

Narrative review: Epidemiology and acting mechanisms of risk factors of hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma is a main human malignant primary liver tumour. The incidence of hepatocellular carcinoma differs among geographic regions, ethnic groups, genders and ages. Approximate 80% of hepatocellular carcinoma cases can be attributed to hepatitis B and C virus infections. Hazardous alcohol consumption, obesity, dietary aflatoxin B1 exposure and hemochromatosis are also significantly associated with development of HCCs. These risk factors alter DNA, modify protein or induce oxidative stress, leading to malignant transformations of hepatocytes.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most prevalent human cancer [1,2]. Nearly 1 million deaths are caused worldwide by HCC each year [3]. Moreover, the worldwide incidence of HCC is increasing by 4.6% per annum [2,4]. Mechanisms of hepatic carcinogenesis are incompletely understood, so that prevention, early detection and treatment of HCCs is still difficult [5-7]. Identifications of risk factors and acting mechanisms of these risk factors are help to decipher the enigma of HCC.

Hepatocellular carcinoma

HCC is an important primary liver cancer. HCC cells originate in hepatic cells and resemble normal hepatocytes, but the cancer cells lose functions of hepatocytes, and grow abnormally [8,9]. Cancers, originated other hepatic cells, are also called as primary liver cancers. These primary cancers include cholangiocarcinoma, angiocarcinoma, hepatoblastoma and lymphoma. Cholangiocarcinoma develops from the bile ducts [10]. Aetiology of cholangiocarcinoma is chronic inflammation of the biliary epithelium [11]. Fibrolamellar carcinoma accounts for approximately 1% of all cases of liver cancers [12]. The aetiology of fibrolamellar carcinoma is not known [9]. Hepatoblastoma arises from incompletely differentiated hepatocyte progenitors or stem cells and comprises approximately 1% of all childhood malignant tumours [13]. Among primary liver cancers, HCC is the most prevalent, cholangiocarcinoma is the second, and other primary liver cancers are rare [8].

Livers also contain metastatic liver cancers. Metastatic liver cancers arise from cancer cells that spread to the liver, but start in other organs, such as a colon, pancreas, stomach, ovary, kidney, lung or breast [14]. Most liver cancers are metastatic. However, among cirrhotic patients, primary liver cancers account for 77% of malignancies [8].

Different frequencies of hepatocellular carcinoma in different regions

The incidence of HCC varies between geographic regions and ethnic groups. Approximately 80% of HCCs occur in Asia (China,

Hong Kong, Taiwan, Korea, and Japan) and sub-Saharan Africa (Mozambique and South Africa) [15]. Intermediate incidences occur in Eastern Europe, Southern Europe, the Caribbean, Central America and Western Asia. HCCs are relatively rare in Western Europe and North America [16]. Among ethnic groups, the incidence of HCC is the highest among Asians; intermediate among African-Americans and Hispanics; and lowest rate among Caucasians [17]. The frequency of HCC also varies within countries and ethnic groups [18]. For example, in China, the highest incidence is in the north-eastern and south-eastern coastal provinces whereas the incidence is lower within inner western regions [18]. A similar situation occurs in Mozambique where the highest incidences are in the coastal town of Inhambane [19].

The increase in incidence of HCC in many developed countries, including western European nations, has been attributed to an increase in injection drug use, leading to the spread of hepatitis C virus infection in youths, and chronic alcohol consumption in adults [20-22]. Conversely, HCC cases are decreasing in many developing countries where the incidences has previously been high due to wide usage of the HBV vaccine in children [23].

HCC is an uncommon cancer in Australia, in which incidence of this cancer is the 18th most common and mortality 11th among all types of diagnosed cancers in 2007 [21]. However, there has been a significant increase in the incidence and mortality of primary liver cancer, the majority of which (approximately 80%) are HCCs. Between 1982 and 2007 the incidence of HCC increased approximately three fold (from 1.8 to 5.2 new cases per 100 000 population/ year) while HCC mortality doubled (from 2.3 to 4.9 deaths per 100 000 population/ year) [21].

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Risk factors of hepatocellular carcinoma

HCC is strongly associated with liver cirrhosis and chronic liver inflammation. Hepatitis B and hepatitis C are main aetiological agents of HCC. About 80% of HCC cases worldwide are associated with chronic infections with HBV and HCV [24]. Other aetiological agents of HCC are alcohol, aflatoxin B1, diabetes, non-alcoholic fatty liver disease, obesity, tobacco, vinyl chloride and thorium dioxide [25], and some inherited metabolic diseases including hemochromatosis, tyrosinemia and α -1-antitrypsin deficiency. Within these disease groups, ethnicity, male gender and age remain important risk factors [26].

