Short communication

JHEP|Reports

Association of physical activity, including amount and maintenance, with the risk of HCC among patients with type 2 diabetes

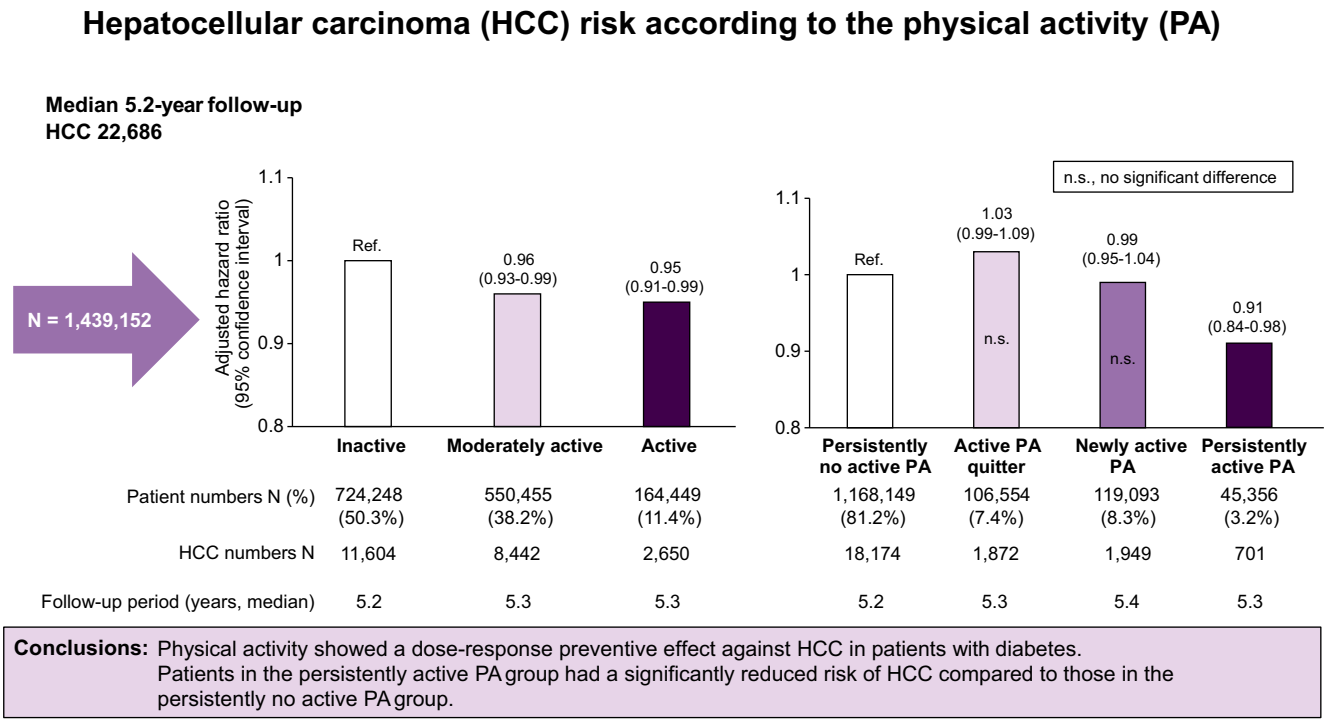
Authors

Wonkyung Han, Kyungdo Han, Seong Gyu Hwang, Sang Hoon Ahn, Mi Na Kim

Correspondence

minakim@yuhs.ac (M.N. Kim).

Graphical abstract



Highlights:

- Physical activity showed a dose-responsive preventive effect against hepatocellular carcinoma in patients with diabetes.
- The persistently active group had a significantly reduced risk of hepatocellular carcinoma compared to the persistently inactive group.
- Maintaining physical activity could be a strategy to prevent hepatocellular carcinoma development in patients with diabetes.

