Lifestyle and Hepatocellular Carcinoma

Subjects: Health Care Sciences & Services | Gastroenterology & Hepatology | Food Science & Technology
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Liver cancer remains a global health challenge, and while infection by hepatitis B virus and hepatitis C virus are the main risk factors for hepatocellular carcinoma (HCC) development, non-alcoholic steatohepatitis is associated with metabolic syndrome or diabetes mellitus is becoming a more frequent risk factor.

obesity dietary composition alcohol

1. Introduction

Liver cancer remains a global health challenge, and while infection by hepatitis B virus and hepatitis C virus are the main risk factors for hepatocellular carcinoma (HCC) development, non-alcoholic steatohepatitis, associated with metabolic syndrome or diabetes mellitus, is becoming a more frequent risk factor [1]. The increasing public health burden of HCC emphasizes the prominent need to define important modifiable risk factors. It is now believed that lifestyle plays a vital role in cancer prevention or progression. Lifestyle includes, among others, physical activity (PA), sedentary behavior, diet and eating habits, all reflected in obesity and abdominal obesity. In addition, smoking and excessive alcohol drinking by themselves or in synergism have been associated with increased risk of HCC.

2. Role of Diet and Lifestyle in General in the Prevention of Hepatocellular Carcinoma

Evidence for a potential association between dietary composition and HCC in humans is mainly derived from large observational prospective cohort studies and meta-analyses. Generally, it is shown that the same dietary characteristics and other lifestyle habits (minimizing obesity, smoking, drinking alcohol, and increasing physical activity) that are beneficial in the treatment of non-alcoholic fatty liver disease (NAFLD) also have the potential to prevent HCC, although the HCC-related studies are not specific to NAFLD patients. The association of lifestyle, as a whole, with HCC risk has been tested in a large prospective study by applying a composite score of healthy lifestyle factors consisting of body mass index (BMI), alcohol consumption, cigarette smoking, Mediterranean diet, and sleep duration. After a mean follow-up of 17.7 years, individuals with higher composite scores, representing healthier lifestyles, were at significantly lower risk of HCC in a dose-response manner. A similar inverse association was observed in participants with negative HBsAg and negative hepatitis C virus (HCV)-serology [2]. Similarly, in a meta-analysis of prospective cohort studies looking at a similar healthy lifestyle composite score, adopting the healthiest lifestyles was associated with a 32% lower risk of liver cancer [3].

These studies highlight the importance of comprehensive lifestyle modification strategies for the primary prevention of HCC. In the following review, the specific lifestyle components and their relation to HCC will be summarized.

A summary of all prospective cohort studies and meta-analyses of cohort studies testing the association of diet with HCC is presented (study description and the nutrient/food intake categories which were compared) in **Table 1**.

Table 1. Prospective cohort studies and meta-analyses of cohort studies testing the association between dietary factors and patterns and hepatocellular carcinoma.

Author, Year of Publication (Ref)	Study Design Cohort Study/Meta-Analysis of Cohort Studies	Study Population and Sample Size	Nutrient/Food Group	Adjusted HR/RR (CI) of Highest Category vs. Lowest Category	Nutrient/Food Intake Categories Which Were Compared (Highest Category vs. Reference Category)
Liu Y., 2021 [4]	Prospective cohort	Nurses' Health Study (*n* = 88,770 women). The Health Professionals Follow-up Study (*n* = 48,197 men)	Plant based low-carbohydrate diet	0.83 (0.70–0.98)	Per 1 standard deviation increase
			Carbohydrates from refined grains	1.18 (1.00–1.39)	Per 1 standard deviation increase
			Plant fat	0.78 (0.65–0.95)	Per 1 standard deviation increase
Shah SC., 2021 [5]	Prospective cohort	The NIH-American Association of Retired Persons (NIH-AARP) Diet and Health Study (*n* = 536,359)	Magnesium (diet + supplements)	0.65 (0.48–0.87)	4th vs. 1st quartile
Luu HN., 2021 [6]	Prospective cohort	Singapore Chinese Health Study (*n* = 63,2570)	Alternative Health Eating Index-2010 (AHEI-2010)	0.69 (0.53–0.89)	4th vs. 1st quartile
			Alternate Mediterranean Diet (aMED)	0.70 (0.52–0.95)	4th vs. 1st quartile
			Dietary Approaches to Stop	0.67 (0.51–0.87)	4th vs. 1st quartile

Author, Year of Publication (Ref)	Study Design Cohort Study/Meta-Analysis of Cohort Studies	Study Population and Sample Size	Nutrient/Food Group	Adjusted HR/RR (CI) of Highest Category vs. Lowest Category	Nutrient/Food Intake Categories Which Were Compared (Highest Category vs. Reference Category)
			Hypertension (DASH)		
Yang W., 2021 [7]	Prospective cohort	Nurses' Health Study (*n* =70,055 women). Health Professionals Follow-up Study (*n* = 49,261 men)	Empirical lifestyle pattern score for hyperinsulinemia (ELIH)	1.89 (1.25–2.87)	3rd vs. 1st tertile
			Empirical lifestyle pattern score for insulin resistance (ELIR)	2.05 (1.34–3.14)	3rd vs. 1st tertile
			Empirical dietary inflammatory pattern (EDIP)	2.03 (1.31–3.16)	3rd vs. 1st tertile
			Total fat	1.33 (1.01–1.75)	4th vs. 1st quartile
Ji XW., 2021 [8]	Prospective cohort	Chinese men (*n* = 59 998)	Saturated fat	1.50 (1.13–1.97)	4th vs. 1st quartile
			Monounsaturated fat	1.26 (0.96–1.65)	4th vs. 1st quartile
			Polyunsaturated fat	1.41 (1.07–1.86)	4th vs. 1st quartile
Luo Y., 2020 [9]	Prospective cohort	Patients with new HCC enrolled in the Guangdong Liver Cancer Cohort (*n* = 887)	Chinese Healthy Eating Index (CHEI-2016)	0.74 (0.56–0.98) Outcome: HCC specific mortality	3rd vs. 1st tertile
			Healthy Eating Index-2015 (HEI-2015)	0.93 (0.71–1.21) Outcome: HCC	3rd vs. 1st tertile

