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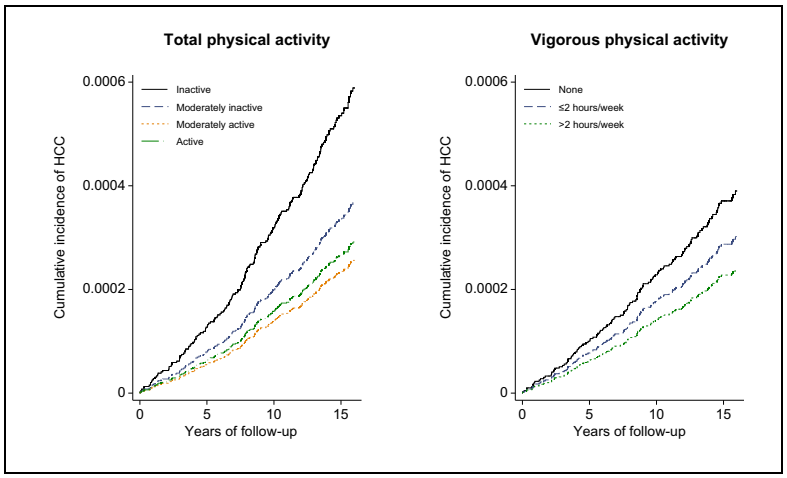
Association between physical activity and risk of hepatobiliary cancers: A multinational cohort study

Graphical abstract



Highlights

- Liver cancer rates are increasing in Western countries, possibly due to increases in obesity, diabetes, and physical inactivity.
- Previous evidence was not convincing to support an effect of physical activity on liver cancer.
- We found that physical activity reduced the risk of hepatocellular carcinoma by about 45%.

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Lay summary

In a pan-European study of 467,336 men and women, we found that physical activity is associated with a reduced risk of developing liver cancers over the next decade. This risk was independent of other liver cancer risk factors, and did not vary by age, gender, smoking status, body weight, and alcohol consumption.

http://dx.doi.org/10.1016/j.jhep.2018.12.014

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Association between physical activity and risk of hepatobiliary cancers: A multinational cohort study

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Keywords: Hepatobiliary cancer; Hepatocellular carcinoma; Liver cancer; Physical activity.
Received 5 July 2018; received in revised form 5 December 2018; accepted 6 December 2018; available online 22 December 2018
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Background & Aims: To date, evidence on the association between physical activity and risk of hepatobiliary cancers has been inconclusive. We examined this association in the European Prospective Investigation into Cancer and Nutrition cohort (EPIC).
Methods: We identified 275 hepatocellular carcinoma (HCC) cases, 93 intrahepatic bile duct cancers (IHBCs), and 164 non-gallbladder extrahepatic bile duct cancers (NGBCs) among 467,336 EPIC participants (median follow-up 14.9 years). We estimated cause-specific hazard ratios (HRs) for total physical activity and vigorous physical activity and performed mediation analysis and secondary analyses to assess robustness to confounding (*e.g.* due to hepatitis virus infection).
Results: In the EPIC cohort, the multivariable-adjusted HR of HCC was 0.55 (95% CI 0.38–0.80) comparing active and inactive individuals. Regarding vigorous physical activity, for those reporting >2 hours/week compared to those with no vigorous activity, the HR for HCC was 0.50 (95% CI 0.33–0.76). Estimates were similar in sensitivity analyses for confounding. Total and vigorous physical activity were unrelated to IHBC and NGBC. In mediation analysis, waist circumference explained about 40% and body mass index 30% of the overall association of total physical activity and HCC.
Conclusions: These findings suggest an inverse association between physical activity and risk of HCC, which is potentially mediated by obesity.
Lay summary: In a pan-European study of 467,336 men and women, we found that physical activity is associated with a reduced risk of developing liver cancers over the next decade. This risk was independent of other liver cancer risk factors, and did not vary by age, gender, smoking status, body weight, and alcohol consumption.