Impact and implications:

Our study investigated the impact of physical activity (PA) levels and changes on the risk of hepatocellular carcinoma (HCC) in patients with type 2 diabetes. PA was associated with a dose-responsive preventive effect against HCC. Patients in the persistently active PA group had a significantly lower risk of HCC than those in the persistently inactive PA group, while newly active patients and PA quitters had similar risks to the persistently inactive group. Our study highlighted the importance of maintaining regular PA as a preventive strategy against HCC.

https://doi.org/10.1016/j.jhepr.2024.101166

JHEP|Reports

Association of physical activity, including amount and maintenance, with the risk of HCC among patients with type 2 diabetes

Wonkyung Han[1,†], **Kyungdo Han**[2,†], Seong Gyu Hwang[1], Sang Hoon Ahn[3,4,5], Mi Na Kim[3,4,5,*]

JHEP Reports **2024**. vol. 6 | 1–5

Background & Aims: We investigated the association of physical activity (PA) levels and changes with the risk of hepatocellular carcinoma (HCC) in patients with type 2 diabetes.

Methods: Patients with type 2 diabetes who had undergone health examinations in 2009 and 2011 were enrolled. In total, 1,439,152 patients were included in the analysis. The level of PA was classified as inactive (<500 metabolic equivalent task [MET]-min/week), moderately active (500-1,500 MET-min/week), and active (≥1,500 MET-min/week). Change in PA was categorized as persistently inactive PA, newly active PA, active PA quitter, and persistently active PA according to change of PA between 2009 and 2011.

Results: During a median of 5.2 years of follow-up, 22,686 patients developed HCC. Compared to the inactive group, the risk of HCC was significantly lower in the moderately active (adjusted hazard ratio [aHR] 0.96, 95% CI 0.93–0.99), and active (aHR 0.95, 95% CI 0.91–0.99) groups. The patients in the persistently active PA group had a significantly lower risk of HCC than those in the persistently inactive PA group (aHR 0.91, 95% CI 0.84–0.98).

Conclusions: Physical activity exhibited a dose-responsive preventive effect against HCC in patients with diabetes.

Introduction

Population-based studies over the past two decades have revealed that diabetes is a strong independent metabolic risk factor of hepatocellular carcinoma (HCC).[1–4] The association was independent of several confounding factors, including alcohol, chronic liver diseases, and metabolic factors.[1,3,5] Thus, establishing strategies for HCC prevention in patients with diabetes is crucial.[6]

Several population-based studies have shown that physical activity (PA) lowers the risk of HCC development.[7–9] A recent meta-analysis including 14 prospective studies reported that high PA reduced the risk of liver cancer, including HCC, by 25% compared to low PA.[10] A pooled analysis of 10 prospective US and European cohorts found that high leisure-time PA was associated with a 27% lower risk of liver cancer incidence compared to low PA.[11] In addition, a preventive effect of PA on HCC has been suggested in several preclinical studies.[12,13] However, no study has investigated the association of PA with the risk of HCC in patients with diabetes. In addition, PA was assessed at a single time point in previous studies, so the effect of change in PA on the risk of HCC is unclear.

Accordingly, we investigated the associations of the amount of and change in PA with the risk of HCC in patients with type 2 diabetes.

Patients and methods

In this nationwide cohort study using the National Health Insurance Service cohort, we selected participants with type 2 diabetes who had undergone health examinations in 2009 and 2011 (Fig. S1). Patients with a history of extrahepatic cancers were also excluded due to the potentially increased risk of secondary cancer development in cancer survivors.[14] Type 2 diabetes was defined as ICD-10-CM codes of E11-E14 and claims for prescription of insulin and/or at least one oral hypoglycemic agent, or a fasting glucose level ≥126 mg/dl.[15] A total of 1,439,152 patients were eligible for the final analysis. Patients were followed up to the date of HCC development, death, or 31 December 2018. The primary outcome was HCC development. HCC was identified in the National Health Insurance Service data based on the ICD-10-CM code C22.0.

The level of PA was classified as inactive (<500 MET-min/week), moderate (500-1,500 MET-min/week), and active (≥1,500 MET-min/week). Change in PA over time was

* Corresponding author. Address: Department of Internal Medicine, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea. Tel.: +82-2-2228-1939.
E-mail address: minakim@yuhs.ac (M.N. Kim).
† These authors contributed equally as first authors.
https://doi.org/10.1016/j.jhepr.2024.101166

categorized as follows: persistently inactive PA as PA <1,500 MET-min/week in both 2009 and 2011; newly active PA as PA <1,500 MET-min/week in 2009 and ≥1,500 MET-min/week in 2011; active PA quitter as PA ≥1,500 MET-min/week in 2009 and <1,500 MET-min/week in 2011; and persistently active PA as reporting PA ≥1,500 MET-min/week in both 2009 and 2011.