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				specific mortality	
Zhong GC., 2020 [10]	Prospective cohort	American adults from the prostate, lung, colorectal and ovarian cancer screening trial (*n* = 103,902)	Dietary inflammatory index (DII) from food and supplements	2.05 (1.23–3.41) Outcome: PLC incidence	3rd vs. 1st tertile
			Dietary inflammatory index (DII) from food and supplements	1.97 (1.13–3.41) Outcome: PLC mortality (*n* = 102)	3rd vs. 1st tertile
			Dietary inflammatory index (DII) from food only	2.57 (1.44–4.60) Outcome: PLC incidence	3rd vs. 1st tertile
Jayedi A., 2020 [11]	Umbrella Review of Meta-Analyses of Prospective Cohort Studies (5 Meta-analyses)	Mixed populations	Fish	0.65 (0.48–0.87)	per 100 gr/day
Zhong GC., 2020 [12]	Prospective cohort	American adults from the prostate, lung, colorectal and ovarian cancer screening trial (*n* = 104,025)	Magnesium (diet + supplements)	0.44 (0.24–0.80) Outcome: PLC incidence	3rd vs. 1st tertile
			Magnesium (diet + supplements)	0.83 (0.67–1.01) Outcome: PLC incidence	Per 100 mg/d

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			Dietary magnesium	0.41 (0.22–0.76) Outcome: PLC incidence	3rd vs. 1st tertile
			Dietary magnesium	0.65 (0.51–0.82) Outcome: PLC incidence	Per 100 mg/d
			Magnesium (diet + supplements)	0.37 (0.19–0.71) Outcome: PLC mortality	3rd vs. 1st tertile
Yang W., 2020 [13]	Prospective cohort	Nurses' Health Study (*n* =88,657 women). Health Professionals Follow-up Study (*n* = 49,826 men)	Vegetable fats	0.61 (0.39–0.96)	17.7 vs. 8.7 (% energy)
			n-3 PUFA	0.63 (0.41–0.96)	0.8 vs. 0.5 (% energy)
			n-6 PUFA	0.54 (0.34–0.86)	6.5 vs. 3.7 (% energy)
			High-fat dairy	1.81 (1.19–2.76)	2.0 vs. 0.4 serving/day
Yang W., 2020 [14]	Prospective cohort	Nurses' Health Study (*n* = 93,427 women). Health Professionals Follow-up Study (*n* = 51,418 men)	Low-fat dairy	1.18 (0.78, 1.78)	1.9 vs. 0.2 serving/day
			Butter	1.58 (1.06–2.36)	0.7 vs. 0 serving/day
			Yogurt	0.72 (0.49–1.05)	0.2 vs. 0 serving/day
Kim TL., 2020 [15]	Umbrella Review of Meta-analyses of	Mixed populations	Green tea	0.87 (0.78–0.98)	High vs. low

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	observational studies (2)				
Guo XF., 2019 [16]	Meta-analysis (9 cohorts)	1,326,176 participants	Vegetable	0.96 (0.95–0.97)	Per 100 gr/d
Ma Y., 2019 [17]	Prospective cohort	Nurses' Health Study (*n* = 92,389 women). Health Professionals Follow-up Study (*n* = 50,468 men).	Processed red meat	1.84 (1.16–2.92)	3rd vs. 1st tertile
			Total white meat	0.61 (0.40–0.91)	3rd vs. 1st tertile
			Unprocessed red meat	1.06 (0.68–1.63)	3rd vs. 1st tertile
			Poultry	0.60 (0.40–0.90)	3rd vs. 1st tertile
			Fish	0.70 (0.47–1.05)	3rd vs. 1st tertile
Ma Y., 2019 [18]	Prospective cohort	Nurses' Health Study (*n* = 121,700 women). Health Professionals Follow-up Study (*n* = 51,529 men)	Alternative Healthy Eating Index-2010 (AHEI-2010)	0.61 (0.39–0.95)	3rd vs. 1st tertile
Tran KT., (2019) [19]	Prospective cohort	UK Biobank population (*n* = 471,779)	Coffee	0.50 (0.29–0.87)	Any consumption vs. none
			Instant coffee	0.51 (0.28–0.93)	Any consumption vs. none
			Ground coffee	0.47 (0.20–1.08)	Any consumption vs. none
Kennedy OJ., 2017	Meta-analysis (18 cohorts)	Mixed populations,	Coffee	0.71 (0.65–0.77)	An extra two cups per day

Author, Year of Publication (Ref)	Study Design Cohort Study/Meta-Analysis of Cohort Studies [29][30]	Study Population and Sample Size	Nutrient/Food Group	Adjusted HR/RR (CI) of Highest Category vs. Lowest Category	Nutrient/Food Intake Categories Which Were Compared (Highest Category vs. Reference Category)
[20]		2,272,642 participants		2	[29]
	2 cohorts [31]	Approximately 850,000 participants	Caffeinated coffee	0.73 (0.63–0.85)	An extra two cups per day
	3 cohorts	Approximately 750,000 participants	Decaffeinated coffee	0.86 (0.74–1.00) [32]	An extra two cups per day
Gao M., 2015 [21]	Meta-analysis (3 cohorts)	Mixed populations, 693,274 participants	Fish	0.73 (0.56–0.90)	Highest vs. lowest consumption
Yang Y., 2014 [22]	Meta-analysis (9 cohorts)	Mixed populations, 1,474,309 participants	Vegetables	0.66 (0.51–0.86)	Highest vs. lowest consumption
Luo J., 2014 [23]	Meta-analysis (7 cohorts)	Mixed populations, 2,677,514 participants	Red meat	[5] 1.43 (1.08–1.90)	Highest vs. lowest consumption
			White meat	0.70 (0.57–0.86)	Highest vs. lowest consumption
			[12] Fish	0.74 (0.61–0.91)	Highest vs. lowest consumption
Bravi F., 2013, [24]	Meta-analysis (8 cohorts)	Mixed populations, 378,392 participants	Coffee [22]	0.64 (0.52–0.7)	No consumption vs. any consumption
Fedirko V., 2013 [25]	Cohort	European Prospective Investigation into Cancer and	Total sugar	1.43 (1.17–1.74)	Per 50 gr/day

