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The association between frequency of vigorous physical activity and hepatobiliary cancers in the NIH-AARP Diet and Health Study

Gundula Behrens¹, Charles E. Matthews², Steven C. Moore², Neal D. Freedman², Katherine A. McGlynn², James E. Everhart³, Albert R. Hollenbeck⁴, and Michael F. Leitzmann¹

¹Department of Epidemiology and Preventive Medicine, Regensburg University Medical Center, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany

²Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA

³Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA

⁴AARP, Washington, D.C., USA

Abstract

Despite a potential preventive effect of physical activity on hepatobiliary cancer, little information is available on the relation between the two. We studied the association between frequency of vigorous physical activity and hepatobiliary cancer among 507,897 participants of the NIH-AARP Diet and Health Study, aged 50 to 71 years at baseline in 1995/1996. During ten years of follow-up, 628 incident cases of liver cancer and 317 cases of extrahepatic biliary tract cancer were registered. Physical activity levels were assigned according to the frequency of engagement in 20 minutes or more of vigorous physical activity per week: never/rarely (lowest level), less than once per week, 1 to 2 times per week, 3 to 4 times per week, 5 or more times per week (highest level). Using Cox regression, multivariate-adjusted relative risks (RR) comparing the highest with the lowest level of physical activity revealed a statistically significant decreased risk for liver cancer (RR=0.64, 95% confidence interval (CI)=0.49–0.84, p-trend<0.001), particularly hepatocellular carcinoma (RR=0.56, 95% CI=0.41–0.78, p-trend<0.001), independent of body mass index. By comparison, multivariate analyses indicated that physical activity was not statistically significantly associated with extrahepatic bile duct cancer (RR=0.86, 95% CI=0.45–1.65), ampulla of Vater cancer (RR=0.66, 95% CI=0.29–1.48), or gallbladder cancer (RR=0.63, 95% CI=0.33–1.21). These results suggest a potential preventive effect of physical activity on liver cancer but not extrahepatic biliary tract cancer, independent of body mass index.

Keywords

Physical activity; liver cancer; biliary cancer; gallbladder cancer; cohort study

Introduction

Physical activity has been reported to reduce total cancer risk [1]. The relations of physical activity to cancers of the lung, colorectum, prostate, breast, endometrium and ovaries have been widely studied [1]. However, surprisingly little is known about any potential preventive effect of physical activity on hepatobiliary cancers, which have very low five-year survival rates of between 5% (intrahepatic bile duct cancer) and 17% (gallbladder cancer) [2].

Of the few epidemiologic studies concerning the relation of physical activity to hepatobiliary cancers, one large prospective investigation involving 444,963 Korean men showed an inverse association between physical activity and liver cancer but not gallbladder cancer [3]. By comparison, a cohort study of 79,771 Japanese men and women observed a risk reduction for liver cancer with high versus low physical activity in men but not women; no risk estimates were reported for biliary tract cancers [4]. Similarly, a cohort study of 38,801 men from the U.S. found a risk reduction for liver but not gallbladder cancer with high versus low cardiorespiratory fitness [5], a potential surrogate for maintained levels of total physical activity. However, those studies did not explore the relation of physical activity to hepatobiliary cancers in any detail. Specifically, no study has comprehensively examined the association between physical activity and hepatobiliary cancers according to liver cancer histology (hepatocellular carcinoma, cholangiocarcinoma) or extrahepatic biliary tract subsite (extrahepatic bile duct, ampulla of Vater, and gallbladder).

Methods

The cohort

The NIH-AARP Diet and Health Study was initiated in 1995–1996 when 3.5 million AARP (formerly known as the American Association of Retired Persons) members aged 50 to 71 years and residing in one of the U.S. states California, Florida, Louisiana, New Jersey, North Carolina, Pennsylvania or in one of the U.S. metropolitan areas Atlanta or Detroit were invited to participate. Of those, 566,399 participants satisfactorily completed a mailed questionnaire providing self-reported information on diet, physical activity, anthropometric measurements, and personal history of diseases [6]. For the current analysis, we excluded all participants with missing information on physical activity ($n=6,509$ subjects excluded) and those with prevalent cancer at study baseline ($n=51,993$ subjects excluded), leaving 507,897 participants for our analytic cohort. The Special Studies Institutional Review Board (IRB) of the U.S. National Cancer Institute approved the study.

Assessment of physical activity

To assess the frequency of vigorous physical activity, the baseline questionnaire inquired how often, during a typical month in the last 12 months, the participant had engaged in 20 minutes or more of physical activity. Participants were asked to include activities at home and work as well as those for exercise and sport that were sufficient to increase their breathing, heart rate, or to work up a sweat. The following response options were listed: never, rarely, 1 to 3 times per month, 1 to 2 times per week, 3 to 4 times per week, and 5 or more times per week. This physical activity assessment is comparable to one with documented reliability and validity [7].

Cohort follow-up

Study members were followed-up from baseline in 1995–1996 through December 31, 2006. Information on participants' residence was updated regularly through change of address notifications, address update services, and through processing of undeliverable mail.

Presumed deaths were verified through linkage to the Social Security Administration Death Master File and to the National Death Index Plus, which also clarified the cause of death, using either the participant's social security number or the participant's name, address history, gender, and date of birth.

Endpoint definition

We identified incident cases of liver or biliary tract cancer through linkage to the cancer registries of the states in which the study population was recruited and, additionally, through linkage to the cancer registries of Arizona and Texas. All registries are certified by the North American Association of Central Cancer Registries (NAACCR) [8]. The linkage procedure validly identifies about 90% of cancer incidences in the cohort [9].

Using all International Classification of Diseases for Oncology (ICD-O-3) morphology codes with malignant behaviour at sites C22.0, C22.1, C23.9, C24.0, C24.1, C24.8, and C24.9, we identified the following endpoints: liver cancer (C22.0 and C22.1), which included both liver cancer and intrahepatic bile duct cancer; extrahepatic bile duct cancer (C24.0); ampulla of Vater cancer (C24.1), gallbladder cancer (C23.9), and unspecified/overlapping biliary tract cancer (C24.8 and C24.9). The dominant histologic type of liver cancer in the U.S., hepatocellular carcinoma, was identified using morphology codes 8170–8175 and topography codes C22.0 and C22.1, while intrahepatic cholangiocarcinoma, the second most frequent histologic type of liver cancer in the U.S., was identified using morphology codes 8160–8161 and topography codes C22.0 and C22.1.

Main statistical analysis

Each study participant accrued follow-up time beginning at the date of return of the baseline questionnaire and ending at the date of the first incidence of any cancer, the date of death, the date at which the participant moved out of the study area, or the end of follow-up, whichever occurred first. Levels of physical activity were defined on the basis of the weekly frequency of vigorous physical activity that lasted at least 20 minutes: 0 (never, rarely), less than once per week (1 to 3 times per month), 1 to 2, 3 to 4, and 5 or more times per week. We assessed the association between the frequency of vigorous physical activity and the first occurrence of liver or extrahepatic biliary tract cancer by estimating relative risks (RR) applying Cox proportional hazards regression models. We verified that the assumption of proportional hazards was not violated using Schoenfeld residuals [10].