Statistical analysis

Baseline characteristics were presented as mean ± SD (for normally distributed continuous variables), or geometric means with 95% CIs (for non-normally distributed continuous variables). Numbers (percentages) were presented for categorical variables. The Cox proportional hazard regression model was used to assess the association of PA with the risk of HCC, and adjusted hazard ratios (aHRs) and 95% CIs were calculated. We adjusted for age, sex, obesity (defined as ≥25 mg/kg^2 in Asian patients), smoking status, alcohol consumption, income, hypertension, dyslipidemia, chronic viral hepatitis, cirrhosis, insulin use, and number of oral antidiabetic agents. Cirrhosis was defined as a claim under ICD-10 code K74. To accurately assess the adjusted risk of HCC, we incorporated known traditional risk factors for HCC development as covariates in Model 2. In Model 3, insulin use and number of oral antidiabetic agents were included to account for the extent of glycemic control in diabetes. Significant alcohol consumption was defined as alcohol intake ≥30 g/day for men or ≥20 g/day for women, according to the definition of nonalcoholic fatty liver disease.[16] Statistical analysis was performed using SAS software (version 9.3; SAS Institute, Cary, NC).

Results

Baseline characteristics

During a median of 5.2 years of follow-up, 22,686 patients developed HCC. The follow-up period for each group is detailed in Table S1. The characteristics of the patients according to HCC development are shown in Table S2. The characteristics of the participants according to amount of PA are listed in Table 1. Among them, 724,248 participants (50.3%) were in the inactive group, 550,455 (38.2%) in the moderately active group, and 164,449 cases (11.4%) were in the active group. Patients who reported more PA were more likely to be male, non-obese, have higher income, to be non-current smoker, have more significant alcohol consumption, and lower fasting glucose levels.

Risk of HCC according to PA

The incidence rate of HCC was 3.2 per 1,000 person-years for the inactive group, 3.0 per 1,000 person-years for the moderately active group, and 3.1 per 1,000 person-years for the active group. Compared to the inactive group, the risk of HCC was significantly lower in the moderately active (aHR 0.96, 95%

Table 1. Baseline characteristics according to the physical activity group.

Variables	Inactive (n = 724,248, 50.3%)	Moderately active (n = 550,455, 38.2%)	Active (n = 164,449, 11.4%)	*p* value
Demographic variable				
Age, years	58.3 ± 12.1	57.2 ± 11.6	58.9 ± 10.8	<0.001
Male	408,245 (56.37)	354,991 (64.49)	111,165 (67.60)	<0.001
Body mass index, kg/m^2	25.1 ± 3.4	24.9 ± 3.2	24.8 ± 3.1	<0.001
Waist circumference, cm	85.3 ± 8.8	84.9 ± 8.4	84.5 ± 8.2	<0.001
Systolic blood pressure, mmHg	128.1 ± 15.4	127.9 ± 14.9	128.1 ± 14.9	<0.001
Diastolic blood pressure, mmHg	78.3 ± 10.0	78.4 ± 9.9	78.0 ± 9.7	<0.001
Low income	150,278 (20.75)	105,066 (19.09)	30,814 (18.74)	<0.001
Smoking status				<0.001
Never	424,369 (58.59)	282,553 (51.33)	85,914 (52.24)	
Former	117,002 (16.15)	127,878 (23.23)	44,061 (26.79)	
Current	182,877 (25.25)	140,024 (25.44)	34,474 (20.96)	
Alcohol intake, g/day				<0.001
None	433,874 (59.91)	281,838 (51.20)	87,073 (52.95)	
Mild	222,925 (30.78)	216,494 (39.33)	61,209 (37.22)	
Significant alcohol consumption	67,449 (9.31)	52,123 (9.47)	16,167 (9.83)	
Comorbidity				
Chronic viral hepatitis	81,315 (11.23)	60,092 (10.92)	18,567 (11.29)	<0.001
Cirrhosis	10,116 (1.40)	7,407 (1.35)	2,347 (1.43)	0.011
Hypertension	415,169 (57.32)	305,899 (55.57)	94,633 (57.55)	<0.001
Dyslipidemia	333,804 (46.09)	245,335 (44.57)	73,196 (44.51)	<0.001
Chronic kidney disease	74,662 (10.31)	46,884 (8.52)	14,879 (9.05)	<0.001
Duration of diabetes ≥5 years	276,312 (38.15)	206,149 (37.45)	68,629 (41.73)	<0.001
Insulin use	53,101 (7.33)	35,450 (6.44)	11,196 (6.81)	<0.001
Oral hypoglycemic agent ≥3	126,244 (17.43)	88,176 (16.02)	26,420 (16.07)	<0.001
Laboratory variable				
Fasting glucose, mg/dl	134.8 ± 47.8	133.4 ± 45.0	130.8 ± 41.1	<0.001
AST, IU/L	25.2 (25.2-25.3)	25.3 (25.3-25.4)	25.3 (25.2-25.3)	<0.001
ALT, IU/L	24.9 (24.9-25.0)	25.1 (25.1-25.1)	24.2 (24.1-24.2)	<0.001

