Review paper

Update in global trends and aetiology of hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver responsible for an increasing number of cancer-related deaths, especially in developing economies of Asia and Africa. A plethora of risk factors have been described in the literature. Some of the important ones include chronic viral hepatitis, liver cirrhosis, environmental toxins such as aflatoxin, non-alcoholic fatty liver disease, lifestyle factors like alcohol consumption, smoking, and dietary factors, metabolic diseases like diabetes mellitus and obesity, and genetic and hereditary disorders. The development of HCC is complex involving sustained inflammatory damage leading to hepatocyte necrosis, regeneration, and fibrotic deposition. It also poses multiple challenges in diagnosis and treatment despite advances in diagnostic, surgical, and other therapeutic advancements. This is a narrative review of findings of multiple studies that were retrieved from electronic databases like PubMed, MEDLINE, Embase, Google Scholar, Scopus, and Cochrane. We summarise the current knowledge regarding the epidemiology and various risk factors for the development of HCC with a brief note on various prevention strategies.

Key words: epidemiology, aetiology, hepatocellular carcinoma, HCC, risk factors, hepatitis C, HBV, incidence, prevalance, mortality.

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Introduction

Hepatocellular carcinoma (HCC) is considered to be the most common primary cancer of the liver. HCC represents the fastest rising cause of cancer-related death in the US and remains difficult to manage [1]. It accounts for 75–85% of primary liver cancers and is the second leading cause of cancer death in East Asia and sub-Saharan Africa and the sixth most common in western countries [1, 2]. The incidence of HCC will continue to escalate as hepatitis C reaches its maturity and as non-alcoholic steatohepatitis (NASH) and obesity become more prevalent in the United States, and the Centre for Disease Control (CDC) has proposed a series of screening recommendations based on risk exposures [3]. The development of HCC is complex, involving sustained inflammatory damage leading to hepatocyte necrosis, regeneration, and fibrotic deposition [4]. This review summarises current knowledge regarding the epidemiology and various risk factors for the development of HCC, with a brief note on various prevention strategies.

Epidemiology

Incidence

The worldwide incidence of HCC is heterogeneous because of the variable prevalence of risk factors. According to Cancer Today, an international agency for research and cancer, 80% of HCC cases occur in sub-Saharan Africa and eastern Asia (Fig. 1), and the major risk factors here are hepatitis B and aflatoxin exposure, whereas hepatitis C is the primary risk factor in the USA, Europe, and Japan [5, 6]. The incidence of HCC in the US has tripled over the last four decades. The burden of HCC in 2012 was 14 million and is expected to rise to 22 million in the next two decades [7]. HCC occurs more often in males than in females, in the ratio of 2.4 : 1. HCC has an average five-year survival of < 15% [8]. The age-adjusted incidence of liver cancer has risen from 1.6 per 100,000 individuals to 4.6 per 100,000 individuals among Native Americans and Alaskan Natives followed by Blacks, Whites, and Hispanics [9]. Liver cancer is predicted to be the sixth most commonly diagnosed cancer and the fourth leading cause of cancer death worldwide in 2018. When compared to other cancers, a total of 841,000 (4.7%) new liver cancers are estimated to have occurred in 2018 in addition to 782,000 (8.2%) deaths [1].

Estimated age-standardised incidence rates (ASIR) per 100,000 people for liver cancer in 2018 were highest in Eastern Asia (17.7) and Micronesia (15.2), followed by other regions in Northern Africa (14.1) and South Eastern Asia (13.3). The lowest rates were observed in South Central Asia (2.5), followed by Central and Eastern Europe and Western Asia (equally about 4.0) [5]. Mongolia has the highest ASIR (93.7), followed by Egypt (32.2), The Gambia (23.9) and Vietnam (23.2). Morocco and Nepal (equally about 1.1) have the lowest ASIR [5].

