.04 (0.96–1.13)	1.03 (0.95–1.12)	1.01 (0.93–1.10)
Stratified by HBV/HCV infection without HBV/HCV infection				
Long ST	868	1 (reference)	1 (reference)	1 (reference)
Medium ST	391	0.89 (0.77–1.03)	0.89 (0.77–1.03)	0.89 (0.77–1.03)
Short ST	535	0.92 (0.82–1.04)	0.92 (0.82–1.04)	0.92 (0.81–1.04)
All women				
Long ST	577	1 (reference)	1 (reference)	1 (reference)
Medium ST	142	**0.79 (0.63–0.99)**	**0.78 (0.62–0.98)**	**0.77 (0.62–0.97)**
Short ST	253	0.97 (0.82–1.15)	0.93 (0.79–1.1)	0.90 (0.76–1.07)
Stratified by HBV/HCV infection without HBV/HCV infection				
Long ST	255	1 (reference)	1 (reference)	1 (reference)
Medium ST	62	**0.71 (0.51–0.99)**	**0.69 (0.49–0.97)**	**0.71 (0.50–0.99)**
Short ST	116	0.91 (0.71–1.17)	0.87 (0.68–1.11)	0.86 (0.67–1.10)

Values in bold represent statistically significant results (two-sided $p < 0.05$)
*Conditional logistic regression matched for sex, age, admission date and admitting hospital.
†Additional adjustment for smoking in Model 1.
‡Additional adjustment for diagnosis of hypertension, type 2 diabetes, dyslipidaemia and obesity in Model 2.
HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ST, sedentary time.

Figure 1

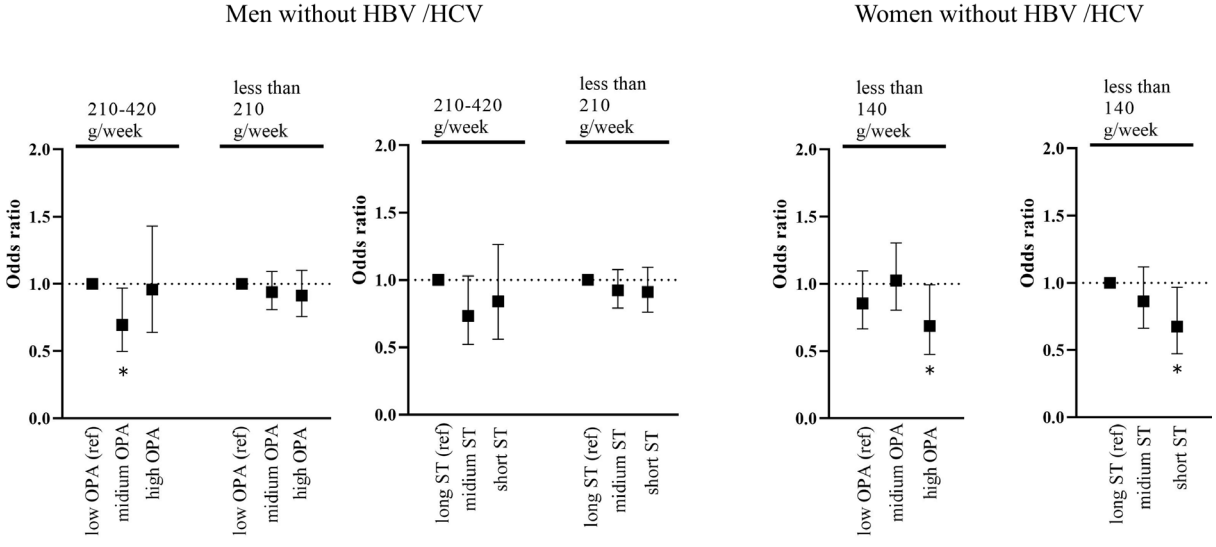

Figure 1 Association of OPA and ST stratified by alcohol consumption (pure ethanol grams per week) with HCC risk in the population without HBV/HCV. The ORs (symbols) and 95% CIs (bars) were estimated using conditional logistic regression analyses matched for sex, age, admission date and admitting hospital. Additional adjustments for smoking, diagnosis of hypertension, type 2 diabetes, dyslipidaemia and obesity were performed. Low OPAs or long STs were used as references. Asterisks (*) represent categories with increased ORs that are statistically significant. HBV, hepatitis B virus; HCV, hepatitis C virus; OPA, occupational physical activity; ST, sedentary time.