Data are presented as mean ± SD, geometric mean and 95% confidence interval, or number (%).
The distribution of continuous variables was evaluated using Kolmogorov-Smirnov test. Continuous variables that were not normally distributed were compared using Mann-Whitney U test, and Student's *t*-test was used to compare normally distributed continuous variables. When less than 20% of cells had an expected frequency <5, chi-square test was used to compare categorical variables; otherwise, Fisher's exact test was used. Two-tailed *p*-values of <0.05 were considered statistically significant.
HCC, hepatocellular carcinoma; MET, metabolic equivalent task; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; gamma GTP, gamma glutamyl transferase.

Table 2. Risk of hepatocellular carcinoma according to the PA group and change of PA.

	N	Event	Person-years	Incidence-rate[†]	Hazard ratio (95% CI)		
					Model 1[‡]	Model 2[§]	Model 3[¶]
PA group							
Inactive	724,248	11,604	3,652,422.3	3.2	1.00 (reference)	1.00 (reference)	1.00 (reference)
Moderately active	550,455	8,442	2,794,653.1	3.0	0.94 (0.91–0.96)	0.95 (0.93–0.98)	0.96 (0.93–0.99)
Active	164,449	2,650	841,400.0	3.1	0.92(0.88–0.96)	0.94 (0.90–0.98)	0.95 (0.91–0.99)
Change in PA							
Persistently inactive PA	1,168,149	18,174	5,900,447.6	3.1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Active PA quitter	106,554	1,872	546,627.8	3.4	1.03 (0.98–1.08)	1.04 (0.99–1.09)	1.03 (0.99–1.09)
Newly active PA	119,093	1,949	608,639.3	3.2	0.97 (0.93–1.02)	0.99 (0.94–1.03)	0.99 (0.95–1.04)
Persistently active PA	45,356	701	232,760.7	3	0.87 (0.81–0.94)	0.90 (0.83–0.97)	0.91 (0.84–0.98)

PA, physical activity.
[†]Incidence per 1,000 person-years.
[‡]Model 1 was adjusted for age and sex.
[§]Model 2 was adjusted for age, sex, obesity, smoking status, alcohol consumption, income, hypertension, dyslipidemia, chronic viral hepatitis, and cirrhosis.
[¶]Model 3 was adjusted for age, sex, obesity, smoking status, alcohol consumption, income, hypertension, dyslipidemia, chronic viral hepatitis, cirrhosis, insulin use, and number of oral antidiabetic agents used.

CI 0.93–0.99) and active (aHR 0.95, 95% CI 0.91–0.99) groups (Table 2). In the subgroup analyses of patients with and without cirrhosis, a similar reduction in the risk of HCC was observed, although this reduction did not reach statistical significance in some groups (Table S3).

The risk of HCC stratified by PA intensity is shown in Table S4. Patients who performed vigorous-intensity PA >3 days per week had a significantly lower risk of HCC than those performing vigorous-intensity PA <3 days per week (aHR 0.95, 95% CI 0.92–0.98). Although the incidence rate of HCC was slightly higher in patients with higher frequencies of light and moderate PA, after adjusting for confounding factors, the risk of HCC decreased in these patients. However, this reduction in risk did not reach statistical significance.