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5. Role of Physical Activity in HCC

Author, Year of Publication (Ref)	Study Design Cohort Study/Meta-Analysis of Cohort Studies [34]	Study Population and Sample Size	Nutrient/Food Group	Adjusted HR/RR (CI) of Highest Category vs. Lowest Category	Nutrient/Food Intake Categories Which Were Compared (Highest Category vs. Reference Category)
[33] [35]		Nutrition cohort (n = 477,206)	Total dietary fiber	0.70 (0.52–0.93)	Per 10 gr/day
Sawada N., 2012 [26]	Prospective cohort	Population-based prospective cohort of Japanese subjects (n = 90,296)	Fish (rich in n-3 PUFA)	0.64 (0.42–0.96)	70.6 vs. 9.6 gr/day
			EPA	0.56 (0.36–0.85)	0.74 vs. 0.14 g/day
			DHA	0.56 (0.35–0.87) [36]	1.19 vs. 0.28 g/day
Freedman ND., 2010 [27]	Cohort [37]	Men and women of the National Institutes of Health–AARP Diet and Health Study [38] (n = 495,006)	White meat	0.52 (0.36–0.77)	65.8 vs. 9.7 g/1000 kcal
			Red meat	1.74 (1.16–2.61)	64.8 vs. 10 g/1000 kcal
Ioannou GN., 2009 [28]	Cohort	General US population from the first National Health and Nutrition Examination Survey (n = 9221)	Cholesterol	2.45 (1.3–4.7)	≥511 vs. <156 mg/d

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assessed ced liver (5 days a week for eight weeks). There was a marked improvement in the biochemical parameters of the trained rats on the low-fat diet (LFD) and high-fat diet (HFD) groups. However, while there was a marked decrease in pre-neoplastic lesion development in the LFD group, no such effect was noticed in the HFD group. The researchers concluded that exercise attenuated liver carcinogenesis together with dietary manipulations [39]. In another study, serum was collected from a young overweight man without metabolic syndrome before and after 3 weeks of LFD and moderate aerobic exercise. Post-intervention serum was added to the HCC cell line HepG-2 and markedly attenuated cell proliferation, lipid accumulation, and signalling of various stress pathways [40]. Both previous studies combined diet and PA as interventions. Indeed, dietary and metabolic signals are known to markedly increase the incidence of HCC. In 2015, Piguet et al. used genetically engineered mice to assess dietary and exercise effects separately. They used hepatocyte-specific PTEN-deficient mice, which develop steatohepatitis and HCC spontaneously. Mice were fed the same diet and were divided into exercise (treadmill running-1 h, five days a week for 32 weeks) or sedentary groups. The exercise group developed hepatic nodules larger than 15 mm^3 in 71% vs. 100% in the sedentary group. There was also a marked decrease in the number of tumors per liver and tumor volume per liver independently of hepatic steatosis. Exercise was associated with increased AMPK and Raptor

phosphorylation and decreased Mammalian Target of Rapamycin (mTOR) activity [41]. Later on, Arfianti A et al. assessed the same effect in a chemically induced DEN HCC model in two groups of genetically engineered mice, obese/diabetic Alms1 mutant (foz/foz) mice, and JNK1 deficient foz/foz mice. Mice were divided to exercise or sedentary groups (exercise wheel from week 4 to 12 or 24 weeks). Exercising, foz/foz mice developed obesity by week 24 but still had less dysplastic hepatocytes and significantly fewer tumors (15% vs. 64% compared to sedentary controls). In contrast to previous studies, these diabetic/obese mice failed to activate AMPK and mTOR Complex 1. Instead, exercise improved insulin sensitivity and steatosis and regulated key signalling pathways, which resulted in decreased hepatocyte proliferation [42]. In another study, tumors derived from an HCC cell line (Morris Hepatoma 3924A) were grown sub-cutaneously and were later resected and surgically implanted in the livers of American cancer Institute rats. The rats were assigned to exercise (treadmill running 1 h, five days a week for four weeks), sedentary or sorafenib± exercise or sorafenib+metformin groups. Tumor area, cell proliferation, and vascular density were all decreased by exercise. AMPK phosphorylation was increased in the exercise group together with the expression of PTEN, while STAT3 and S6 ribosomal proteins were decreased. Transcriptomic analysis showed that exercise affected non-tumoral tissue rather than the tumor itself. The anti-tumoral effects of exercise in the sorafenib group were similar to the effect of metformin, suggesting that metformin induces an exercise-like effect [43]. In a similar study, mice on a choline deficient high-fat diet (CD-HFD) were divided to exercise or sedentary groups. CD-HFD mice developed steatohepatitis and hepatic pre-neoplastic lesions. Exercise improved their metabolic parameters and improved steatohepatitis and hepatic inflammation as manifested by decreased aminotransferases. Similar to the previous study, there were fewer hepatic adenomas with increased AMPK activity and mTOR inhibition. The authors concluded that exercise reduced the transition from fatty liver to non-alcoholic steatohepatitis (NASH) and decreased progression to fibrosis and tumorigenesis [44]. In two recent studies, the intensity and method of exercise were assessed. HCC was induced by DEN in C57BL/6 mice, which were subjected to high-intensity interval training (HIIT) or endurance training on a treadmill (from 8–26 weeks). Endurance training resulted in lower cancer incidence and growth and less fibrosis. Furthermore, endurance training resulted in less lipotoxicity and improved body composition, inflammation, and metabolomics compared to the HIIT group. The authors suggested that moderate-intensity endurance training may be superior to HIIT in its anti-tumoral effect [45]. Similarly, Cao et al. assessed moderate endurance training compared to HIIT, arguing that HIIT may induce an acidic micro-environment that may be tumor-promoting. The DEN induced HCC model was utilized in C57BL/6 mice that were subjected to HIIT or moderate endurance training on a treadmill for 18 weeks. Again, endurance training decreased tumor incidence and size as compared to HIIT. There were no significant differences in the mRNA levels of key gluconeogenesis enzymes [46].