In age- and sex-adjusted analyses, we adjusted for age using five-year age groups at baseline. In multivariate analyses, we additionally adjusted for marital status (married or living as married, never married or separated or divorced or widowed), education (high-school or less than high-school, college education/vocational training, postgraduate education), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian, other ethnic background), body mass index (BMI) (<18.5, 18.5–24.9, 25.0–29.0, 30.0–34.9, 35.0+ kg/m²), alcohol intake (0, 0.1–14.9, 15.0–29.9, 30.0–59.9, 60+ grams of alcohol per day), smoking status (never, past smoking with an intensity of ≤20 cigarettes per day, past smoking with an intensity of more than 20 cigarettes per day, current smoking with an intensity of ≤20 cigarettes per day, current smoking with an intensity of more than 20 cigarettes per day), history of type 2 diabetes mellitus (yes, no), use of multivitamin dietary supplements (yes, no), total coffee intake (0, <1, 2–3, 4+ cups per day), red meat intake (ounces per 1000 kcal of energy intake in quintiles), white meat (including fish) intake (ounces per 1000 kcal of energy intake in quintiles), fruit (excluding juice) intake (ounces per 1000 kcal of energy intake in quintiles), vegetable (excluding legume) intake (ounces per 1000 kcal of energy intake in quintiles), and folate intake (micrograms per 1000 kcal of energy intake in quintiles). Because gallstone disease could be an intermediate step in the

causal pathway linking increased physical activity to decreased risk for extrahepatic biliary tract cancer, this variable was not included in our primary analyses. However, in an additional model, we adjusted for history of gallstones (yes, no) to assess the impact of physical activity on extrahepatic biliary cancer independent of its effect on gallstone disease. For tests of linear trend across levels of physical activity, we assigned each physical activity level its midpoint value and calculated the p-value of the resulting continuous variable using the Wald test.

We report RRs with corresponding 95% confidence intervals (CI). All p-values correspond to two-sided tests at the 5% significance level. We performed all analyses using SAS release 9.2 (SAS Institute, Cary, NC).

Statistical sub-analyses

In sub-analyses, we assessed whether BMI or history of diabetes affected the relationship of the frequency of vigorous physical activity to liver cancer by individually and jointly removing these variables from the multivariate model.

To examine the possibility that people with poor health (i.e., chronic liver disease) could have reduced their level of physical activity, thereby biasing our results, we excluded participants reporting poor health at baseline from the analysis and additionally explored the sensitivity of the risk estimates to the exclusion of the first 2, 4, and 6 years of follow-up.

To assess the effect of adherence to the vigorous physical activity recommendations of engaging in 20 minutes or more of vigorous exercise at least three times per week, as issued by the American College of Sports Medicine [11], we calculated multivariate-adjusted relative risks and multivariate-adjusted population-attributable risks [12] for participants adhering to the physical activity guidelines in comparison to participants not meeting those recommendations.

Furthermore, we conducted subgroup analyses of the association between physical activity and each of the following subtypes of hepatobiliary cancers: hepatocellular carcinoma, intrahepatic cholangiocarcinoma, other liver cancer, extrahepatic bile duct cancer, ampulla of Vater cancer, and gallbladder cancer. In further sub-analyses, we included exposure to menopausal hormone therapy (never, former, current) in the multivariate model to examine if hormone therapy confounded the relationship between physical activity and hepatobiliary cancers. In stratified analyses, we investigated whether the association of physical activity with total liver cancer was modified by other potential risk factors. We employed likelihood-ratio tests to assess whether interaction terms added any information to the model.

Hepatitis B and C virus infection status

We were interested in whether hepatitis B and C virus infection status, a risk factor for the development of hepatocellular carcinoma, was cross-sectionally associated with physical activity level, in which case hepatitis B and C virus infection status would qualify as a potential confounder of the relationship between physical activity and liver cancer. Because we lacked information on hepatitis B and C virus infection status in our U.S. cohort, we investigated the cross-sectional association between physical activity and hepatitis B and C virus infection status in a different U.S. study, the cross-sectional continuous National Health and Nutrition Examination Survey (NHANES) [13] conducted between 1999 and 2006, for which the required information was available. In NHANES, vigorous physical activity was assessed in a standardized interview inquiring on type, frequency, and duration of vigorous physical activities within the past 30 days. Information on hepatitis B and C virus infection status was obtained by measuring serum hepatitis B virus surface antigen seropositivity and serum hepatitis C virus antibody seropositivity. Applying multivariate

logistic regression, we examined the association between the frequency of vigorous leisure time physical activity and hepatitis B and C virus infection status in those 15,346 NHANES participants aged 21 to 79 years with available information on physical activity and hepatitis B and C virus infection status. The multivariate analyses were adjusted for age, sex, marital status, education, race/ethnicity, BMI, alcohol intake, smoking status, history of type 2 diabetes mellitus, use of multivitamin dietary supplements, total coffee intake, and energy-adjusted intakes of red meat, white meat (including fish), fruit (excluding juice), vegetables, and folate. For analysis, we used the statistical software R [14] and its “survey” package [15] to account for the complex sampling design of NHANES.

Results

Distribution of events

Between 1995 and 2006, the analytic NIH-AARP cohort accumulated 4,604,015 person-years of follow-up. The mean follow-up time was 9.1 (standard deviation SD=2.9) years. At the beginning of follow-up, the mean age was 62.0 (SD=5.4) years; at the end of follow-up, it was 71.1 (SD=5.8) years. During follow-up, 628 incident cases of primary liver cancer were reported, of which 415 were hepatocellular carcinoma, 90 were cholangiocarcinoma, and 123 were other liver cancers. In addition, a total of 317 cases of primary biliary tract cancer were ascertained, the locations of which were distributed as follows: extrahepatic bile duct, 32.2%; ampulla of Vater, 23.7%; gallbladder, 38.8%; and overlapping or not otherwise specified, 5.4%.

Distribution of risk factors at baseline

NIH-AARP participants who exercised at least five times per week were more likely to be married, to hold a postgraduate degree, to have a lower BMI, to consume more alcohol, and they were less likely to smoke cigarettes than physically inactive participants (Table 1).

Incidence of liver cancer and incidence of biliary tract cancer

Multivariate-adjusted analyses (Table 2) using NIH-AARP data revealed that the highest level of physical activity was significantly associated with a 36% risk reduction in total liver cancer (RR=0.64, 95% CI=0.49–0.84, p-trend<0.001) compared to the physically inactive group. For hepatocellular carcinoma, the corresponding risk estimate was stronger (RR=0.56, 95% CI=0.41–0.78, p-trend<0.001), while no significant association was observed with cholangiocarcinoma (RR=1.34, 95% CI=0.64–2.79, p-trend=0.39) or other liver cancer (RR=0.61, 95% CI=0.32–1.15, p-trend=0.13).

Table 3 shows the relationships of frequency of vigorous physical activity to extrahepatic biliary tract cancer and its anatomic subsites in the NIH-AARP Diet and Health Study. Multivariate analyses indicated that physical activity was not associated with total extrahepatic biliary tract cancer (RR=0.73, 95% CI=0.50–1.08), extrahepatic bile duct cancer (RR=0.86, 95% CI=0.45–1.65), ampulla of Vater cancer (RR=0.66, 95% CI=0.29–1.48), or gallbladder cancer (RR=0.63, 95% CI=0.33–1.21).