Cirrhosis

Approximately 80% of HCCs occur in a cirrhotic liver, with up to 20% occurring in non-cirrhotic or normal livers [27,28]. Some HCC in non-cirrhotic livers still occur in association with liver fibrosis, steatosis or liver cell dysplasia [29]. Cirrhosis has nearly the same causative agents as HCC. For example, most HCCs associated with cirrhosis are also associated with viral hepatitis B [30,31] and C [32], and alcohol abuse [33]. In Asia and Africa, hepatitis B and C are the major risk factors of liver cirrhosis, while in the western world, alcohol is a major risk factor for cirrhosis [34,35]. Obesity [36,37], haemochromatosis [38] and autoimmune hepatitis [39] are also risk factors for cirrhosis.

Hepatitis B virus

Hepatitis B virus infection is the most major risk factor of HCC. 53% of worldwide HCC cases attributed to this infection [40]. The association between HBV and HCC was first recognised in the 1970's [25, 41]. At that time, studies found that the risk of developing HCC was higher in patients with hepatitis B virus surface antigen (HBsAg) compared to patients without HBsAg [42,43]. The World Health Organization reported in 2000 that worldwide, approximately 2 billion people have been infected with the hepatitis B virus, with more than 350 million of them chronic carriers [44]. Cases of HCCs associated with hepatitis B virus infection are the most prevalent in India, Singapore and Mongolia, [40]. Hepatitis B associated HCCs have the second highest prevalence in Korea, China, and Vietnam, Turkey, Thailand, Greece, Pakistan, Peru, Brazil and most African countries [41]. However, in western countries the prevalence of chronic hepatitis B virus infection is relatively low [45]. The incidence of HCC has been shown to be significantly reduced following immunization of infants with HBV vaccines in the 1980's [46]. In addition, antiviral therapy against Hepatitis B virus also appears to reduce the risk of HCC [47,48].

HBV is a DNA virus of the *Hepadnaviridae* family [49], which is the smallest circular DNA of known human viruses [50]. Possible mechanisms of hepatocarcinogenesis related to HBV include insertion of HBV DNA into the genome of hepatocytes, oncogenic effects of HBx protein and oxidative stress induced by immune response to HBV. HBV encodes the 154 amino acid HBx protein [51]. Genomic integration of HBV into the DNA of host cells occurs in most HCCs associated with HBV, but is rare in non-tumour tissues [52,53]. The process of HBV viral integration is enhanced by chronic inflammation [54], and exposure to oxidative stress [55]. Integration of the HBV viral DNA into hepatocyte genome induces genetic instability [56,57]. Furthermore, the HBx protein can interfere with DNA repair [58], and with transcription and signalling pathways [59]. These alterations in turn enhance the malignant transformation of hepatocytes [59].

Hepatitis C virus

Hepatitis C virus infection is another major risk factor for HCC,

being associated with 25% of all cases [41]. HCC cases caused by HCV infection comprise approximately 50% of HCC cases in the United States [60], 59% in Mexico [61], 74% in Italy [62,63], 75% in Spain [64], 53% in India [64], and 88% in Japan [65]. However, the rate is 4.28% in China, 10% in Hong Kong, 10% in Korea, 2% in Malaysia, 13% in Singapore and 15% in Thailand [18]. The World Health Organization estimated that there are currently 170 million people chronically infected with HCV in the world [66]. The prevalence of HCV is high in the Middle East, particular in Egypt; but low in Europe, Northern America, Africa, and South East Asia [67]. In the United States, 1.6% of national population has anti-HCV antibodies. Nearly 50% of have a history of injection drug use, or other significant risk factors such as blood transfusion [68]. In patients with HCV, additional risk factors for HCC include older age [69] and male gender [70]. Co-infection of HCV with HBV may increase the risk for developing HCC [71], although not all studies have found this [72]. HCV infection results in chronic liver inflammation, in which fibrosis occurs and progresses to cirrhosis and HCC [73].

The incidence of hepatitis C infection in people living in Australia declined from 57.5 new cases per 100 000 population in 2007 to 45.7 new cases per 100 000 population in 2011 [74]. It has been estimated that by the end of 2011, approximate 304 000 Australians had been exposed to HCV, with the majority of these (estimated to be 226 700) going on to develop chronic hepatitis C infection with varying degrees of liver injury [74].

Hepatitis C virus is a RNA virus that belongs to the *Flaviviridae* family [75]. It is composed of a 9.6 kb RNA strand [76], three structural proteins (core protein, envelope 1 and 2) and seven non-structural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B) [77]. The viral RNA of HCV does not integrate into the genome of hepatocytes as HBV does, but structural and non-structural proteins of HCV contribute to malignant transformation of hepatocytes [78]. Another possible mechanism involved in malignant transformation of hepatocyte is oxidative stress caused by chronic HCV infection [79]. Thus, HCV infects hepatocyte which initiates an immune response. Subsequently, inflammatory cells release ROS and RNS which damage DNA, protein and lipid, facilitating the development of HCC. In summary, HCV exerts important effects in malignant transformation of hepatocytes but the molecular mechanisms are still unclear.

