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Hepatocellular Carcinoma: Causes and Prevention

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Abstract

Hepatocellular carcinoma (HCC) is a primary malignancy of the liver and occurs predominantly in patients with underlying chronic liver disease and cirrhosis. It is considered as the second leading cause of cancer-related death worldwide with over 500,000 people affected. Incidence of the HCC is highest in Asia and Africa, where the endemic high prevalence of hepatitis B and C strongly predisposes to development of the chronic liver disease and subsequent development of HCC. In most cases, the cause of liver cancer is long-term damage and scarring of the liver cirrhosis that may be caused by viral infections (Virus B or C) or non-viral causes such as non-Alcoholic Fatty Liver Disease (NAFLD), autoimmune diseases, inflammation of the liver (chronic), obesity, diabetes, alcohol consumption, smoking, iron overload in the body (hemochromatosis) and the exposure to aflatoxin. The recent studies concluded that vaccination and the antiviral treatment are the most important ways for the HCC prevention.

1 Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy that is considered as the second leading cause of cancer-related death worldwide[1]. The studies which were carried out with over half a million new cases diagnosed annually worldwide, it was reported that HCC is the fifth most common cancer in men and seventh among women[2]. The HCC is particularly lethal with a 5-year survival of less than 5% of the patients who are not transplant candidates[3]. A total of 30 new liver cancers and 640 intrahepatic bile duct cancers were estimated during 2013[4]. In 2010, Ferlay *et al*.[5] documented that HCC occurred more often in males than females (2.4:1) with a higher incidence in Eastern and Southern Asia, Middle and Western Africa, Melanesia and Micronesia/Polynesia.

Moreover, it was found that the age-adjusted incidence of liver cancer has risen from 1.6 per 100,000 individuals to 4.6 per 100,000 individuals among American Indians and Alaskan Natives followed by blacks, whites and hispanics[6]. In the United States, incidence of the HCC increases with a more than two fold from 1976 to 2002[7-9]. A significant proportion of this increase is accounted for by the growing prevalence of hepatitis C virus (HCV) infection[10]. However, other potential causes of HCC are garnering close attention. Increased body mass index and diabetes with subsequent development of non-alcoholic steatohepatitis (NASH) represent significant risk factors for incidence of HCC. This is especially concerning in light of the growing epidemic of obesity in adults and children over the past 25 years[7,10-13].

Other non viral causes of HCC include iron overload syndromes, alcohol use, tobacco use, oral contraceptive use, aflatoxin exposure and betel quid chewing, a prevalent habit in the world. Emerging evidence suggests that etiology of many cases of HCC is in fact multifactorial, including both viral infections and non-viral environmental and dietary exposures (Fig 1).

2 Viral causes of hepatocellular carcinoma

2.1 Hepatitis B Virus (HBV)

Hepatitis B virus (HBV) is a double-stranded, circular DNA molecule with eight genotypes (A to H). Genotypes A and D are more common in Europe and the Middle East, while genotypes B and C are more common in Asia[14]. Hepatitis B is transmitted via contaminated blood transfusions, intravenous injections and sexual contact. Vertical transmission from mother to fetus is the leading cause for HBV infection worldwide. Five percent of the world's population is infected with hepatitis B[15]. HBV is the leading risk factor for HCC globally and accounts for at least 50% cases of HCC[16]. In endemic areas, HBV is mostly acquired by vertical and perinatal transmission with > 90% of these cases becoming chronic HBV carriers.

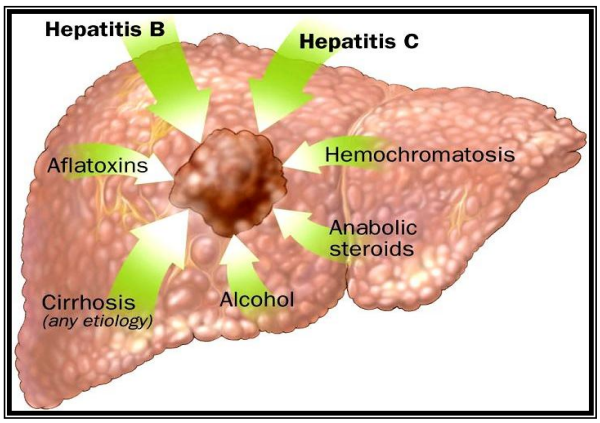

Fig 1: Causes of liver cancer (hepatocellular carcinoma)