Removing variables representing BMI and history of type 2 diabetes mellitus individually or jointly from the multivariate models did not materially alter the risk estimates of physical activity in relation to total liver cancer. In these models, the relative risk estimates for liver cancer comparing extreme categories of physical activity were RR=0.61 (95% CI=0.47–0.79, BMI removed) and RR=0.61 (95% CI=0.47–0.80, history of diabetes removed). The corresponding risk estimates for total biliary tract cancer were RR=0.69 (95% CI=0.47–1.02) and RR=0.72 (95% CI=0.49–1.07). Removing BMI and history of type 2 diabetes jointly from the multivariate model yielded a relative risk for liver cancer of 0.56 (95%

CI=0.43–0.73) and a relative risk for biliary tract cancer of 0.68 (95% CI=0.46–0.99). Furthermore, adding history of gallstones to the multivariate biliary tract cancer model did not alter the estimated relative risk of biliary tract cancer comparing extreme categories of physical activity (RR=0.73, 95% CI=0.50–1.08). Inclusion of menopausal hormone therapy in the model did not affect the relationship between a physical activity and hepatobiliary cancers. In particular, after inclusion of menopausal hormone therapy, relative risks comparing extreme categories of physical activity remained constant for total liver cancer (RR=0.64, 95% CI=0.49–0.84), total biliary tract cancer (RR=0.74, 95% CI=0.50–1.08), and gallbladder cancer (RR=0.64, 95% CI=0.34–1.22).

The risk estimate for total liver cancer was unaltered after exclusion of participants stating poor health at baseline (RR=0.64, 95% CI=0.49–0.85). Likewise, the association proved relatively stable after additional exclusion of the first 2, 4, and 6 years of follow-up, with corresponding risk estimates of RR=0.66 (95% CI=0.49–0.89), RR=0.58 (95% CI=0.41–0.82), and RR=0.52 (95% CI=0.34–0.80), respectively.

Multivariate analyses revealed that adherence to the vigorous physical activity guidelines of the American College of Sports Medicine recommending engaging in 20 minutes or more of vigorous exercise at least three times per week was related to a 23% reduction in total liver cancer (RR=0.77, 95% CI=0.65–0.91) compared to those not meeting the guidelines. If all participants had engaged in 20 minutes or more of vigorous exercise at least three times per week, 14% (95% CI=5%–23%) of liver cancer incidences could have been avoided.

In the NIH-AARP Diet and Health Study, we further examined whether the association between the frequency of vigorous physical activity and liver cancer was modified by potential liver cancer risk factors (Table 4). We detected a statistically significant heterogeneity of effects for smoking status (p-interaction=0.004). Among never-smokers, we observed a decreasing risk of liver cancer with increasing physical activity (p-trend<0.001). However, no significant associations between physical activity and liver cancer were found among past (p-trend=0.10) or current smokers (p-trend=0.56). In addition, an inverse association between physical activity and liver cancer was present among participants with vegetable intake less than the median (p-trend<0.001) but not among participants with vegetable intake greater than the median (p-trend=0.49). By comparison, no statistically significant heterogeneity of the physical activity and liver cancer relation was observed across levels of alcohol intake (p-interaction=0.75), coffee intake (p-interaction=0.06), or diabetes status (p-interaction=0.13). Tests for statistical interaction between physical activity and any of the remaining potential risk factors also proved to be statistically non-significant.

Among the 15,347 participants of the continuous NHANES surveys, we investigated the association between the frequency of vigorous leisure time physical activity and hepatitis B virus infection status (n=63 cases) and between leisure time physical activity and hepatitis C virus infection status (n=311 cases) in multivariate-adjusted analyses. No consistent relations emerged. As compared with the physically inactive group, the relative risks of hepatitis B virus infection for those who engaged in physical activity less than 1 time, 1 to 2 times, 3 to 4 times, and 5 or more times per week were 0.35 (95% CI=0.10–1.18), 0.50 (95% CI=0.08–3.27), 0.84 (95% CI=0.34–2.05), and 0.74 (95% CI=0.24–2.24), respectively (p-trend=0.80). The corresponding risk estimates for hepatitis C virus infection were 0.57 (95% CI=0.34–0.95), 0.93 (95% CI=0.53–1.64), 1.04 (95% CI=0.63–1.71), and 0.74 (95% CI=0.45–1.22), respectively (p-trend=0.47).

Discussion

Main results

These data support the hypothesis that physical activity decreases the incidence of liver cancer. Comparing the highest to the lowest physical activity levels, we observed a 36% decrease in risk for total liver cancer and a 44% decrease in risk for hepatocellular carcinoma. Conversely, we found no association between physical activity and total biliary tract cancer or biliary tract cancer anatomic subsites.

Our results are consistent with those from a large prospective study among 444,963 Korean men [3] that examined more than two versus less than two sessions of leisure-time physical activity per week in relation to liver cancer risk. That study found an inverse association for liver cancer (RR=0.88, 95% CI=0.81–0.95) based on multivariate models that adjusted for age, employment status, smoking status, alcohol intake, BMI, fasting glucose level, and dietary preference (vegetables/mixture of vegetables and meat/meat), but did not adjust for hepatitis B and C virus infection status. Similarly, a prospective study among 79,771 Japanese men and women compared the highest with the lowest quartile of Metabolic Equivalent of Task hours per day without adjustment for hepatitis B and C virus infection status and reported a beneficial effect of total physical activity on liver cancer that was statistically significant among men (RR=0.62, 95% CI=0.40–0.96) but not among women (RR=0.54, 95% CI=0.23–1.29) [4]. Cardiorespiratory fitness, an exposure related to physical activity, was inversely associated with liver cancer mortality (RR=0.28, 95% CI=0.11–0.72) in a U.S. study of 38,801 men without a history of hepatitis [5]. In conclusion, there are now at least four prospective studies that provide evidence for a potential benefit of physical activity on risk for liver cancer.

We are unaware of any previous investigation of the relationship between physical activity and extrahepatic biliary tract cancers. The association between physical activity and gallbladder cancer has been examined in two previous studies, and investigators reported null associations [3, 5].

Potential biological mechanisms

Although speculative, physical activity could reduce liver cancer risk through its beneficial effects on body weight and insulin sensitivity. Obesity and insulin resistance are major risk factors for liver cancer [16, 17]. Regular physical activity helps treat or prevent obesity [18, 19] and it improves glucose utilization [20], independent of the effect of weight loss on insulin sensitivity [21].

A further possibility through which physical activity may affect liver cancer risk is via reduced chronic inflammation. Low-grade chronic inflammation of the liver may be caused by chronic hepatitis B or C infection, excess alcohol consumption, or non-alcoholic steatohepatitis [22, 23]. Because increased levels of physical activity have been found to reduce liver fat stores [24], it is plausible that regular exercise may lower risk for liver cancer by reducing steatohepatitis. Results from observational and interventional studies suggest that the potentially beneficial effects of physical activity on chronic inflammation are mediated mainly through weight reduction [25].