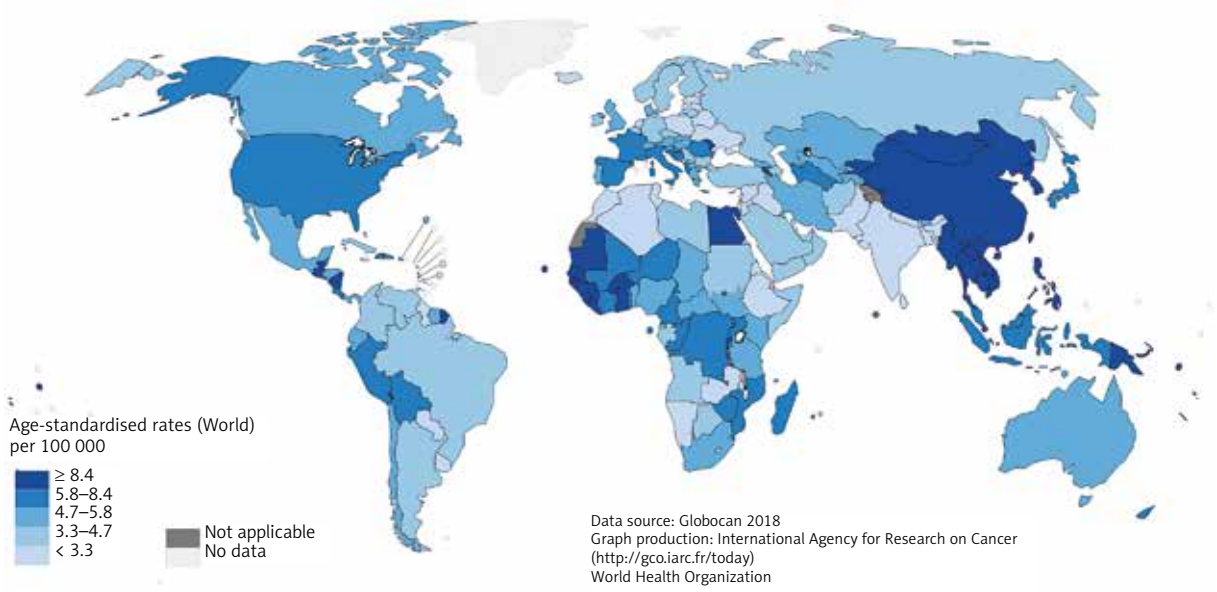
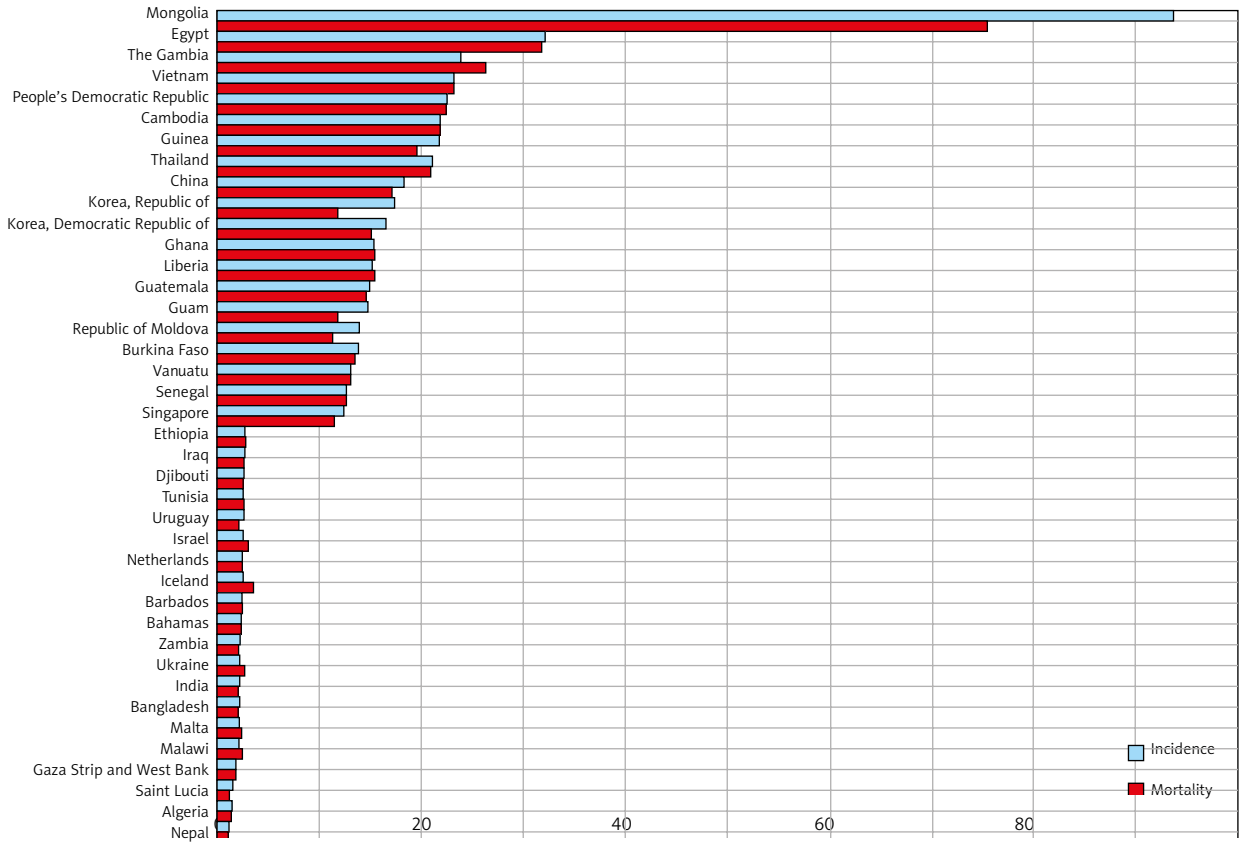
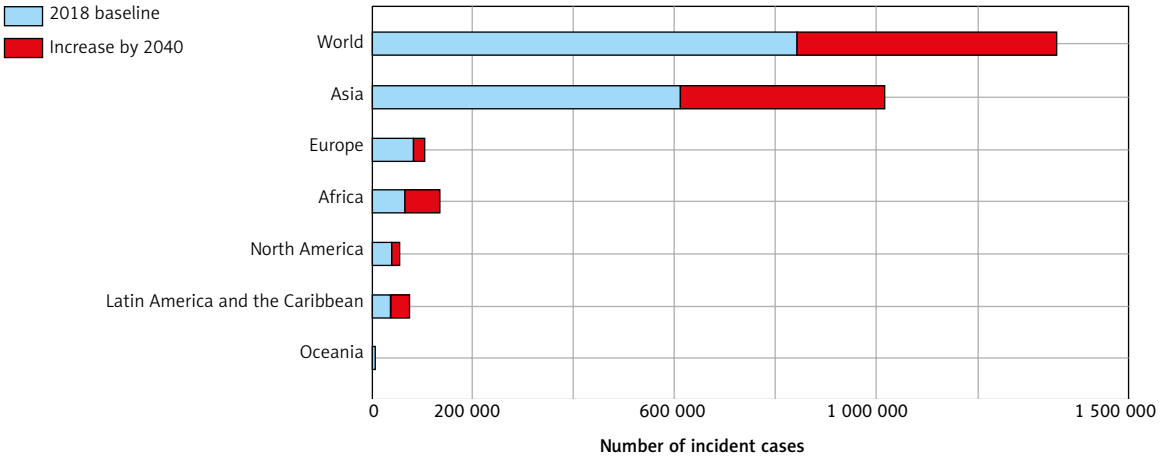