Introduction

Liver cancer was the fourth leading cause of cancer death in 2015.[1] Liver cancer is responsible for around 47,000 deaths per year in the European Union.[2] Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer derived from hepatocytes and it accounts for 85–90% of all primary liver cancers worldwide. It is the fifth most common cancer in men and the seventh most common cancer in women.[1] The distribution of HCC varies greatly according to geographic location and it is more common in low- and middle-income countries than in developed countries. HCC more frequently occurs in Asia and Africa than in Europe and the United States. The strongest risk factor for HCC is cirrhosis, a condition that is related to hepatitis B virus (HBV), hepatitis C virus (HCV), excessive consumption of alcohol, and exposure to aflatoxin B1.[1] The geographic variability of HCC incidence has been widely associated to the different distribution of HBV and HCV infections.[1,3] In high-income countries, the main risk factors for HCC are smoking, alcoholic cirrhosis, diabetes, obesity, and non-alcoholic hepatic steatosis.[1,4,5] The recent increase in HCC incidence is thought to be caused by increases in obesity, diabetes, and physical inactivity.[6,7] The Physical Activity Collaboration of the National Cancer Institute's Cohort Consortium performed a pooled analysis of 10 prospective US and European cohorts and found that high compared with low leisure-time physical activity was associated with a 27% lower risk of liver cancer incidence.[8] Other prospective studies from the United States and East Asian countries support an association between physical activity and lower risk of hepatobiliary cancers.[8–13] However, the World Cancer Research Fund International judged that the evidence was not convincing to support an effect of physical activity on liver cancer.[14] Similarly, an umbrella review provided limited evidence for an association between physical activity and liver cancer.[15] We report results from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort to provide additional evidence on the relationship between physical activity and HCC and other hepatobiliary cancers.

Patients and methods

Study population and data collection

The EPIC is a multinational prospective cohort study designed to investigate the link between diet, lifestyle and environmental factors, and cancer risk and other chronic diseases. Detailed information on the study design, rationale, and methods of the EPIC cohort have been presented previously.[16] In brief, between 1992 and 2000, >520,000 men and women, aged 25–70 years, were recruited from 23 centres throughout 10 countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom). Data on physical activity, education, smoking, alcohol consumption, coffee intake, anthropometric measurements, and medical history were collected at baseline, before disease onset, or at diagnosis. All cohort members provided written informed consent. Ethical approval was obtained from the International Agency for Research on Cancer review board (Lyon, France) and participating centres. A total of 467,336 participants were included in the main analyses for total physical activity and hepatobiliary cancer risk after applying the following exclusions: 25,184 participants with prevalent cancer other than non-melanoma skin cancer; 20 individuals with missing date of diagnosis; and 4,128 individuals without follow-up. Four EPIC study centres (Naples, Umea, southeast of Norway, and northwest of Norway) did not measure vigorous physical activity. Thus, the analysis of vigorous physical activity and hepatobiliary cancer risk was limited to 341,533 participants for whom data on this exposure were available. For further details regarding the materials used, please refer to the CTAT table and Supplementary information.

In a subset[17] of the EPIC cohort as of 2006, sera samples for HBV (ARCHITECT HBsAg, Abbott Diagnostics, France) and HCV (anti-HCV chemiluminescent microparticle immunoassays, Abbott Diagnostics, France) serologic tests were available: 115 HCC cases were matched using incidence density sampling with 230 controls based on age at blood collection, sex, study centre, time of the day at blood collection, and fasting status at blood collection; among women, in addition to the aforementioned menopausal status and hormone replacement therapy use at time of blood collection were used. These data were used in nested case-control analyses to examine potential confounding by viral hepatitis status for the association between physical activity and HCC.

Follow-up of study population and case ascertainment

Incident first primary hepatobiliary cancer cases and vital status were ascertained through record linkage with cancer and death registries in most centres.[16] In France, Germany, and Greece, ascertainment was done using a combination of methods including health insurance records, pathology registries, and active follow-up through mailed questionnaires/telephone inter-

views.[16] Incident cancers were subsequently verified through medical records, pathology reports, and discharge diagnosis.[16] In all centres, cancer diagnosis required confirmation through comprehensive pathology review.[16] A detailed protocol entitled *Guidelines for Collection of End-point Data in the EPIC study* for the collection and standardisation of clinical and pathological data for each cancer site was prepared by a special EPIC working group.[16] Cancer incidence was coded according to the International Classification of Diseases-Oncology-2. HCC was defined as C22.0. Intrahepatic bile duct cancer (IHBC) was defined as C22.1. Non-gallbladder extrahepatic bile duct cancer (NGBC) was defined as tumours in the extrahepatic bile duct (C24.0), ampulla of Vater (C24.1), or overlapping lesions of the biliary tract (C24.8), and the biliary tract not specified (C24.9). We did not consider cancers of the gallbladder (C23.9) as an endpoint because we assumed different underlying mechanisms.[10]

