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**Lifestyle factors in hepatocellular carcinoma: From pathogenesis to prognosis**

Zhao H *et al.* Lifestyle Factors in HCC

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## Abstract

<sup>2</sup> Hepatocellular carcinoma (HCC) represents a major global health burden, ranking third as the leading cause of cancer-related mortality worldwide. This comprehensive review examines the substantial body of evidence linking modifiable lifestyle factors to HCC pathogenesis and clinical outcomes. We systematically evaluate dietary components, alcohol consumption patterns, tobacco use, physical activity levels, and emerging factors including metabolic disorders, psychological stress, and sleep disturbances. These factors collectively influence hepatocarcinogenesis through diverse biological mechanisms, including genotoxic damage, metabolic dysregulation, chronic inflammatory responses, and gut microbiome-mediated pathways. The accumulated data underscore the urgent need to integrate lifestyle interventions into multidisciplinary HCC management.

**Key Words:** Hepatocellular carcinoma; Lifestyle; Dietary factors; Physical activity; Behavioral modification; Pathogenesis; Prognosis

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**Core Tip:** This review highlights key modifiable factors affecting hepatocellular carcinoma risk and outcomes. A diet that avoids aflatoxins while being rich in fiber, vegetables, coffee and tea provides protective benefits. Alcohol and tobacco cessation, along with regular exercise, significantly reduce risk and improve outcomes. Obesity, diabetes, poor mental health and sleep disorders worsen prognosis, particularly when interacting with viral hepatitis. These findings underscore the importance of personalized prevention strategies and the integration of lifestyle interventions into hepatocellular carcinoma management to address this global health challenge.

## INTRODUCTION

Liver cancer is one of the most common malignant tumors worldwide. According to the 2022 global cancer statistics, liver cancer causes around 865269 new cases and 757948 deaths annually, ranking as the sixth most diagnosed cancer and the third leading cause of cancer-related mortality[1]. Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, accounting for approximately 75%-85% of all cases[2]. The disease burden is particularly severe in East Asia and Africa. The prognosis of HCC remains extremely poor, with a 5-year survival rate of only around 20%, and the median survival for advanced-stage patients is only about two years[3]. This dismal outcome is attributed to the insidious onset of the disease, low early diagnosis rates (only 30% of cases are detected at a curable stage), and strong treatment resistance[4]. Therefore, further exploration of HCC pathogenesis, the development of novel biomarkers, and the optimization of treatment strategies remain critical research priorities.

Lifestyle factors play a significant role in both the risk of developing cancer and the outcome of cancer patients. Key modifiable behaviors, including tobacco use, alcohol consumption, dietary habits, physical activity levels, and sleep patterns, have been extensively studied in terms of their associations with cancer incidence, progression, and survival rates[5]. Multiple lifestyle factors, such as alcohol intake, dietary habits (e.g., aflatoxin contamination), sedentary behavior and obesity, are recognized as key modulators of HCC incidence and progression[6]. Emerging evidence further suggests that additional modifiable lifestyle elements may influence HCC pathogenesis and disease outcomes. For instance, higher dietary fiber and whole grain intake have been inversely associated with liver cancer risk[7,8]. Additionally, psychiatric disorders are linked to an elevated HCC incidence (standardized incidence ratio 1.42, 95% confidence interval (CI) 1.28-1.57,  $P < 0.001$ )[9]. Sleep patterns also appear relevant: Both short (< 5 hours) and prolonged (> 9 hours) nighttime sleep durations exhibit u-shaped associations with HCC risk, while daytime napping is associated with increased HCC incidence[10]. Given the established significance of these modifiable lifestyle factors, this review aims to provide a comprehensive and systematic evaluation of their critical roles in HCC risk modulation and treatment outcomes. By synthesizing current evidence, we seek to

deliver actionable insights and evidence-based recommendations for HCC patients. These findings may serve as a practical reference for lifestyle modifications that could potentially contribute to HCC prevention, treatment optimization, and quality of life improvement in affected individuals.