Risk of HCC according to change in PA

Table S5 shows the baseline characteristics of the patients according to the change in PA. Patients in the persistently active PA group were likely to be male, have significant alcohol consumption, and have diabetes for >5 years. They were less likely to be current smokers, use insulin, and use more than three oral hypoglycemic agents. The fasting glucose level was lower in patients in the persistently active PA group and newly active PA groups.

The incidence rate of HCC was 3.1 per 1,000 person-years in the persistently inactive PA group, 3.2 per 1,000 person-years in the newly active PA group, 3.4 per 1,000 person-years in the active PA quitter group, and 3.0 per 1,000 person-years in the persistently active PA group (Table 2). The patients in the persistently active PA group had a significantly lower risk of HCC than those in the persistently inactive PA group (aHR 0.91, 95% CI 0.84–0.98), while patients in the newly active PA and active PA quitter groups had similar risks of HCC as those in the persistently inactive PA group (all p >0.05).

Risk of HCC according to change in PA stratified by intensity

Active PA according to intensity was categorized as follows: 5 or more times a week of light-intensity PA, such as walking for ≥10 min at a time and ≥30 min a day; 5 or more times a week of moderate-intensity PA, such as brisk walking, tennis doubles, or cycling at a normal speed for ≥30 min; and 3 or more times a week of vigorous-intensity PA, such as running, aerobics, fast bicycling, or climbing for ≥20 min.

Persistently active PA was associated with the greatest reduction in risk of HCC regardless of PA intensity. Compared to patients in the persistently inactive light PA group (HCC incidence-rate of 3.4 per 1,000 person-years), the risk of HCC was significantly lower in those in the persistently active light PA group (HCC incidence rate of 3.0 per 1,000 person-years; aHR 0.93, 95% CI 0.89–0.97) (Fig. 1A). Similarly, compared to patients in the persistently inactive moderate PA group (HCC incidence rate of 3.3 per 1,000 person-years), the risk of HCC was significantly lower in those in the persistently active moderate PA group (HCC incidence rate of 2.8 per 1,000 person-years; aHR 0.91, 95% CI 0.88–0.95) (Fig. 1B). Furthermore, compared to patients in the persistently inactive vigorous PA group (HCC incidence rate of 3.3 per 1,000 person-years), the risk of HCC was significantly lower in those in the persistently active vigorous PA group (HCC incidence rate of 2.8 per 1,000 person-years; aHR 0.91, 95% CI 0.87–0.94) (Fig. 1C). Although the HCC incidence rate of patients in the active PA quitter and newly active PA groups across all PA intensity levels was lower than those in the persistently inactive PA group, statistical significance was only achieved in the moderate and vigorous PA intensity groups.

Discussion

In this nationwide population-based cohort study, the risk of HCC was significantly lower in patients who were physically active compared to those who were not, among patients with diabetes. The inverse association of the total amount of PA with the risk of HCC was dose-dependent. Moreover, patients in the persistently active PA group had a significantly lower risk of HCC than those in the persistently inactive PA group, whereas patients in the newly active PA and active PA quitter groups had similar risks.

Population-based studies have shown that diabetes is strongly associated with the risk of HCC.[1–3,5,17] In a recent meta-analysis, patients with diabetes had a 2.3-fold higher risk of HCC compared to individuals without diabetes. In a recent prospective cohort study, diabetes was associated with an increased HCC risk, as was an increasing diabetes duration.[2] Diabetes appears to be linked to an increased risk of HCC