Assessment of physical activity

The validated EPIC Physical Activity Questionnaire (EPIC-PAQ) was used to assess recreational, household, and occupational physical activity during the past year in all EPIC centres, except in the Norwegian centres.[18–20] Recreational physical activity was assessed by asking participants how much time, in hours per week, they spent cycling and/or performing other physical exercises (*e.g.* jogging, swimming) during the winter and summer. Recreational physical activity was summarised into 4 groups: inactive, moderately inactive, moderately active, and active.[21,22] Participants reported their level of occupational physical activity as either sedentary, standing, manual work, or heavy manual work. They were also asked whether engaging in household and recreational activities had caused them to experience increases in sweating or heartbeat, and, if so, how many hours per week they dedicated to these vigorous activities. We derived measures of total physical activity and vigorous physical activity from the EPIC-PAQ. The Cambridge Index was used as a measure of total physical activity by combining recreational physical activity and occupational physical activity.[20,22] The Cambridge Index was developed[22] and validated[19] by comparing the EPIC-PAQ with objective measures of cardiorespiratory fitness and physical activity energy expenditure. The Spearman correlation between the Cambridge Index and physical activity energy expenditure was 0.33 (95% confidence interval [CI] 0.28–0.38).[19] The Norwegian EPIC centres measured total physical activity using a scale that ranged from 1 to 10;[23] and the Cambridge Index for the Norwegian centres was derived as described previously.[21] Vigorous physical activity was categorised into 0, ≤2 (below the median), or >2 (above the median) hours per week.[21,24]

Statistical analysis

Hazard ratios (HRs) and 95% CIs were estimated using cause-specific Cox proportional hazard models, with age as the underlying time metric. Time of study entry was age at recruitment and exit time was age at cancer diagnosis or the last date at which follow-up was considered complete in each centre. Models were stratified by centre and sex to minimise departure from proportionality and to control for differences between centres, such as follow-up procedures and questionnaire design. Trend tests across exposure groups were performed by modelling the categorical physical activity variables as continuous covariables. We estimated cumulative incidence functions, adjusted for baseline confounders, accounting for competing risk of death from causes other than hepatobiliary cancer using a Fine–Gray subdistribution hazard model. The basic multivariable models were adjusted for education (no school degree, primary school, technical/professional/secondary, university), smoking status, and intensity (never, current [1–15, 16–25, or ≥26 cigarettes/-day], or former [≤10 or >10 years]; current pipe, cigar, or occasional smoking), current alcohol consumption (grams per day modelled continuously using restricted cubic splines), lifetime alcohol use patterns (never, former, >0–6 [men]/>0–3 [women], >6–12 [men]/>3–12 [women], >12–24, >24–60, >60 g/day), and daily number of cups of coffee (1 cup was defined as 150 ml). For covariates with missing data (Table 1), multiple imputation of covariates by fully conditional specification with accommodation of the substantive model[25] and 25 sets of imputed data were used. We examined multiplicative effect modification by testing interaction terms of physical activity variables with sex, age (continuous), waist circumference (continuous), body mass index (continuous), baseline alcohol consumption (continuous), and lifetime alcohol consumption (categorical) using likelihood ratio tests; for continuous covariates a procedure based on fractional polynomials was used.[26]

Because obesity and diabetes may be potential intermediates,[4,27,28] our primary multivariable model did not control for them. Causal mediation analysis methods, as described for survival data,[29] were used to examine the proportions of the association of physical activity with hepatobiliary cancer risk that was mediated by waist circumference, body mass index, and diabetes. These mediators were selected *a priori* based on subject knowledge[4,27,28] and were assessed using multiple linear regression (waist circumference and body mass index) and logistic regression (diabetes) for the mediator models and accelerated failure time models with Weibull distribution for time to event[29,30]. Proportion mediated was calculated as indirect natural effect divided by the sum of the direct and indirect natural effect,[29] and 500 simulations were used to derive quasi-Bayesian CI.[30] To facilitate the interpretation of mediation analyses, the categories 'active' *vs.* 'inactive' of the Cambridge Index and '>2 hours/week' *vs.* 'no' vigorous physical activity were compared. The mediation method assumes no unmeasured confounding in the exposure–outcome, mediator–outcome, and exposure–mediator relations, and no effect of the exposure on confounders of the mediator–outcome relation. We did not detect any exposure–mediator interactions.