## DIETARY FACTORS IN HCC

### *Dietary components*

**Aflatoxin contamination:** Aflatoxins, particularly aflatoxin B1 (AFB1), constitute a major global public health challenge due to their potent hepatocarcinogenic properties. These mycotoxins, produced by *Aspergillus* fungi, frequently contaminate dietary staples including rice, corn, peanuts, and spices. This contamination poses particularly severe risks in low-income regions where suboptimal food storage conditions prevail[11]. It is estimated that approximately 4.5 billion people worldwide are at risk of consuming AFB1-contaminated foods[12]. AFB1 exerts hepatocarcinogenic effects primarily through cytochrome P450-mediated metabolic activation, generating the reactive AFB1-8,9-epoxide that forms DNA adducts (e.g., AFB1-N7-guanine)[13]. These lesions drive characteristic *TP53* mutations, notably G to T transversions at codon 249, and genomic analyses reveal AFB1-specific mutational signatures including C > A transversions in GCN sequences and recurrent adhesion G protein-coupled receptor B1 mutations linked to tumor angiogenesis[14,15]. Crucially, AFB1 synergizes with hepatitis b virus (HBV) infection, evidenced by accelerated HCC progression [odds ratio (OR) = 5.47] in individuals with elevated AFB1-albumin adducts[16]. Independent carcinogenicity persists in hepatitis c virus (HCV)/non-viral HCC cases, with alcohol consumption exacerbating risks[17]. These findings underscore the necessity to integrate molecular epidemiology with precision prevention approaches, particularly for high-risk populations with concurrent viral hepatitis or alcohol exposure. Implementation of comprehensive intervention strategies, encompassing improved agricultural practices, evidence-based chemoprevention, and strengthened food safety regulations, represents a critical pathway for reducing the global burden of AFB1-associated HCC.

**Dietary carbohydrates:** Dietary carbohydrates consumed by humans are classified into sugar (monosaccharides and disaccharides), and polysaccharides including digestible starches and indigestible dietary fibers. While sugars provide quick energy, complex carbohydrates from whole grains and fiber-rich foods offer sustained energy and health benefits. Sugars are rapidly digested and absorbed to provide immediate energy, whereas dietary fiber, although non-caloric, modulates sugar metabolism by slowing glucose absorption and improving glycemic control. Emerging evidence suggests that dietary carbohydrates play differential roles in HCC development. While refined sugars exhibit detrimental effects, dietary fiber and whole grains demonstrate protective potential. Large prospective cohort studies have revealed significant inverse associations between fiber intake and HCC risk. The National Institutes of Health- American Association of Retired Persons (NIH-AARP) prospective observational cohort study ( $n = 485717$ ) in the United States found highest quintile fiber consumers had 31% lower HCC risk [hazard ratio (HR) = 0.69, 95%CI: 0.53-0.90][7]. Similarly, a meta-analysis of 2383 HCC cases demonstrated a 17% risk reduction per 10 g/day fiber intake (HR = 0.83, 95%CI: 0.76-0.91)[8]. Mechanistically, fiber may protect through improved glycemic control, reduced inflammation, and gut microbiota modulation. Conversely, sugar intake appears harmful. The European Prospective Investigation into Cancer and Nutrition (EPIC) prospective observational cohort study ( $n = 477206$ ) in Europe reported a 43% increased HCC risk per 50 g/day total sugar, with sugar-sweetened beverage consumers showing a particularly elevated risk[18]. Excessive fructose consumption, prevalent in modern diets, may promote HCC *via* metabolic dysfunction including insulin resistance, non-alcoholic fatty liver disease (NAFLD) progression, and obesity, all established HCC risk factors[19]. Current evidence supports prioritizing fiber-rich whole foods while limiting added sugars as a practical dietary strategy for HCC prevention, especially in high-risk populations.