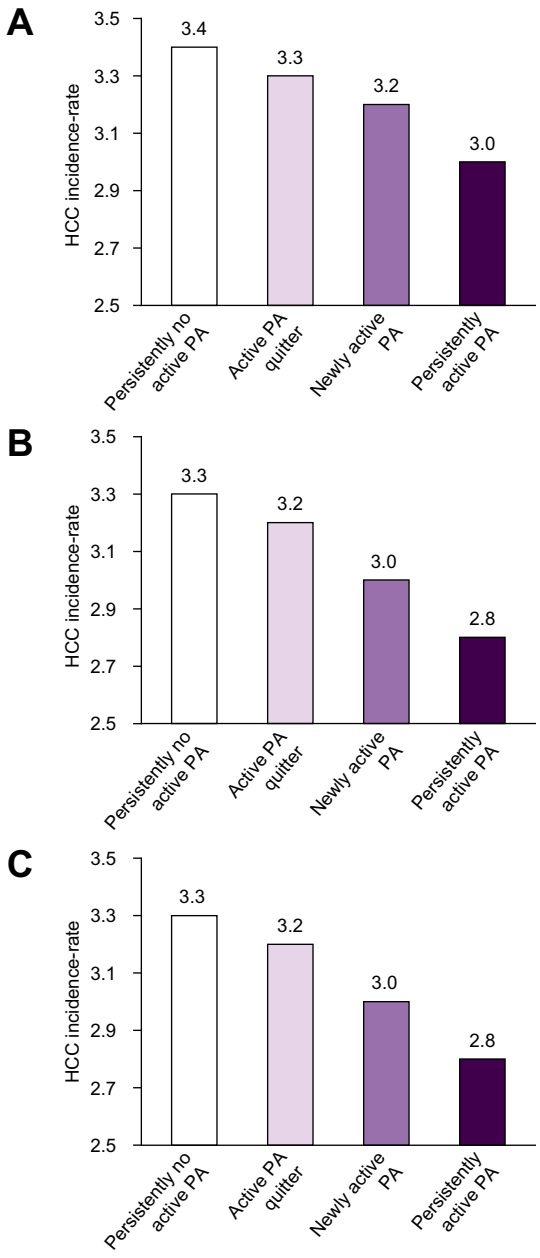


Fig. 1. The incidence rate of HCC (per 1,000 person-years) according to the change in PA stratified by intensity. (A) light intensity PA, (B) moderate intensity PA, (C) vigorous intensity PA. HCC, hepatocellular carcinoma; PA, physical activity.

via insulin resistance-induced hyperinsulinemia and oxidative stress.[18]

An inverse association of PA with the risk of HCC has been reported in several studies. In a European cohort study, the active PA group had a 45% lower risk of HCC compared to the inactive group. Vigorous PA for >2 h per week lowered the risk of HCC by about 50% compared to no vigorous-intensity PA.[8] A US cohort study revealed that brisk walking (moderate-intensity PA) reduced the risk of HCC by about 50%.[9] Recent meta-analysis showed that the mean HR for high compared to low PA was 0.75. Our findings are in line with prior studies of an inverse dose-response association between the amount of PA and the risk of HCC.[8,9,19] In addition, regular vigorous PA was associated with a reduced risk of HCC, whereas moderate and light PA were not, which implies that high-intensity PA can prevent HCC.

Several mechanisms might explain the inverse association between PA and the risk of HCC. PA improves insulin resistance and decreases steatosis,[19,20] potentially preventing HCC development. In addition, a PA-mediated decrease in the IL-6 level may reduce the HCC risk.[21] IL-6 is known to be the main cytokine involved in HCC development and can modulate cancer stem cells.[22,23] Chronic PA reduces the IL-6 level in both animal and human studies.[24,25]

The strength of this study is the analysis of a large cohort with available data on PA and sufficient HCC cases. In addition, we collected information on PA at two time points, allowing us to investigate the association between change in PA over time and the risk of HCC. Although previous studies investigated the association of the amount of PA with the risk of HCC,[8,9,19] our study is the first report on the importance of maintaining PA to prevent HCC development.

We acknowledge several limitations. First, we lacked detailed clinical information due to the nature of the nationwide cohort data. Liver imaging or histological data was not available in this nationwide cohort, precluding the assessment of metabolic-associated steatohepatitis diagnoses. In addition, detailed data on factors among patients with chronic viral hepatitis and/or cirrhosis, such as viral load, virological response, the stages of cirrhosis including decompensation status and Child-Pugh scores were not available for our cohort. Although we have adjusted for the presence of chronic viral hepatitis and cirrhosis, and have presented the results stratified by the presence of cirrhosis, the absence of detailed information regarding liver diseases may pose a barrier to accurately assessing the risk of HCC. Second, despite adjustment for diabetes duration and medication use, we lacked data on hemoglobin A1c level, which is an important indicator of severity of diabetes. Third, as our cohort was provided with only anthropometric data for 2009 and 2011 according to our study design, we could not further evaluate the impact of long-term changes in PA on the risk of HCC. Fourth, although the adjusted risk did not significantly increase for patients with newly active PA and those who quit active PA, the increased incidence of HCC in these groups could not be clearly explained due to the lack of detailed information on the development of other comorbidities and decompensated liver cirrhosis. Fifth, this study was a retrospective observational study, which may be biased due to residual confounders not included in the analysis that may have influenced the results. Lastly, the risk of mortality could not be assessed with this database.

