Risk Factors for Hepatocellular Carcinoma in India

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Hepatocellular carcinoma (HCC) is an important cause of death all over the world, more so in Asia and Africa. The representative data on epidemiology of HCC in India is very scanty and cancer is not a reportable disease in India and the cancer registries in India are mostly urban. 45 million people who are suffering from chronic Hepatitis B virus (HBV) infection and approximately 15 million people who are afflicted with chronic Hepatitis C virus (HCV) infection in India. HBV and HCV infection is considered an important etiologic factor in HCC. Positive association between HCC and consumption of alcohol where alcohol contribute as a cofactor for hepatotoxins and hepatitis viruses. Aflatoxin contamination in the diets, Hepatitis B virus infection and liver cirrhosis in Andhra Pradesh, India and direct chronic exposure to aflatoxins was shown to cause liver cirrhosis. Cirrhosis of liver of any cause lead to develop about 70%–90% of HCC. Aflatoxin interact synergistically with Hepatitis B virus (HBV)/Hepatitis C virus (HCV) infection which increase the risk of HCC. HBV infection, HBV infection with Aflatoxin exposure, viral infection and alcohol consumption leading to overt cirrhosis of the liver, alcohol consumption leading to cirrhosis of the liver with viral infection are the predominant risk factor for the development of HCC. HCV and alcohol are also associated with HCC in India. Indians develop diabetes at younger age, Asians have strong genetic susceptibility for type II diabetes. Diabetes mellitus is identified as a risk factor for HCC. Prevention of viral infection by universal vaccination against hepatitis virus, HCC surveillance program, preventing alcoholic liver diseases, fungal contamination of grains and ground crops to prevent basically Aflatoxin exposure are important measures to prevent liver diseases and HCC among those at risk. (J Clin Exp Hepatol 2014;4:S34–S42)

WHAT ARE THE RISK FACTORS FOR HEPATOCELLULAR CARCINOMA IN INDIA?

Hepatocellular carcinoma (HCC) is an important cause of death all over the world, more so in Asia and Africa.[1] Chronic viral hepatitis as an important etiologic risk factor in the causation of HCC, especially in endemic areas has been reported.[2,3] Nearly 45 million people are suffering from chronic Hepatitis B virus (HBV) infection and approximately 15 million people are with chronic Hepatitis C virus (HCV) infection in India. Hepatitis B virus is known to cause genomic integration in the liver tissue resulting in chromosomal deletions and in turn metaplasia. The p53 tumor suppressor gene can be altered in HCC under the transactivating potential of the HBx protein.[4–6] Chronic Hepatitis C virus infection is now considered an important etiologic factor in HCC.[7] HCV-related carcinogenesis is possibly related to chronic inflammation and cirrhosis.[8] Nalpas et al 2001[9] reported a positive association between HCC and consumption of alcohol in which alcohol works as a cofactor for hepatotoxins and hepatitis viruses.

Chronic alcoholism is also on the rise in India. Guptan et al 1996[10] reported that although the possible role of these viral infections and alcohol in the causation of HCC has not been assessed in detail but nearly 25% of all HBV-related chronic liver disease in India is caused by mutant forms of HBV.[10]

HBV infection is the predominant risk factor for the development of HCC, often related to mutant forms of HBV in India. Chronic hepatitis B or C, alcohol, obesity (non-alcoholic fatty liver disease), aflatoxin (cofactor with HBV), tobacco, tyrosinosis, hemochromatosis (iron overload), α1-antitrypsin deficiency, autoimmune chronic active hepatitis, primary biliary cirrhosis, alcoholic cirrhosis, non-alcoholic steatohepatitis, diabetes, viral load, male sex, older age, exposure to aflatoxins, concurrent alcohol abuse are the main risk factors for HCC has been reported by World Gastroenterology Organization: global guidelines.[11]

The most important factor responsible for the development of hepatocellular carcinoma in the predominant

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Abbreviations: AFB1: aflatoxin B1; DM: diabetes mellitus; GT: glucose tolerance; HBsAg: hepatitis-B surface antigen; HBV: Hepatitis B virus; HCC: hepatocellular carcinoma; HCV: Hepatitis C virus; IARC: International Agency for Research on Cancer; NAFLD: non-alcoholic fatty liver disease; RR: relative risk
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north Indian population is chronic Hepatitis B virus infection, with tumors developing more often in a cirrhotic (76%) than in a non-cirrhotic liver has been reported in a prospective comprehensive study from the Indian subcontinent. This pattern is supported by quite similar study from areas where HBV infection is endemic, such as the far east and sub-Saharan Africa. A positive association of cirrhosis of the liver in 80–90% of patients with HCC has been demonstrated in reports from Northern regions.[12–17] Oka et al. 1990[18] found the yearly incidence rate of HCC in cirrhotics varies from 3% in the West[19] to as high as 11% in Japan. Tsukuma et al1990[8] in a prospective study from Japan reported liver cirrhosis and viral hepatitis as risk factors for HCC, each carrying a 3-year cumulative risk of 12.5 and 3.8%, respectively. Colombo et al 1991[19] described that the development of HCC during the course of cirrhosis is not necessarily related to end-stage liver disease. Cirrhotic liver contains various kinds of hepatocellular nodules and these nodules were known to cause HCC.[20,21]