The data presented from mouse and cellular models, although preliminary, show a beneficial effect of exercise on HCC initiation and progression in chemically, metabolically, and surgically implanted HCC induced models. While these models do not bear a good resemblance to human HCC, the data is compelling. Furthermore, recent, small publications suggest that exercise type is important, as endurance training showed better anti-tumoral effects than HIIT. Finally, several of the models suggest a synergistic effect to a healthy diet on tumor incidence in these models.

5.3. Physical Activity and HCC Incidence and Prevention in Humans

Initial data on the effect of PA on HCC risk in humans came from prospective studies in Korea and Japan. In Korea, a prospective study of 444,963 men older than 40 showed that moderate-high leisure-time physical activity (LPA) (>2 times/week, >30 min) had a significant protective effect against several cancers, including HCC as compared to low LPA (<2 per week, <30 min) [47]. In Japan, 79,771 men and women aged 45–74 responded to a questionnaire and were followed until 2004. LPA was assessed using a metabolic equivalents/day score. Increased PA was associated with a decrease in the risk for various cancers and was more pronounced in women, especially among the elderly and those who exercised regularly. HCC was decreased only in men and reached significance only in the group who were in the highest quartile of PA compared to the lowest [48]. Wen et al. developed prediction models to assess the risk of HCC in a large cohort in Taiwan. Their cohort consisted of 428,584 individuals that were divided into two groups, one with HCV (130,533) and the other without. Data were collected from a standard medical screening program, and the average follow-up was 8.5 years. During this period, 1668 HCC cases were identified. The data included PA, which was categorized as inactive, low-active, and active according to the intensity in a metabolically equivalent task (MET); X represented the duration of exercise in hours per week (METs hours/week). Although individuals with low active and active PA showed significantly reduced risk for HCC in the initial model, this difference became non-significant when other variables (age, sex, health history, HBV and HCV, AFP and transaminases) were added to the model [49]. A study conducted in the USA in 2013 focused on 507,897 participants aged 50–71 in the NIH-AARP diet and health study that were followed for ten years. A total of 628 cases of HCC were identified during the study period. Physical exercise was defined as the performance of 20 min of vigorous activity per week. Groups were classified between “rarely perform” (lowest level) to >5 times per week (highest level). Comparison of the lowest to highest group of PA showed a significant decrease in the risk for HCC (RR = 0.64; 95% CI, 0.49–0.84) independently of BMI [50]. Arem et al. looked at PA in almost 300,000 men and women in the same NIH-AARP study in order to assess PA patterns over the life course and their association with HCC. They used modelling starting from teenage years to middle age and identified seven distinct PA trajectories. They showed that those who maintained PA levels over life had an approximately 30% reduction in HCC risk compared to those with consistently low PA. The specific pattern of PA (increased or decreased PA through life) had different evolving risks of HCC. Their results suggest that maintaining PA from early age onwards had the best protective effect and warn that increasing PA later in life may not yield the same protective effect [51].

Recent years have shown a plethora of studies assessing the role of PA in association with hepato-pancreato-biliary (HPB) cancers. Data from the EPIC cohort looked at cause-specific hazard ratios (HR) among 467,000 participants focusing on HPB cancers. They identified 275 HCCs among 532 all HPB cancers during follow-up. There was a 45% decrease in the risk for HCC comparing active to inactive participants and a 50% decrease for those engaging in vigorous PA (defined a >2 h/week). Markers associated with obesity such as BMI and waist circumference partially explained the reduced risk [52]. In a rigorous prospective study spanning almost 30 years, the authors assessed the effect of various lifestyle parameters, including PA, on liver-related mortality in over 125,000 participants. HCC accounted for a third of the deaths. The risk for overall liver-related mortality declined progressively with increasing PA and increased with higher BMI. The HR for liver-related mortality tripled in obese sedentary compared to lean, active participants. Findings were similar for HCC or cirrhosis-specific mortality. The

authors suggested that engaging in average pace walking >3 h/week could have prevented 25% of liver-related deaths [53]. More recently, the emphasis focused on the intensity, mode, and duration of PA. Luo et al. looked at moderate intensity PA in two well-defined cohorts of the NHS and the HPFS over an average of 23 years. Surprisingly, total and vigorous PA was not associated with a reduced risk of HCC, while moderate-intensity PA showed an inverse association with HCC. The reduced risk was especially associated with brisk walking, suggesting that the mode of PA may play a role in HCC prevention [54]. Lee et al. wanted to establish whether there is a minimum PA threshold for the prevention of HCC. They conducted a meta-analysis and divided the PA performed in the selected studies into three groups: high >3 h/week, moderate 2–3 h/week, or low <2 h/week. A total of 10 prospective cohort studies were included. PA was associated with a dose-dependent decrease in HCC risk and mortality. High and moderate PA reduced the risk of HCC by 54% and 45%, respectively. According to their data, the authors state that 2 h/week PA is mandatory to reduce HCC risk [55]. An interesting recent study looked at variability in the association of obesity and PA and HCC at the state level in the US. Trends of HCC incidence from 2001–2017 were calculated using data from the Centers for Disease Control (CDC) and the National Cancer Institute Surveillance. There were striking state-level disparities in HCC incidence ranging from 6.3 to 0.9 in various states and ethnicities. There was a moderate inverse correlation with state-level PA and the incidence of HCC ($r = -0.40$, $p = 0.004$) [56].