In conclusion, PA showed a dose-responsive preventive effect against HCC in patients with diabetes. Patients in the persistently active PA group had a significantly reduced risk of HCC compared to those in the persistently inactive PA group. Our findings suggest that maintaining active PA could prevent HCC development in patients with diabetes.

Affiliations

[1]*Division of Gastroenterology, Department of Internal Medicine, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Republic of Korea;* [2]*Department of Statistics and Actuarial Science, Soongsil University, Seoul, Republic of Korea;* [3]*Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea;* [4]*Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Republic of Korea;* [5]*Yonsei Liver Center, Severance Hospital, Seoul, Republic of Korea*

Abbreviations

aHR, adjusted hazard ratio; HCC, hepatocellular carcinoma; MET, metabolic equivalent task; PA, physical activity.

Financial support

This study was supported by a faculty research grant of Yonsei University College of Medicine (6-2023-0097). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest

The authors have no conflicts of interest to disclose.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

WH: data interpretation, drafting of the manuscript. KH: data analysis and interpretation. YH: data interpretation. YEC: data interpretation. JHL: data interpretation. KSL: data interpretation. MNK: study design, data analysis and interpretation, drafting of the manuscript, review of the manuscript, overall study oversight and guarantor of the manuscript.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101166.

References

Author names in bold designate shared co-first authorship

[1] Wang P, Kang D, Cao W, et al. Diabetes mellitus and risk of hepatocellular carcinoma: a systematic review and meta-analysis. Diabetes Metab Res Rev 2012;28(2):109–122. https://doi.org/10.1002/dmrr.1291.

[2] Simon TG, King LY, Chong DQ, et al. Diabetes, metabolic comorbidities, and risk of hepatocellular carcinoma: results from two prospective cohort studies. Hepatology 2018;67(5):1797–1806. https://doi.org/10.1002/hep.29660.

[3] Wang C, Wang X, Gong G, et al. Increased risk of hepatocellular carcinoma in patients with diabetes mellitus: a systematic review and meta-analysis of cohort studies. Int J Cancer 2012;130(7):1639–1648. https://doi.org/10.1002/ijc.26165.

[4] Seif El Dahan K, Daher D, Singal AG. Hepatocellular carcinoma surveillance in patients with non-alcoholic fatty liver disease. Clin Mol Hepatol 2023;29(Suppl):S207–S219. https://doi.org/10.3350/cmh.2022.0247.

[5] El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. Clin Gastroenterol Hepatol 2006;4(3):369–380. https://doi.org/10.1016/j.cgh.2005.12.007.

[6] **Sohn W**, **Kang D**, **Kang M**, et al. Impact of nationwide hepatocellular carcinoma surveillance on the prognosis in patients with chronic liver disease. Clin Mol Hepatol 2022;28(4):851–863. https://doi.org/10.3350/cmh.2022.0037.

[7] Behrens G, Matthews CE, Moore SC, et al. The association between frequency of vigorous physical activity and hepatobiliary cancers in the NIH-AARP Diet and Health Study. Eur J Epidemiol 2013;28(1):55–66. https://doi.org/10.1007/s10654-013-9767-1.

[8] **Baumeister SE**, **Schlesinger S**, **Aleksandrova K**, et al. Association between physical activity and risk of hepatobiliary cancers: a multinational cohort study. J Hepatol 2019;70(5):885–892. https://doi.org/10.1016/j.jhep.2018.12.014.

[9] Luo X, Yang W, Ma Y, et al. Physical activity and risk of hepatocellular carcinoma among U.S. Men and women. Cancer Prev Res (Phila) 2020;13(8):707–714. https://doi.org/10.1158/1940-6207.Capr-19-0447.

[10] Baumeister SE, Leitzmann MF, Linseisen J, et al. Physical activity and the risk of liver cancer: a systematic review and meta-analysis of prospective studies and a bias analysis. J Natl Cancer Inst 2019;111(11):1142–1151. https://doi.org/10.1093/jnci/djz111.