Physical activity may confer protection against liver cancer development by affecting estrogen levels through a reduction of adipose tissue [26, 27]. However, the theoretical role of estrogens in liver carcinogenesis is ambiguous [28–30]. While anti-inflammatory and anti-oxidative effects of estrogens may protect against liver cancer in the early stages, elevated estrogen levels in combination with chronic liver disease are suspected to accelerate the progression from liver cirrhosis to liver cancer, particularly in men.

Epidemiologic findings on the relationship between reproductive factors and liver cancer development have been inconsistent, with some studies suggesting an inverse [31, 32], others a positive association [33, 34] between the two.

Physical activity may also decrease risk for liver cancer through a mechanism involving a reduction in oxidative stress. Various sources of oxidative stress may induce liver cancer [35–37]. In rat livers, regular exercise reverses oxidative stress induced by age [38], ethanol [39, 40], or a diet deficient in vitamins and minerals [41]. Human studies also show that regular exercise increases oxidative liver metabolism [42, 43] and reduces circulating markers of oxidative stress [44, 45].

Tobacco use has been shown to be related to liver cancer [46]. Many tobacco composites and metabolites damage human DNA, with the degree and type of damage depending on the affected tissue type and the tissue's capacity for DNA repair response [47, 48]. Yun and coworkers [3] reported that physical activity decreased liver cancer risk significantly in non-smokers but not in current smokers. We also observed that the apparent beneficial effect of physical activity on liver cancer was present in never smokers but not among past or current smokers. This suggests that the mechanism through which physical activity affects liver cancer risk is inhibited by tobacco use, possibly through tobacco-induced irreversible DNA damage.

It is challenging to interpret our observation of an inverse association between physical activity and liver cancer among subjects with low vegetable intake, but no relation of physical activity to liver cancer among those with high vegetable intake. Other than chance, one possible explanation for the latter finding is that increased physical activity reduces liver cancer risk partly through the same biological mechanisms that link high vegetable intake to decreased liver cancer risk [49, 50], such as increased antioxidant capacity [49], a circumstance that may obscure any association between physical activity and liver cancer among high vegetable consumers.

A major strength of our study is its large sample size of over 500,000 participants, which allowed a detailed investigation of liver and extrahepatic biliary tract cancer and its subgroups. Furthermore, cohort follow-up through regular address updates and linkages to cancer and death registries was reasonably complete. Our prospective study design minimized recall bias.

One limitation of our study includes the lack of data on chronic liver disease and hepatitis B and C virus infection status. However, in a multivariate model adjusting for the same risk factors which we adjusted for in our NIH-AARP study, physical activity was not associated with hepatitis B and C virus infection status in the NHANES surveys. Those data suggest that hepatitis B and C virus infection status do not represent major confounders of the physical activity and liver cancer relation. To our knowledge, only one previous investigation [5] on cardiorespiratory fitness and liver cancer was able to account for hepatitis virus infection status. That study [5] excluded participants with prevalent hepatitis and found an inverse association between fitness and liver cancer.

A further potential limitation of our study is that the frequency of vigorous physical activity was assessed using a self-report questionnaire. However, a previous study proved a very similar physical activity self-report questionnaire to be valid and reliable [7]. Our physical activity assessment was further limited by the unavailability of data on how physical activity levels changed during the ten-year follow-up. A continuous evaluation of physical activity level might have yielded more precise risk estimates. Also, our investigation was unable to address specific types of physical activity in relation to hepatobiliary cancers. It has, for example, been shown that aerobic training reduces liver cancer risk factors such as insulin

resistance, liver fat stores, and abdominal fat stores more effectively than resistance training [51].

Previous studies have established the preventive potential of physical activity on major multi-factorial diseases, such as cardiovascular disease [52] or cancers of the lung, colorectum, prostate, breast, endometrium and ovaries [1]. Our study is the largest investigation to date to evaluate physical activity in relation to hepatobiliary cancers. Our findings add support to the limited available evidence that increased physical activity is related to decreased risk of liver cancer, independent of body mass index, and that physical activity is probably unrelated to extrahepatic biliary tract cancer. We estimated that 14% of liver cancer incidences in our cohort could have been prevented if all participants had engaged in 20 minutes or more of vigorous exercise at least three times per week, as recommended by the American College of Sports Medicine [11]. Our results imply that adherence to the physical activity recommendations by those who are presently sedentary represents a significant individual-level and public health strategy for liver cancer prevention. Additional large epidemiologic studies that adjust for hepatitis B and C virus infection status and chronic liver disease (including hepatitis B and C) are necessary to confirm our findings. A future promising area of research is the identification of the specific types, frequencies, doses, and intensities of physical activity needed to reduce liver cancer risk. Also, future interventional and experimental research will be required to examine the biological mechanisms underlying these possible associations.

References

1. Courneya, KS.; Friedenreich, CM., editors. Physical Activity and Cancer. Berlin: Springer; 2011.
2. Howlader, N.; Noone, A.; Krapcho, M.; Neyman, N.; Aminou, R.; Waldron, W., et al., editors. SEER Cancer Statistics Review, 1975–2008. National Cancer Institute; Bethesda, MD: 2011. http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site
3. Yun YH, Lim MK, Won YJ, Park SM, Chang YJ, Oh SW, et al. Dietary preference, physical activity, and cancer risk in men: National Health Insurance Corporation Study. BMC Cancer. 2008; 8:366. [PubMed: 19077256]
4. Inoue M, Yamamoto S, Kurahashi N, Iwasaki M, Sasazuki S, Tsugane S. Daily total physical activity level and total cancer risk in men and women: results from a large-scale population-based cohort study in Japan. Am J Epidemiol. 2008; 168(4):391–403. [PubMed: 18599492]
5. Peel JB, Sui X, Matthews CE, Adams SA, Hebert JR, Hardin JW, et al. Cardiorespiratory fitness and digestive cancer mortality: findings from the Aerobics Center Longitudinal Study. Cancer Epidemiol Biomarkers Prev. 2009; 18(4):1111–7. [PubMed: 19293313]
6. Schatzkin A, Subar AF, Thompson FE, Harlan LC, Tangrea J, Hollenbeck AR, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions : the National Institutes of Health-American Association of Retired Persons Diet and Health Study. Am J Epidemiol. 2001; 154(12):1119–25. [PubMed: 11744517]
7. Marshall AL, Smith BJ, Bauman AE, Kaur S. Reliability and validity of a brief physical activity assessment for use by family doctors. Br J Sports Med. 2005; 39(5):294–7. [PubMed: 15849294]
8. North American Association of Central Cancer Registries. Standards for Completeness, Quality, Analysis, and Management of Data. Springfield, IL: North American Association of Central Cancer Registries; 2004.
9. Michaud DS, Midthune D, Hermansen S, Leitzmann M, Harlan LC, Kipnis V, et al. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH-AARP Diet and Health Study. Journal of Registry Management. 2005; 32(2):70–5.
10. Schoenfeld DA. Partial residuals for the proportional hazards regression model. Biometrika. 1982; 69(1):239–41.
11. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and

maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc.* 2011; 43(7):1334–59. [PubMed: 21694556]