Fig. 1. Estimated age-standardised rates of incident cases, both sexes, liver cancer, worldwide in 2018



Data source: Globocan 2018
Graph production: Global Cancer Observatory (http://gco.iarc.fr)
World Health Organization

Fig. 2. Estimated age-standardised incidence and mortality rates (World) in 2018, liver, both sexes, all ages



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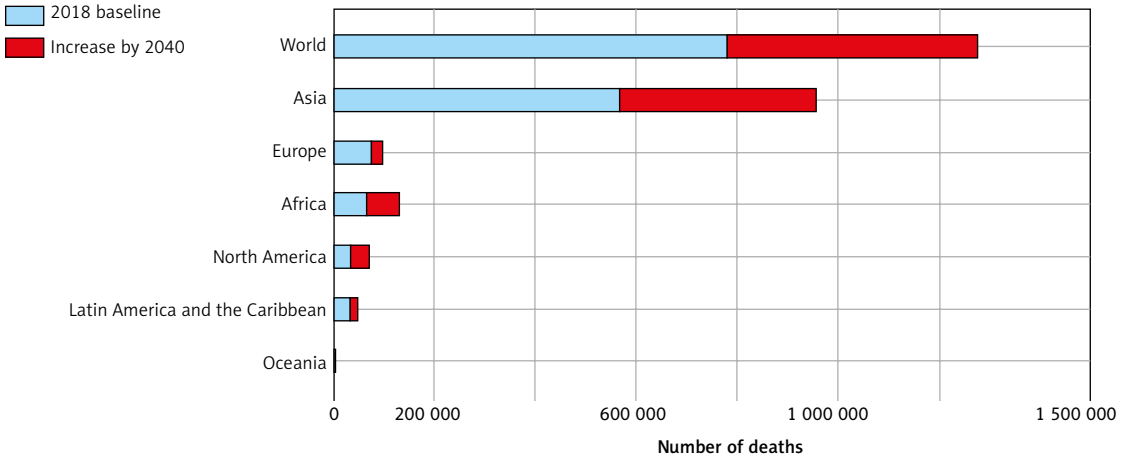

Data source: Globocan 2018
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Fig. 3. Estimated number of incident cases and deaths from 2018 to 2040, liver, both sexes, all ages

Mortality

Age-standardised mortality rates (ASMR) from liver cancer in 2018 in both genders were highest in Eastern Asia (16.0) and Northern Africa (13.9) followed by South Eastern Asia (13.2) and Micronesia (12.0). The lowest ASMR was observed in South Central Asia (2.3), followed by Central, Northern, and Eastern Europe and Western Asia (around 3.8–4.0). ASMR was highest in Mongolia and Egypt and lowest in Morocco and Nepal [5]. Figure 2 depicts the estimated age-standardized incidence and mortality rates (World) in 2018, liver, both sexes, all ages.