**Dietary fats:** Dietary fats comprise different ratios of saturated and unsaturated fatty acids, including both monounsaturated and polyunsaturated varieties. Emerging evidence suggests differential effects of dietary fat subtypes on hepatocarcinogenesis. Large cohort studies reveal complex associations. While the Nurses' Health Study and the Health Professionals Follow-up Study cohorts, which prospectively recruited 138483 healthy adults, found inverse associations for n-3 polyunsaturated fatty acids (PUFA) (HR = 0.63, 95%CI: 0.41-0.96) and n-6 PUFA (HR = 0.54, 95%CI: 0.34-0.86) with HCC risk[20], the Singapore Chinese Health Study ( $n = 63257$ ) reported increased HCC risk with higher n-6 PUFA intake (Q4 vs Q1 HR = 1.49, 95%CI: 1.08-2.07), particularly in HBV/HCV-negative individuals (OR = 4.36, 95%CI: 1.59-11.94)[21]. The anti-HCC mechanisms of n-3 PUFAs may involve suppression of  $\beta$ -catenin and cyclooxygenase-2 pathways, anti-inflammatory effects *via* inhibition of interleukin-1 and tumor necrosis factor, and modulation of cell membrane lipid rafts, which regulate proliferation and apoptosis[20]. Saturated fats show more consistent harm, with the NIH-AARP study ( $n = 495006$ ) demonstrating an 87% increased HCC risk for high saturated fat consumers (HR = 1.87, 95%CI: 1.23-2.85)[22], although a Swedish cohort ( $n = 77059$ ) found no significant associations[23]. Current evidence supports prioritizing unsaturated fats over saturated fats for HCC prevention. The protective potential of dietary modifications, particularly in high-risk NAFLD populations, warrants further investigation.

**Vitamins:** Emerging evidence highlights the significant role of vitamins, particularly vitamin A and folate (vitamin B9), in HCC progression and survival. Vitamin A and its precursors demonstrate protective effects through multiple mechanisms. Clinical data reveal that patients in the highest quartile of  $\beta$ -carotene intake showed significantly improved overall survival (HR = 0.72, 95%CI: 0.54-0.96) and HCC-specific survival (HR = 0.69, 95%CI: 0.51-0.94) compared to the lowest quartile[24].  $\beta$ -Carotene metabolizes to retinol, activating retinoic acid receptor/retinoid X receptor; all-trans retinoic acid inhibits HCC proliferation *via* retinoid X receptor dephosphorylation through rat sarcoma virus/extracellular signal-regulated kinase (ERK) suppression[25], while

vitamin A derivatives block metastasis by reversing epithelial-mesenchymal transition[26]. Folate (vitamin B9) status also significantly impacts HCC outcomes. The Guangdong Liver Cancer Cohort study ( $n = 982$ ) demonstrated that patients in the lowest serum folate quartile had worse liver cancer-specific survival (HR = 1.48, 95%CI: 1.05-2.09) and overall survival (HR = 1.43, 95%CI: 1.03-1.99) compared to the third quartile[27]. These associations were particularly pronounced in patients with systemic inflammation or current smokers, suggesting folate's role in mitigating oxidative stress and inflammation-related carcinogenesis.

### *Food items*

**Fish:** Growing evidence suggests that fish consumption, particularly n-3 PUFA-rich fish, is inversely associated with HCC risk in a dose-dependent manner. Several studies indicate that higher intake of n-3 PUFAs, eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid, is associated with a dose-dependent reduction in HCC incidence. A prospective study reported HRs of 0.64 (95%CI: 0.42-0.96) for n-3 PUFA-rich fish, 0.56 (95%CI: 0.36-0.85) for eicosapentaenoic acid, 0.64 (95%CI: 0.41-0.98) for docosapentaenoic acid, and 0.56 (95%CI: 0.35-0.87) for docosahexaenoic acid, with consistent effects regardless of HBV or HCV infection[28]. Similarly, another study found a significant inverse association between total fish intake (per 20 g/day increase) and HCC risk (HR = 0.83 before calibration)[29]. An umbrella meta-analysis further supported this, showing that each 100 g/day increase in fish intake correlated with a 35% lower liver cancer risk[30]. A meta-analysis of 11 studies reported a 35% HCC risk reduction with high fish consumption (summary relative risk = 0.65, 95%CI: 0.51-0.79) and a 51% reduction with n-3 PUFA intake (summary relative risk = 0.49, 95%CI: 0.19-0.79)[31]. Therefore, most evidence supports a protective role of fish and n-3 PUFAs against HCC.

