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REVIEW

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Environmental exposures and the risk of hepatocellular carcinoma

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Abstract

The global epidemiology of HCC is shifting due to changes in both established and emerging risk factors. This transformation is marked by an emerging prevalence of metabolic dysfunction–associated steatotic liver disease (MASLD) and type 2 diabetes, alongside traditional risks such as viral hepatitis (HBV and HCV), and exposure to chemical agents like aflatoxin, alcohol, tobacco, and air pollution. This review examines how environmental exposures and evolving liver pathology, exacerbated by lifestyle and metabolic conditions, are contributing to the rising worldwide incidence of HCC. Effective prevention strategies must not only address traditional risk factors through vaccination and therapeutic measures but also confront metabolic and socioeconomic disparities through comprehensive public health efforts. As the burden of liver cancer continues to grow, particularly in resource-limited settings, an expansive and inclusive approach is vital for mitigating its impact across diverse populations.

Keywords: aflatoxin, environmental exposure, liver cancer, metabolic dysfunction-associated steatotic liver disease, viral hepatitis

INTRODUCTION

An epidemiologic transition is underway in the etiology of liver cancer, particularly HCC, that impacts future cancer therapeutics, prevention, and control interventions for this often fatal disease. The rising proportion of people across the globe with metabolic syndrome, obesity, diabetes, and metabolic dysfunction–associated steatotic liver disease (MASLD) is accelerating the risk for liver cancer in people exposed to established hepatocarcinogens. The established carcinogens implicated in this context include viruses such as HBV and HCV, individual chemical agents like aflatoxin B1 (AFB1) and alcohol, as well as complex mixtures such as tobacco smoke. Additionally, emerging exposures to other complex mixtures, notably air pollution, may also play a significant

Abbreviations: AFB1, aflatoxin B1; IARC, International Agency for Research on Cancer; MASLD, metabolic dysfunction–associated steatotic liver disease; $PM_{2.5}$, particulate matter.

role in contributing to future cases of HCC. Each of these risk factors varies in their global prevalence, OR for developing HCC, and population attributable fraction both in the United States and globally (Table 1).

Burden of HCC

Liver cancer remains one of the three leading causes of cancer mortality worldwide and about 85% of liver cancer is HCC, thus the diagnosis and management is an important public health problem.[16] Over the past 75 years, the incidence and mortality rates of HCC were greater in low-income and middle-income countries.[17] The rates of HCC, however, rose rapidly in the late 20th and early 21st centuries in many formerly low-rate countries.[18–22] In the United States, individuals with Hispanic ancestry account for the second-highest number of liver cancer deaths.[23–26] In the most recent report on Cancer Health Disparities in the United States, the American Association for Cancer Research outlined that Hispanic persons have twice the rate of liver cancer mortality compared to other ethnic groups.[27] While projections of future numbers of cases have wide confidence intervals, a recent study forecasts that by 2040 the number of liver cancer cases in the world will increase by nearly 55%, based on projections of growth and aging of populations.[28] This increase might also be affected by the increasing numbers of MASLD.

The impact of HCC incidence by sex has been well documented.[16] In many populations, there is a 2- to 5-fold greater prevalence of HCC in men.[29] In contrast, across Central American countries where liver cancer rates are the highest in the Western Hemisphere, the incidence in men and women is almost equivalent.[29,30] Since an increasing proportion of the US population is projected to have either immigrated from or be of, Central American ancestry, identifying their unique risk factors is crucial for early detection and prevention strategies, benefiting these high-risk communities and the US health care system.

This review examines the established and emerging environmental risk factors for HCC, with a focus on agents classified as group 1 human carcinogens by the International Agency for Research on Cancer (IARC). We define environmental exposures broadly to encompass all nongenetic factors that contribute to hepatocarcinogenesis. These include well-documented chemical carcinogens such as aflatoxins, alcohol, and tobacco constituents, as well as physical agents like particulate matter and air pollution. Additionally, we consider biological factors such as HBV, HCV, and metabolic conditions, including diabetes and MASLD, which, while not traditionally viewed as environmental, are significantly influenced by exogenous factors and lifestyle choices (Figure 1). We explore how established and emerging environmental factors interact with changing liver pathology, potentially increasing the overall risk of disease.

