Review

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Hepatocellular carcinoma and lifestyles

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Summary

The majority of hepatocellular carcinoma occurs over pre-existing chronic liver diseases that share cirrhosis as an endpoint. In the last decade, a strong association between lifestyle and hepatocellular carcinoma has become evident. Abundance of energy-rich food and sedentary lifestyles have caused metabolic conditions such as obesity and diabetes mellitus to become global epidemics. Obesity and diabetes mellitus are both tightly linked to non-alcoholic fatty liver disease and also increase hepatocellular carcinoma risk independent of cirrhosis. Emerging data suggest that physical activity not only counteracts obesity, diabetes mellitus and non-alcoholic fatty liver disease, but also reduces cancer risk. Physical activity exerts significant anticancer effects in the absence of metabolic disorders. Here, we present a systematic review on lifestyles and hepatocellular carcinoma.

Introduction

Cancers result from the interactions of host features with environment factors. Lifestyles, which comprise the habits by which a person chooses to live, define these interactions. Therefore, lifestyles such as dietary choices, smoking, alcohol consumption and physical activity have a profound influence on cancer development, including hepatocellular carcinoma (HCC). The capacity to survive famine was one of the strongest selection traits during evolution. This changed drastically about 50 years ago with generalization of a lifestyle characterized by the abundance of food and lack of exercise. Human physiology has not changed in such a short period of time. As a consequence, we are maladapted to our new environment and this maladaptation leads to the epidemics of obesity and diabetes mellitus (DM). Obesity has been consistently associated with a 1.5–4.5 times increase of HCC risk [1–7]. Even an increase in body mass index (BMI) during childhood was associated with an elevated risk of HCC during adulthood [8]. DM was also linked to a 2–3-fold increase of HCC risk [9–11], independently of the underlying liver disease [11] and even in lean individuals [12]. Moreover, treating diabetic patients with insulin and/or insulin sensitizers may further increase the risk to develop HCC. This highlights how strongly lifestyles influence the risk of developing HCC.

Key points

- The growing epidemic of metabolic conditions such as obesity and DM and their close link to NAFLD in turn contribute to the increased risk of HCC development independent of cirrhosis
- Both human and animal studies have demonstrated an inverse association between physical activity and liver cancer
- Smoking increases the risk of developing HCC
- Coffee intake is associated with a decreased risk of developing HCC
- The molecular mechanisms underlying the effects of lifestyles and HCC involve changes in metabolism, in particular, the activation of AMPK, changes in the immune system and in inflammation

Smoking

Smoking is associated with the development of several types of cancers, particularly those arising in organs directly exposed to smoke. Smoking also increases the risk of developing HCC

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Abbreviations: ACC, acetyl coenzyme A carboxylase; BMI, body mass index; DM, diabetes mellitus; FAS, fatty acid synthase; β-HAD, β-hydroxyacyl-CoA dehydrogenase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IHF, intrahepatic fat; MDA, malondialdehyde; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; FFA, free fatty acids; OLETF, Otsuka Long-Evans Tokushima Fatty; NEFA, non-esterified fatty acids; PA, physical activity; SCD-1, stearoyl-CoA desaturase-1; SREBPF, sterol regulatory element-binding transcription factor 1; TNF-α, tumor necrosis factor-α.

Table 1. Human studies focusing on the effect of smoking on HCC.