Figure 2

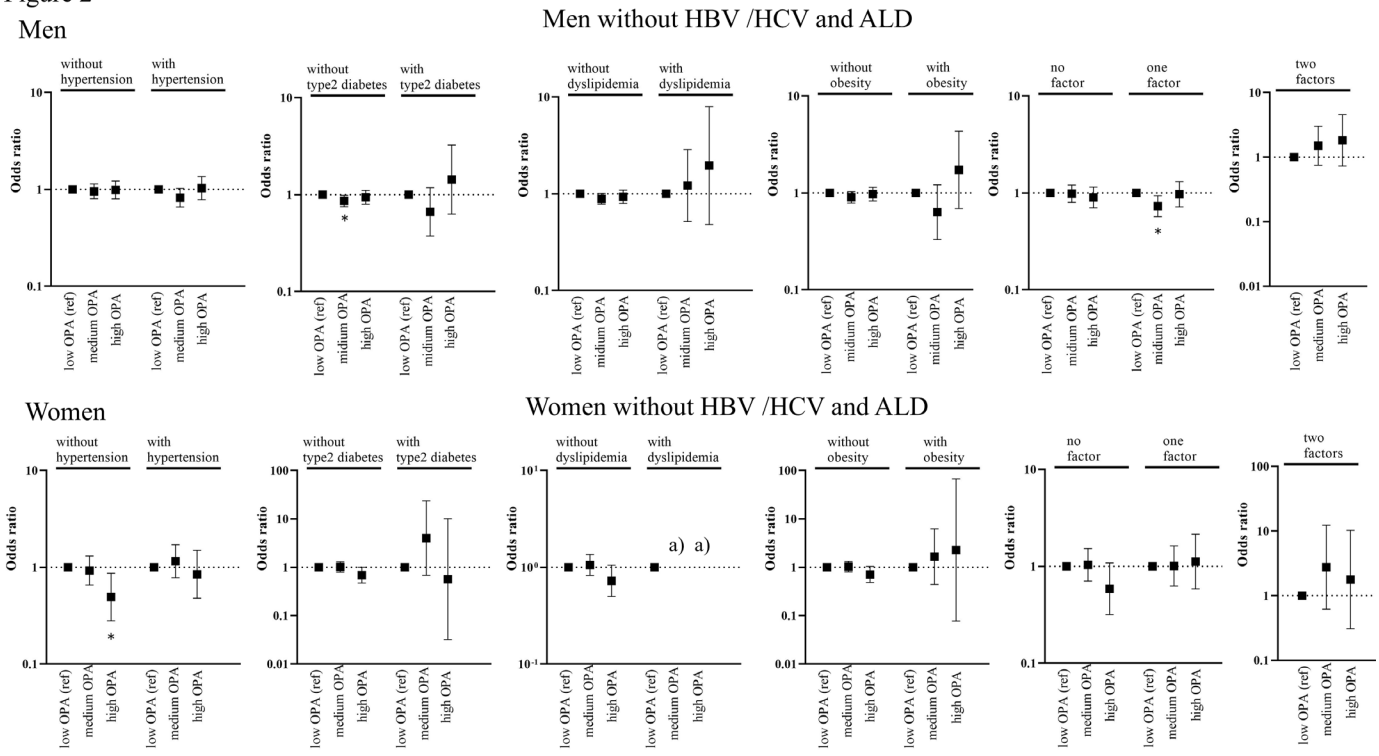

Figure 2 Association between OPA and HCC risk, stratified with hypertension, type 2 diabetes, dyslipidaemia, obesity, the number of these four factors in the population without HBV/HCV infection and alcohol consumption of the ALD amount (<420 g of pure ethanol per week in men and <350 g/week in women). The ORs (symbols) and 95% CIs (bars) were estimated using conditional logistic regression analyses matched for sex, age, admission date and admitting hospital. We adjusted for smoking and additionally adjusted for the diagnosis of hypertension, type 2 diabetes, dyslipidaemia and obesity, which were not stratified. Low OPA was used as the reference. Asterisks (*) represent categories with increased ORs that are statistically significant. [a]ORs and 95% CIs could not be calculated because of insufficient number of cases and matched controls. ALD, alcohol-related liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; OPA, occupational physical activity.