AFLATOXIN

Discovery and relation to liver cancer

Aflatoxins, mycotoxins produced by fungi of the *Aspergillus* species, contaminate a variety of human foodstuffs, most notably, maize, ground nuts, and tree nuts.[31] Although most extensively investigated in Africa and Asia, AFB_1 contamination occurs in many locations around the world, especially in regions with warm, humid environments such as Central America.[32] Animal studies first demonstrated AFB1's hepatotoxicity and lethality at high doses. Human research lagged due to insufficient data on aflatoxin metabolism and susceptibility factors. The heterogeneous nature of food contamination made dietary assessments inadequate for establishing an AFB1-HCC link. However, the development of aflatoxin-specific biomarkers eventually enabled studies to provide convincing evidence of this association.[32] Using AFB_1 biomarkers, 2 cohort studies examined urinary levels of AFB_1 and serum levels of

TABLE 1 Risk factors with epidemiologic metrics

Risk Factors	Prevalence (%)	OR of HCC	PAF in United States (%)[1]	PAF globally (%)[2]
HBV	3.3[3]	23[4]	4.3-6.3	44
HCV	0.7[3]	17[4]	20.5-35.4	21
Aflatoxin	55[5]	5.5[6]	—	4.6-28.2
Air pollution	99[7]	—	—	—
Alcohol consumption	17[8]	3-10[9]	13.4-26	26
Tobacco use	22.3[10]	1.39-1.9[11]	9	13
MASLD	25.2-29.8[12]	3.63[13]	42.1[a]	16[a]
Type II Diabetes Mellitus	10.5[14]	1.53[15]		

Note: Denotes lack of sufficient data.
[a]PAF for MASLD and type II diabetes mellitus merged based on overlapping data in metabolic factors data.
Abbreviations: MASLD, metabolic associated steatotic liver disease; PAF, population attributable fraction.

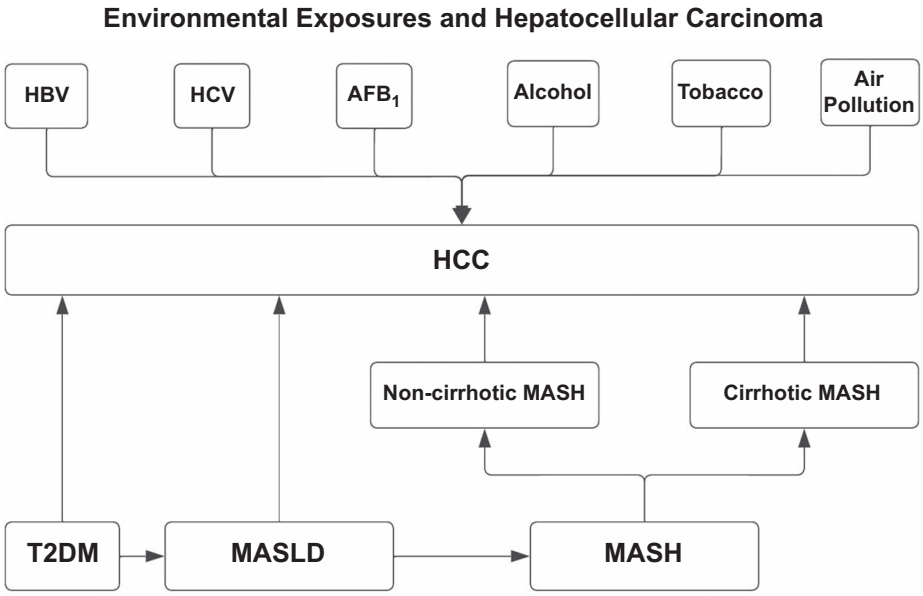

FIGURE 1 Integrated model of major risk factors for liver cancer. Abbreviations: AFB1, aflatoxin; MASLD, metabolic dysfunction–associated steatotic liver disease; MASH, metabolic dysfunction–associated steatohepatitis; T2DM, type 2 diabetes mellitus.