Two studies looked at the effect of PA on specific, at-risk populations. In the first, Feng et al. looked at the effect of PA on alcohol-related cancer (including liver cancer). Data were collected from British and Scottish population-based surveys spanning the years 1994–2008. Alcohol consumption was categorized from “never drinkers” to “harmful” (>35 units/week for women; >49 units/week for men) and PA to lower (7.5 METs h/week) or upper recommended limits (15 METs h/week). There were 54,686 participants, and hazardous/harmful alcohol consumption was associated with a marked increase in cancer-related mortality. Although cancers were not separated by type, the increased risk was eliminated among participants who exercised more than 7.5 METs hours/week and persisted in the upper recommended limits group [57].

Lastly, a recent study looked at whether PA is associated with HCC risk in patients with chronic HBV infection. The authors looked at 9727 treatment-naïve Korean HBV carriers who started treatment with nucleoside/tide analogous from 2012–2017. During the study period, the cumulative HCC incidence was 8.3%. There was an inverse correlation between carriers engaged in PA measured in METs and those without PA. PA had a protective effect in patients with and without cirrhosis that resulted in an approximately 40% reduction in risk for HCC. The authors conclude that PA was significantly associated with a reduced risk of HCC in HBV carriers, treated with anti-viral medications [58].

The data presented here from multiple studies, cohorts, and meta-analyses, clearly shows a beneficial effect for PA in reducing the risk of HCC. The data comes from diverse populations with different gender and ethnic backgrounds. However, there are multiple questions remaining to be answered, especially the obesity independent effect of PA that was only partially shown. Other issues include the duration, mode, and intensity of PA and whether PA is effective in reducing the risk for HCC across multiple liver diseases.

5.4. Physical Activity Following HCC Treatment in Humans

Following the promising data on HCC prevention prior to tumor development, researchers set out to assess whether PA can improve recovery, prevent a recurrence, and possibly prolong survival in patients with HCC that were treated with or without curative intent.

Kiabori et al. from Japan, looked at 51 patients who underwent hepatectomy for HCC. The patients were randomized to diet alone or diet and PA after the operation. PA was started one week before the operation, resumed one week post-operatively, and continued for six months. The authors show that patients in the PA group had significantly improved metabolic parameters such as whole-body mass, fat mas, insulin resistance and insulin levels and recommend early resumption of PA after HCC resection [59]. The same group assessed whether perioperative PA was associated with long-term survival in a larger group of HCC patients undergoing hepatectomy. One hundred and six patients underwent cardiopulmonary exercise assessment utilizing various methods pre and six months post-hepatectomy. Patients were classified as the maintenance group if they had >90% anaerobic threshold six months post-operatively compared to pre-operatively (n = 78) or a decreased group if the threshold was below 90% (n = 28). 5-year recurrence-free survival and overall survival were significantly improved in the maintenance group compared to the decreased group (39.9% vs. 9.9% p = 0.018, and 81.9% vs. 61.7% p = 0.006 respectively). Thus the maintenance of the anaerobic threshold, which is maintained by PA, was an independent positive prognostic marker [60].

Some concern was raised, whether PA could exacerbate CLD in patients with HCC. It was thought that exercise might increase portal pressures and decrease glomerular filtration rate and thus may expose cirrhotic patients to the risk of variceal bleeding and the development of hepatorenal syndrome.

References

1. Llovet, J.M.; Kelley, R.K.; Villanueva, A.; Singal, A.G.; Pikarsky, E.; Roayaie, S.; Lencioni, R.; Koike, K.; Zucman-Rossi, J.; Finn, R.S. Hepatocellular carcinoma. Nat. Rev. Dis. Primers 2021, 7, 6.
2. Luu, H.N.; Behari, J.; Goh, G.B.; Wang, R.; Jin, A.; Thomas, C.E.; Clemente, J.C.; Odegaard, A.O.; Koh, W.P.; Yuan, J.M. Composite Score of Healthy Lifestyle Factors and Risk of Hepatocellular Carcinoma: Findings from a Prospective Cohort Study. Cancer Epidemiol. Biomarkers Prev. 2021, 30, 380–387.
3. Zhang, Y.B.; Pan, X.F.; Chen, J.; Cao, A.; Zhang, Y.G.; Xia, L.; Wang, J.; Li, H.; Liu, G.; Pan, A. Combined lifestyle factors, incident cancer, and cancer mortality: A systematic review and meta-analysis of prospective cohort studies. Br. J. Cancer 2020, 122, 1085–1093.
4. Liu, Y.; Yang, W.; VoPham, T.; Ma, Y.; Simon, T.G.; Gao, X.; Chan, A.T.; Meyerhardt, J.A.; Giovannucci, E.L.; Zhang, X. Plant-Based and Animal-Based Low-Carbohydrate Diets and Risk of

Hepatocellular Carcinoma Among US Men and Women. Hepatology 2021, 73, 175–185.