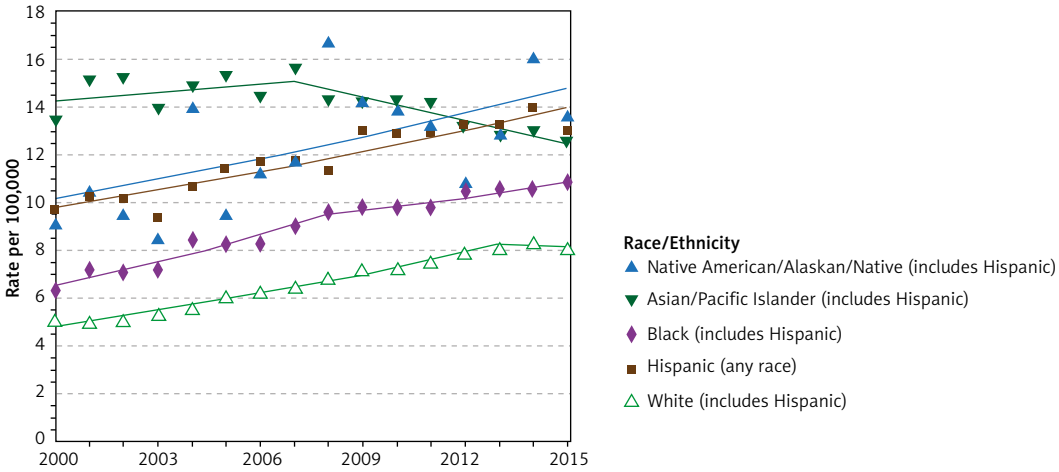
Trends

The number of incident cases of liver cancer in both sexes and all age groups is estimated to increase from 841,080 in 2018 to 1,361,836 in 2040 (an overall change of +61.9%) [10]. Estimated number of deaths from liver cancer in both sexes and all age groups is estimated to increase from 781,631 in 2018 to 1,284,252 in 2040 (an overall change of +64.3%) [10]. Figure 3 shows the estimated number of incident cases and deaths from 2018 to 2040. Figure 4 shows the time trend of rise in liver and intrahepatic bile duct cancer by race and ethnicity across all age groups and both sexes, as published by the National Cancer Institute through the Surveillance, Epidemiology, and End Results (SEER) program [11].

Risk factors

Hepatitis B

Hepatitis B virus (HBV) is an enveloped DNA virus belonging to the *Hepadnaviridae* family [12]. A strong association between HBV and HCC was described by Beasley *et al.* in their landmark study in Taiwan with 22,707 men [13]. It was also seen that the relative risk for HCC in this



SEER 18 areas [http://seer.cancer.gov/registries/terms.html] (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana, New Jersey and Georgia excluding ATL/RG).
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups – Census P25-1130).
The Annual Percent Change (APC) estimates were calculated from the underlying rates using the Joinpoint Trend Analysis Software [http://surveillance.cancer.gov/joinpoint], Version 4.6, February 2018, National Cancer Institute.
The APC's direction is "rising" when the entire 95% confidence interval (C.I.) is above 0, "falling" when the entire 95% C.I. is lower than 0, otherwise, the trend is considered stable.
Rates for American Indians/Alaska Natives only include cases that are in a Contract Health Service Delivery Area (CHSDA). See SEER Race Recode Documentation for American Indian/Alaskan Native Statistics [http://seer.cancer.gov/seerstat/variables/seer/race_ ethnicityfitai-an].
Hispanics and Non-Hispanics are not mutually exclusive from Whites, Blacks, Asian/Pacific Islanders, and Native American /Alaska Natives. Incidence data for Hispanics and Non-Hispanics are based on the NAACCR Hispanic Latino Identification Algorithm (NHIA) and exclude cases from the Alaska Native Registry. See SEER Race Recode Documentation for Spanish-Hispanic-Latino Ethnicity [http://seer.cancer.gov/seerstat/variables/seer/race_ethnicityllthispanic].
Cancer sites are defined using the SEER Site Recode ICD-O-3/WHO 2008 Definition [https://seer.cancer.gov/siterecode/icdo3_ dwhoheme/index.html].
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Fig. 4. Recent trends in incidence rates (2000–2015) of liver and intrahepatic bile duct cancer by race and ethnicity in both sexes and all ages

population was 63, compared to uninfected controls. Also, Franceschi *et al.* also reported a 30-fold increased risk of HCC in chronic HBV carriers [14]. A systematic review estimated the incidence rates of HCC in subjects with chronic HBV infection in East Asian countries to be 0.2 per 100 person-years in inactive carriers (HBsAg-positive but with normal levels of ALT), and 3.7 person-years for those with compensated cirrhosis [15].

A recent meta-analysis revealed the global prevalence of Hepatitis B surface Antigen (HBsAg) positivity to be 3.61%. There are over 248 million people currently living with chronic HBV carriers [16]. Africa has the highest endemicity, with an HBsAg prevalence of 8.83%. However, the country with the largest number of people living with chronic HBV is China, at 95 million people, with an HBsAg prevalence of 5.49%. India and Nigeria have the second and third highest populations of HBsAg-positive individuals, respectively, at 17 and 15 million people. The CDC in the year 2015 reported that 850,000 individuals are living with HBV [17], although other studies report it to be 2.2 million [18]. The HBV X protein (HBx), a 154 amino acid polypeptide, plays a critical role in the development of HCC. HBx regulates cellular transcription, protein degradation, cellular proliferation, and apoptosis. HBx activation of Wnt/β-catenin (transcription coactivator) may directly promote the transformation of hepatocytes into cancer-initiating cells [19]. The Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) study carried out in Taiwan revealed that elevated serum HBV DNA level (≥ 10,000 copies/ml) is a strong risk predictor of HCC [20]. A study by Papatheodoridis *et al.* in a European, 10-centre cohort concluded that HCC risk decreases beyond year five of entecavir/tenofovir therapy in Caucasian chronic hepatitis B patients, particularly in those with compensated cirrhosis [21]. The incidence of HBV infection and subsequent development of HCC has significantly decreased due to the development of the HBV vaccine [22].