**Red meat and poultry:** The relationship between red meat, poultry intake, and HCC risk remains inconsistent across studies. A large United States cohort study reported an

almost two-fold HCC risk with higher processed red meat intake (3<sup>rd</sup> vs 1<sup>st</sup> tertile), while unprocessed red meat exhibited no association (HR = 1.06, 95%CI: 0.68-1.63)[32]. A case-control study of cirrhotic viral hepatitis patients found that N-acetyltransferase 2 rapid acetylators with high red meat intake dose-dependently increased HCC risk (OR = 3.89 for high intake; *P*-trend = 0.016), highlighting gene-diet interactions in hepatocarcinogenesis[33]. Conversely, a Chinese prospective cohort (*n* = 510048) observed no overall association between red meat, poultry, or fish and HCC, although rural residents showed a potential protective effect from poultry (*P*-interaction = 0.046)[34]. Recent substitution analyses found no significant link between replacing red meat with legumes and HCC risk (HR = 1.02, 95%CI: 0.96-1.08)[35]. Processed red meat may elevate HCC risk, particularly in genetically susceptible individuals, and unprocessed red meat and poultry show neutral or protective associations, respectively.

**Vegetables and fruits:** Accumulating evidence suggests that higher vegetable intake is associated with a reduced risk of HCC, while fruit consumption shows inconsistent associations. A meta-analysis of nine prospective cohort studies (1703 HCC cases) found a 39% lower HCC risk with high vegetable intake (95%CI: 0.50-0.75), with a 4% risk reduction per 100 g/day increase (*P*-trend < 0.001)[36]. This protective effect was particularly strong in males (50% risk reduction) but not significant in females. Similarly, the EPIC study (*n* = 486799) observed a 17% lower HCC risk per 100 g/day vegetable increase (HR = 0.83, 95%CI: 0.71-0.98), whereas fruit intake showed no association (HR = 1.01, 95%CI: 0.92-1.11)[37]. Specific vegetable subgroups, particularly cruciferous vegetables (*e.g.*, broccoli, cauliflower, cabbage) and lettuce, appear to drive this protective effect. The NIH-AARP study (*n* = 485403) reported a 28% lower HCC risk with high total vegetable intake (HR = 0.72, 95%CI: 0.59-0.89), with cruciferous vegetables and lettuce showing the strongest inverse associations (*P*-trend < 0.005)[38]. Additionally, dietary antioxidants (*e.g.*, flavanols) and high dietary fiber intake (particularly from cereals and vegetables) have been linked to reduced HCC risk. The EPIC cohort found that flavanol intake was inversely associated with HCC (HR = 0.62, 95%CI: 0.39-0.99)[39], while a

United States prospective cohort study of health professionals ( $n = 125455$ ) noted that whole grain and cereal fiber intake reduced HCC risk by 37% (HR = 0.63, 95%CI: 0.41-0.96)[40]. Therefore, current evidence strongly supports an inverse association between vegetable consumption (especially cruciferous vegetables and lettuce) and HCC risk, likely mediated by bioactive compounds and fiber. In contrast, fruit intake does not consistently show protective effects. These findings highlight the potential role of plant-based diets in HCC prevention[7].

**Coffee:** Current research shows a consistent inverse association between coffee consumption and HCC risk. A Finnish randomized controlled study (27037 male smokers), originally designed to assess the effect of vitamin E on lung cancer risk, found that each daily cup of coffee reduced HCC risk by 18% (relative risk = 0.82, 95%CI: 0.73-0.93)[41]. No significant difference was observed between boiled *vs* filtered coffee, suggesting bioactive compounds remain effective regardless of preparation. Consistently, a meta-analysis of 32 studies involving 2492625 participants revealed that higher coffee intake was associated with a 47% reduction in HCC risk (relative risk = 0.53; 95%CI: 0.47-0.59), with similar protective effects observed across different study designs[42]. Another meta-analysis reported a 28% risk reduction per daily cup of coffee consumed (relative risk = 0.72; 95%CI: 0.66-0.79)[43]. The protective mechanisms of coffee against HCC appear multifaceted. Caffeine, a key bioactive component, functions as a non-selective adenosine receptor inhibitor, blocking adenosine-mediated immunosuppression and initiating antitumor immune responses[44]. Experimental studies demonstrate caffeine's ability to inhibit HCC cell proliferation by activating the mitogen activated protein kinase/ERK/epidermal growth factor receptor signaling pathway[45]. The chemopreventive effects of coffee may also be attributed to its polyphenol content, which exhibits antioxidant and anti-inflammatory properties. These compounds may counteract dietary inflammatory patterns that increase HCC risk[46].

