Risk Factors in Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma is the fifth most common cancer in the world. The aim of this study was to identify the possible risk factors causing HCC. Certain metabolic diseases like hepatitis B, Hepatitis C infection lead to liver cancer without causing liver cirrhosis and increases risk of HCC by 27 fold. Cirrhosis itself is an independent risk factor of inducing HCC by 5-fold. Drugs used for the treatment of diabetes have shown to cause HCC. Certain toxins like aflatoxins increase the risk of liver cancer. Anabolic steroids are known to cause HCC by mimicking the action of some hormones. Some of organic and inorganic compounds like vinyl chloride and Arsenic cause HCC. This article summarizes the risk factors of Hepato Cellular Carcinoma.

Keywords: Hepatocellular Carcinoma; Liver cancer; Hepatitis B; Hepatitis C; Diabetes; Aflatoxin; Steroids; Smoking; Vinyl Chloride; Arsenic

Abbreviations: THCC: Hepato Cellular Carcinoma; LC: Liver Cancer; As2O3: Arsenic Trioxide; As: Arsenic; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HBsAg: Hepatitis B Surface Antigen; TP53: Tumor protein 53; CYP1A2: Cytochrome 450 1A2; CYP3A4: Cytochrome 450 3A4; GSTP1: Glutathione S-transferase P

Introduction

Liver cancer (LC) ranks fifth in frequency in the world. In developing countries, incidence rates are two- to three-fold higher than in developed countries [1]. Hepatocellular carcinoma, like any other cancer, develops when there is a mutation to the cellular machinery that causes the cell to replicate at a higher rate and results in the cell growth avoiding apoptosis [2]. In particular, chronic infections of hepatitis B, C can aid the development of hepatocellular carcinoma by repeatedly causing the body’s own immune system to attack the liver cells, some of which are infected by the virus, others merely bystanders [3,4].

The early detection of HCC is highly desirable, patients with this disease are often asymptomatic and consequently HCC is frequently diagnosed late, by which time it is often untreated [5]. Suspicions of disease may first arise in patients with liver cirrhosis who develop ascites, encephalopathy or jaundice [6]. Some patients initially present with upper abdominal pain, weight loss, early satiety or a palpable mass in the upper abdomen. Other symptoms include obstructive jaundice, diarrhea, bone pain, dyspnea, intraperitoneal bleeding, paraneoplastic syndromes e.g. hypoglycemia, erythrocytosis, hypercalcemia, severe watery diarrhea, or cutaneous features.

Causes for Hepatocellular Carcinoma

The causes for hepatocellular carcinoma are unknown but several risk factors were identified:

- Chronic hepatitis B and C infection
- Cirrhosis of the liver
- Diabetes mellitus
- Exposure to toxins, such as certain types of fungi (aflatoxin), vinyl chloride, anabolic steroids, and arsenic
- Smoking

Chronic Hepatitis B and C infection

Hepatitis B and C virus (HBV & HCV) may be one of the agents involved in the etiology of human primary liver cancer [7]. This hypothesis is supported by the similarity between the geographical distribution of chronic carriers of the viral surface antigen (HBsAg) and that of hepatocellular carcinoma (HCC), but not all the viruses were related to risk [8]. Researchers have previously identified eight genotypes of HBV and a variety of mutations in two regions of the viral genome are associated with liver cancer. People who have hepatitis B virus face up to a 100 fold increased risk of developing HCC [9,10]. HBsAg which is present in the people infect with hepatitis virus is known to play an important role in developing HCC [11,12]. There were some epidemiological indications of an association between HBV infection and hepatocellular carcinoma are supported by the detection of HBV markers such as HBsAg or viral DNA sequences, although in a non-integrated form in tumor tissue [13]. HBsAg is known to activate oncogenes such as c-myc and that HBsAg could "transform" nontumorigenic cell lines into lines capable of growing as tumors in nude mice which supported the hypothesis that HBsAg play an important role in pathogenesis of HBV-associated liver cancer [14,15].