In contrast, areas of low prevalence such as western countries, it is usually acquired in adulthood by horizontal transmission (through sexual and parenteral routes) with >90% of acute infections resolving spontaneously. HBV is a notorious HCC cause in the absence of cirrhosis; however, most (70%-90%) HBV-related HCC develops in cirrhotic livers[17]. Several factors have been reported to increase HCC risk among HBV carriers, including demographic (male gender, older age, Asian or African ancestry, family history of HCC), viral (higher levels of HBV replication, HBV genotype, longer duration of infection, co-infection with HCV, HIV or HDV), clinical (cirrhosis) and environmental or life-style factors (exposure to aflatoxin, heavy alcohol drinking or tobacco smoking). In Asian studies, genotype C is associated with more severe liver disease, cirrhosis and the development of HCC, compared with genotype B; whereas in Western Europe and North America, genotype D is more associated with a higher incidence of HCC than genotype A, as well as the development of HCC in young carriers without cirrhosis[18].

2.2 Hepatitis C Virus (HCV)

Hepatitis C virus (HCV) is a small, single-stranded RNAvirus, which exhibits high genetic variability[19]. There are six different genotypes of HCV isolated. Genotypes I, II and III are predominant in the Western countries and the Far East, while type IV is predominant in the Middle East. The highest rates of chronic hepatitis C infection occur in Egypt (18%), with lower rates occur in Europe (0.5%-2.5%), the United States (1.8%) and Canada (0.8%)[20]. Once infected with HCV, 80% of patients progress to chronic hepatitis, with ~20% developing cirrhosis[21]. In hepatitis C, the HCC development occurs almost exclusively in the liver with established cirrhosis. HCV increases risk of the HCC by inducing hepatic inflammation and importantly fibrosis, but also promoting malignant transformation of infected cells[22]. Other risk factors that increase risk of HCC in infected patients include male sex, co-infection with HIV, HBV, HCV genotype 1b, old age, presence of diabetes and obesity, and a high level of chronic alcohol consumption. But, the risk of HCC is reduced significantly in patients who obtained a sustained viral response after treatment of HCV with a 54% reduction in all-cause mortality[23].

3 Non-viral causes of hepatocellular carcinoma

3.1 Non-Alcoholic Fatty Liver Disease (NAFLD)

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disorder in western countries, with ~20% of individuals affected[24]. It occurs in absence of alcohol use, although the hepatic histology appears consistent with alcoholic hepatitis[25], with changes in histology including hepatic steatosis, inflammation, hepatocyte injury as exemplified by cytologic ballooning and Mallory's hyaline and fibrosis[26]. Thus, NAFLD comprises a spectrum of conditions ranging from fat alone to fat plus inflammation and fat plus ballooning degeneration[25, 27]. Epidemiologic studies showed that NAFLD is closely linked with the metabolic syndrome, particularly type 2 diabetes mellitus and obesity[28], with NAFLD occurring almost universally among diabetic patients who are morbidly obese[29]. Moreover, NASH in association with multiple components of the metabolic syndrome is thought to increase the risk for developing chronic liver disease, cirrhosis and HCC[28].

Although the pathophysiologic mechanisms driving NAFLD and the associated progressive hepatocellular damage are not fully understood, a number of processes have been described. A well-established driver of NAFLD is Insulin Resistance (IR) (Fig 2). IR is a complex process that likely involves both insulin secretion and action, and is closely associated with obesity[29]. IR causes increased peripheral lipolysis and increases circulating fatty acids that are taken up by the liver. At the same time, there is an increase in de novo liponeogenesis in the hepatocytes and a reduction in the hepatic secretion of very-low-density lipoproteins, resulting in hepatic triglyceride accumulation or fatty liver. Increased intrahepatic fatty acid levels are also thought to provide a source of the oxidative stress which may play an important role in the development from steatosis to steatohepatitis associated with progression to cirrhosis[30]. The reactive oxygen species (ROS) produced by the mitochondria

oxidize fat deposits to release lipid peroxidation products which together with ROS impair the respiratory chain via oxidative damage to the mitochondrial genome[31]. ROS and lipid peroxidation products also increase production of various cytokines including TNF-α, TGF-β and Fas ligand. Furthermore, the proinflammatory cytokines activate the hepatic stellate cells which produce a collagen matrix and drive the fibrosis development[32].