We conducted several sensitivity analyses to test the robustness of our primary models. First, to minimise the influence of reverse causation, we excluded hepatobiliary cancer events that occurred during the first 2 years of follow-up. Second, although our primary analysis assumed that obesity and diabetes mediate the association between physical activity and hepatobiliary cancer risk, it is also plausible to hypothesise that overweight/obesity and diabetes render physical activity difficult (*i.e.* confound the association).[31] Accordingly, we performed secondary analyses with additional adjustment for waist circumference and diabetes. Third, we assessed the robustness of observed associations to unmeasured confounding. Specially, we calculated E-values,[32] which indicate the minimum strength of association than an unmeasured confounder would need to have with the exposure and the outcome on the risk ratio scale to fully account for an observed exposure–outcome association, above and beyond the measured covariates. In addition, we used data from the EPIC nested case-control study[17] to adjust associations for HBV/HCV status. Odds ratios for HCC were

Table 1. Age-adjusted baseline characteristics of the EPIC cohort by total physical activity (n = 467,336).

		Total physical activity (Cambridge Physical Activity Index)			
	Total N	Inactive	Moderately inactive	Moderately active	Active
Vigorous physical activity (%)					
None	182,178	55.9	42.5	30.0	28.5
≤2 h/week	88,245	18.1	19.9	19.0	18.7
>2 h/week	71,110	11.2	14.6	17.0	17.1
Missing	125,803	14.8	23.0	34.0	35.7
Sex (%)					
Men	139,168	26.8	27.7	27.5	40.4
Women	328,168	73.2	72.3	72.5	59.6
Education (%)					
No school degree/unknown	20,859	7.3	3.7	3.6	4.2
Primary school	120,284	35.7	23.1	23.1	25.8
Technical/professional/secondary	198,720	40.0	43.7	43.8	43.6
University	112,121	15.6	26.3	26.8	24.1
Missing	10,658	1.3	2.6	2.6	2.3
Smoking (%)					
Never	202,567	48.6	43.5	40.9	40.5
Current					
<15 cigarettes/day	53,680	10.2	11.1	12.1	12.9
≥15 cigarettes/day	37,534	9.4	7.7	7.4	7.9
Current pipe, cigar, or occasional smoking	40,040	7.3	9.6	9.4	6.8
Former					
<10 years	44,584	8.2	9.4	9.9	10.8
≥10 years	75,403	13.6	16.0	16.9	18.4
Missing	13,528	2.6	2.7	3.4	2.8
Baseline alcohol consumption (g/day)		3.1	5.8	5.4	7.3
Average lifetime alcohol consumption (g/day)					
Non-drinkers	28,146	8.7	6.4	4.3	4.6
Former	17,026	5.1	3.9	2.7	2.9
>0–6 (men)/> 0–3 (women)	93,442	25.4	21.3	16.3	17.2
>6–12 (men)/>3–12 (women)	110,070	24.6	24.3	22.2	22.6
>12–24	63,487	12.0	13.4	14.3	14.2
>24–60	41,822	7.2	8.6	10.1	9.8
>60	8,977	1.5	1.8	2.2	2.2
Missing	104,366	15.4	20.2	27.8	26.4
Coffee (ml/day)		179.3	281.1	316.9	409.4
Waist circumference (cm)		87.2	83.3	82.9	84.2
Missing	108,439				
Body mass index (kg/m^2)					
Missing	82,692	26.4	25.1	24.8	24.9
Diabetes (%)		5.4	2.6	2.0	1.9
Missing	36,517				

Entries are adjusted medians for continuous variables and adjusted percentages for categorical variables. Adjustment for age using median regression (continuous covariates), binary logistic regression (dichotomous covariates), ordinal logistic regression (ordered categorical covariates), and multinomial logistic regression (unordered categorical covariates).
EPIC, European Prospective Investigation into Cancer and Nutrition.