5. Shah, S.C.; Zhu, X.; Dai, Q.; Peek, R.M.; Shrubsole, M.J. Magnesium intake is associated with a reduced risk of incident liver cancer, based on an analysis of the NIH-American Association of Retired Persons (NIH-AARP) Diet and Health Study prospective cohort. Am. J. Clin. Nutr. 2021, 113, 630–638.
6. Luu, H.N.; Neelakantan, N.; Geng, T.T.; Wang, R.; Goh, G.B.; Clemente, J.C.; Jin, A.; van Dam, R.M.; Jia, W.; Behari, J.; et al. Quality diet indexes and risk of hepatocellular carcinoma: Findings from the Singapore Chinese Health Study. Int. J. Cancer 2021, 148, 2102–2114.
7. Yang, W.; Sui, J.; Zhao, L.; Ma, Y.; Tabung, F.K.; Simon, T.G.; Lee, D.H.; Zeng, X.; Nguyen, L.H.; Meyerhardt, J.A.; et al. Association of Inflammatory and Insulinemic Potential of Diet and Lifestyle with Risk of Hepatocellular Carcinoma. Cancer Epidemiol. Biomarkers Prev. 2021, 30, 789–796.
8. Ji, X.W.; Wang, J.; Shen, Q.M.; Li, Z.Y.; Jiang, Y.F.; Liu, D.K.; Tan, Y.T.; Li, H.L.; Xiang, Y.B. Dietary fat intake and liver cancer incidence: A population-based cohort study in Chinese men. Int. J. Cancer 2021, 148, 2982–2996.
9. Luo, Y.; Zhang, Y.J.; Zhang, D.M.; Yishake, D.; Liu, Z.Y.; Chen, M.S.; Wang, F.; Zhou, Z.G.; Long, J.A.; Zhong, R.H.; et al. Association between dietary patterns and prognosis of hepatocellular carcinoma in the Guangdong liver cancer cohort study. Hepatol. Res. 2020, 50, 1164–1175.
10. Zhong, G.C.; Wang, K.; Peng, Y.; Shivappa, N.; Hebert, J.R.; Wu, Y.Q.; Gong, J.P. Dietary inflammatory index and incidence of and death from primary liver cancer: A prospective study of 103,902 American adults. Int. J. Cancer 2020, 147, 1050–1058.
11. Jayedi, A.; Shab-Bidar, S. Fish Consumption and the Risk of Chronic Disease: An Umbrella Review of Meta-Analyses of Prospective Cohort Studies. Adv. Nutr. 2020, 11, 1123–1133.
12. Zhong, G.C.; Peng, Y.; Wang, K.; Wan, L.; Wu, Y.Q.; Hao, F.B.; Hu, J.J.; Gu, H.T. Magnesium intake and primary liver cancer incidence and mortality in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Int. J. Cancer 2020, 147, 1577–1586.
13. Yang, W.; Sui, J.; Ma, Y.; Simon, T.G.; Petrick, J.L.; Lai, M.; McGlynn, K.A.; Campbell, P.T.; Giovannucci, E.L.; Chan, A.T.; et al. High Dietary Intake of Vegetable or Polyunsaturated Fats Is Associated With Reduced Risk of Hepatocellular Carcinoma. Clin. Gastroenterol. Hepatol. 2020, 18, 2775–2783.e2711.
14. Yang, W.; Sui, J.; Ma, Y.; Simon, T.G.; Chong, D.; Meyerhardt, J.A.; Willett, W.C.; Giovannucci, E.L.; Chan, A.T.; Zhang, X. A prospective study of dairy product intake and the risk of hepatocellular carcinoma in U.S. men and women. Int. J. Cancer 2020, 146, 1241–1249.
15. Kim, T.L.; Jeong, G.H.; Yang, J.W.; Lee, K.H.; Kronbichler, A.; van der Vliet, H.J.; Grosso, G.; Galvano, F.; Aune, D.; Kim, J.Y.; et al. Tea Consumption and Risk of Cancer: An Umbrella Review and Meta-Analysis of Observational Studies. Adv. Nutr. 2020, 11, 1437–1452.

16. Guo, X.F.; Shao, X.F.; Li, J.M.; Li, S.; Li, K.L.; Li, D. Fruit and vegetable intake and liver cancer risk: A meta-analysis of prospective cohort studies. Food Funct. 2019, 10, 4478–4485.
17. Ma, Y.; Yang, W.; Li, T.; Liu, Y.; Simon, T.G.; Sui, J.; Wu, K.; Giovannucci, E.L.; Chan, A.T.; Zhang, X. Meat intake and risk of hepatocellular carcinoma in two large US prospective cohorts of women and men. Int. J. Epidemiol. 2019, 48, 1863–1871.
18. Ma, Y.; Yang, W.; Simon, T.G.; Smith-Warner, S.A.; Fung, T.T.; Sui, J.; Chong, D.; VoPham, T.; Meyerhardt, J.A.; Wen, D.; et al. Dietary Patterns and Risk of Hepatocellular Carcinoma Among, U.S. Men and Women. Hepatology 2019, 70, 577–586.
19. Tran, K.T.; Coleman, H.G.; McMenamin, Ú.C.; Cardwell, C.R. Coffee consumption by type and risk of digestive cancer: A large prospective cohort study. Br. J. Cancer 2019, 120, 1059–1066.
20. Kennedy, O.J.; Roderick, P.; Buchanan, R.; Fallowfield, J.A.; Hayes, P.C.; Parkes, J. Coffee, including caffeinated and decaffeinated coffee, and the risk of hepatocellular carcinoma: A systematic review and dose-response meta-analysis. BMJ Open 2017, 7, e013739.
21. Gao, M.; Sun, K.; Guo, M.; Gao, H.; Liu, K.; Yang, C.; Li, S.; Liu, N. Fish consumption and n-3 polyunsaturated fatty acids, and risk of hepatocellular carcinoma: Systematic review and meta-analysis. Cancer Causes Control 2015, 26, 367–376.
22. Yang, Y.; Zhang, D.; Feng, N.; Chen, G.; Liu, J.; Chen, G.; Zhu, Y. Increased intake of vegetables, but not fruit, reduces risk for hepatocellular carcinoma: A meta-analysis. Gastroenterology 2014, 147, 1031–1042.
23. Luo, J.; Yang, Y.; Liu, J.; Lu, K.; Tang, Z.; Liu, P.; Liu, L.; Zhu, Y. Systematic review with meta-analysis: Meat consumption and the risk of hepatocellular carcinoma. Aliment. Pharmacol. Ther. 2014, 39, 913–922.
24. Bravi, F.; Bosetti, C.; Tavani, A.; Gallus, S.; La Vecchia, C. Coffee reduces risk for hepatocellular carcinoma: An updated meta-analysis. Clin. Gastroenterol. Hepatol. 2013, 11, 1413–1421.e1.
25. Fedirko, V.; Lukanova, A.; Bamia, C.; Trichopolou, A.; Trepo, E.; Nothlings, U.; Schlesinger, S.; Aleksandrova, K.; Boffetta, P.; Tjonneland, A.; et al. Glycemic index, glycemic load, dietary carbohydrate, and dietary fiber intake and risk of liver and biliary tract cancers in Western Europeans. Ann. Oncol. 2013, 24, 543–553.
26. Sawada, N.; Inoue, M.; Iwasaki, M.; Sasazuki, S.; Shimazu, T.; Yamaji, T.; Takachi, R.; Tanaka, Y.; Mizokami, M.; Tsugane, S.; et al. Consumption of n-3 fatty acids and fish reduces risk of hepatocellular carcinoma. Gastroenterology 2012, 142, 1468–1475.
27. Freedman, N.D.; Cross, A.J.; McGlynn, K.A.; Abnet, C.C.; Park, Y.; Hollenbeck, A.R.; Schatzkin, A.; Everhart, J.E.; Sinha, R. Association of meat and fat intake with liver disease and hepatocellular carcinoma in the NIH-AARP cohort. J. Natl. Cancer Inst. 2010, 102, 1354–1365.