Hepatitis C

Hepatitis C virus is a single-stranded, RNA virus belonging to the Hepacivirus genus, with seven major genotypes. An estimated 143 billion people are infected with the HCV as of 2015 [23]. It is estimated that around 1.9 million individuals are viraemic in the United States. Despite the availability of efficacious antiviral agents, the cost and high frequency of unrecognised cases hamper control of virus [24]. With 3–4 million new cases each year, the burden will be high even in the next decade, even in developed countries [25]. HCV-induced progressive liver cirrhosis is a well-established risk factor for HCC, hence attaining sustained viral response (SVR) with therapy is essential. It is also important to note that SVR does not necessarily mean the elimination of HCC risk despite the substantially decreased incidence. In fact, HCC can occur more than 10 years after successful HCV clearance, with an annual incidence of 1% [26]. Older age, alcohol abuse, accompanying metabolic disorders (especially diabetes), and persisting liver inflammation (elevated aminotransferase and serum α-fetoprotein levels) pre- and post-SVR have been

implicated as risk indicators for post SVR HCC [26]. Interferon-based therapy had been the mainstay, yielding SVR in 50% of patients, which has been mostly replaced by the recently developed direct antiviral agents (DAAs) targeting the non-structural viral proteins (NS 3–5), yielding an SVR of greater than 90% [27]. In patients treated with DAA, SVR was associated with a considerable reduction in the risk of HCC [28]. However, there is some controversy regarding this because some studies have shown that patients with prior HCC treated with DAAs have a high rate of cancer recurrence [29]. The development of HCV vaccine remains an important goal for global control and eradication of infection [27].

Liver cirrhosis

Liver cirrhosis represents the final stage of liver fibrosis, which occurs in response to chronic liver injury. The process of fibrosis occurs following a long-standing asymptomatic period called the 'compensated' phase, followed by a progressive 'decompensated' phase, which is associated with progressive decline in hepatic function and complications (ascites, encephalopathy, variceal bleed, jaundice, and HCC) [30]. According to the National Health and Nutrition Examination Survey (NHANES), the prevalence of cirrhosis in the USA is approximately 0.27%, corresponding to 633,323 adults [31]. Liver cirrhosis is a well-known risk factor for primary liver cancer, but it also increases the risk of extrahepatic malignancies [32]. Unlike other solid malignancies, the prognosis in HCC is also determined by the underlying liver cirrhosis and its complications [33]. Also, liver cirrhosis limits the applicability of certain standard therapies for HCC because they may cause collateral damage to non-cancerous tissue, thereby aggravating liver dysfunction (ex: transarterial chemoembolisation [TACE]) [33].

Environmental toxins

The major environmental toxins discussed here include aflatoxin, areca nut (betel nut), and contaminated water. Aflatoxin is a family of toxins produced predominantly by two fungi: Aspergillus flavus and Aspergillus parasiticus. Individuals are exposed to aflatoxins by consumption of contaminated animal and plant products [34]. Of the four aflatoxins (B1, B2, G1, and G2) that are known to be carcinogenic to both humans and animals, aflatoxin B1 (AFB1) is the most potent liver carcinogen [35]. Studies in areas with high AFB1 exposure reveal mutations affecting the *p53* gene. Mutations such as transversion in codon 249 are present in 50% of HCCs [36]. AFB1 is metabolised in the liver by cytochrome – P450 to produce intermediate metabolites (aflatoxin B1-8, 9-oxide, AFBO), which interact with the guanine base and cause mutational effects. Chemoprevention of AFB1-induced HCC plays an important role. Recent studies with human hepatocytes demonstrated that naturally occurring biologically active compounds phenethyl isothiocyanate (PEITC) and sulforaphane (SFN) have chemoprotective effects against AFB-DNA adduct formation [37].

Besides alcohol intake and smoking, betel (areca) quid chewing is an integral component of the cultural fabric in 10–20% of the human population [38]. Experimental studies have demonstrated persistent hepatocyte necroinflammation secondary to areca nut-derived nitrosamines that methylate and cyanoethylate DNA resulting in hepatotoxicity [38]. Betel leaves also contain a high concentration of safrole (15 mg/g fresh weight), which is known to be rodent hepatocarcinogen; 37.5% of the areca nut sample was infested with aflatoxin B1 – producing fungus [39, 40]. A population-based study in Taiwan, which screened 60,000 community dwellers, reported that betel chewing increased cirrhosis and HCC risk 4.25-fold (95% confidence interval [CI] = 2.9, 6.2) in current chewers and 1.89-fold (95% CI = 1.13, 3.16) in ex-chewers, when compared with never-chewers [41]. A case-control study in 263 patients diagnosed with HCC indicated that betel quid chewing (odds ratio [OR] = 3.49; 95% CI = 1.74–6.96) is an independent risk factor risk for HCC [42]. Several mechanisms that contribute to hepatic fibrosis have been hypothesised, such as increase in circulating tissue inhibitor of metalloproteinase (TIMP-1) [43] and excess collagen production through NADPH oxidase by angiotensin-2 produced from hepatic stellate cells [44], and hypovitaminosis D as activated vitamin D is known to inhibit nitroso-related hepatocarcinogenesis [45].