HBV among a cohort of men in Shanghai, China. The study found that the risk of liver cancer was 3.4-fold higher among the men who tested positive for AFB_1, 7-fold higher among the men who tested positive for HBV, and 59-fold higher among the men who tested positive for both AFB_1 and HBV.[33] Several years later, a subsequent cohort study from Taiwan confirmed the results.[34] As was demonstrated by the studies in China and Taiwan, AFB_1 is particularly carcinogenic when it co-occurs with chronic HBV infection, as the combination of the 2 factors has a synergistic effect on HCC risk.[33,34] Based on the evidence presented by biomarker-based studies, an IARC expert working group concluded that there was sufficient evidence to classify aflatoxin as a group 1 human carcinogen.[35] A 2012 meta-analysis estimated that AFB_1 alone increased HCC risk by 6-fold, HBV alone by 11-fold, and the 2 factors together by 54-fold.[36]

Studies of HCC tumors identified a specific AFB_1 exposure marker: a characteristic mutation in codon 249 of the *TP53* tumor suppressor gene. High frequencies of the signature *TP53* guanine to thymine transversion in codon 249 were observed in tumors from aflatoxin-exposed populations, but absent in HCCs from areas with little aflatoxin exposure.[37] Notably, African immigrants to France show a decreasing likelihood of displaying the AFB1 signature in their tumors the longer they reside in France.[38] Experimental models further confirm this link, demonstrating consistent mutational signature in liver tumors with aflatoxin exposure.[39] In addition, whole genome sequencing of human HCC has identified a mutational signature of aflatoxin that correlates with the duration of time since AFB_1 exposure.[39]

Beyond numerous studies linking AFB1 exposure to an increased risk of HCC, a natural experiment in the 1980s demonstrated that removing AFB1 from the environment reduces this risk. When the government facilitated a dietary switch from maize to rice in high-HCC regions, daily aflatoxin exposure decreased by nearly 4000% by 2012.[40] This led to a 50% reduction in HCC mortality, occurring before HBV vaccination could influence rates. The dietary change accounted for an estimated 65% of the reduced liver cancer mortality, with 83% of this benefit conferred on HBV-infected individuals.[41] Globally, the AFB1 population attributable fraction for HCC is estimated at 17%, ranging from 8% in HBV-absent populations to 21% in HBV-present populations.[36]

Climate change is expected to expand AFB1's impact. Warmer, more humid conditions favorable for AFB1 contamination are increasing globally, potentially raising its population attributable fraction. In previously low-risk regions like Central America, extreme weather events, increased rainfall, and higher temperatures are likely to promote mold growth and crop contamination.[42] It is well documented that extreme weather events can lead to plant-related stress that increases the probability of mold growth on maize and peanuts. As mold spores are ubiquitous in soil, weather events that lead to a breakdown of the normal physical barriers in plants may increase aflatoxin contamination. A Texas study (2004–2014) showed significant increases in aflatoxin detection rates and median aflatoxin-albumin adduct biomarker levels over time. As maize cultivation expands into traditionally colder climates, aflatoxin contamination risks may spread geographically.[43] Moreover, rising temperatures favor cyanobacterial blooms, potentially

increasing exposure to liver-damaging cyanotoxins. Recent research confirms increased cyanotoxin prevalence due to climate-driven changes, aligning with studies linking environmental toxin exposures to higher liver disease risks. These findings underscore the need for integrated monitoring and response strategies to address these emerging health risks in Central America and beyond.

AIR POLLUTION

While air pollution is well-established as a risk factor for lung cancer, growing evidence suggests associations with other cancers, including liver cancer. The Effects of Low Level of Air Pollution: A Study in Europe collaboration, encompassing 6 European cohorts, has identified links between long-term exposure to air pollutants and increased liver cancer risk.[44] Notably, this risk persists even at levels below current European Union air quality standards for nitrogen dioxide and fine particulate matter ($PM_{2.5}$).[44]

The Effects of Low Level of Air Pollution: A Study in Europe study revealed statistically significant hazard ratios for various $PM_{2.5}$ elemental components, with sulfur and vanadium showing the strongest correlations.[44] In the United States, an ecological study demonstrated increased HCC incidence with rising ambient PM2.5 levels, though it lacked control for individual-level risk factors.[45] A prospective cohort study in Taiwan further corroborated these findings, showing that higher residential ambient PM2.5 levels were associated with increased HCC risk (HR 1.22, 95% CI: 1.02–1.47).[46]

The mechanistic role of these pollutants appears to be mediated via inflammation and fibrosis.[47] This inflammatory pathway may explain the carcinogenic potential of air pollutants in liver tissue. However, the complex nature of environmental exposures and potential confounding factors necessitate further well-designed prospective studies to definitively establish air pollutants as hepatocarcinogens.