HCC risk according to MASLD

Figure 2 shows the association between OPA and the HCC risk caused by MASLD, stratified by hypertension, type 2 diabetes, dyslipidaemia and obesity in the population without HBV/HCV infection and alcohol consumption below the ALD amount. In men, medium OPA was associated with a lower risk of HCC in the absence of type 2 diabetes (0.86 (0.75–0.98)). Additionally, women with a high OPA had a lower risk of HCC in the absence of hypertension (0.49 (0.28–0.87)) (online supplemental tables 13 and 14). For ST, women with high OPA had a lower risk of HCC in the absence of hypertension (0.56 (0.34–0.94)) or type 2 diabetes (0.68 (0.47–0.98)) (online supplemental tables 16 and 17). A medium OPA decreased HCC risk in men with one metabolic disease (0.73 (0.57–0.94)). A medium ST decreased HCC risk in women without comorbidities (0.4 (0.22–0.73)) (online supplemental table 15 and 18). Furthermore, a medium OPA decreased the risk of HCC in men with MASLD while ST was not associated with HCC risk in patients with MASLD (online supplemental tables 19 and 20). In the sensitivity analysis, when we replaced the controls with those who had liver disease but without HCC, the associations between OPA or ST and the risk of viral or non-viral HCC were not observed in either men or women (online supplemental tables 21–23).

DISCUSSION

Our large-scale case-control study showed that the association between OPA and HCC risk differed according to the viral infection status (HBV/HCV), the amount of alcohol consumption and the presence of comorbid diseases. Although OPA and ST did not have any impact on the risk of HCC caused by ALD or MASLD with comorbidities except for medium OPA in men with MASLD, OPA and ST decreased the risk for non-viral HCC in women with alcohol consumption below the MetALD threshold and others, suggesting MASLD without comorbid diseases.

In 2012, the cause of HCC was HBV/HCV in 90% of the cases and alcohol consumption in 10% of the cases; other causes accounted for <10% in the Asian regions.[24] However, the prevalence of HBV/HCV infections is decreasing.[25 26] Herein, 51.4% of HCC cases had HBV/HCV infection, and 3.2% involved heavy alcohol use. The Rosai Hospitals, which served as the study's setting, are located in major cities across Japan, and their occupational distributions are similar to Japan's representative

values.[21] Thus, the participants in this study are considered representatives of Japan. These results indicate that the proportion of HCC caused by MASLD is increasing in Japan as well as in other countries.[2] Areas with a high prevalence of HCC coincide with those with a high prevalence of HCV[27] and alcohol consumption in our study.

Several epidemiological studies from various countries showed that PA plays an important role in the prevalence of NAFLD/NASH. A study based on the UK biobank calculated total PA, LTPA and ST and showed that long ST increased the risk of NASH/NAFLD.[28] In the USA, physically active participants (≥600 MET min/week) had a lower risk of NAFLD than inactive participants (<600 MET min/week).[29] A study in Korea showed a significant positive association between the amount of PA (exercise) and improvements in fatty liver. Furthermore, exercising five times per week suppressed the incidence of NAFLD and led to its improvement compared with no exercise.[30]

However, measuring exposure to PA or exercise, such as intensity, duration and frequency, can be challenging. Thus, studies on PA involve various intensities, each yielding different results. The results of OPA and LTPA have been reported to vary. Regarding CVD risk, the differences in the results of OPA and LTPA are known as the OPA paradox.[31] Harden *et al* showed that moderate-intensity LTPA decreased homocysteine or C-reactive protein levels in patients with NAFLD, but light LTPA was not effective.[32] Furthermore, Lee *et al* showed that individuals involved in moderate-to-vigorous OPA had higher C-reactive protein levels than those without; however, those involved in moderate-to-vigorous LTPA showed no significant association with C-reactive protein levels.[33] Another study showed that high OPA/total PA had no significant effect on the improvement of MASLD, whereas LTPA decreased the risk of MASLD.[34] In addition, LTPA≥300 min/week prevented metabolic syndrome by 0.6 times; however, high OPA did not affect metabolic syndrome.[35] Animal studies have yielded similar findings. More recently, Tsutsui *et al* demonstrated that exercise intensity mimicking LTPA changed the intrahepatic immune cell profile and inhibited the progression of NASH in a mouse model.[36] The difference between OPA and LTPA is based on the duration of intense activity; thus, self-determination is difficult. High OPA could be, in some cases, taxing on the body, resulting in no alterations in the immune cell profile. Therefore, although moderate-intensity exercise reduces the risk of metabolic diseases, high OPA might not affect metabolic diseases.