Contamination of groundwater due to pollution, mainly industrial waste, is a well-known factor causing ill-health in humans. Organic solvents, such as trichloroethylene (TCE), are known to bring about peroxisome proliferation induction, oxidative stress, alterations in cell replication, and DNA mutagenic effects [46]. Although a slightly higher risk has been found in workers exposed to TCE, there is insufficient epidemiological data to arrive at a causal relationship [47]. Porru *et al.* showed that, in workers chronically exposed to organic solvents like toluene and xylene, there is an increased risk of HCC and that the risk is time-dependent [48]. Groundwater contamination with inorganic arsenic has been extensively reported in epidemiological studies, especially in Asian cohorts, to be significantly associated with increased risk of HCC [49]. Recent laboratory data have also confirmed that the liver is a major target for inorganic arsenic carcinogenesis in rodents and cell model systems [50].

Occupational exposure to chemicals is yet another risk factor for HCC. Some examples include exposure to pesticides like Dichloro diphenyl trichloroethane (DDT) in agriculture, whose mechanism of causation, although not very clearly delineated, is thought to be mediated through the *CYP3A1* gene, which is involved in inflammatory and immune responses in the liver [51]. Nitrosamines are yet another carcinogenic chemical compound produced when nitrite, a food preservative, combines with amino acids in the stomach. Nitrosamines can also be found in latex products and tobacco smoke and are implicated in nasopharyngeal, oesophageal, stomach, liver, and urinary bladder cancers [52]. Recent studies have reported a correlation between HCC and exposure to N-nitrosamines, which might be due to the shortening of telomeres among workers in the rubber industry. Telomeres are critical in maintaining the integrity of chromosomes, and telomere length abnormalities are associated with carcinogenesis [53].

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is fatty infiltrations in the liver unrelated to alcohol use, which can then lead to non-alcoholic steatohepatitis (NASH), where there is liver inflammation [54]. NASH is pathologically characterised by steatosis with a necro-inflammatory component, with or without fibrosis, and is known to account for 75% of the cryptogenic cirrhosis cases [55]. NAFLD affects approximately 20% of the population worldwide [56], and 34% of Americans suffer one of the several forms of NAFLD [57]. In a recent meta-analysis of 86 studies, comprising 8,515,431 persons from 22 countries, the global prevalence of NAFLD was 25.24% (95% CI = 22.10–28.65) with the highest occurrence in the Middle East and South America and the lowest in Africa [58]. 10–30% of patients with NAFLD have NASH that can progress to cirrhosis. In the United States, approximately 6 million people are estimated to have NASH [57]. NAFLD does not carry the same risk of HCC as HCV or HBV, but the burden of NAFLD makes it one of the major causes of HCC in the United States [59]. In a recent global meta-analysis, the HCC incidence among NAFLD patients reached 0.44 (range, 0.29–0.66) per 1000 person-years [60]. Risk factors such as morbid obesity (body mass index 40 kg/m^2 or higher) and diabetes mellitus are known to cause NAFLD, but it has also been observed in the non-obese and in non-diabetics with insulin resistance [61]. Several mechanisms such as increased levels of TNF-α and IL-6, and increased levels of leptin, an iron compound deposition that predisposes to oxidative DNA damage, have been implicated in carcinogenesis in NASH [62].

Lifestyle factors (alcohol consumption, smoking, and dietary factors)

Alcohol consumption and the resulting cirrhosis have a causal relationship in the development of HCC [63]. The induction of CYP2E1, due to chronic alcohol consumption, involves the generation of free radicals, thereby resulting in the formation of DNA adducts and resulting in oxidative damage [63]. The pro-inflammatory environment activates Kupffer cells that release cytokines and chemokines, reducing the survival of hepatocytes. A case-control study in Italy, involving 464 subjects (380 men) with a first diagnosis of HCC as cases and 824 subjects (686 men) as controls, with alcohol intake of > 60 g/day, was associated with an OR for HCC of 7.0 (95% CI = 4.5–11.1) compared with those with an intake of ≤ 60 g/day [64].

Several epidemiological studies have revealed a mild risk in the development of HCC with smoking. A meta-analysis in 2009, which included 38 cohort studies and 58 case-control studies on liver cancer and cigarette smoking, demonstrated the adjusted relative risk for liver cancer to be 1.51 (95% CI = 1.37–1.67) for current smokers and 1.12 (95% CI = 0.78–1.60) for former smokers [65]. The chemicals in tobacco smoke, 4-aminobiphenyl (4-ABP) and polycyclic aromatic hydrocarbons (PAH), which are converted to reactive species, explain the biologically plausible relationship [66].