12. Greenland S. Variance estimators for attributable fraction estimates consistent in both large strata and sparse data. *Stat Med.* 1987; 6(6):701–8. [PubMed: 2825320]
13. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: 2012.
14. R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2011.
15. Lumley T. Analysis of Complex Survey Samples. *Journal of Statistical Software.* 2004; 9(8):1–19.
16. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology.* 2004; 126(2):460–8. [PubMed: 14762783]
17. Welzel TM, Graubard BI, Zeuzem S, El-Serag HB, Davila JA, McGlynn KA. Metabolic syndrome increases the risk of primary liver cancer in the United States: A study in the SEER-medicare database. *Hepatology.* 2011; 54(2):463–71. [PubMed: 21538440]
18. Wareham NJ, van Sluijs EM, Ekelund U. Physical activity and obesity prevention: a review of the current evidence. *Proc Nutr Soc.* 2005; 64(2):229–47. [PubMed: 15960868]
19. Wing RR. Physical activity in the treatment of the adulthood overweight and obesity: current evidence and research issues. *Med Sci Sports Exerc.* 1999; 31(11 Suppl):S547–52. [PubMed: 10593526]
20. Rosenthal M, Haskell WL, Solomon R, Widstrom A, Reaven GM. Demonstration of a relationship between level of physical training and insulin-stimulated glucose utilization in normal humans. *Diabetes.* 1983; 32(5):408–11. [PubMed: 6341123]
21. Kang J, Robertson RJ, Hagberg JM, Kelley DE, Goss FL, DaSilva SG, et al. Effect of exercise intensity on glucose and insulin metabolism in obese individuals and obese NIDDM patients. *Diabetes Care.* 1996; 19(4):341–9. [PubMed: 8729157]
22. Weber A, Boege Y, Reisinger F, Heikenwalder M. Chronic liver inflammation and hepatocellular carcinoma: persistence matters. *Swiss Med Wkly.* 2011; 141:w13197. [PubMed: 21557112]
23. Alison MR, Nicholson LJ, Lin WR. Chronic inflammation and hepatocellular carcinoma. *Recent Results Cancer Res.* 2011; 185:135–48. [PubMed: 21822824]
24. Johnson NA, Sachinwalla T, Walton DW, Smith K, Armstrong A, Thompson MW, et al. Aerobic exercise training reduces hepatic and visceral lipids in obese individuals without weight loss. *Hepatology.* 2009; 50(4):1105–12. [PubMed: 19637289]
25. Wetmore CM, Ulrich CM. Mechanisms associating physical activity with cancer incidence: Exercise and immune function. *Cancer Prevention and Management through Exercise and Weight Control.* 2006; 5:157–75.
26. McTiernan A. Mechanisms linking physical activity with cancer. *Nat Rev Cancer.* 2008; 8(3):205–11. [PubMed: 18235448]
27. Rundle, A. Physical Activity, Dietary Calorie Restriction, and Cancer. New York: Springer; 2011. Mechanisms Underlying the Effects of Physical Activity on Cancer.
28. Villa E, Grottola A, Colantoni A, De Maria N, Buttafoco P, Ferretti I, et al. Hepatocellular carcinoma: role of estrogen receptors in the liver. *Ann N Y Acad Sci.* 2002; 963:37–45. [PubMed: 12095926]
29. De Maria N, Manno M, Villa E. Sex hormones and liver cancer. *Mol Cell Endocrinol.* 2002; 193(1–2):59–63. [PubMed: 12161002]
30. Kalra M, Mayes J, Assefa S, Kaul AK, Kaul R. Role of sex steroid receptors in pathobiology of hepatocellular carcinoma. *World J Gastroenterol.* 2008; 14(39):5945–61. [PubMed: 18932272]
31. Yu MW, Chang HC, Chang SC, Liaw YF, Lin SM, Liu CJ, et al. Role of reproductive factors in hepatocellular carcinoma: Impact on hepatitis B- and C-related risk. *Hepatology.* 2003; 38(6): 1393–400. [PubMed: 14647050]
32. Wu CH, Chan TF, Changchien CC, Yang CY. Parity, age at first birth, and risk of death from liver cancer: Evidence from a cohort in Taiwan. *J Gastroenterol Hepatol.* 2011; 26(2):334–9. [PubMed: 21261724]

33. Stanford JL, Thomas DB. Reproductive factors in the etiology of hepatocellular carcinoma. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. *Cancer Causes Control*. 1992; 3(1):37–42. [PubMed: 1311212]
34. La Vecchia C, Negri E, Franceschi S, Parazzini F. Long-term impact of reproductive factors on cancer risk. *Int J Cancer*. 1993; 53(2):215–9. [PubMed: 8425757]
35. Sanchez-Perez Y, Carrasco-Legleu C, Garcia-Cuellar C, Perez-Carreón J, Hernandez-Garcia S, Salcido-Neyoy M, et al. Oxidative stress in carcinogenesis. Correlation between lipid peroxidation and induction of preneoplastic lesions in rat hepatocarcinogenesis. *Cancer Lett*. 2005; 217(1):25–32. [PubMed: 15596293]
36. Farinati F, Cardin R, Bortolami M, Burra P, Russo FP, Rugge M, et al. Hepatitis C virus: from oxygen free radicals to hepatocellular carcinoma. *J Viral Hepat*. 2007; 14(12):821–9. [PubMed: 18070284]
37. Asare GA, Mossanda KS, Kew MC, Paterson AC, Kahler-Venter CP, Siziba K. Hepatocellular carcinoma caused by iron overload: a possible mechanism of direct hepatocarcinogenicity. *Toxicology*. 2006; 219(1–3):41–52. [PubMed: 16337327]
38. Radak Z, Chung HY, Naito H, Takahashi R, Jung KJ, Kim HJ, et al. Age-associated increase in oxidative stress and nuclear factor kappaB activation are attenuated in rat liver by regular exercise. *FASEB J*. 2004; 18(6):749–50. [PubMed: 14766800]
39. Duncan K, Harris S, Ardies CM. Running exercise may reduce risk for lung and liver cancer by inducing activity of antioxidant and phase II enzymes. *Cancer Lett*. 1997; 116(2):151–8. [PubMed: 9215858]
40. Husain K, Somani SM. Interaction of exercise training and chronic ethanol ingestion on hepatic and plasma antioxidant system in rat. *J Appl Toxicol*. 1997; 17(3):189–94. [PubMed: 9250541]
41. Teixeira A, Muller L, dos Santos AA, Reckziegel P, Emanuelli T, Rocha JB, et al. Beneficial effects of gradual intense exercise in tissues of rats fed with a diet deficient in vitamins and minerals: a pilot study. *Nutrition*. 2009; 25(5):590–6. [PubMed: 19131214]
42. Mauriz JL, Tabernero B, Garcia-Lopez J, Jorquera F, Villa JG, Gonzalez-Gallego J. Physical exercise and improvement of liver oxidative metabolism in the elderly. *Eur J Appl Physiol*. 2000; 81(1–2):62–6. [PubMed: 10552268]
43. Villa JG, Cuadrado G, Bayon JE, Gonzalez-Gallego J. The effect of physical conditioning on antipyrine clearance. *Eur J Appl Physiol Occup Physiol*. 1998; 77(1–2):106–11. [PubMed: 9459529]
44. Miyazaki H, Oh-ishi S, Ookawara T, Kizaki T, Toshinai K, Ha S, et al. Strenuous endurance training in humans reduces oxidative stress following exhausting exercise. *Eur J Appl Physiol*. 2001; 84(1–2):1–6. [PubMed: 11394236]
45. Djordjevic D, Cubrilo D, Macura M, Barudic N, Djuric D, Jakovljevic V. The influence of training status on oxidative stress in young male handball players. *Mol Cell Biochem*. 2011; 351(1–2):251–9. [PubMed: 21264496]
46. Lee YC, Cohet C, Yang YC, Stayner L, Hashibe M, Straif K. Meta-analysis of epidemiologic studies on cigarette smoking and liver cancer. *Int J Epidemiol*. 2009; 38(6):1497–511. [PubMed: 19720726]
47. Shrivastav N, Li D, Essigmann JM. Chemical biology of mutagenesis and DNA repair: cellular responses to DNA alkylation. *Carcinogenesis*. 2010; 31(1):59–70. [PubMed: 19875697]
48. Hang B. Formation and repair of tobacco carcinogen-derived bulky DNA adducts. *J Nucleic Acids*. 2010; 2010:709521. [PubMed: 21234336]
49. Kurahashi N, Inoue M, Iwasaki M, Tanaka Y, Mizokami M, Tsugane S. Vegetable, fruit and antioxidant nutrient consumption and subsequent risk of hepatocellular carcinoma: a prospective cohort study in Japan. *Br J Cancer*. 2009; 100(1):181–4. [PubMed: 19127270]
50. La Vecchia C, Negri E, Decarli A, D'Avanzo B, Franceschi S. Risk factors for hepatocellular carcinoma in northern Italy. *Int J Cancer*. 1988; 42(6):872–6. [PubMed: 2847988]
51. Slentz CA, Bateman LA, Willis LH, Shields AT, Tanner CJ, Piner LW, et al. Effects of aerobic vs. resistance training on visceral and liver fat stores, liver enzymes, and insulin resistance by HOMA in overweight adults from STRRIDE AT/RT. *Am J Physiol Endocrinol Metab*. 2011; 301(5):E1033–9. [PubMed: 21846904]