[11] Moore SC, Lee IM, Weiderpass E, et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. JAMA Intern Med 2016;176(6):816–825. https://doi.org/10.1001/jamainternmed.2016.1548.

[12] Piguet AC, Saran U, Simillion C, et al. Regular exercise decreases liver tumors development in hepatocyte-specific PTEN-deficient mice independently of steatosis. J Hepatol 2015;62(6):1296–1303. https://doi.org/10.1016/j.jhep.2015.01.017.

[13] Arfianti A, Pok S, Barn V, et al. Exercise retards hepatocarcinogenesis in obese mice independently of weight control. J Hepatol 2020;73(1):140–148. https://doi.org/10.1016/j.jhep.2020.02.006.

[14] Demoor-Goldschmidt C, de Vathaire F. Review of risk factors of secondary cancers among cancer survivors. Br J Radiol 2019;92(1093):20180390. https://doi.org/10.1259/bjr.20180390.

[15] Choi EK. Cardiovascular research using the Korean national health information database. Korean Circ J 2020;50(9):754–772. https://doi.org/10.4070/kcj.2020.0171.

[16] Kim MN, Lo CH, Corey KE, et al. Weight gain during early adulthood, trajectory of body shape and the risk of nonalcoholic fatty liver disease: a prospective cohort study among women. Metabolism 2020;113:154398. https://doi.org/10.1016/j.metabol.2020.154398.

[17] Lai SW, Chen PC, Liao KF, et al. Risk of hepatocellular carcinoma in diabetic patients and risk reduction associated with anti-diabetic therapy: a population-based cohort study. Am J Gastroenterol 2012;107(1):46–52. https://doi.org/10.1038/ajg.2011.384.

[18] Kasuga M, Ueki K, Tajima N, et al. Report of the Japan diabetes society/Japanese cancer association joint committee on diabetes and cancer. Cancer Sci 2013;104(7):965–976. https://doi.org/10.1111/cas.12203.

[19] Zelber-Sagi S, Nitzan-Kaluski D, Goldsmith R, et al. Role of leisure-time physical activity in nonalcoholic fatty liver disease: a population-based study. Hepatology 2008;48(6):1791–1798. https://doi.org/10.1002/hep.22525.

[20] van der Heijden GJ, Wang ZJ, Chu ZD, et al. A 12-week aerobic exercise program reduces hepatic fat accumulation and insulin resistance in obese, Hispanic adolescents. Obesity (Silver Spring) 2010;18(2):384–390. https://doi.org/10.1038/oby.2009.274.

[21] DiJoseph K, Thorp A, Harrington A, et al. Physical activity and risk of hepatocellular carcinoma: a systematic review and meta-analysis. Dig Dis Sci 2022. https://doi.org/10.1007/s10620-022-07601-w.

[22] Liu Y, Fuchs J, Li C, Lin J. IL-6, a risk factor for hepatocellular carcinoma: FLLL32 inhibits IL-6-induced STAT3 phosphorylation in human hepatocellular cancer cells. Cell Cycle 2010;9(17):3423–3427. https://doi.org/10.4161/cc.9.17.12946.

[23] Wan S, Zhao E, Kryczek I, et al. Tumor-associated macrophages produce interleukin 6 and signal via STAT3 to promote expansion of human hepatocellular carcinoma stem cells. Gastroenterology 2014;147(6):1393–1404. https://doi.org/10.1053/j.gastro.2014.08.039.

[24] **Oberbach A**, **Lehmann S**, **Kirsch K**, et al. Long-term exercise training decreases interleukin-6 (IL-6) serum levels in subjects with impaired glucose tolerance: effect of the -174G/C variant in IL-6 gene. Eur J Endocrinol 2008;159(2):129–136. https://doi.org/10.1530/eje-08-0220.

[25] Pattamaprapanont P, Muanprasat C, Soodvilai S, et al. Effect of exercise training on signaling of interleukin-6 in skeletal muscles of type 2 diabetic rats. Rev Diabet Stud 2016;13(2–3):197–206. https://doi.org/10.1900/rds.2016.13.197.

Keywords: Physical activity; Hepatocellular carcinoma; Diabetes.

Received 29 October 2023; received in revised form 1 July 2024; accepted 1 July 2024; Available online 3 July 2024