In industrialised countries, fatty liver disease, apart from viral hepatitis, is closely related to nutritional factors [67]. A meta-analysis with 19 studies involving 1,290,045 participants and 3912 cases of HCC concluded that the risk of HCC decreases by 8% for every 100 g/day increase in vegetable intake [68]. Larger studies conducted in Europe and the United States demonstrate different results. The European Prospective Investigation into Cancer and Nutrition (EPIC) study recruited 477,206 patients from all over Europe and demonstrated an inverse association between total fat intake (per 10 g/day hazards ratio [HR] = 0.80; 95% CI = 0.65–0.99), while there was no association with meat intake [69]. The NIH-AARP study, which prospectively enrolled almost 500,000 men and women, reported an increased risk for HCC associated with intake of saturated fat and red meat [70]. A prospective, randomised, controlled trial in postmenopausal women could not show any beneficial effect of a low-fat diet on the incidence of liver cancer (HR = 0.95, 95% CI = 0.89–1.01; p = 0.10) [71]. The EPIC trial also revealed that higher baseline levels of 25(OH) D is associated with a lower risk of HCC (per 10 nmol/l increase IRR 0.80; 95% CI = 0.68–0.94) [72]. Due to the evidence mentioned above, demonstrating conflicting results, evidence-driven recommendations pertaining to prevention of HCC are lacking.

Metabolic diseases (diabetes and obesity)

There is now clear evidence that type 2 diabetes mellitus (T2DM) and HCC are closely linked due to their association with obesity, impaired insulin sensitivity, and non-alcoholic fatty liver disease (NAFLD) [73]. A recent meta-analysis involving 17 case-control studies and 32 cohort studies showed an increased risk of HCC prevalence among diabetic individuals (RR = 2.31, 95% CI = 1.87–2.84). Metformin treatment was potentially protective. The study also demonstrated an increased risk of HCC mortality (RR = 2.43, 95% CI = 1.66–3.55) among T2DM patients [74]. The presence of obesity and hepatic steatosis (along with T2DM) were also thought to be independent predictors of incident HCC [75]. Several studies suggest that factors such as increased hepatic/peripheral insulin resistance, lipotoxicity, increased oxidative stress, and chronic low-grade inflammatory state contribute to the development of HCC [76]. Hyperinsulinaemia also stimulates insulin receptor substrate-1 (IRS-1), which plays a key role in the activation of some intracellular cytokine signalling pathways implicated in hepatic carcinogenesis [77]. In addition to these factors, reactive oxygen species (ROS) promote DNA damage with mitochondrial dysfunction (i.e. structural mitochondrial lesions, decreased activity of the respiratory chain enzymes, and abnormal mitochondrial β-oxidation), which results in the development of HCC [78]. Recently, accumulating evidence suggests that gut microbiota also play a role in carcinogenesis. The pathophysiology involves a complex process which includes abnormalities in toll-like receptors (TLRs), increased levels of gut bacterial metabolites, and increased levels of secondary bile acids [79]. It is plausible to assume that gut microbiota increases the production of fibrotic and growth mediators by hepatic stellate cells [80]. The EPIC study indicated that obesity might account for ~16% of HCC cases in Europe [81]. Similarly,

data from the U.S. SEER-Medicare estimated that diabetes and/or obesity might be attributed to 36.6% of HCCs in the U.S [82]. The mechanism implicated in obese individuals are very similar to those involved in diabetes leading to HCC. A nested case-control study involving a total of 125 HCC cases showed that higher baseline serum levels of C-reactive protein, IL-6, and C-peptide, and high molecular weight adiponectin were associated with increased risk of developing HCC in the general population [83].

Genetic and related factors

About 20% of cases diagnosed in the United States have no known predisposing risk factors, including alcohol use or viral hepatitis [84]. Strong evidence from rodent models has supported the role of genetic factors in the risk of HCC [85]. Here we discuss certain monogenic risk factors that determine the risk of HCC development.

Haemochromatosis is an inherited disorder of iron metabolism, characterised by increased iron storage in all organs except for the brain and nervous tissue. Limited liver dysfunction is present in the early stages but may develop into hepatic cirrhosis followed by HCC. The haemochromatosis gene (HFE) is located on chromosome 6p21.3 and haemochromatosis is inherited as an autosomal recessive trait [86]. The risk of HCC in haemochromatosis patients is approximately 20-fold higher than in the general population [87].

Alpha 1 antitrypsin deficiency (AAT) is an autosomal recessive disorder due to defects in SERPINA 1 located on chromosome 14q32.1 [88]. A study in Swedish patients demonstrated a higher risk odds ratio (OR) of 5.0 (95% CI = 1.6–15.8; $p = 0.008$), especially in males with AAT deficiency, compared to the general population [89].

Glycogen storage disease type I (Von Gierke's disease) is inherited as an autosomal recessive trait, resulting in impairment of glucose-6-phosphatase activity, with consequent excess glycogen storage in the liver [90]. Liver functions are usually normal or show only minor deviations, and cirrhosis does not develop. By the second or third decade of life, patients develop hepatocellular adenomas with prevalence increasing with age and ranging from 16% to 75% [91].