52. Li J, Siegrist J. Physical activity and risk of cardiovascular disease--a meta-analysis of prospective cohort studies. *Int J Environ Res Public Health*. 2012; 9(2):391–407. [PubMed: 22470299]

Age-standardized^a baseline characteristics by frequency of vigorous physical activity, 1995–1996, NIH-AARP Diet and Health Study.

Table 1

Subjects	Frequency of vigorous physical activity ^b , times per week					
	0	<1	1–2	3–4	5+	
N	93,536	69,574	109,851	136,171	98,765	
Age at baseline (yrs), mean ± standard deviation	62 ± 5	61 ± 5	62 ± 5	62 ± 5	62 ± 5	
Sex, percent						
Men	51	59	62	63	67	
Women	49	41	38	37	33	
Marital status, percent						
Married or living as married	62	68	70	72	73	
Not married	38	32	30	28	27	
Education, percent						
12 years or less	40	29	26	25	26	
College graduate/vocational training	48	53	54	53	51	
Postgraduate	12	18	20	22	23	
Ethnicity, percent						
Caucasian	89	92	92	92	92	
Non-Caucasian	9	7	7	7	7	
BMI (kg/m ²), mean ± standard deviation	28.5 ± 6.3	27.8 ± 5.2	27.2 ± 4.8	26.5 ± 4.5	26.0 ± 4.2	
Alcohol (g/day), percent						
0.0	32	23	22	22	24	
0.1–14.9	50	56	56	56	52	
15.0–29.9	7	10	11	12	12	
30.0–59.9	5	6	6	6	7	
60+	5	5	5	4	5	
Smoking status, percent						
Never	32	34	36	36	36	
Past	45	48	48	51	52	
Current	19	15	12	9	8	

		Frequency of vigorous physical activity ^b , times per week				
		0	<1	1-2	3-4	5+
Use of dietary supplements, percent						
Multivitamins						
Total coffee intake (cups per day), percent		49	53	55	58	58
0		11	10	10	10	12
<1		33	32	32	33	33
2-3		38	41	42	42	40
4+		17	17	16	15	16

^aUsing direct standardization to the baseline age distribution of the cohort.

^b Vigorous physical activity was defined as 20 minutes or more of exercise that was sufficient to increase breathing, increase heart rate, or work up a sweat.

Table 2

Relative risk of total liver cancer (including intrahepatic bile duct cancer) and sub-types of liver cancer in relation to frequency of vigorous physical activity^a, NIH-AARP Diet and Health Study, 1995–2006.

Frequency of vigorous physical activity ^a , times per week	Age- and sex-standardized ^b Incidence Rate per 100,000 Person- Years (95% Confidence Interval)			Relative Risk (95% Confidence Interval)	
	Cases	Person-years		Age-and sex-adjusted ^c	Multivariate-adjusted ^d
Total liver cancer					
0	155	818,247	21.0 (17.7–24.4)	1.00 (ref.)	1.00 (ref.)
<1	90	632,732	15.5 (12.3–18.7)	0.73 (0.56–0.95)	0.87 (0.67–1.13)
1–2	144	1,003,396	14.8 (12.4–17.2)	0.70 (0.56–0.88)	0.91 (0.72–1.15)
3–4	147	1,246,016	11.3 (9.5–13.2)	0.54 (0.43–0.68)	0.77 (0.61–0.97)
5+	92	903,624	9.3 (7.4–11.2)	0.45 (0.35–0.58)	0.64 (0.49–0.84)
p-trend				<0.001	<0.001
Hepatocellular carcinoma					
0	110	818,247	15.1 (12.3–18.0)	1.00 (ref.)	1.00 (ref.)
<1	59	632,732	10.2 (7.6–12.8)	0.67 (0.49–0.91)	0.81 (0.59–1.11)
1–2	98	1,003,396	10.1 (8.1–12.1)	0.66 (0.50–0.86)	0.87 (0.66–1.15)
3–4	90	1,246,016	6.9 (5.4–8.3)	0.45 (0.34–0.60)	0.65 (0.49–0.87)
5+	58	903,624	5.9 (4.3–7.4)	0.38 (0.28–0.53)	0.56 (0.41–0.78)
p-trend				<0.001	<0.001
Cholangiocarcinoma					
0	13	818,247	1.8 (0.8–2.8)	1.00 (ref.)	1.00 (ref.)
<1	12	632,732	2.1 (0.9–3.3)	1.19 (0.54–2.62)	1.24 (0.56–2.74)
1–2	18	1,003,396	1.8 (1.0–2.7)	1.09 (0.53–2.23)	1.18 (0.57–2.43)
3–4	28	1,246,016	2.2 (1.4–3.0)	1.31 (0.68–2.54)	1.47 (0.74–2.90)
5+	19	903,624	1.9 (1.0–2.8)	1.20 (0.59–2.44)	1.34 (0.64–2.79)
p-trend				0.57	0.39
Other liver cancer					
0	32	818,247	4.1 (2.7–5.6)	1.00 (ref.)	1.00 (ref.)
<1	19	632,732	3.2 (1.7–4.6)	0.77 (0.44–1.36)	0.94 (0.53–1.67)
1–2	28	1,003,396	2.9 (1.8–3.9)	0.69 (0.41–1.15)	0.95 (0.57–1.60)
3–4	29	1,246,016	2.3 (1.4–3.1)	0.55 (0.33–0.91)	0.87 (0.52–1.48)
5+	15	903,624	1.6 (0.8–2.4)	0.38 (0.20–0.70)	0.61 (0.32–1.15)

Frequency of vigorous physical activity ^a , times per week	Cases	Person-years	Age- and sex-standardized ^b Incidence Rate per 100,000 Person-Years (95% Confidence Interval)	Relative Risk (95% Confidence Interval)	
				Age-and sex-adjusted ^c	Multivariate-adjusted ^d
p-trend				0.001	0.13

^aPhysical activity was defined as 20 minutes or more of exercise that was sufficient to increase breathing, increase heart rate, or work up a sweat.