**Tea:** Tea consumption, particularly green tea, represents a promising dietary strategy for HCC prevention[47]. A comprehensive umbrella meta-analysis of observational studies established that high green tea consumption correlates with a 13% reduction in liver cancer risk, although the authors highlighted the necessity for more rigorous prospective studies to account for potential biases[48,49]. Subsequent meta-analyses encompassing over 2.4 million participants demonstrated a 20% decrease in HCC risk associated with green tea intake (relative risk = 0.80, 95%CI: 0.67-0.95), with consistent protective effects observed across both cohort and case-control study designs[42]. The Shanghai Women's Health Study, a prospective cohort of 71841 middle-aged Chinese women, provided compelling longitudinal evidence, revealing that cumulative consumption exceeding 30 kg of dried tea leaves corresponded to a 44% lower HCC risk (adjusted HR = 0.56, 95% CI: 0.32-0.97). This protective association was even more pronounced among exclusive green tea drinkers (adjusted HR = 0.54, 95%CI: 0.30-0.98)[50]. While most evidence originates from Asian populations, the European EPIC study ( $n = 486799$ ) corroborated these findings, demonstrating 72% and 59% risk reductions for the highest vs lowest quintiles of coffee and tea consumption, respectively[51]. The chemopreventive mechanisms of tea appear to operate through multiple bioactive compounds[47]. Theabrownin, a tea polyphenol, mediates tumor-inhibitory effects by activating the ataxia telangiectasia mutated-checkpoint kinase 2-p53 signaling axis and regulating c-Jun N-terminal kinase pathways, thereby inducing cellular senescence and apoptosis in HCC cells[52]. Similarly, epigallocatechin-3-gallate exhibits potent anti-HCC activity through three distinct mechanisms, suppression of osteopontin-mediated metastasis, enhancement of 5-fluorouracil chemosensitivity and induction of apoptosis *via* nuclear factor- $\kappa$ B pathway inactivation[53-55].

### **Alcohol consumption**

The relationship between alcohol consumption and HCC has been well-established through multiple epidemiological and mechanistic studies. Alcohol-related HCC (A-HCC) accounts for approximately 19% of global liver cancer deaths, making it the third

leading cause of HCC after HBV and HCV infections, and the primary cause in Europe[56]. Patients with alcohol-associated cirrhosis face a 1%, 3%, and 9% cumulative HCC incidence at 1, 5, and 10 years, respectively[57]. A-HCC is typically diagnosed at advanced stages, with only 24.5% receiving curative treatments *vs* 33.9% in non-A-HCC cases, leading to higher mortality (HR = 1.3; 95%CI: 1.1=1.5)[58]. The risk increases linearly with alcohol intake, with heavy drinkers ( $\geq 3$  drinks/day) showing a 16% higher risk compared to non-drinkers[59], while former and always heavy drinkers face 3.2-fold and 5.5-fold increased risks, respectively[60]. Abstinence improves survival (5-year mortality: 52% *vs* 78% in active drinkers) but does not significantly enhance treatment access[61]. In addition, alcohol exacerbates HCC risk in metabolic disorders, with diabetics showing a 3.3-fold increased risk with heavy drinking *vs* non-drinking normoglycemic individuals[62]. Ethanol metabolism generates carcinogenic acetaldehyde and reactive oxygen species through antidiuretic hormone/cytochrome P450 2E1-mediated oxidation, causing DNA damage *via* N<sup>2</sup>-ethylidenedeoxyguanosine adduct formation and chromosomal instability. Concurrently, aldehyde dehydrogenase-mediated conversion of acetaldehyde to acetate fuels tumor bioenergetics and epigenetic regulation *via* histone acetylation (H3K9/27/56) of lipogenic genes (*FASN*, *ACACA*), promoting HCC survival under hypoxia[63]. Alcohol also induces immune dysfunction by suppressing natural killer-cell activity and promoting a tumor-permissive microenvironment rich in M2 macrophages and toll-like receptor 4-activated pathways[64]. Alcohol promotes HCC through direct genotoxicity, metabolic reprogramming, and immune suppression, with outcomes worsened by delayed diagnosis and limited curative options.