Hepatic porphyrias are a group of inherited diseases resulting from defects in the heme biosynthesis pathway. It is inherited as an autosomal dominant trait, resulting in a deficiency of hydroxymethylbilane synthase (HMBS) enzyme due to a mutation on chromosome 11q23.3. Acute intermittent hepatic porphyria (AIP) is the most common form of porphyria. Cirrhosis is not frequent in patients with AIP, but morphologic abnormalities of hepatocytes on liver biopsy and altered liver biochemical function have been reported [92]. Compared with the total population, the risk of HCC is increased > 30-fold in AIP patients [93]. Familial porphyria cutanea tarda (PCT) is transmitted as an autosomal dominant trait, resulting in mutations in the uroporphyrinogen decarboxylase gene (UROD), causing a deficiency of the relevant enzyme activity. PCT is associated with subacute hepatitis and liver cirrhosis, earlier studies demonstrated a 100- to 200-fold relative risk of HCC in PCT patients [94], whereas a case-control study in 2001 showed a lower risk (OR = 5.3, 95% CI = 1.4–19.3) [95].

Hereditary tyrosinemia type I is an autosomal recessive disorder resulting in a deficiency of tyrosine, fumarylacetoacetate hydrolase (FAH), located on chromosome 15q23–q25. The disease is devastating, resulting either in acute hepatic failure in infancy or chronic liver disease associated with cirrhosis and HCC development [96]. The risk of HCC is very high, with an incidence of 40% in those who survive beyond two years of age developing HCC in childhood [97].

Miscellaneous factors (epidermal growth factor polymorphism, gallstones, and cholecystectomy)

Epidermal growth factor receptor (EGFR) is a tyrosine kinase transmembrane receptor, which regulates several processes in carcinogenesis [98]. Activation of the EGFR pathway also leads to the up-regulation of the ligand vascular endothelial growth factor (VEGF) and its receptor (VEGFR2) on endothelial cells, thus stimulating angiogenesis. In the case of HCC, the elevated serum level of VEGF is considered an independent marker of HCC survival [99]. However, the association between the EGFR genotype and prognosis so far has not been described in HCC patients and is controversial [100].

With regards to gallstones and cholecystectomy, they have been hypothesised as risk factors of several cancers of the gastrointestinal tract, such as intrahepatic cholangiocarcinoma, pancreatic and colorectal cancer [101]. Gallstones and cholecystectomy are known to increase bile duct pressure and dilation of the common bile duct, predisposing to chronic inflammation [102]. It has also been proposed that the accumulation of bile and secondary bile acids, in particular deoxycholic acid, can act as carcinogens [103]. A recent large, population-based, case-control study utilising SEER database involving 236,850 cancer cases, revealed that the association between gallstones and HCC appeared to be stronger (OR = 2.91, 95% CI = 2.68–3.16) than the association with cholecystectomy (OR = 1.34, 95% CI = 1.17–1.52) [101]. A Meta-analysis involving 15 studies (five case-control and 10 cohort studies) with 4,487,662 subjects and 17,945 diagnoses of liver cancer, indicated significant risk in those with history of gallstones (OR = 2.54; 95% CI = 1.71–3.79; $n = 11$ studies), as well as cholecystectomy (OR = 1.62; 95% CI = 1.29–2.02; $n = 12$ studies) [104].

Hepatic dysfunction is common in patients with congenital heart disease, either resulting from the primary cardiac defect itself or the complex palliative surgical procedures performed during infancy or childhood, and studies have shown that there is a risk for development of HCC in these patients [105].

Prevention strategies

Dietary modifications, as mentioned, provide conflicting evidence on their protective effect towards the development of HCC. HBV and HCV infections can be treated with DAAs for prevention of chronic carrier state. The current treatment modalities aimed at HBV are prophylactic and curative therapy. HBV vaccination administered as

three doses during infancy has a global coverage rate for the third dose to be about 78%. However, to date, there is no HCV vaccination [106]. Statins are also thought to exert antitumour effects through the following mechanisms: 1) Down-regulation of the RAF/mitogen-activated protein kinase 1/extracellular signal-regulated kinase (ERK) pathway; 2) Limiting the degradation of the cyclin-dependent kinase inhibitors p21 and p27 (growth-inhibitory and tumour-suppressor effects); 3) prevention of phosphorylation and activation of c-Myc, which is a critical step in hepatocarcinogenesis; and 4) anti-inflammatory and antioxidant effects [107]. The evidence pertaining to risk reduction was obtained from a meta-analysis of 10 studies, evaluating 4298 cases of HCC in 1,459,417 patients, in which statin use decreased the risk for HCC by 37% in both Asian and Western populations. A higher reduction was noticed in the Asian (adjusted odds ratio [AOR] 0.52) as compared to the western population (AOR 0.67) [107]. Statins may well be considered as an adjuvant in the treatment of liver cancer. However, additional well-designed RCTs are warranted to establish the role of statins in chemoprevention of HCC.

Conclusions

Chronic viral hepatitis and alcohol consumption have been the two most important risk factors for the development of liver cirrhosis and subsequent HCC globally. Lifestyle factors, environmental factors, and genetic factors continue to contribute as other important but modifiable risk factors for HCC. Recent drug developments in the pharmacotherapy of treatment of chronic viral hepatitis have come a long way in limiting the number of progressive liver diseases and HCC. In-depth knowledge on the molecular mechanisms of development of HCC has prompted for more active surveillance among patients with established risk factors as discussed in this review. Prevention of alcoholic liver disease combined with healthy diet and lifestyle and better environmental conditions are some important strategies that would help further curb the menace of increasing incidence of HCC, especially in developing nations.

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