Cirrhosis of the Liver

Usually, individuals at risk for developing liver cancer are those with cirrhosis (advanced liver disease with permanent liver scarring) [16]. In other words, cirrhosis is a precancerous condition. In fact, patients with cirrhosis regardless of the underlying cause are at increased risk of developing liver cancer [17]. Cirrhosis increases the risk of developing liver cancer by at least 40 times over the risk of an average person. Of all people with cirrhosis, 3 percent will develop liver cancer every year. A good percentage of alcoholics will eventually develop cirrhosis that has increased risk of HCC [18,19]. Cirrhotic liver contains various kinds of hepatocellular nodules, including HCC the hepatocell-
lular nodules which were divided into adenomatous hyperplasia, atypical adenomatous hyperplasia [20]. These nodules were known to cause HCC [21,22].

**Diabetes Mellitus**

Several studies have suggested that diabetes mellitus may alter the risk of developing a variety of cancers, and the associations are biologically plausible [23]. The relation between diabetes and cancer mortality is still under studies. Diabetes is associated with alterations in liver metabolism and immune response that may influence post-operative recovery and long-term survival after hepatectomy for cancer [24]. Patients with type I or type II diabetes mellitus submitted to a potentially curative hepatic resection for metastatic colorectal cancer were identified from the prospective database, and compared with patients with hepatic colorectal metastases submitted to resection during the same time interval, but without diabetes mellitus [25]. 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 [26]. 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 [27,28].

Several confounding factors, having general or site-specific relevance assess cancer risk in diabetic patients. These factors include diabetes duration, varying levels of metabolic control, different drugs used for therapy, and the possible presence of chronic complications [29,30]. Hyperinsulinemia most likely favors cancer in diabetic patients as insulin is a growth factor with pre-competitive metabolic but also mitogenic effects, and its action in malignant cells is favored by mechanisms acting at both the receptor and post-receptor level [31,32]. Insulin's mitogenic action is specifically involved in the higher incidence of liver cancer in diabetic patients since healthy liver cells are physiologically exposed to higher insulin concentrations than other tissues [33,34]. The three major oral anti-diabetic drug families such as sulfonylureas, biguanides, and thiazolidinediones have a different mechanism of action. Sulfonylureas stimulate endogenous insulin secretion, while the other two categories of compounds are insulin sensitizers, i.e., they make tissues more responsive to insulin and, therefore, decrease hyperinsulinemia [35]. If Hyperinsulinemia plays a role in increasing cancer risk and progression in diabetic patients, it is reasonable to expect that these drugs will have a different effect on association between diabetes and cancer [36,37].

**Aflatoxin**

Aflatoxin represents a group of secondary fungal metabolites which were discovered as contaminants of certain lots of animal feeds. These compounds have a high order of acute toxicity to animal species, and have been shown to possess potent carcinogenic properties in several animal species [38,39]. Aflatoxin forms adducts with DNA and with proteins, and these are the direct products of (or surrogate markers for) damage to a crucial, cellular macromolecular target. Aflatoxin B1 undergoes an initial two-electron oxidation by the cytochrome P450-family members CYP1A2 and CYP3A4, yielding aflatoxin-B1-8,9-oxide [40]. This epoxide reacts with the N7 atom of guanine to form a pro-mutagenic DNA adduct (aflatoxin-N7-guanine). The aflatoxin-DNA adduct is unstable and undergoes depurination, leading to its urinary excretion which act as a biomarker. Several mutational assays have shown that aflotoxins induce mainly G-T transversions. A G-T transversion mutation in codon 249 of the TP53 tumor-suppressor gene results in a loss of function, and this mutation has been found in ~50% of patients with HCC [41,42].

**Vinyl Chloride**

Vinyl chloride is associated with liver cancer in humans and has been classified as a Group 1 carcinogen by IARC, Category 1 (carcinogenic to man) by the EU and a Group A carcinogen (carcinogenic to humans) by the EPA (EPA, 1987) [43,44]. Occupational vinyl chloride exposure was first associated with development of liver cancer in 1974, when rare liver angiosarcomas were detected in three workers who worked in a vinyl chloride polymerization plant [45]. This is known to cause liver cancer in infants and younger ones. Vinyl chloride produces DNA adducts and has been positive in gene mutation and chromosomal aberration assays [46]. Chromosomal aberrations have also been observed in peripheral lymphocytes of exposed workers in some studies. The mutations caused by vinyl chloride are different from those of sporadic liver cancers. The mutations caused by vinyl chloride have been found in p53 and Ki-ras genes [47].