### *Dietary patterns*

Emerging evidence demonstrates significant associations between dietary patterns and HCC risk, with distinct protective effects observed across cultural contexts. A case-control study from Italy and Greece (518 HCC cases) revealed that high adherence to a Mediterranean diet reduced HCC risk by 50%, with particularly pronounced benefits in

chronic hepatitis B/C patients[65]. The NIH-AARP study ( $n = 494942$ ) found that higher Healthy Eating Index-2010 scores were associated with a 28% lower HCC risk (HR = 0.72, 95%CI: 0.53-0.97) and 43% reduced chronic liver disease mortality[66]. Similarly, the Alternative Healthy Eating Index-2010 (AHEI-2010) demonstrated a 39% lower HCC risk for highest vs lowest adherence (HR = 0.61, 95%CI: 0.39-0.95) in United States cohorts[67]. The multiethnic cohort study confirmed these associations across racial groups, with alternate Mediterranean diet scores showing a 32% lower HCC risk overall (HR = 0.68, 95%CI: 0.51-0.90)[68]. In contrast, Chinese studies yielded culturally specific insights: Higher Chinese Healthy Eating Index scores were associated with 26% lower HCC-specific mortality (HR = 0.74, 95%CI: 0.56-0.98)[69] and 57% reduced primary liver cancer risk in case-control analyses (OR = 0.43, 95%CI: 0.38-0.50 per 5-point increase)[70]. The empirical dietary inflammatory pattern was associated with a two-fold HCC risk (HR = 2.03, 95%CI: 1.31-3.16)[71]. These findings consistently demonstrate that adherence to culturally rooted healthy dietary patterns can reduce HCC risk across diverse populations. Public health strategies promoting regionally tailored dietary guidelines may substantially impact HCC prevention, especially in high-risk groups.

### **TOBACCO USE AND HCC**

A meta-analysis of 81 studies revealed current smokers had 55% higher HCC incidence (OR = 1.55, 95%CI: 1.46-1.65) and 29% greater mortality (OR = 1.29, 95%CI: 1.23-1.34) compared to non-smokers[72]. Subsequent research corroborated a 2.46-fold higher HCC risk in current smokers (HR = 2.46, 95%CI: 1.77-3.43)[60]. Effects were most pronounced in viral hepatitis patients[73,74]. Smoking promotes HCC through direct DNA damage/p53 inactivation[75], HBV-related immunosuppression (elevated viral load, impaired natural killer cells)[76], and inflammation/fibrosis (stellate cell activation, iron overload)[75]. It synergizes with viral hepatitis but not alcohol[60]. While some studies show mixed survival outcomes[77], the overwhelming body of evidence shows that tobacco use substantially elevates HCC risk and adversely impacts disease progression.

## PHYSICAL ACTIVITY AND HCC

Current scientific evidence demonstrates a robust inverse association between physical activity and HCC risk. A meta-analysis of 14 prospective studies involving 6440 liver cancer cases revealed that high levels of physical activity were associated with a 25% reduction in HCC risk (HR = 0.75, 95%CI: 0.63-0.89)[78]. Another meta-analysis of 7 studies with 777662 participants confirmed this protective effect, showing 35% lower odds of HCC among more active individuals (OR = 0.65, 95%CI: 0.45-0.95)[79]. The benefits appear dose-dependent, with studies suggesting a minimum threshold of 2 hours/week of physical activity to significantly reduce liver cancer mortality[80]. Notably, moderate-intensity activities such as brisk walking (> 1 hour/week) show particularly strong associations with HCC risk reduction (HR = 0.50, 95%CI: 0.31-0.78), while vigorous-intensity exercise exhibits less consistent effects[81]. This suggests that accessible forms of physical activity may be particularly beneficial for HCC prevention.