Recent research has also begun to explore the potential synergistic effects of air pollution with other known liver cancer risk factors, such as HBV and MASLD.[46,48,49] These interactions could amplify the carcinogenic impact of air pollutants on liver tissue. Additionally, emerging evidence suggests that certain populations may be more susceptible to the hepatotoxic effects of air pollution, including those with pre-existing liver conditions or genetic predispositions. With increasing urbanization and climate change impacting air quality, understanding the air pollution-liver cancer relationship is crucial. Future research must focus on specific pollutant mixtures and interventions for high-risk populations to address this emerging public health concern.

ALCOHOL CONSUMPTION

Excessive consumption of alcohol (ie, >45 or 50 g/d) increases the risk of liver cancer, with women showing a higher OR (3.89) than men (1.59).[50] While women show higher individual risk, likely due to differences in alcohol metabolism, body composition, and hormonal factors; men face greater overall attributable risk due to their higher prevalence of alcohol consumption.[51] A 2016 US study reported that 17% of HCCs among men were alcohol-associated, while only 6.2% of HCC among women were alcohol-associated.[1] On the global scale, it has been estimated that 17% of liver cancer is related to alcohol, with a greater percentage among men (22.7%) than women (5.0%).[51]

The exact mechanism or mechanisms linking alcohol consumption to liver cancer are complex and multifaceted, although alcohol is metabolized to acetaldehyde, which is an established group 1 carcinogen that can directly damage DNA and proteins.[52] In addition to the role that acetaldehyde may play, chronic alcohol consumption may (1) increase pro-oxidant states leading to oxidative stress and cellular damage, (2) alter the gut microbiome, resulting in deleterious consequences to the liver, (3) impair immune function, reducing the physiological response to detect and eliminate precancerous cells, and (4) induce chronic inflammation and fibrosis, leading to procarcinogenic environment in the liver.[53–57]

The impact of alcohol reduction or cessation on liver cancer risk remains understudied, with limited longitudinal data available.[58] Current evidence suggests that alcohol abstinence may reduce HCC risk, particularly in patients with early-stage alcohol-associated liver disease. A retrospective study by Ganne-Carrié et al[59] found that alcohol abstinence was associated with a decreased HCC incidence in patients with alcohol-associated cirrhosis (HR 0.58, 95% CI: 0.38–0.88). However, the risk reduction magnitude and time frame vary depending on factors such as the degree of pre-existing liver fibrosis, duration of heavy alcohol use, and potential genetic predispositions. For instance, Marot et al[60] observed that the beneficial effects of abstinence on HCC risk were most pronounced in patients who had abstained for more than 1.5 years. Future prospective studies are needed to elucidate the molecular mechanisms underlying potential risk reduction, identify relevant biomarkers for monitoring, and establish evidence-based guidelines for alcohol cessation in HCC prevention strategies.

TOBACCO

Tobacco smoking is estimated to increase the risk of liver cancer with an estimated 70% higher risk among smokers compared to nonsmokes.[61] Globally, 13% of

liver cancers are related to smoking.[2] Several mechanisms are hypothesized to explain the liver cancer-smoking association.[62] The liver metabolizes a number of tobacco constituents, including 4-aminobiphenyl and polycyclic aromatic hydrocarbons, which are converted into reactive species. Other tobacco constituents, such as nitrosamines and benzene, undergo hepatic activation to procarcinogens by *CYP2E1*. In addition, tobacco exposure has been associated with immunosuppression and telomere shortening and can lead to the production of proinflammatory cytokines, such as IL-33, IL-1β, and TNFα. Mutational signature studies of liver cancer tumors have also noted the presence of signatures that could be related to tobacco smoking.[38]

The impact of smoking cessation on liver cancer risk has been investigated, with encouraging results. A US study reported an inverse association between the duration of smoking cessation and HCC risk. Individuals who ceased smoking for more than 30 years exhibited an HCC risk similar to that of never-smokers.[63] This suggests a potential reversibility of smoking-induced liver cancer risk, though the time frame for risk reduction may be prolonged.