derived from multivariable conditional logistic regression, adjusted for matching variables, age, sex, smoking status, current alcohol use, and coffee intake. Analysis of the nested case-control subset was performed among all participants with additional adjustment for HBV/HCV; and among HBV/HCV-negative individuals. Fourth, as an alternative to the stratified Cox model, we modelled unobserved heterogeneity across centres using a Cox model with a shared frailty. Fifth, because of different methods used for assessment of total physical activity in the Norwegian centres, we re-estimated our Cox models for total physical activity after excluding data from the Norwegian centres. Sixth, we performed complete cases analysis when covariates had missing values. All p values <0.05 are reported as statistically significant. Analyses were performed using R (version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria), SAS (version 9.4; SAS Institute, Cary, NC, USA), and Stata (version 15.1; StataCorp, College Station, TX, USA).

Results

EPIC study

Characteristics of participants

Among the 467,336 participants in the EPIC study, the mean (standard deviation) age was 51.3 (9.9) years, and 70.2% were women. During a median follow-up time of 14.9 years, participants contributed 6,508,182 person-years, and 275 HCC, 93 IHBC, and 164 NGBC cancer cases were reported. Age-adjusted baseline characteristics of the analytical sample are summarised in Table 1.

Physical activity and hepatobiliary cancer risk

Total physical activity and vigorous physical activity were inversely associated with HCC but not with IHBC and NBGC. The adjusted HR for HCC comparing 'active' with 'inactive' individuals was 0.55 (95% CI 0.38–0.80, p for trend <0.001; Table 2). The adjusted HR for HCC comparing '>2 hours/week' of vigorous

Table 2. Association of total physical activity and hepatocellular carcinoma, intrahepatic bile duct cancers, and non-gallbladder extrahepatic bile duct cancer risk in the EPIC cohort (n = 467,336).

	Total physical activity (Cambridge Index)				*p* value for trend
	Inactive (ref.)	Moderately inactive	Moderately active	Active	
HCC (n)	91	83	48	53	
HR (95% CI)	1.00	0.65 (0.48–0.89)	0.49 (0.34–0.71)	0.55 (0.38–0.80)	<0.001
IHBC (n)	26	27	21	19	
HR (95% CI)	1.00	0.72 (0.41–1.26)	0.66 (0.36–1.21)	0.82 (0.43–1.53)	0.477
NGBC (n)	39	46	36	43	
HR (95% CI)	1.00	0.67 (0.43–1.05)	0.67 (0.42–1.08)	0.88 (0.55–1.39)	0.761

CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HCC, hepatocellular carcinoma (C22.0); IHBC, intrahepatic bile duct cancer (C22.1). NGBC, non-gallbladder extrahepatic bile duct cancer (C24.0, C24.1, C24.8, C24.9). HR, cause-specific hazard ratio, which was obtained from the centre- and sex-stratified Cox proportional hazards model, with age as time metric, adjusted for education, smoking, baseline alcohol consumption, lifetime alcohol consumption, and coffee intake. Missing covariate was imputed using multiple imputation.

Table 3. Association of vigorous physical activity and hepatocellular carcinoma, intrahepatic bile duct cancers, and non-gallbladder extrahepatic bile duct cancer risk in the EPIC cohort (n = 341,533).

	Vigorous physical activity			*p* value for trend
	None (ref.)	≤2 h/wk	>2 h/wk	
HCC (n)	122	33	32	
HR (95% CI)	1.00	0.50 (0.33–0.75)	0.50 (0.33–0.76)	<0.001
IHBC (n)	46	11	14	
HR (95% CI)	1.00	0.52 (0.26–1.06)	0.75 (0.39–1.44)	0.271
NGBC (n)	64	26	24	
HR (95% CI)	1.00	0.78 (0.47–1.30)	0.80 (0.48–1.35)	0.368

CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HCC, hepatocellular carcinoma (C22.0); IHBC, intrahepatic bile duct cancer (C22.1). NGBC, non-gallbladder extrahepatic bile duct cancer (C24.0, C24.1, C24.8, C24.9). HR, cause-specific hazard ratio, which was obtained from the centre- and sex-stratified Cox proportional hazards model, with age as time metric, adjusted for education, smoking, baseline alcohol consumption, lifetime alcohol consumption, and coffee intake. Missing covariate was imputed using multiple imputation.

activity with no vigorous activity was 0.50 (95% CI 0.33–0.76, *p* for trend <0.001; Table 3). The adjusted cumulative incidence functions indicate that the physically inactive group showed excess HCC incidence compared with more active groups (Fig. 1). The relationships between total physical activity/vigorous physical activity and outcomes were not modified by sex, age, waist circumference, body mass index, smoking, current alcohol consumption, or lifetime alcohol consumption (all *p* for interaction >0.1).