^bThe incidence rates were standardized by age (5-year groups) and sex (female, male).

^cThe age- and sex-adjusted analysis was adjusted for age (5-year groups) and sex (female, male).

^dThe multivariate-adjusted analysis was adjusted for age (5-year groups), sex (female, male), marital status (married or living as married, never married or separated or divorced or widowed), education (high-school or less than high-school, college education/vocational training, postgraduate education), ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian, other ethnic background), body mass index (BMI) (<18.5, 18.5–24.9, 25.0–29.0, 30.0–34.9, 35.0+ kg/m²), alcohol intake (0, 0.1–14.9, 15.0–29.9, 30.0–59.9, 60+ grams of alcohol per day), smoking status (never, past smoking with an intensity of 20 cigarettes per day, past smoking with an intensity of more than 20 cigarettes per day, current smoking with an intensity of 20 cigarettes per day, current smoking with an intensity of more than 20 cigarettes per day), history of type 2 diabetes mellitus (yes, no), use of multivitamin dietary supplements (yes, no), total coffee intake (0,<1, 2–3, 4+ cups per day), red meat intake (ounces per 1000 kcal of energy intake in quintiles), white meat (including fish) intake (ounces per 1000 kcal of energy intake in quintiles), fruit (excluding juice) intake (ounces per 1000 kcal of energy intake in quintiles), vegetable (excluding legume) intake (ounces per 1000 kcal of energy intake in quintiles), and folate intake (micrograms per 1000 kcal of energy intake in quintiles).

Table 3

Relative risk of total biliary tract cancer and anatomic subsites of biliary tract cancer in relation to frequency of vigorous physical activity^a, NIH-AARP Diet and Health Study, 1995–2006.

Frequency of vigorous physical activity ^a , times per week	Cases	Person-years	Age- and sex-standardized ^b Years (95% Confidence Interval)	Relative Risk (95% Confidence Interval)	
				Age- and sex-adjusted ^c	Multivariate-adjusted ^d
Total biliary tract cancer					
0	66	818,247	8.3 (6.3–10.4)	1.00 (ref.)	1.00 (ref.)
<1	41	632,732	7.1 (4.9–9.3)	0.84 (0.57–1.24)	0.90 (0.60–1.33)
1–2	69	1,003,396	7.0 (5.4–8.7)	0.86 (0.61–1.20)	0.95 (0.67–1.34)
3–4	93	1,246,016	7.2 (5.7–8.7)	0.88 (0.64–1.20)	1.01 (0.73–1.41)
5+	48	903,624	5.0 (3.6–6.5)	0.61 (0.42–0.89)	0.73 (0.50–1.08)
p-trend				0.03	0.25
Extrahepatic bile duct cancer					
0	20	818,247	2.5 (1.4–3.6)	1.00 (ref.)	1.00 (ref.)
<1	15	632,732	2.6 (1.3–3.9)	0.98 (0.50–1.91)	1.04 (0.53–2.04)
1–2	20	1,003,396	2.1 (1.2–2.9)	0.78 (0.42–1.45)	0.84 (0.45–1.58)
3–4	27	1,246,016	2.1 (1.3–2.8)	0.79 (0.44–1.41)	0.86 (0.47–1.57)
5+	20	903,624	2.0 (1.1–2.8)	0.78 (0.42–1.45)	0.86 (0.45–1.65)
p-trend				0.40	0.60
Ampulla of Vater cancer					
0	14	818,247	2.0 (0.9–3.1)	1.00 (ref.)	1.00 (ref.)
<1	7	632,732	1.3 (0.3–2.2)	0.65 (0.26–1.61)	0.67 (0.27–1.66)
1–2	15	1,003,396	1.5 (0.8–2.3)	0.82 (0.40–1.71)	0.86 (0.41–1.80)
3–4	28	1,246,016	2.1 (1.3–2.9)	1.14 (0.60–2.17)	1.23 (0.63–2.40)
5+	11	903,624	1.2 (0.5–1.9)	0.59 (0.27–1.30)	0.66 (0.29–1.48)
p-trend				0.64	0.87
Gallbladder cancer					
0	30	818,247	3.7 (2.3–5.0)	1.00 (ref.)	1.00 (ref.)
<1	17	632,732	2.9 (1.5–4.3)	0.81 (0.45–1.47)	0.89 (0.49–1.63)
1–2	31	1,003,396	3.2 (2.1–4.3)	0.91 (0.55–1.51)	1.07 (0.64–1.79)
3–4	30	1,246,016	2.4 (1.5–3.2)	0.68 (0.41–1.14)	0.86 (0.51–1.46)
5+	15	903,624	1.7 (0.8–2.6)	0.47 (0.25–0.88)	0.63 (0.33–1.21)

Frequency of vigorous physical activity ^a , times per week	Cases	Person-years	Age- and sex-standardized ^b Incidence Rate per 100,000 Person-Years (95% Confidence Interval)	Relative Risk (95% Confidence Interval)	
				Age-and sex-adjusted ^c	Multivariate-adjusted ^d
p-trend				0.01	0.16

^aPhysical activity was defined as 20 minutes or more of exercise that was sufficient to increase breathing, increase heart rate, or work up a sweat.

^bThe incidence rates were standardized by age (5-year groups) and sex (female, male).

^cThe age- and sex-adjusted analysis was adjusted for age (5-year groups) and sex (female, male).

^dThe multivariate-adjusted analysis was adjusted for age (5-year groups), sex (female, male), marital status (married or living as married, never married or separated or divorced or widowed), education (high-school or less than high-school, college education/vocational training, postgraduate education), ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian, other ethnic background), body mass index (BMI) (<18.5, 18.5–24.9, 25.0–29.0, 30.0–34.9, 35.0+ kg/m²), alcohol intake (0, 0.1–14.9, 15.0–29.9, 30.0–59.9, 60+ grams of alcohol per day), smoking status (never, past smoking with an intensity of 20 cigarettes per day, past smoking with an intensity of more than 20 cigarettes per day, current smoking with an intensity of 20 cigarettes per day, current smoking with an intensity of more than 20 cigarettes per day), history of type 2 diabetes mellitus (yes, no), use of multivitamin dietary supplements (yes, no), total coffee intake (0,<1, 2–3, 4+ cups per day), red meat intake (ounces per 1000 kcal of energy intake in quintiles), white meat (including fish) intake (ounces per 1000 kcal of energy intake in quintiles), fruit (excluding juice) intake (ounces per 1000 kcal of energy intake in quintiles), vegetable (excluding legume) intake (ounces per 1000 kcal of energy intake in quintiles), and folate intake (micrograms per 1000 kcal of energy intake in quintiles).