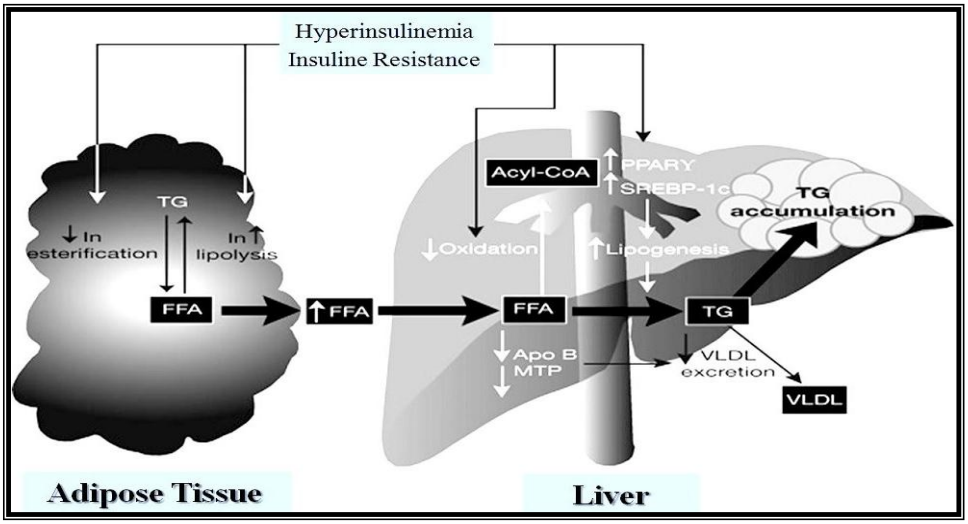

Fig. 2. Insulin resistance and the development of nonalcoholic steatohepatitis[28].; Apo B: apolipoprotein B, FFA: free fatty acids, MTP: microsomal triglyceride transfer protein, PPARγ: peroxisome proliferator-activated receptor gamma, SREBP-1c: sterol regulatory element binding protein-1c, TG: triglycerides, VLDL: very low-density lipoprotein.

3.2 Obesity

Prevalence of obesity has increased to epidemic proportions over the last three decades. Excess body mass is classified as overweight if the BMI is > 25 kg/m2 and <30 kg/m2, or obese if the BMI is ≥ 30 kg/m2. In addition to the increase in an array of disease processes observed with being overweight or obese, both classifications of excess body mass are associated with a higher risk of developing all cancers including liver cancer[33,34]. In addition to an increased risk of developing HCC, overweight or obese patients appear to be at increased risk for HCC-related mortality. In a population-based study of cancer mortality and BMI, men with a BMI of 30-34.9 were found to have a two fold increase in the risk of death from HCC, with a 4.5-fold increase noted in men with BMI > 35[33].

3.3 Diabetes

Diabetes has been found to increase the risk of developingchronic liver disease and HCC[35]. Diabetes mellitus directly affects the liver because of the essential role that the liver plays in glucose metabolism. It can lead to chronic hepatitis, fatty liver, liver failure and cirrhosis[36,37]. Patients with diabetes have between a 1.8- and 4-fold increased risk of HCC. As compared to HCV, NASH-related HCC liver transplants increased by nearly four times in the decade from 2002 to 2012[38]. Hyperinsulinemia has been associated with a three fold increased risk of HCC. It is believed that the pleotropic effects of insulin that regulate the anti-inflammatory cascade and other pathways inducing cellular proliferation play a role incarcinogenesis. Insulin-like growth factor and insulin receptorsubstrate-1 promote cellular proliferation and inhibit apoptosis,respectively[39,40].

3.4 Diet

Some studies have examined whether alterations in diethave an effect on the risk of HCC. A trial from Italy hasexamined a broad range of dietary habits among 185patients with HCC and 412 patients without cancer[41,42]. Those with HCC were more likely to consume a largeamount of calories, were five times more likely to beformer drinkers, and were 30 times more likely to beinfected with either HCV or hepatitis B virus (HBV).Among dietary compounds, consumption of iron andthiamine were associated with a significant threefoldand twofold increase in risk of HCC, respectively. Conversely,β-carotene and linoleic acid consumption wasassociated with a reduced risk of HCC[41]. Another study had been reported that the subjects with consumptionin the highest quartile for yogurt and milk, whitemeat and eggs had a significantly lower likelihood ofdeveloping HCC. This effect was observed in patientswith and without viral hepatitis[43].