[Ref]	Design	Population	Total	Conclusions drawn	Limitation of study
[14]	Case study	110 HCC patients and 42 patients with metastatic liver tumors / intrahepatic stones who underwent surgery between 1984-1995	152/110	4-aminobiphenyl exposure (result of cigarette smoking) plays a role in the development of HCC in humans. OR = 4.14 (1.15-15.50) and OR = 9.71 (2.82-34.86) for medium and high 4-aminobiphenyl-DNA adducts levels respectively.	Retrospective case control study, no clear definition of smoking, information about smoking duration/quantity was not available for all subjects.
[15]	Case control	36,000 adults who died from liver cancer (cases) and 17,000 who died from cirrhosis (controls)	53,000/36,000	For men smokers, RR = 1.36 (1.29-1.43) to die from liver cancer. Looking at consumption (cigarettes/day): RR = 1.5 (1.39-1.62) for 20/day and RR = 1.32 (1.23-1.41) for 10/days. For women smoker RR = 1.17 (1.06-1.29), RR = 1.45 (1.18-1.79) for 22/day and RR = 1.09 (0.94-1.25) for 8/day.	Retrospective study
[16]	Prospective cohort	63,257 adults aged 45-74 years in Singapore	61,321/394	Current *vs.* never smokers have an increased risk of HCC HR = 1.63 (1.27-2.10) after adjusting for alcohol consumption and other cofounders. Result was dose-dependent (p <0.001) and duration of smoking dependent (p = 0.002).	Smoke habit evaluated only at enrollment
[17]	Prospective nested case-control study	115 HCC matched with 229 controls from the European Prospective Investigation into Cancer and nutrition EPIC cohort.	115/229	Smokers have a higher risk to develop HCC. OR = 4.55 (1.90- 10.91). Former smokers have a higher risk to develop HCC. OR = 1.98 (0.90-4.39).	Information about comorbidities such as diabetes was not available for all subjects, HCC treatment was not taken into account
[18]	Prospective cohort	2273 HCC patients aged 20-75.	2273/2273	Looking at survival after HCC diagnosis, HR = 1.20 (1.05-1.37) for current smoker and 1.16 (0.98-1.38) for ex-smokers compared to never smokers.	Lack of evaluation of interactions with other possible factors (cirrhosis, diabetes, diet)
[19]	Prospective cohort	302 patients with HBV infection who underwent surgical resection for HCC	302/302	Heaving smoking (PY ≥20) was the most significant factor associated with HBV-related HCC recurrence after surgical resection (p = 0.001). Median recurrence-free survival was worse for ex- and current-smoker than for non-smoker (24, 26, 34 months respectively, p = 0.033).	Small number of ex-smoker (n = 25), tumour burden in that specific group was worse than the other groups, Short-term follow-up.

Total column: number of subjects in study/number of subjects with HCC. OR, odds ratio; RR, relative risk; HR, hazard ratio.

(Table 1). Tobacco smoke contains chemicals that become activated as carcinogens when metabolized in the liver [13]. A linear relation between 4-aminobiphenyl-DNA adduct levels in liver tissue and HCC risk was reported, which was also significant after adjustment for covariates, including hepatitis B surface antigen status [14]. In a large Chinese retrospective study, smokers had a higher risk ratio for HCC than nonsmokers; this concerned males as well as females and the risk correlated with the degree of cigarette consumption [15]. This was confirmed in two Asian prospective studies which adjusted for alcohol consumption [16,17]. Data from the European Prospective Investigation into Cancer and Nutrition (EPIC) suggested that, in Europe, smoking contributes to nearly half the cases of HCC, which is actually more than hepatitis B and C viruses [18]. Moreover, smokers who underwent HCC resection had a higher rate of recurrence and liver-specific mortality [19].

Alcohol

Alcohol is linked to HCC via the development of cirrhosis. The published evidence does not support a role for alcohol as a direct carcinogen for HCC. Alcohol-induced liver disease is one of the most prevalent causes of cirrhosis and alcohol-induced cirrhosis is associated with a five-year cumulative risk for HCC of 8% [20]. The odds ratios for HCC increase linearly with alcohol intake and are higher in cases of DM or infection with hepatitis B or C virus [21,22].

Coffee

Since 2002, when a protective effect of coffee against HCC was first reported [23], epidemiological studies, covering different geographical areas and different HCC etiologies and with different designs, have substantiated this observation. Three meta-analyses comprising studies from Europe and Asia found a statistically significant association between coffee consumption and an approximately 40% reduced liver cancer risk [24–26]. Prospective studies confirmed the benefit of coffee consumption. A prospective cohort that enrolled Finnish male smokers reported that coffee intake (boiled or filtered) was inversely associated with incident liver cancer [27]. Comparing high coffee consumers with low coffee consumers in the EPIC study, Bamia *et al.* found a