28. Ioannou, G.N.; Morrow, O.B.; Connole, M.L.; Lee, S.P. Association between dietary nutrient composition and the incidence of cirrhosis or liver cancer in the United States population. Hepatology 2009, 50, 175–184.
29. Yang, C.; Lu, Y.; Xia, H.; Liu, H.; Pan, D.; Yang, X.; Sun, G. Excess Body Weight and the Risk of Liver Cancer: Systematic Review and a Meta-Analysis of Cohort Studies. Nutr. Cancer 2020, 72, 1085–1097.
30. Sohn, W.; Lee, H.W.; Lee, S.; Lim, J.H.; Lee, M.W.; Park, C.H.; Yoon, S.K. Obesity and the risk of primary liver cancer: A systematic review and meta-analysis. Clin. Mol. Hepatol. 2021, 27, 157.
31. Parra-Soto, S.; Cowley, E.S.; Rezende, L.F.M.; Ferreccio, C.; Mathers, J.C.; Pell, J.P.; Ho, F.K.; Celis-Morales, C. Associations of six adiposity-related markers with incidence and mortality from 24 cancers-findings from the UK Biobank prospective cohort study. BMC Med. 2021, 19, 7.
32. Rahmani, J.; Kord Varkaneh, H.; Kontogiannis, V.; Ryan, P.M.; Bawadi, H.; Fatahi, S.; Zhang, Y. Waist Circumference and Risk of Liver Cancer: A Systematic Review and Meta-Analysis of over 2 Million Cohort Study Participants. Liver Cancer 2020, 9, 6–14.
33. Dyrstad, S.M.; Hansen, B.H.; Holme, I.M.; Anderssen, S.A. Comparison of self-reported versus accelerometer-measured physical activity. Med. Sci. Sports Exerc. 2014, 46, 99–106.
34. Saran, U.; Humar, B.; Kolly, P.; Dufour, J.-F. Hepatocellular carcinoma and lifestyles. J. Hepatol. 2016, 64, 203–214.
35. Lange, N.F.; Radu, P.; Dufour, J.F. Prevention of NAFLD-associated HCC: Role of lifestyle and chemoprevention. J. Hepatol. 2021, 75, 1217–1227.
36. Moore, S.C.; Lee, I.-M.; Weiderpass, E.; Campbell, P.T.; Sampson, J.N.; Kitahara, C.M.; Keadle, S.K.; Arem, H.; De Gonzalez, A.B.; Hartge, P. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. JAMA Intern. Med. 2016, 176, 816–825.
37. Kerr, J.; Anderson, C.; Lippman, S.M. Physic.cal activity, sedentary behaviour, diet, and cancer: An update and emerging new evidence. Lancet Oncol. 2017, 18, e457–e471.
38. Eliassen, A.H.; Hankinson, S.E.; Rosner, B.; Holmes, M.D.; Willett, W.C. Physical activity and risk of breast cancer among postmenopausal women. Arch. Intern. Med. 2010, 170, 1758–1764.
39. Aguiar e Silva, M.A.; Vechetti-Junior, I.J.; Nascimento, A.F.d.; Furtado, K.S.; Azevedo, L.; Ribeiro, D.A.; Barbisan, L.F. Effects of swim training on liver carcinogenesis in male Wistar rats fed a low-fat or high-fat diet. Appl.Physiol.Nutr. Metab. 2012, 37, 1101–1109.
40. Monda, M.; Messina, G.; Scognamiglio, I.; Lombardi, A.; Martin, G.A.; Sperlongano, P.; Porcelli, M.; Caraglia, M.; Stiuso, P. Short-term diet and moderate exercise in young overweight men modulate cardiocyte and hepatocarcinoma survival by oxidative stress. Oxidative Med. Cell. Longev. 2014.