Alcohol consumption has been implicated as a risk factor for developing HCC in many studies.[22] Fifteen of HCC patients had a history of chronic alcohol abuse and nearly 80% of them had evidence of concomitant HBV or HCV infection. A high prevalence of HBV and HCV in alcoholic patients with HCC was demonstrated by Paterlini et al 1993.[5] Alcohol seems to be a cocarcinogen in the pathogenesis of HCC, by inducing cirrhosis, and by increasing the risk of viral infections (HBV and HCV), as well as via its effects on P450 mixed function oxidase system, thus causing enhanced activation of chemical carcinogens.[5]

Ozturk et al 1991[23] described Aflatoxin has been shown to cause hepatocarcinogenesis by a guanine-to-thymidine mutation at the third base of codon 249 in the p53 tumor suppressor gene. The risk of HCC is highest when Aflatoxin exposure is associated with the presence of HBsAg, suggesting a viral–chemical interaction.[24,25]

The predominant factor responsible for the development of HCC in India is chronic HBV infection.[26] A fair proportion of HCC patients in India are either HBeAg negative or have undetectable HBsAg. Three quarters of the HCC patients in the population had distinct features of underlying cirrhosis. It is also reported that the people who have Hepatitis B virus face up to a 100-fold increased risk of developing HCC.[27] Edman et al1980[28] defined that HBsAg which is present in the people infect with hepatitis virus is known to play important role in developing HCC. Ishikawa et al 2009[29] described oncogenes such as c-myc activation in presence of HBsAg since it transform nontumorigenic cell lines into lines capable of growing as tumors in nude mice. It was supported by the hypothesis that HBsAg play an important role in pathogenesis of HBV-associated liver cancer.[29]

Several studies have also suggested that diabetes mellitus may alter the risk of developing a variety of cancers, and the associations are biologically plausible.[30] Diabetes is associated with alterations in liver metabolism and immune response that may influence postoperative recovery and long-term survival after hepatectomy for cancer.[31] Cancer patients who already have diabetes have a greater chance of dying of the disease than cancer patients who do not have the blood-sugar disorder.[32] The risk of liver cancer is common in people with diabetes who are heavy drinkers and who may or may not have hepatitis. Insulin made by the pancreas moves through the portal vein to the liver and exposes the liver to high levels of the insulin hormone. Non-alcoholic fatty liver disease, cirrhosis and abnormal fat retention are diabetes related factors that increase the risk of liver cancer. Obesity is a shared risk factor for both diabetes and liver cancer.[33,34]

ARE INDIANS GENETICALLY MORE PRONE TO HEPATOCELLULAR CARCINOMA?

The representative data on epidemiology of HCC in India is not available. Cancer is not a reportable disease in India and the cancer registries in India are mostly urban. Several etiologic factors including hepatitis viruses, alcohol and aflatoxin have been implicated in the pathogenesis of hepatocellular carcinoma (HCC). There is, however, limited information from the Indian subcontinent.[26] Chronic Hepatitis C virus infection is possibly related to chronic inflammation and cirrhosis[7] now considered an important etiologic factor in HBV-negative HCC cases.[8] A positive association between HCC and consumption of alcohol has been reported from some countries. However, alcohol probably works as a cofactor for hepatotoxins and hepatitis viruses. Viral infection and chronic alcoholism may contribute to alteration in terms of mutation in genome at molecular level.[9]

In India HBV infection, overt cirrhosis of the liver, HCV and alcohol is the predominant factor for the development of HCC.[26] Asians have a strong genetic susceptibility for type II diabetes[35] and DM is a risk factor for HCC in India.

Infection with HBV and HCV are the major risk factors for the development of HCC in Indian patients. Presence of HBV antibodies even in the absence of HBsAg conferred increased risk for HCC in the presence or absence of cirrhosis. Anti-HCV positivity in the absence of HCV RNA conferred no increased risk. HCV RNA positivity and heavy alcohol use significantly increased the risk of HCC among cirrhotic patients, but not non-cirrhotic patients.[36] The association of HBV and HCV as risk for hepatocellular carcinoma and their interaction with genetic factor needs to be further explored in our country.

Genetic variant in low penetrance gene such as GSTM1 and GSTT1 is associated with an increased risk of liver cancer. The influence of GSTM1/T1 null genotypes may contribute in the etiology of HCC in patients with higher levels of AFB1-N7-guanine adducts, who are heavy smokers and those who consume alcohol.[37,38]