Clinical studies highlight the therapeutic potential of physical activity in HCC management. Among patients receiving lenvatinib plus anti-programmed death-1 therapy, those maintaining regular activity had significantly longer overall survival (HR = 0.22), progression-free survival (HR = 0.16), and higher objective response rates (OR = 4.57) compared to sedentary patients[82]. Exercise interventions also improve various health parameters in HCC patients, including metabolic syndrome, muscle wasting, and quality of life[83]. Recent research indicates that supervised exercise programs are feasible and safe for HCC patients, with multiple studies demonstrating improvements in muscle mass and physical function[84]. These findings suggest that physical activity may serve as both a preventive measure and adjunct therapy for HCC.

The protective effects of physical activity against HCC operate through multiple interconnected biological mechanisms. At the molecular level, exercise activates critical tumor suppressor pathways, including p53-mediated upregulation of p27 to inhibit hepatocyte proliferation, while simultaneously enhancing adenosine monophosphate-activated protein kinase activity and suppressing mammalian target of rapamycin complex 1 signaling to block pro-growth pathways[85]. Regular physical activity also

modulates circadian gene expression to degrade oncoproteins E2F transcription factor 1 and cellular myelocytomatosis oncogene[86], creating an unfavorable environment for tumor development. Beyond direct molecular effects, physical activity improves metabolic health by enhancing insulin sensitivity and mitigating obesity-related metabolic dysfunction, both established risk factors for HCC[87], with animal models demonstrating these benefits can occur independently of weight changes[88]. The immune system represents another key mediator, as exercise reduces transforming growth factor- $\beta$ 1 release and activates dopamine receptor signaling pathways, thereby strengthening anti-tumor immunity and inhibiting HCC progression and metastasis[89]. These multifaceted mechanisms collectively contribute to physical activity's protective role against HCC across different stages of disease development and progression.

## **OTHER LIFESTYLE DETERMINANTS OF HCC**

### *Metabolic disorders*

Obesity represents an independent risk factor, with meta-analyses showing an 89% higher HCC risk in obese individuals compared to normal-weight subjects[90]. Notably, men with a body mass index  $\geq 35$  kg/m<sup>2</sup> face a 4.5-fold increased risk[91], with population-attributable fractions suggesting approximately 15.6% of HCC cases may be linked to overweight/obesity[92]. A nationwide prospective cohort study of 119316 health professionals found that higher dietary inflammatory (empirical dietary inflammatory pattern: HR = 2.03) and hyperinsulinemic patterns (empirical dietary index for hyperinsulinemia: HR = 1.61; empirical dietary index for insulin resistance: HR = 1.62) significantly increased HCC risk, with diabetes and adiposity partially mediating these associations[71]. The growing global prevalence of metabolic syndrome components suggests an increasing burden of metabolic-associated HCC, necessitating targeted interventions addressing insulin resistance, obesity, and associated inflammatory pathways for effective prevention strategies. The pathophysiological mechanisms connecting metabolic disorders to HCC are multifactorial. NAFLD, present in 70%-80% of obese individuals[93], serves as a critical intermediary, with studies confirming that

NAFLD can progress to HCC even without cirrhosis[94]. Adipose tissue dysfunction contributes through altered adipokine secretion (increased leptin, decreased adiponectin) and chronic low-grade inflammation[19]. Leptin promotes angiogenesis and activates oncogenic pathways (c-Jun N-terminal kinase, protein kinase B, ERK) in hepatocytes[95], while insulin resistance drives carcinogenesis through hyperinsulinemia and inflammatory cascades[96,97]. Diabetes mellitus independently doubles HCC risk after adjusting for viral hepatitis and alcohol use[98]. These metabolic disturbances often synergize with other risk factors, obesity potentiates alcohol-related hepatocarcinogenesis[99].