Our results showed that high OPA had a suppressive effect only on HCC caused by suggested MASLDs without metabolic diseases (cryptogenic SLD). NASH and metabolic syndrome are similarly categorised as MASLD because, in both cases, overnutrition, obesity and a lack of exercise cause insulin resistance and fat-induced inflammation.[3 37] However, in some cases, NASH occurs without an accompanying metabolic syndrome. In the carcinogenic process of NASH, inflammation and oxidative stress are the primary factors in the mechanism by which hepatic fibrosis occurs in a fatty liver.[38] The pathological differences between NASH with and without metabolic disease remain unclear. We speculate that, in patients with metabolic diseases, liver fibrosis possibly increases through a synergistic effect, whereas in the livers of individuals without metabolic diseases, the degree of inflammation caused by fat (the first hit) might vary according to individuals,[39] for example, in people with the PNPLA3G allele who are susceptible to developing NASH.[40] In Japan, individuals without obesity showed a 15% prevalence of fatty liver; additionally, the prevalence of the PNPLA3G allele is higher,[41] or the mechanism of fatty liver may be different between Asians and Westerners.[42] Thus, fibrosis progression is considered to precede the onset of metabolic diseases, leading to the early initiation of carcinogenic processes. As mentioned above, because high OPA has different effects on metabolic factors compared with high LTPA,[43] high OPA might have little effect on the immune profile related to inflammation in metabolic diseases; however, it might reduce fat deposits, resulting in the suppression of inflammation. We demonstrated in the sensitivity analysis that high OPA or ST were not associated with a reduced risk of HCC compared with controls with liver disease. These results suggest that OPA does not prevent the development of liver cancer. High OPA might not be related to the onset or improvement of metabolic diseases or the carcinogenic processes of HCC caused by NASH.

STRENGTHS AND LIMITATIONS OF THIS STUDY

This study's main strength is that the database contained detailed occupational histories. Trained registrars collected the occupational data, ensuring high accuracy. Furthermore, a reliable diagnosis of HCC was available for all admissions to estimate the influence of OPA. Because this survey started data collection for ST in 2020, we could estimate the risk associated with sedentary behaviour. OPA and ST were found to be inversely proportional, and a short ST decreased HCC risk, especially in women.

However, this study has some limitations. First, HCC cases were not diagnosed as NASH by hepatic biopsy; HCC cases with no viral infection and low alcohol consumption were considered NASH. Although 24.8% of cases did not have liver disease or HBV/HCV, patients with NASH might still have been present within these groups. Second, because participants were all inpatients, selection bias may have occurred. The results might not be applicable to the general population, as the controls were inpatients, and the results may have been biased either towards or away from the null. In addition, cases and controls were selected from the same hospital admission to adjust for background confounding factors. The large sample size provided significant accuracy to minimise the bias. We selected cases from all admissions to minimise selection bias. Third, no information on the types of alcohol, such as wine and beer, was available. A study showed that consuming wine with <30 g of pure

alcohol decreased HCC risk.[44] Lastly, due to a lack of information on clinical results such as blood tests, the severity of metabolic diseases and liver cirrhosis could not be determined. Further studies are needed to examine the impact of different types of alcohol and the severity of comorbidity.

In conclusion, our results suggest that activeness during work decreases HCC risk among the women without established risk factors for HCC, such as HBV/HCV, or NASH. These findings indicate that careful follow-up should be considered for patients with NASH whose occupations are less active and/or sedentary.

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Acknowledgements We would like to express our gratitude to all study staff in the Japan Organization of Occupational Health and Safety for their commitment to the data collection. We also thank Editage (http://www.editage.com) for English language editing.

Contributors NK, KH, AT and MT acquired funding and collected the data. SN, KF, KS, YF and MT designed the study and analysed the data. SN, KF, KS and MT wrote the manuscript. KF, NK, KH, MK, AT and MT supervised the study and provided critical comments. All the authors have reviewed and approved the final manuscript. KF is responsible for the overall content of the manuscript as guarantor.

Funding This work was supported by the Research Project on Inpatient Clinico-Occupational Database of Rosai Hospital Group (2021); Epidemiological Study on Prevention of Disease and Return to Work by the Hospitalized Patient Medical History Study; Grants-in-Aid for Scientific Research from the Ministry of Health, Labour and Welfare (grant number: 23HC1001); and Industrial Disease Clinical Research Grants from the Ministry of Health, Labour and Welfare (No.220101-01).The funding sources had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; or the decision to submit the manuscript for publication.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. Ethical approval for this study was provided by the Research Ethics Committee of Japan Organization of Occupational Health and Safety (Protocol Number 2022-11) on 17 March 2022 and the Research Ethics Committees of the Tokai University School of Medicine, Kanagawa, Japan (Protocol Number 18R-309 R-309) on 14 March 2019. All research was conducted in accordance with both the Declarations of Helsinki and Istanbul. All participants gave their written consent until 2015. From 2016 to 2021, the consent acquisition method was changed to broad consent (opt-out). Access to the data set was provided via a research agreement between the study authors and Japan Organization of Occupational Health and Safety.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data sets used in this study are not publicly available because of license restrictions for the current study. These data are available upon request from the corresponding author.

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