Chronic alcohol consumption

Chronic alcohol consumption increases the risk of HCC in proportion to alcohol intake. A number of cancers are linked to alcohol consumption including primary cancers of the liver, colon, rectum, breast, oral cavity, oesophagus and larynx. Another study of women in the United Kingdom found that while chronic alcohol consumption increased the risk of liver cancer, it reduced the risk of other cancers including thyroid, non - Hodgkin lymphoma and renal cell [80]. Studies have shown that alcohol alone is not genotoxic [81]. However, alcohol acts synergistically with other risk factors to increase the risk of HCC [82]. Chronic alcohol consumption increases the risk of HCC in patients with coexisting hepatitis B [83], hepatitis C [82,84] and haemochromatosis [85]. Worldwide, 3.6% of all cancers and 3.2% of all deaths per year are attributed to chronic alcohol consumption [86]. In addition to cancers, chronic alcoholism also induces steatosis, steatohepatitis, hepatic fibrosis and cirrhosis [87].

The exact hepatocarcinogenesis mechanisms induced by chronic alcohol consumption are not known. It is currently believed that alcohol is involved in malignant transformation of hepatocytes via

a series of direct reactions with hepatocyte molecules and activation of the immune response. Alcohol is oxidized to yield acetaldehyde which can bind DNA to form DNA adducts [88]. Alcohol also interferes with methyl group transfer and may alter gene expression [89,90]. Most importantly, alcohol triggers chronic liver inflammation which generates ROS [91], RNS [92] and inflammatory cytokines [93]. Oxidative stress results in damage of DNA, protein and lipid of hepatocytes. Inflammatory cytokines regulate immune response of inflammatory cells, and growth, differentiation and proliferation of hepatocytes. Thus, alcohol induces malignant transformation of hepatocytes via direct genotoxicity of alcohol, and indirectly via oxidative stress and cytokine release from an activate immune response.

Iron overload

Hemochromatosis (HH) is a genetic disease that leads to iron overload, with a prevalence of 0.2 - 0.5% among Caucasians [94,95]. In Australia, the prevalence of HH is approximately 0.5% [96]. The incidence of HCC among HH patients is approximately 20 - 200 fold higher than the general population [97,98], and also higher than in non-HH chronic liver disease patients [38]. Other co-factors including alcohol abuse, viral hepatitis and age over 55 years old increase risk of HCC in patients with HH [99]. Altogether, approximately 6% of males with HH 1.5% of females with HH develop HCC [38].

Iron can catalyse the degradation of H_2O_2 and O_2^- produced in mitochondria and other organelles, to OH via the Fenton and Haber-Weiss reactions [100]. OH strongly damages DNA, protein and lipids, affecting the function of hepatocyte genes associated with tumour suppression, cell cycle regulation, DNA repair, and apoptosis. For example, approximate 70% of HCC case with HH showed mutations of tumour suppressor gene p53 [101,102]. In addition, Iron has been shown to enhance growth of human hepatoma cells [103].

Aflatoxin B₁

Aflatoxin B₁ is produced by the soil fungus *Aspergillus flavus*, which contaminates foods such as peanuts, rice, soybeans, corn, and wheat if these are not properly stored [104]. Aflatoxin causes 4.6–28.2% of all global HCC cases, with most of these cases occurring in sub-Saharan Africa, Southeast Asia, and China [105]. In these regions, HBV infection is also endemic [106]. The risk of HCC is significantly higher in patients with aflatoxin exposure and HBV infection than patients with aflatoxin exposure without HBV [107,108]. A study demonstrated that HBV infection increases activation of the enzyme cytochrome P450 to convert aflatoxin to hepatocarcinogenic aflatoxin B₁-8,9-epoxide [109]. HCV infection also enhances hepatocarcinogenesis of aflatoxin [110,111].

The hepatocarcinogenesis mechanisms of aflatoxin B₁ are not fully clear. Currently, it is believed that aflatoxin causes hepatocarcinogenesis via two pathways, *i.e.*, direct reaction of aflatoxin with DNA; and oxidative stress resulting from immune responses induced by the aflatoxin. Aflatoxin B₁ is oxidized by cytochrome P450 enzymes into aflatoxin B₁-8,9-epoxide [112], which can bind to DNA forming the aflatoxin B₁-N⁷-dG DNA adduct [113]. This ultimately can lead to a G to T mutation at the third position of codon 249 of p53 tumour suppressor gene [114,115]. This mutation enhances hepatocyte dysplastic growth. In addition, a current study has demonstrated that aflatoxin B₁, B₂, G₁ significantly increases releasing of cytokines from murine macrophages [116].