Mediation of the association between physical activity and HCC risk

We used mediation analysis to estimate the proportions of the associations with HCC that were mediated by waist circumference, body mass index, and diabetes (Table 4). Waist circumference explained 40% and body mass index 30% of the overall association of total physical activity and HCC. The proportions of the total effect of vigorous physical activity on HCC mediated by waist circumference and body mass index were 17% and 12%, respectively. Diabetes did not seem to mediate the observed associations.

Sensitivity analyses

In sensitivity analyses, the associations of total physical activity and vigorous physical activity with HCC, IHBC, and NBGC were virtually unchanged when events occurring during the first 2 years of follow-up were excluded (Tables S1 and S2). In models additionally adjusted for waist circumference and diabetes, the HR for HCC were attenuated but remained statistically significant. In the Cox model for total physical activity and HCC, for an unmeasured confounder to explain the HR estimate of 0.55, the unmeasured confounder would have to increase the likelihood of physical activity and decrease the likelihood of HCC by 3-fold, above and beyond the measured confounders. For an unmeasured confounder to move the upper confidence limit of 0.80 for this estimate to above 1.0, the unmeasured confounder would still have to both increase the likelihood of physical activity and decrease the likelihood of HCC by 1.8-fold, conditional on the measured covariates. Similarly, an unobserved confounder would need to be associated with an RR of 3.4 with vigorous physical activity and HCC to explain the estimated HR of 0.50 and an RR of 1.9 to move the upper confidence limit above 1.0, conditional on the measured covariates. We used the EPIC nested case-control study to perform additional adjustment for HBV/HCV. The results of these analyses were similar in direction and magnitude to those reported for the entire cohort, but they were not statistically significant because of the small sample size (Table S3). However, the data from the case-control data set provide further support for the notion that additional confounding by HBV/HCV might not be sufficient to explain the observed association of physical activity and HCC. Estimates from frailty models to account for between-centre heterogeneity were similar those from the stratified Cox models. After exclusion of Norwegian centres and in complete case analyses, HR were almost identical to the primary analysis. The HR and CI from the complete case analyses were similar to those from primary models employing multiple imputation (Tables S1 and S2).

Discussion

In this analysis of a multinational European cohort, higher total physical activity and vigorous physical activity were associated with a lower risk of HCC. We observed a 45% lower risk of HCC

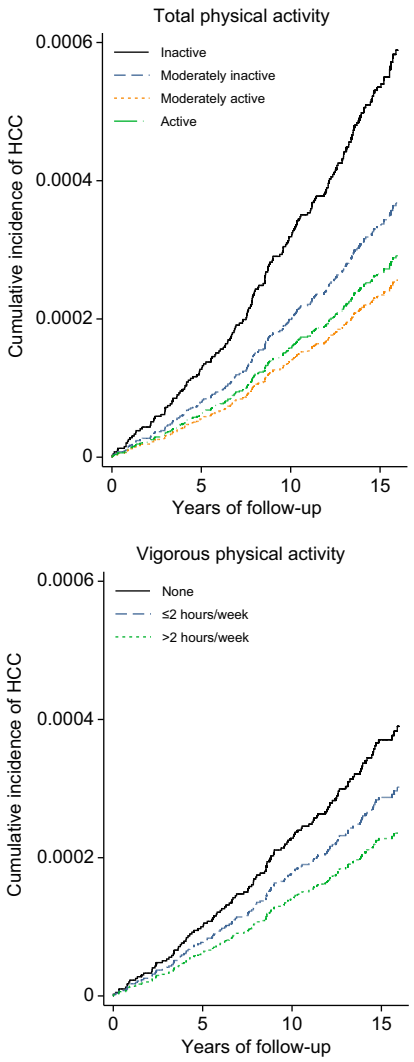

Fig. 1. Cumulative incidence of hepatocellular carcinoma according to total physical activity and vigorous physical activity. Adjusted cumulative incidence from a Fine–Gray model, with age as time metric, adjusted for education, smoking, baseline alcohol consumption, lifetime alcohol consumption, and coffee intake. (This figure appears in colour on the web.)