Future research priorities include identifying the molecular mechanisms of tobacco-induced hepatocarcinogenesis, quantifying synergistic effects between smoking and viral hepatitis or alcohol consumption, and even assessing the hepatotoxic potential of e-cigarettes. Longitudinal studies are needed to determine the optimal duration of smoking cessation for significant HCC risk reduction. Additionally, investigating genetic susceptibility factors may help stratify smokers for targeted HCC prevention strategies.

OCCUPATIONAL CARCINOGENIC HAZARDS TO HUMANS

IARC has convened expert panels to evaluate carcinogenic risk to humans for more than 50 years, and many of these monographs summarize available epidemiologic data linking specific exposures to liver cancer (http://monographs.iarc.fr). While the preceding sections in this review summarize the dominant risk factors for human liver cancer, the following provides specific cases identified through epidemiologic and occupational studies. These include vinyl chloride as a risk factor for hepatic angiosarcoma, various pesticides, and a number of radioactive substances. Collectively, these represent at the present time a small fraction of the risk factors that contribute to liver cancer diagnosis. With the development of better biomarkers and higher throughput analytic methodologies, new causal associations will be characterized over the next decade.

Vinyl chloride Vinyl chloride exposure in occupational settings has been associated with angiosarcomas of the liver.[64–66] Further, studies have reported a multiplicative interaction between vinyl chloride exposure in the workplace and alcohol consumption in the enhancement of HCC.[67] Finally, a synergistic interaction between vinyl chloride workplace exposure and HBV status has been reported in a cohort in Taiwan.[68]

Arsenic: Chronic arsenic exposure, primarily through contaminated drinking water, has been established as a risk factor for HCC development through epidemiological studies in endemic regions. Studies from Taiwan and Bangladesh have demonstrated dose-dependent relationships between arsenic exposure and liver cancer mortality, with significantly increased risks observed at concentrations exceeding 50 μg/L in drinking water.[69,70] Mechanistically, arsenic promotes hepatocarcinogenesis through oxidative stress, DNA damage, and epigenetic modifications, with enhanced risk observed in populations with concurrent HBV infection or heavy alcohol consumption. Recent prospective studies have further elucidated synergistic interactions between arsenic exposure and other environmental toxicants in HCC development.

Pesticide exposures: A number of epidemiologic studies, particularly among agricultural workers and other occupational settings, have reported associations between liver cancer and DDT and it's most persistent metabolite, dichlorodiphenyldichloroethylene. All 3 studies found significant associations with either DDT or dichlorodiphenyldichloroethylene, suggesting that other organochlorine pesticides might have similar effects.[71]

EXPOSURES TO RADIOACTIVE SUBSTANCES: PLUTONIUM, THORIUM-232, AND THOROTRAST

There have been a number of reports of both occupational and iatrogenic exposures to specific forms of radiation-causing liver cancers. This has been observed among workers exposed to alpha emitters such as plutonium.[72] In these circumstances, the ongoing exposure assessments required for these workers helped to define the dose of radiation, and ongoing health assessments facilitated disease diagnoses. Similar to this exposure and dose situation, the alpha-emitter Thorium-232 that historically was incorporated into an imaging product for the liver was subsequently shown to induce HCC in experimental models and in patients.[73,74] These studies illustrate that high-quality exposure and health assessment can identify these etiologies, and in turn, this accelerates preventive interventions.

HEPATITIS B VIRUS

Chronic infection with HBV is associated with more than half (56%) of the HCCs in the world, making it the

dominant risk factor.[75] The lifetime risk of developing HCC among persons with chronic HBV infections varies between 10% and 25%,[21] depending on characteristics of the virus, other concomitant viral infections, demographic characteristics, and the presence of other HCC risk factors, such as aflatoxin B_1.[76]

Approximately 300 million individuals are chronically infected with HBV, with the highest infection rates (>8%) in sub-Saharan Africa and the Western Pacific. Early-life transmission is a key factor in developing chronic infections, particularly in high-prevalence regions. HBV vaccination, available since 1981, offers primary prevention. Taiwan's pioneering neonatal HBV vaccination program, implemented in 1984, demonstrated a decline in HCC incidence in vaccinated cohorts after 2 decades. As of 2022, 190 WHO member states have introduced neonatal HBV vaccination, although complete coverage remains a challenge in some countries. For individuals with established chronic HBV infections, antiviral treatment reduces risk of HCC, although long-term therapy must be maintained.[77–79]