Table 4

Multivariate-adjusted^a relative risk (95% confidence interval) of total liver cancer in relation to frequency of vigorous physical activity^b by selected variables, NIH-AARP Diet and Health Study, 1995–2006.

Stratum	Cases ^c	Frequency of vigorous physical activity ^b , times per week					p-trend	p-interaction
		0	<1	1–2	3–4	5+		
Age (years)								
50–65	328	1.00 (ref.)	0.75 (0.53–1.07)	0.78 (0.57–1.06)	0.69 (0.50–0.95)	0.50 (0.34–0.73)	<0.001	
66+	300	1.00 (ref.)	1.02 (0.69–1.52)	1.09 (0.77–1.54)	0.88 (0.63–1.25)	0.84 (0.58–1.23)	0.19	0.51
Sex								
Men	493	1.00 (ref.)	0.88 (0.66–1.18)	0.87 (0.67–1.14)	0.75 (0.57–0.98)	0.60 (0.44–0.81)	<0.001	
Women	135	1.00 (ref.)	0.84 (0.47–1.50)	1.08 (0.67–1.75)	0.87 (0.53–1.44)	0.87 (0.49–1.54)	0.60	0.59
Education								
12 years or less	189	1.00 (ref.)	0.65 (0.39–1.07)	1.08 (0.73–1.59)	0.65 (0.42–0.99)	0.74 (0.47–1.17)	0.14	
College graduate/vocational training	318	1.00 (ref.)	1.10 (0.76–1.59)	0.99 (0.71–1.39)	0.89 (0.64–1.25)	0.64 (0.43–0.96)	0.01	
Postgraduate	97	1.00 (ref.)	0.71 (0.36–1.39)	0.51 (0.27–0.98)	0.60 (0.33–1.09)	0.59 (0.30–1.13)	0.24	0.20
Ethnicity								
Non-Caucasian	81	1.00 (ref.)	0.89 (0.44–1.81)	0.82 (0.43–1.57)	0.60 (0.31–1.16)	0.66 (0.33–1.34)	0.14	
Caucasian	539	1.00 (ref.)	0.86 (0.65–1.15)	0.93 (0.73–1.20)	0.79 (0.61–1.02)	0.65 (0.48–0.87)	0.003	0.93
BMI (kg/m ²)								
18.5–24.9	140	1.00 (ref.)	0.94 (0.49–1.80)	1.15 (0.66–1.98)	1.02 (0.60–1.74)	1.16 (0.67–1.99)	0.62	
25.0+	465	1.00 (ref.)	0.87 (0.65–1.16)	0.85 (0.65–1.10)	0.72 (0.55–0.94)	0.54 (0.39–0.74)	<0.001	0.32
Alcohol (g/day)								
0.0	202	1.00 (ref.)	0.95 (0.60–1.51)	0.96 (0.64–1.44)	0.82 (0.54–1.22)	0.70 (0.44–1.10)	0.09	
0.1–14.9	276	1.00 (ref.)	0.67 (0.44–1.02)	0.85 (0.60–1.20)	0.70 (0.49–0.99)	0.59 (0.39–0.89)	0.02	
15+	150	1.00 (ref.)	1.17 (0.70–1.96)	0.95 (0.58–1.55)	0.84 (0.51–1.38)	0.68 (0.38–1.21)	0.07	0.75
Smoking status								
Never	158	1.00 (ref.)	0.69 (0.42–1.14)	0.68 (0.44–1.06)	0.34 (0.20–0.56)	0.52 (0.32–0.85)	0.001	
Past	341	1.00 (ref.)	1.10 (0.76–1.59)	1.07 (0.77–1.49)	0.92 (0.66–1.27)	0.82 (0.57–1.18)	0.10	
Current	103	1.00 (ref.)	0.82 (0.44–1.52)	0.87 (0.50–1.53)	1.42 (0.85–2.38)	0.42 (0.17–1.01)	0.56	0.004
Total coffee intake (cups per day)								
<1	279	1.00 (ref.)	1.09 (0.75–1.59)	1.01 (0.71–1.43)	0.80 (0.56–1.14)	0.51 (0.33–0.79)	<0.001	

Stratum	Cases ^c	Frequency of vigorous physical activity ^b , times per week					p-trend	p-interaction
		0	<1	1-2	3-4	5+		
2-3	246	1.00 (ref.)	0.85 (0.56-1.30)	0.89 (0.62-1.29)	0.65 (0.44-0.96)	0.74 (0.49-1.12)	0.07	
4+	103	1.00 (ref.)	0.42 (0.19-0.93)	0.72 (0.40-1.30)	1.00 (0.59-1.71)	0.75 (0.40-1.38)	0.84	0.06
History of diabetes mellitus								
No	474	1.00 (ref.)	0.79 (0.58-1.07)	0.85 (0.65-1.12)	0.83 (0.63-1.08)	0.63 (0.46-0.86)	0.01	
Yes	154	1.00 (ref.)	1.14 (0.70-1.86)	1.10 (0.71-1.72)	0.56 (0.34-0.94)	0.71 (0.41-1.20)	0.02	0.13
Vegetables excl. legumes intake								
Less than median (energy-adjusted)	369	1.00 (ref.)	0.75 (0.55-1.04)	0.71 (0.53-0.95)	0.62 (0.46-0.84)	0.49 (0.34-0.70)	<0.001	
Greater than median (energy-adjusted)	259	1.00 (ref.)	1.24 (0.77-1.98)	1.47 (0.97-2.21)	1.18 (0.78-1.77)	1.03 (0.66-1.59)	0.49	0.02

^aModels were adjusted for age (5-year groups), sex (female, male), marital status (married or living as married, never married or separated or divorced or widowed), education (high-school or less than high-school, college education/vocational training, postgraduate education), ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian, other ethnic background), body mass index (BMI) (<18.5, 18.5-24.9, 25.0-29.0, 30.0-34.9, 35.0+ kg/m²), alcohol intake (0, 0.1-14.9, 15.0-29.9, 30.0-59.9, 60+ grams of alcohol per day), smoking status (never, past smoking with an intensity of ≤ 20 cigarettes per day, past smoking with an intensity of more than 20 cigarettes per day, current smoking with an intensity of more than 20 cigarettes per day), history of type 2 diabetes mellitus (yes, no), use of multivitamin dietary supplements (yes, no), total coffee intake (0, <1, 2-3, 4+ cups per day), red meat intake (ounces per 1000 kcal of energy intake in quintiles), white meat (including fish) intake (ounces per 1000 kcal of energy intake in quintiles), fruit (excluding juice) intake (ounces per 1000 kcal of energy intake in quintiles), vegetable (excluding legume) intake (ounces per 1000 kcal of energy intake in quintiles), and folate intake (micrograms per 1000 kcal of energy intake in quintiles). In each case, the stratification variable was removed from the multivariate model.

^bVigorous physical activity was defined as 20 minutes or more of exercise that was sufficient to increase breathing, increase heart rate, or work up a sweat.

^cParticipants with missing stratum information were excluded, which led to the exclusion of the following cases: 24 cases for education, 8 cases for ethnicity, 23 cases for BMI, and 26 cases for smoking status.