41. Piguet, A.-C.; Saran, U.; Simillion, C.; Keller, I.; Terracciano, L.; Reeves, H.L.; Dufour, J.-F. Regular exercise decreases liver tumors development in hepatocyte-specific PTEN-deficient mice independently of steatosis. J. Hepatol. 2015, 62, 1296–1303.
42. Arfianti, A.; Pok, S.; Barn, V.; Haigh, W.G.; Yeh, M.M.; Ioannou, G.N.; Teoh, N.C.; Farrell, G.C. Exercise retards hepatocarcinogenesis in obese mice independently of weight control. J. Hepatol. 2020, 73, 140–148.
43. Saran, U.; Guarino, M.; Rodríguez, S.; Simillion, C.; Montani, M.; Foti, M.; Humar, B.; St-Pierre, M.V.; Dufour, J.F. Anti-tumoral effects of exercise on hepatocellular carcinoma growth. Hepatol. Commun. 2018, 2, 607–620.
44. Guarino, M.; Kumar, P.; Felser, A.; Terracciano, L.M.; Guixé-Muntet, S.; Humar, B.; Foti, M.; Nuoffer, J.-M.; St-Pierre, M.V.; Dufour, J.-F. Exercise attenuates the transition from Fatty Liver to Steatohepatitis and reduces tumor formation in Mice. Cancers 2020, 12, 1407.
45. Zhang, X.; Cao, L.; Ji, B.; Li, L.; Qi, Z.; Ding, S. Endurance training but not high-intensity interval training reduces liver carcinogenesis in mice with hepatocellular carcinogen diethylnitrosamine. Exp. Gerontol. 2020, 133, 110853.
46. Cao, L.; Zhang, X.; Ji, B.; Ding, S.; Qi, Z. Mod.derate endurance training reduced hepatic tumourigenesis associated with lower lactate overload compared to high-intensity interval training. Clin. Exp. Pharmacol. Physiol. 2021, 48, 1239–1250.
47. Yun, Y.H.; Lim, M.K.; Won, Y.-J.; Park, S.M.; Chang, Y.J.; Oh, S.W.; Shin, S.A. Dietary preference, physical activity, and cancer risk in men: National health insurance corporation study. BMC Cancer 2008, 8, 1–17.
48. Inoue, M. Impact of lifestyle on overall cancer risk among Japanese: The Japan Public Health Center-based Prospective Study (JPHC Study). J. Epidemiol. 2010, 20, 90–96.
49. Wen, C.-P.; Lin, J.; Yang, Y.C.; Tsai, M.K.; Tsao, C.K.; Etzel, C.; Huang, M.; Hsu, C.Y.; Ye, Y.; Mishra, L. Hepatocellular carcinoma risk prediction model for the general population: The predictive power of transaminases. J. Natl. Cancer Inst. 2012, 104, 1599–1611.
50. Behrens, G.; Matthews, C.E.; Moore, S.C.; Freedman, N.D.; McGlynn, K.A.; Everhart, J.E.; Hollenbeck, A.R.; Leitzmann, M.F. The association between frequency of vigorous physical activity and hepatobiliary cancers in the NIH-AARP Diet and Health Study. Eur. J. Epidemiol. 2013, 28, 55–66.
51. Arem, H.; Loftfield, E.; Saint-Maurice, P.F.; Freedman, N.D.; Matthews, C.E. Physical activity across the lifespan and liver cancer incidence in the NIH-AARP Diet and Health Study cohort. Cancer Med. 2018, 7, 1450–1457.
52. Baumeister, S.E.; Schlesinger, S.; Aleksandrova, K.; Jochem, C.; Jenab, M.; Gunter, M.J.; Overvad, K.; Tjønneland, A.; Boutron-Ruault, M.-C.; Carbonnel, F. Association between physical

activity and risk of hepatobiliary cancers: A multinational cohort study. J. Hepatol. 2019, 70, 885–892.

53. Simon, T.G.; Kim, M.N.; Luo, X.; Yang, W.; Ma, Y.; Chong, D.Q.; Fuchs, C.S.; Meyerhardt, J.A.; Corey, K.E.; Chung, R.T. Physical activity compared to adiposity and risk of liver-related mortality: Results from two prospective, nationwide cohorts. J. Hepatol. 2020, 72, 1062–1069.
54. Luo, X.; Yang, W.; Ma, Y.; Simon, T.G.; Meyerhardt, J.A.; Chan, A.T.; Giovannucci, E.L.; Zhang, X. Physical activity and risk of hepatocellular carcinoma among US men and women. Cancer Prev. Res. 2020, 13, 707–714.
55. Lee, J. Associations between Physical Activity and Liver Cancer Risks and Mortality: A Systematic Review and Meta-Analysis. Int. J. Environ. Res. Public Health 2020, 17, 8943.
56. Lee, Y.T.; Wang, J.J.; Luu, M.; Tseng, H.R.; Rich, N.E.; Lu, S.C.; Nissen, N.N.; Noureddin, M.; Singal, A.G.; Yang, J.D. State-Level HCC Incidence and Association With Obesity and Physical Activity in the United States. Hepatology 2021, 74, 1384–1394.
57. Feng, Y.; Powell, L.; Vassallo, A.J.; Hamer, M.; Stamatakis, E. Does adequate physical activity attenuate the associations of alcohol and alcohol-related cancer mortality? A pooled study of 54 686 British adults. Int. J. Cancer 2020, 147, 2754–2763.
58. Chun, H.S.; Park, S.; Lee, M.; Cho, Y.; Kim, H.S.; Choe, A.R.; Kim, H.Y.; Yoo, K.; Kim, T.H. Association of Physical Activity with the Risk of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B. Cancers 2021, 13, 3424.
59. Kaibori, M.; Ishizaki, M.; Matsui, K.; Nakatake, R.; Yoshiuchi, S.; Kimura, Y.; Kwon, A.-H. Perioperative exercise for chronic liver injury patients with hepatocellular carcinoma undergoing hepatectomy. Am. J. Surg. 2013, 206, 202–209.
60. Kaibori, M.; Matsui, K.; Yoshii, K.; Ishizaki, M.; Iwasaka, J.; Miyauchi, T.; Kimura, Y. Perioperative exercise capacity in chronic liver injury patients with hepatocellular carcinoma undergoing hepatectomy. PLoS ONE 2019, 14, e0221079.