### *Mental and psychological status*

A nationwide United States study of 11609 HCC patients found that 18.6% developed psychiatric diagnoses post-cancer detection, with depression (58.3%) and anxiety (53.0%) being most prevalent[100]. The relationship between psychological status and HCC appears bidirectional. Psychiatric patients demonstrate significantly elevated HCC risk, particularly those with substance-induced disorders[9]. Mendelian randomization studies further support causality, showing psychological distress increases HCC odds (OR = 1.006,  $P = 0.033$ ) while social/leisure activities are protective (OR = 0.994,  $P = 0.035$ )[101]. Conversely, HCC diagnosis often triggers mental health challenges, with structural equation modeling revealing fear of progression mediates between psychological resilience/social support and psychosocial adjustment[102].

Mental health comorbidities significantly impact HCC outcomes. Multivariable analyses have demonstrated that psychiatric diagnoses worsen survival (HR = 1.10, 95%CI: 1.04-1.16), with dose-dependent effects ( $\geq 2$  diagnoses: HR = 1.20, 95%CI: 1.08-1.32)[103]. Tumor-related psychiatric symptoms, particularly depression (49% contribution), substantially reduce health-related quality of life ( $\beta = -5.07$ , 95%CI: -10.01 to -0.13) independently of health behaviors[104]. In addition, nearly 20% of patients discontinue psychiatric medications post-HCC diagnosis[100]. Promisingly, interventions such as reminiscence therapy significantly reduce anxiety and improve

global health status in elderly HCC patients[105]. These findings highlight the critical need for enhanced mental health screening in HCC patients, integrated psycho-oncological care models, and targeted interventions addressing fear of progression and treatment-related distress.

### *Sleep health*

Sleep disorders, particularly short or disrupted sleep, are increasingly recognized as risk factors for chronic diseases, including HCC. Current evidence suggests a bidirectional relationship between sleep disorders and HCC, although direct causal mechanisms remain under investigation. A prospective study of 205 HCC patients post-hepatectomy identified sleep disorders as one of four key tumor-related psychiatric symptoms independently associated with decreased health-related quality of life[104]. Studies indicate that HCC patients frequently experience sleep disturbances, with 89.3% classified as poor sleepers (Pittsburgh sleep quality index > 5), compared to only 30.3% in healthy individuals[106]. Sleep disturbances in HCC are linked to worse clinical outcomes. Patients with poor sleep report higher symptom distress, depression, and reduced quality of life, particularly after treatments like transarterial chemoembolization[107]. The pathophysiological links may involve multiple mechanisms. Sleep deprivation further exacerbates HCC progression by impairing immune surveillance. Chronic sleep deprivation in murine models promotes tumor growth by reducing antitumor CD3+ T and natural killer cells while increasing immunosuppressive CD11b+ cells in the tumor microenvironment[108]. Psychosocial factors also play a role, as fear of cancer progression, which commonly disrupts sleep, was identified as a mediator between psychological resilience and psychosocial adjustment in HCC patients[102].

### **CONCLUSION**

This review highlights the critical role of lifestyle factors in HCC prevention and management as shown in Figure 1. According to current evidence, key dietary strategies

include avoiding aflatoxin exposure, increasing fiber and vegetable intake, and consuming coffee, green tea, and n-3 PUFA-rich fish, while limiting alcohol and processed red meats, as summarized in Table 1. Smoking cessation and regular physical activity may further reduce HCC risk, with exercise also improving treatment outcomes. Metabolic disorders, psychological stress, and poor sleep quality could exacerbate HCC progression, emphasizing the need for holistic interventions. Beyond the lifestyle factors discussed in this review, such as diet, smoking, metabolic health, physical activity, mental status, and sleep, emerging environmental exposures, including particulate matter, polycyclic aromatic hydrocarbons, heavy metals, industrial chemicals, and electromagnetic radiation, may influence HCC development and prognosis. Future studies should evaluate the roles of these emerging environmental exposures, refine lifestyle assessments with quantitative measures, explore diet-treatment interactions, and prioritize randomized controlled trials to establish causality between modifiable lifestyle factors and HCC risk. Additionally, personalized interventions must integrate genetic profiles and socioeconomic influences, particularly how income disparities and healthcare access mediate lifestyle behaviors and hepatocarcinogenesis. We believe that implementing these evidence-based strategies through public health initiatives and clinical practice will significantly reduce the burden of HCC and improve treatment outcomes.

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