Other studies from Japan and Europe have found those who consume a large amount of green vegetables havea significantly lower likelihood of developing HCC[44-46]. One study has shown that eating green vegetables daily, ascompared with consumption fewer times per week, had aprotective effect against the development of HCC (OR:0.75, 95% CI: 0.60-0.95)[44]. On the contrary, a Greek studyhas found no association between vegetable intake and reductionin the risk of developing HCC[47]. So, there is evidence to suggest that consumptionof yogurt and milk as well as vitamin supplementsoffers a

protective effect against HCC. The enthusiasmfor these findings however should be tempered bythe fact that the majority of these studies were retrospectivein nature[48].

3.5 Coffee

Coffee consumption has also been studied and appears to have a potentially favorable effect on the prevention of liver diseases, including HCC[49,50]. There are several hypotheses that could explain why consuming coffee attenuates the risk of developing HCC. One hypothesis argues that coffee intake lowers serum levels of γ-glutamyltransferase (GGT), which is associated with a lower incidence of HCC[50-53]]. Coffee consumption has also been linked to a lower incidence of cirrhosis which is a major risk factor for the development of HCC[50]. In addition, coffee consumption lowers insulin levels and reduces the risk of diabetes, a known risk factors for HCC[54]. Animal studies also suggest that coffee contains compounds with anticarcinogenic properties. Chronic HCV patients who consumed high levels of coffee were found to have lower fibrosis score[55]. Ameta-analysis of studies on risk of HCC among coffee drinkers in European and Japanese studies showed a reduced risk of HCC. They concluded that relative risk of HCC among lowor moderate coffee drinkers (defined as 1-2 cups / day) was 0.70 (95% CI 0.57-0.85), andthat for high drinkers (defined as ≥ 3 cups / day) was 0.45 (95% CI 0.38-0.53) as comparedto non-drinkers[56].

3.6 Alcohol

Alcohol consumption remains an important risk factorfor the development of HCC[57]. As illustrated in Fig 3, there is relationship between alcohol and liver disease and this correlates with amount of alcohol consumed over a lifetime, with heavy alcohol use rather than social drinking being the main risk of HCC[58]. The prevalence rate of alcohol abuse in the United States is five times higher than that of hepatitis C[59]. Alcohol abuse accounts for 40-50% of all HCC cases in Europe[60]. Studies in Europe reported an increase in the relative risk of developing liver disease above 7-13 drinks per week in women and 14-27 drinks per week in men[59,61]. In the United States, studies showed that the risk of liver cancer is increased two to four fold among persons drinking more than 60 g/d of ethanol[62]. A meta-analysis of 19 prospective studies showed that consumption of three or more drinks per day resulted in a 16% increase risk of liver cancer and consumption of six or more drinks per day resulted in a 22% increase risk[63].

3.7 Smoking

Other risk factors may include smoking. Cigarette smoking is associated with a significant increase in the development of HCC. A recent meta-analysis that reviewed the association between smoking and liver cancer demonstrated an OR of 1.6 (95% confidence interval [CI], 1.3-1.9) for current smokers and 1.5 (95% CI, 1.1-2.1) for former smokers. Studies investigating the use of oral contraceptive pills and the risk for development of HCC have previously been inconclusive; however, a recent review of six studies showed a significant increase in HCC risk with a longer duration (>5 years) of exposure to oral contraceptives[64].

3.8 Aflatoxin

Aflatoxin B1 (AFB1) is the major metabolite of the molds *Aspergillus fumigatus* and *Aspergillus parasiticus.* These moldsgrow on a variety of food products that are stored inwarm and damp conditions or are cultivated in countrieswith hot and humid climates[65,66]. AFB1 induces a singlenucleotide substitution in codon 249 in the p53 tumor suppressor gene, which results in the change of the aminoacid arginine to serine[67,68]. This mutation is present in upto 50% of patients with HCC who are indigenous to geographicregions with high exposure to AFB1[69-70].On theother hand, this mutation is absent in patients with HCC from regions with low exposure to AFB1[71,72]. Moreover,it has been recently demonstrated that AFB1-albumin adductsin patients with HCC correlate significantly with thepresence of plasma DNA hypermethylation and mutationsin the p16 and p53 tumor suppressor genes[73].

3.9 Host genetic factors

Host geneticmakeup may be an important factor that influences progression to HCC. Two meta-analysisindentified variants of tumor necrosis factor (TNF) associated with higher risk of HCC.They showed that TNFα-308 AA and AG variants (vs. GG) were associated with asignificantly increased risk of HCC[74,75].