Gender

HCC cases occur 80% more in males than females [117]. The

prevalence of HCC among males is higher than among females. It is estimated that worldwide, HCC is the fifth most prevalent cancer in men and the eighth in women [118], this varies depending on disease aetiology and geographic region [118]. For example, the male to female ratio of HCC in Thailand is 6.7:1 [119], whereas this ratio is 4:1 in Egypt [120]. The frequency of HCC of Australian males was 3 times more than that of females [21].

The differences between men and women are attributed to genetic and environmental factors. Estrogen receptor- α is significantly expressed in chronic liver diseases and HCC [121]. Estrogens inhibits secretion of interleukin 6 by activated Kupffer cells [122], whereas interleukin-6 is an important pro-inflammatory factor [123]. Thus, estrogen may decrease risk of HCC through inhibiting liver inflammation, and provide a protective effect in women. Additionally, males are more likely than females to drink alcohol and smoke, which are associated with increased risk of HCC [124,125]. Additionally, smoking produces ROS [126].

Obesity

Obesity is a risk factor of HCC [127,128]. Incidences of HCC are rising with increasing of obesity prevalence [129]. The World Health Organization estimates that in 2000, at least 400 million adults were obese [130], while this was up to 1.5 billion in 2008 [131]. Obesity is a recognised risk factor for a range of cancers including oesophageal, stomach, colorectal, liver, gallbladder, pancreatic, prostate, and kidney cancer, non-Hodgkin's lymphoma, multiple myeloma, and leukaemia [128].

Obesity is considered a chronic inflammatory state that contributes to oxidative stress. Obesity is associated with elevated levels of inflammatory cytokines such as interleukin-6 and tumour necrosis factor [132] (interleukin-6 promotes hepatocarcinogenesis [122] while tumour necrosis factor regulates hepatocyte apoptosis [133]). Additionally, obesity elevates levels of oxidation products of protein and lipid, such as 4-hydroxynonenal [134], which in turn may be mutagenic [135].

Age

The incidence of hepatocellular carcinoma increases progressively with age. HCC rarely occurs in people less than 40 years old, except in some areas where *hepatitis B virus* infection is hyperendemic [4, 117]. In general, HCC patients are one to two decades younger in areas of high HCC incidence than in low incidence areas [4]. This may be because *hepatitis C* and alcoholic cirrhosis typically occur late in life in low incidence areas; whereas, HBV infection, which is a major HCC risk factor, frequently occurs either at birth or during early childhood [16].

Other known risk factors

Other risk factors of HCC include tobacco smoking [136,137], α_1 antitrypsin deficiency [138] and diabetes [139, 140]. It is still being debated whether the oral contraceptive pill increases the risk of developing HCC [141]. Tobacco smoking brings various carcinogens into bodies, inducing DNA damage [142], immune responses [143] and oxidative stress [144]. α_1 antitrypsin deficiency, an autosomal dominant genetic disorder [145], induces inflammation [146]. Diabetes may accumulate free fatty acids and subsequently induce oxidation of lipid, increasing risks of fibrosis and cirrhosis [147,148].

Conclusion

HCC cases are more in developing countries than western

developed countries, males than females, and elders than youths. The incidence of HCC is the highest among Asians; intermediate among African-Americans and Hispanics; and lowest rate among Caucasians. Most HCCs arise in cirrhosis whereas cirrhosis owns the same risk factors as HCC. Incidents of HCC are associated with its various risk factors. HBV and HCV are main risk factors of HCC. Studies indicate that viral DNA of HBV inserts into hepatocyte genome to induce genetic modification, and that the HBx protein can interfere with DNA repair, and with transcription and signalling pathways. Protein of HCV is perhaps involved in malignant transformation of hepatocytes. In addition, HCV infection causes oxidative stress to induce malignant transformation of hepatocyte. Other risk factors include alcohol, aflatoxin B1, iron overload, diabetes, non-alcoholic fatty liver disease, obesity, tobacco, vinyl chloride and thorium dioxide. Alcohol induces genotoxicity and oxidative stress. Oxidative product of Aflatoxin B1 perhaps cause a G to T mutation of p53 tumour suppressor. Iron can via the Fenton and Haber-Weiss reactions of H₂O₂ to produce OH that strongly damages DNA, protein and lipids of hepatocytes, leading to malignant transformations of hepatocytes. Estrogen receptor- α of women is involved in HCC. Obesity induces oxidative stress. Tobacco, vinyl chloride and thorium dioxide are genotoxicity. Risk factors also include some inherited metabolic diseases including hemochromatosis, tyrosinemia and α -1-antitrypsin deficiency. The mechanisms of HCC are not completely known.

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