when comparing high and low levels of total physical activity. The highest level of vigorous physical activity was associated with a 50% lower risk for HCC. Moreover, we observed that inverse associations of total physical activity and vigorous physical activity with HCC did not differ substantially between subgroups based on gender, lifestyle, and anthropometric variables. Findings from the sensitivity analyses suggest that the association of physical activity and HCC might be robust to reverse causation and unobserved confounding (*e.g.* by hepatitis virus infection). Our study also explored the roles of obesity and diabetes in physical activity's association with HCC. Our findings indicate that waist circumference mediated about 40% and body mass index (BMI) about 30% of the overall association of total physical activity and HCC. By contrast, diabetes did not seem to play an important role as a mediating factor.

These findings are in line with a pooled analysis of 10 cohorts with a total of 1,384 cases that reported a 27% lower risk of liver cancer comparing high and low levels of leisure-time physical activity.[8] In the National Institutes of Health (NIH)-AARP Diet and Health Study, high *vs.* no vigorous physical activity was related to a 44% lower risk of HCC.[10] Similar to our study, no association between physical activity and biliary tract cancer was shown in a previous analysis of the NIH-AARP Diet and Health Study.[10]

Several biological mechanisms might explain the inverse association between physical activity and hepatobiliary cancer, including systemic and local effects.[28,33] The interrelated mechanisms most extensively studied are changes in whole-body and visceral fatness, metabolic dysregulation (*e.g.* insulin, glucose, insulin-like growth factors), adipokines (*e.g.* leptin, adiponectin), sex hormones (*e.g.* oestrogen, testosterone), chronic low-grade inflammation, oxidative stress causing DNA damage and gene mutations (*e.g.* tumour suppression genes), impaired immune function, diluting effects on carcinogenic bile acids, and decreased intestinal transit time.[33–35] Evidence from prospective observational studies and randomised controlled trials suggests that the most relevant mechanism by which physical activity positively affects liver cancer risk is lowering body weight.[27,36–38] This study systematically explored the role of markers of overall adiposity (body mass index), indirect measures of central obesity (waist circumference), and metabolic dysregulation (diabetes) in the overall association between physical activity and HCC. We found that central obesity might account for a large proportion of the direct effect of physical activity on HCC. The mechanisms underlying the association between central obesity and hepatobiliary cancer, particularly HCC, may occur through accumulation of excessive liver fat that increases pro-inflammatory molecules, leptin, and adiponectin.[27]

The analysis of this large multinational European cohort provided sufficient events to examine the association of physical activity with hepatobiliary cancers. The cohort study also provided first insights into the relative importance of different intensities of physical activity. We performed sensitivity analyses to address potential selection bias, differences in case ascertainment between centres, and additional unobserved confounding. Although HBV and HCV are considered among the strongest risk factors for HCC,[3] previous studies[8–13,37] were

Table 4. Mediation analysis for the association of total physical activity and vigorous physical activity and HCC in the EPIC cohort.

	Total physical activity (Cambridge Index) (n = 363,228)		Vigorous physical activity (n = 275,433)	
Mediator	**Proportion mediated (%)**	***p* value for indirect effect**	**Proportion mediated (%)**	***p* value for indirect effect**
Waist circumference	40.0	0.02	16.7	0.01
Body mass index	29.7	0.02	11.9	<0.01
Diabetes	4.2	0.21	0.6	0.23

Adjusted for age, sex, education, smoking, baseline alcohol consumption, lifetime alcohol consumption, and coffee intake. Complete case analysis was used for mediation analysis.
EPIC, European Prospective Investigation into Cancer and Nutrition; HCC, hepatocellular carcinoma (C22.0).