**Anabolic Steroids in Liver Cancer**

Anabolic steroids are technically known as Anabolic-Androgen steroids [48]; these steroids mimic the effects of some hormones and increase protein synthesis in the cells particularly in muscles [49-51]. High doses of oral steroids can cause liver damage as they are metabolized in the digestive system increasing bioavailability and stability [52-55]. Steroids are known to cause hepatic adenomas which are not cancerous but it is dangerous as this causes serious bleeding in the liver when they are ruptured [56-59]. C17 alpha alkylated compounds, like Anadrol 50 can lead to stressed liver, even liver damage and very rare cases lead to liver cancer [60,61].

**Arsenic in Liver Cancer**

Liver cancers can develop from specific chronic liver diseases. Epidemiology studies have clearly indicated an association between chronic arsenic exposure and abnormal liver function, hepatomegaly, hepatopetal sclerosis, liver fibrosis and cirrhosis [62]. Arsenic is well absorbed from the gastrointestinal tract, and first reaches the liver. Arsenate is reduced to arsenite in the liver by glutathione which detoxifies it [63]. Liver is rich in glutathione; it is a major site of arsenic detoxification, either from glutathione acting as an antioxidant, or by glutathione-arsenic conjugation for cellular efflux and biliary excretion. Arsenic trioxide (As$_2$O$_3$) is a novel anticancer agent in inducing HCC. As$_2$O$_3$ is used in the complete remission in acute promyelocytic leukemia patients who were refractory to conventional chemotherapy or all-trans retinoic acid. The role of arsenic in the treatment of this unique form of leukemia is still under investigation [64,65]. Arsenic compounds have been tested in other hematological malignancies in vitro. It is not known at present whether these compounds will prove useful in the treatment of solid tumors. Arsenic trioxide causes cancer by methylation of CpG islands in promoter region of p16 RASSF1A, E Cadherin and GSTP1 genes [66]. Experimental studies with cell lines have showed that high concentration of As$_2$O$_3$ causes methylation of the above genes and thus induces cancer [67].

**Smoking**

Smoking of tobacco is practiced worldwide by over one thousand million people. Tobacco is most commonly smoked as cigarettes; both
manufactured which are a highly sophisticated nicotine delivery system and hand-rolled [68]. Pipes, cigars, bidis and other products are used to a lesser extent or predominantly in particular regions. Smoking cigarettes increases the liver damage caused by a common chronic liver disease, hepatitis C. There is a statistically significant and dose dependent association between tobacco smoking and HBsAg negative HCC [69]. Smoking mainly induces p53 mutations which lead to HCC and other type of cancers. Apart from hepatocarcinoma smoking mainly induces lung cancer [70], cancers in nasal cavities, parasanal sinus, nasopharynx, stomach cancer, cervical cancer, kidney cancer, Myeloid leukemia, etc. Lung cancer is the most common of all the cancers and all the investigations have showed a clear cut response relationship between the amounts smoked daily [71,72]. The smoke released by cigars is a complex mixture of several hundred of different molecules which include several carcinogens such as polycyclic aromatic hydrophobic compounds or N-nitrosoamines. Benzopyrenes remains has highly carcinogenic compound known [73].

Conclusion

HCC is one of the commonest cancers worldwide. It is a major health problem and its incidence is increasing day by day. The presence of cirrhosis is the major risk factor and worldwide this is largely due to chronic HCV and HBV infection. HCC carcinogenesis is likely to involve interplay of viral, environmental and host factors. The advent of mass-vaccination programmes for hepatitis B is beginning to due to chronic HCV and HBV infection. HCC carcinogenesis is likely to involve interplay of viral, environmental and host factors. The advent of mass-vaccination programmes for hepatitis B is beginning to

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