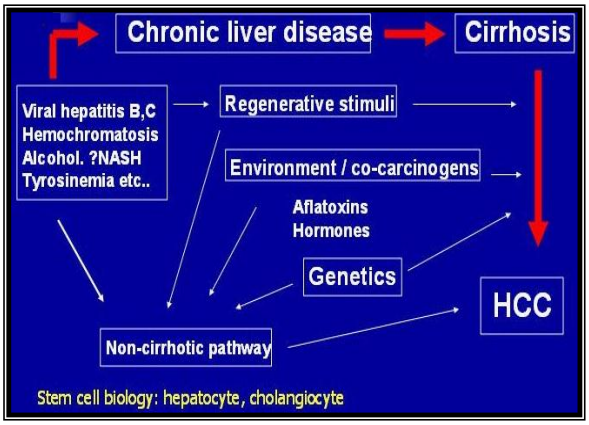

Fig 3: Pathobiology of hepatocellular carcinoma

4 Prevention of HCC

As illustrated in Fig 4, prevention of HCC is an important goal and the opportunities exist for the further development of preventative measures[76].

4.1 HBV vaccination

Development of HBV vaccine has been a major success in reducing the incidence of HBV infection and subsequent development of HCC. The vaccine is safe and effective against

all HBV genotypes and serotypes. HBV vaccine is recommended for all newborns, pregnantwomen at their first pre-natal visit, and high-risk individuals. Neonates born to HBV infected mothers should get a dose of hepatitis B immune globulin in addition to vaccination. Countries like Taiwan that have implemented universal hepatitis B vaccination program have demonstrated its success. Twenty years after adopting the program, HBV carrier rate among children in Taiwan has decreased to 1.2% and incidence of HCC among the vaccinated children has dropped by 70%[77].

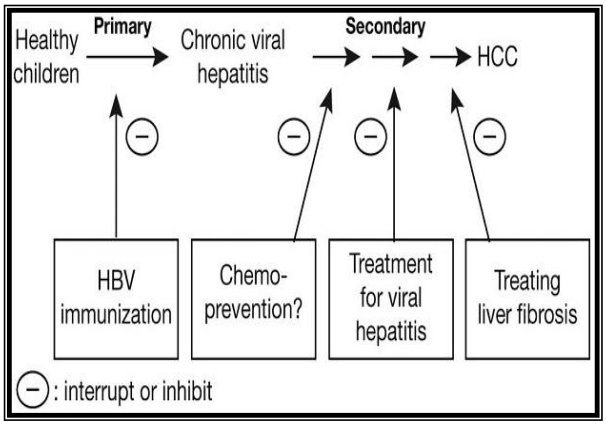

Fig 4: Strategies for primary and secondary liver cancerprevention in healthy subjects and in those with chronic hepatitisinfection[76].; HBV: hepatitis B virus, HCC: hepatocellular carcinoma.

4.2 Antiviral treatment

Antiviral treatment is also considered as one of the most important ways for the HCC prevention. A met analysis of non-randomized trials and observational studies demonstrated reduced risk of HCC after anti-viral treatment for HBV infection. A multicenter randomized controlled study on patients with chronic HBV and advanced hepatic fibrosis showed that 3.9% developed HCC on lamivudine therapy as compared to 7.4% in placebo arm when treated up to 5 years[78].

In addition, the randomized and non-randomized studies have shown that achieving sustained viral response in chronic HCV patients, both with and without cirrhosis, leads to a substantial reduction in risk of HCC[79,80]. Although viremia of any level is a risk factor for HCC, viral load is not associated with HCC. HCV+ patients with advanced fibrosis who clear viremia with anti-viral treatment have a reduced, but not eliminated risk, of HCC and should undergo surveillance for HCC[81].

5 Conclusion

The study concluded that cause of the liver cancer is long-term damage and scarring of the liver cirrhosis that may be caused by viral infections (Virus B or C) or non-viral causes such as NAFLD, autoimmune diseases, inflammation of the liver (chronic), obesity, diabetes, alcohol consumption, smoking, iron overload in the body and the exposure to aflatoxin. Furthermore, vaccination and the antiviral treatment are the most important ways for prevention of the HCC.

6 Conflict of interests

The authors declare that there is no conflict of interest among them and no any compelling interest exists.

7 Authors contributions

NEI collected ideas and information from previous review articles. WMA and RKS write the manuscript. Both of them read and approved the final form of manuscript. RKS communicated with journal's editor to publish the manuscript. WMA carried out the corrections required.

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