HEPATITIS C VIRUS

Chronic infection with HCV is associated with 20% of HCCs in the world.[75] In the majority (90%) of cases, HCV-associated HCC is preceded by cirrhosis, with the annual incidence of HCC ranging from 0.5% to 10%.[19] As cirrhosis is almost invariably present in HCV-associated HCC, hepatocarcinogenesis is likely the result of repetitive damage, which results in regeneration, fibrosis, and cirrhosis.[80,81] There is no HCV vaccine at the current time, but curative therapy exists. Direct-acting antiviral therapy, first introduced in 2014, effectively eradicates the virus. HCC risk is reduced by 50-80% among persons who achieve a sustained virologic response.[82] However, it's important to note that HCC risk persists even after viral clearance, particularly in patients with advanced fibrosis or cirrhosis. In the majority (90%) of cases, HCV-associated HCC is preceded by cirrhosis, with the annual incidence of HCC ranging from 1% to 7%, emphasizing the need for continued surveillance in high-risk individuals even after successful HCV treatment.[19]

TYPE 2 DIABETES

Approximately 7% of liver cancers in the world have been linked to diabetes, which is associated with a 2 to 3-fold increased risk of HCC.[2] The risk is significantly greater among men than women and among persons with long-standing and poorly controlled diseases.[83] The association between type 2 diabetes and HCC may be due to various mechanisms, many of which are related to insulin resistance and activation of the insulin receptor and IGF 1 pathways.[2] Chronic hyperinsulinemia in type 2 diabetes promotes hepatic lipogenesis and inflammation, creating a procarcinogenic environment. Additionally, diabetes-associated oxidative stress and advanced glycation end products contribute to DNA damage and genomic instability in hepatocytes. Recent studies suggest that metformin, a common diabetes medication, may have a protective effect against HCC development, potentially through its anti-inflammatory and antiproliferative properties.[84,85]

METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE

MASLD, thought to be the hepatic manifestation of metabolic syndrome, is the most rapidly rising risk factor for HCC in the world. MASLD is defined as hepatic steatosis in the presence of other cardiometabolic risk factors or without discernible secondary causes.[86,87] The global prevalence of MASLD is approximately 30%, with the highest prevalence in the world estimated to be in Latin America.[12,88,89] HCC risk is significantly higher in persons with MASLD who also have diabetes, obesity, dyslipidemia, and hypertension.[90] Diabetes doubles the risk of HCC, and when associated with MASLD, it increases HCC risk nearly fivefold.[91] The prevalence of MASLD in persons with type 2 diabetes mellitus is estimated to be 55%–68%, with 37% having metabolic dysfunction–associated steatohepatitis, with 17% demonstrating fibrosis.[92]

Obesity also significantly impacts HCC risk in patients with MASLD. Body mass index >30 tracks with a 2-fold increase in HCC risk, and body mass index >35 is correlated with a fourfold increase in HCC risk.[12,91] In the United States, MASLD-related HCC accounts for 19.2%–35.6% of HCC cases in Medicare patients.[91,93] Importantly, MASLD-related HCC was associated with the lowest rates of surveillance when compared to other major etiologies of HCC.[93]

While MASLD and obesity are strongly associated, "lean" MASLD also occurs in 7%–12% of normal-weight individuals in the United States.[94,95] In a recent study by Gobali et al,[95] lean MASLD was associated with higher rates of diabetes and insulin resistance, hypertension, and cardiovascular events when compared to lean individuals without MASLD. Interestingly, patients with cirrhosis with lean MASLD and obesity-related MASLD have similar HCC rates, approximately 20%.[94,95] The annual incidence of HCC among persons with metabolic dysfunction–associated steatohepatitis cirrhosis ranges from 0.5% to 2.6%.[12] The rising prevalence of MASLD, particularly in urban environments, underscores the urgent need for effective prevention, screening, and treatment strategies, especially for high-risk groups such as individuals with diabetes.