unable to adjust for HBV and HCV. In the EPIC nested case-control study, the size and direction of the effect size for the association between physical activity and HCC were similar to those of the entire EPIC cohort; however, it was not statistically significant. Our sensitivity analyses for unobserved confounding using E-values[32] further support the notion that any unmeasured confounding would need to be substantial to explain the inverse association between physical activity and HCC. The study had additional limitations. We were not able to adjust for other potentially important confounding factors (*e.g.* pleiotropic effects of statins) and to examine the role of intermediate phenotypes (non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, cirrhosis). Further, compared with the general population, women were overrepresented in our sample, although men have a higher risk of HCC.[39] Another limitation is that we were not able to examine in detail the type, intensity, and amount of physical activity needed to reduce HCC risk. Physical activity and anthropometric measures were assessed only once at baseline. Repeated measurements of physical activity, anthropometric measures, and other potential biological intermediates over time would have strengthened our understanding of the underlying mechanisms. A recent analysis of the NIH-AARP Diet and Health Study[9] revealed that consistent participation in physical activity throughout the life course might be needed to reduce the risk of liver cancer incidence. We performed mediation analysis for indirect effects acting through general and central obesity, but we were unable to study trajectories of physical activity and body weight that could help to better separate the role of obesity as a confounder and mediator of the association between physical activity and risk of hepatobiliary cancer.[8]

In conclusion, our analysis suggests that physical activity reduces the risk of HCC. Studies with more detailed and objectively measured physical activity assessed at multiple time points throughout the life course are warranted to confirm our findings and may help establish the optimal dose, type, intensity, and timing of physical activity that is needed to prevent HCC.

Financial support

This work was in part supported by the French National Cancer Institute (L'Institut National du Cancer; INCA – grant number 2009-139; principal investigator: MJ). The coordination of EPIC is financially supported by the European Commission (DG-SANCO) and the International Agency for Research on Cancer. The national cohorts are supported by the Danish Cancer Society (Denmark); Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM) (France); Deutsche Krebshilfe, Deutsches Krebsforschungszentrum and Federal Ministry of Education and Research (Germany); the Hellenic Health Foundation (Greece); Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland); World Cancer Research Fund (WCRF); Statistics Netherlands (The Netherlands); Nordic Centre of Excellence programme on Food, Nutrition and Health (Norway); Health Research Fund (FIS) PI13/00061 to Granada, Regional Governments of Andalucía, Asturias, Basque Country, Murcia (no. 6236) and Navarra, ISCIII RETIC (RD06/0020) (Spain); Swedish Cancer Society, Swedish Scientific Council and County Councils of Skåne and Västerbotten (Sweden); Cancer Research UK (14136 to EPIC-Norfolk; C570/A16491 and C8221/A19170 to EPIC-Oxford); Medical Research Council (1000143 to EPIC-Norfolk and MR/M012190/1 to EPIC-Oxford; United Kingdom); Medical Research Council (1000143 to EPIC-Norfolk; United Kingdom).

For information on how to submit an application for gaining access to EPIC data and/or bio-specimens, please follow the instructions at http://epic.iarc.fr/access/index.php.

Conflicts of interest

The authors declare no conflicts of interest that pertain to this work.

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

Authors' contributions

Conception and design: SEB, SS, KA, CJ, MJ, PF, MJG, MS, HF, MFL. Analysis and interpretation of the data: SEB, SS, KA, MJ, PF, MJG, MS, HF, MFL. Drafting of the manuscript: SEB, SS, KA, MFL. Critical revision of the manuscript for important intellectual content: CJ, MJ, MJG, KO, AT, M-CB-R, FC, AF, TK, RK, TP, HB, AT, CB, CLV, GM, SP, FF, RT, SG, BBM, RV, AM, KBB, SOO, EA, MR-B, MDCL, MF-N, ES, BO, OH, MW, AP-C, PF, MS, HF, KKT, HW, ER, EW. Final approval of the manuscript: SEB, SS, KA, CJ, MJ, MJG, KO, AT, M-CB-R, FC, AF, TK, RK, TP, HB, AT, CB, CLV, GM, SP, FF, RT, SG, BBM, RV, AM, KBB, SOO, EA, MR-B, MDCL, MF-N, ES, BO, OH, MW, AP-C, PF, MS, HF, KKT, HW, ER, EW, MFL. Statistical expertise: SEB, SS, KA, MFL. Administrative, technical, or logistical support: CJ, MJ, PF, MJG, MS, HF, EW, TK, RK, BBM, GM, M-CB-R, FC, AF, SP, RV, AM, MDCL, FF, MF-N, ES, BO, ER.

Acknowledgements

We thank all study participants and members of the EPIC study teams.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.12.014.

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