CONCLUSION AND PERSPECTIVES FOR FUTURE

The landscape of HCC risk factors is shifting globally. While viral hepatitis prevalence is decreasing, MASLD is emerging as a dominant driver of HCC. Traditional factors like alcohol and aflatoxins remain significant, while air pollution and climate change-induced mycotoxin spread present new challenges. These evolving risk factors intersect with broader societal issues, particularly socioeconomic disparities, creating a complex web of HCC determinants. This disparity underscores the need for targeted interventions in vulnerable populations, as addressing socioeconomic factors is crucial for comprehensive HCC prevention.

Key priorities for prevention should include beyond expanding HBV vaccination and HCV treatment access to implementing effective MASLD screening programs and addressing lifestyle and metabolic factors. For air pollution, prevention strategies should focus on policy-level interventions, such as enforcing stricter emissions standards, promoting clean energy technologies, and improving urban planning to reduce exposure. Individual-level measures like using air purifiers and limiting outdoor activities during high pollution days can also help mitigate risk. Aflatoxin prevention requires a multifaceted approach. Implementing better agricultural practices, such as proper crop rotation and storage techniques, can reduce contamination. Biocontrol methods, like introducing nontoxigenic fungal strains, have shown promise in reducing aflatoxin levels. Additionally, improving food safety regulations and increasing public awareness about proper food storage and handling can further reduce exposure. Table 2 summarizes various categories to effectively mitigate the risk factors that may guide the next steps (Table 2).

TABLE 2 Comprehensive strategies for reducing HCC environmental and lifestyle risk factors

Risk factor	Solution	Details
Aflatoxin	Agriculture	Control crop drying/storage, use biocontrol agents
	Diet	Promote dietary diversity, educate about moldy food risks
	Regulation	Enforce aflatoxin limits, adopt aflatoxin-resistant crops
Air pollution	Emissions	Enforce stricter industrial and vehicle emission controls, promote clean energy technologist including electric vehicles (EVs)
	Urban planning	Increase green spaces, enforce zoning laws
	Health	Monitor air quality, educate on exposure reduction
Alcohol	Policy	Implement minimum unit pricing, restrict availability and advertising
	Health care	Screen for alcohol use disorders, provide interventions and referrals
	Education	Raise awareness about safe drinking limits and risks
Tobacco	Cessation	Offer counseling, nicotine replacement therapy (NRT), pharmacotherapy
	Policy	Increase taxes, enact smoke-free laws, restrict advertising
Occupational exposure to carcinogenic	Enhanced protective equipment	Use advanced personal protective equipment (PPE), such as respirators and full-body suits, minimizes exposure to radioactive substances and hazardous chemicals
	Engineering controls	Implement changes to the workplace, such as installing adequate ventilation systems, containment structures, and shielding barriers, effectively reduces airborne exposure and contamination risks
Type 2 diabetes	Prevention	Promote healthy diet and physical activity, workplace wellness programs
	Screening	Conduct regular screenings in high-risk populations for early intervention
	Management	Improve access to care, encourage medication adherence and lifestyle changes
MASLD	Diet	Promote Mediterranean diet, reduce processed foods and sugary drinks
	Exercise	Promote physical activity, improve access to fitness and safe outdoor spaces
	Screening	Develop improved screening protocols specific to MASLD and obese patients
	Treatment	Improve access to weight loss interventions, including behavioral therapy and bariatric surgery
Viral hepatitis	HBV	Expand HBV vaccination, screen and treat chronic infections
	HCV	Implement widespread HCV screening, improve access to direct-acting antiviral treatments, provide clean needle access
	Education	Raise awareness about transmission and prevention

Abbreviations: EVs, electric vehicles; MASLD, metabolic dysfunction–associated steatotic liver disease; NRT, nicotine replacement therapy; PPE, personal protective equipment.

Implementing these comprehensive prevention programs presents significant challenges, particularly in resource-limited countries where the burden of HCC is projected to increase. Reducing the global impact of HCC necessitates a coordinated international effort, with high-income countries collaborating closely with lower-income nations to address both environmental risk factors and socioeconomic disparities. By focusing on these diverse risk factors through targeted, evidence-based interventions, the global health community can strive to substantially reduce HCC incidence in the coming decades. While the task ics formidable, the potential to save lives and reduce the societal burden of HCC makes these efforts imperative.

CONFLICTS OF INTEREST

The authors have no conflicts to report.

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