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Review article

Hepatocellular carcinoma: An overview of disease epidemiology and risk factors

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ABSTRACT

Hepatocellular carcinoma (HCC) is the most common type of liver cancer. Consequently, the epidemiology of this fatal disease is well considered and studied. Although hepatitis B virus (HBV) and hepatitis C virus (HCV) are amongst the most prominent risk factors for this cancer, there are some other factors participating in the high incidence of HCC such as cirrhosis, cigarette smoking, alcohol drinking, obesity and metabolic disorders.

Keywords: Hepatocellular carcinoma, Hepatitis C virus, Risk factors.

Introduction

Hepatocellular carcinoma (HCC), also called malignant hepatoma is a primary malignancy of the hepatocyte, the major cell type in the liver[1]. HCC accounts for 85-90% of all primary liver cancers with a survival range 6-20 months[2].

Incidence

In terms of global prevalence, HCC ranks as the eighth most common cancer[3]. It is often clinically silent until it is well advanced or tumor diameter exceeds 10 cm. HCC has a poor prognosis with shorter survival, high recurrence rates after treatment[4]. HCC is the third leading cause of cancer-related mortality, responsible for about 600,000 deaths annually[5].

Epidemiology

A-Geographic Distribution

HCC burden is not distributed evenly throughout the world[6]. The geographic distribution of HCC is highly uneven: three geographic areas with different incidence rates (low, intermediate and high) have been recognized[7]. More than 80% of HCC cases occurs in sub-Saharan Africa and Eastern Asia where the highest incidence rate has been reported[6][8]. Areas with intermediate risk include France, United Kingdom and Germany[9], whereas a much lower HCC incidence characterizes North and South America, Northern Europe and Oceania[6]. Strong geographic correlations have been found between the incidence of HCC and the prevalence of hepatitis B surface antigen (HBsAg) or antibody to HCV[10].

B- Age

The incidence of HCC increases with age[9]. The mean age of onset of HCC increased from 43.7 to 49.1[11].

C-Sex

This malignancy occurs more often among men than women[8]. The male to female ratio in liver cancer incidence is about 2:4[12]. HCC is the sixth

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most common cancer among men and the eleventh among women[3].

D-Race / Ethnicity

HCC incidence rate also varies greatly among different populations living in the same region[2]. HCC rates are two times higher in Asian than African Americans, whose rates are two times higher than those are in whites. The reasons for this ethnic variability likely include difference in the prevalence and acquisition time of major risk factors for liver diseases and HCC[2][9].

Risk factors

HCC is a complex disease associated with many risk factors and cofactors[5]. HCC is one of the few cancers with clearly defined major risk factors[3]. Any agent leading to chronic injury and eventually cirrhosis constitutes an oncogenic agent[13]. The chronic infection with HCV and HBV developed cirrhosis, which is the major risk factor for HCC[9][14]. The fraction of HCC estimated to HBV and HCV in 2002 to be 23% and 20% in developed countries, respectively and 59% and 33% in developing countries[15].

HBV infection

In patients with active HBV viral replication, cirrhosis will develop and the incidence of HCC is greatly increased, HBV can cause HCC also in the absence of cirrhosis[16][17]. The risk of HCC in patients with chronic HBV infection is increased in male or elderly, a long time infection, having a family history of HCC, exposed to the mycotoxin aflatoxin (AF), used alcohol or tobacco, co-infected with HCV or hepatitis Delta Virus and have high levels of HBV hepatocellular replication[18].

The role of HBV in tumor formation remains unclear. There is a good evidence that the virus itself exerts a direct hepatocarcinogenic effect and it may have an indirect effect, through the process of the inflammation, regeneration and fibrosis associated with cirrhosis[19].

HCV infection

The prevalence of HCV-infection has been accepted to be a horrible morbidifying factor in hepatic carcinogenesis[20]. The estimated risk of HCC is 15 to 20 times as high among persons infected with HCV as it is among those who are not infected[21]. HCV genomes can be detected in the tumor and surrounding liver tissue[22]. There are several risk factors for developing HCC in HCV infected individuals. These include advanced hepatic fibrosis (including cirrhosis), heavy alcohol use, diabetes mellitus, obesity, low platelets count, elevated alpha fetoprotein (AFP) level, male sex, older age and increased hepatic iron stores[23]. Also cirrhotic patients infected with HCV subtype 1b carry a significantly higher risk of developing HCC than patients infected by other HCV types[24].

Hepatocarcinogenesis is mainly through indirect pathways: chronic inflammation cell deaths, proliferation and cirrhosis. The Direct pathway result of oncogenic potential of core protein[25]. The core protein is capable of inducing this active production of free radicals per se[26]. Its expression would be inducted HCC, even in the absence of a complete set of genetic aberrations, required for carcinogenesis[22].

Cirrhosis

Cirrhosis is an end stage of chronic diffuse liver disease[27]. A 5% of cirrhotic patients developed HCC[28]. Main causes of liver cirrhosis are alcohol use, chronic hepatitis B, C and nonalcoholic steatohepatitis[29]. Cirrhosis occurs in 80–90% of HCC patients[30].

Aflatoxin (AF)

AF is a group of mycotoxins produced by the fungi Aspergillus Flavus and Parasiticus[12]. Storage of crops in hot humid conditions can promote growth of the AF-producing fungi[31]. AF is a group of approximately 20 related fungal metabolites. The four major AF are known as B1, B2, G1 and G2[32]. AF B1 (AF B1), the most abundant form, is metabolized by liver enzymes to generate an epoxide which is highly reactive with DNA, forming adducts at N7 position of guanine. Lack of repair of this lesion may lead to permanent DNA mutations[33]. AF exposure in food is a significant risk factor for HCC[34]. The risk of liver cancer in individuals exposed to chronic HBV infection and AF has up to 30 times greater than the risk in individuals exposed to AF only[35]. AF also appears to have a synergistic effect on HCV-induced liver cancer[32].

Pesticides

Occupational exposure pesticides may have a contributory role in the etiology or progression of HCC[36]. Pesticides have been considered possible epigenetic carcinogens through one or several mechanisms. Some of these mechanisms are spontaneous initiation of genetic changes, cytotoxicity with persistence cell proliferation, oxidative stress, inhibition of apoptosis,

suppression of intracellular communication and construction of activated receptors[37].

Alcohol drinking

Alcohol consumption is an important risk factor for numerous cancers worldwide[38]. Its first metabolite (acetaldehyde) is a local carcinogen in humans[39]. There are synergistic interactions between alcohol intake and smoking[12].

Tobacco Smoking

It is causally associated with liver cancer[12]. An Italian study reported that an interaction between tobacco smoking and infection with HBV and HCV could increase the risk of HCC[40].

Obesity

Several large-scale epidemiological studies have associated the increasingly prevalent overweight and obesity with a higher risk of HCC[41].

Diabetes mellitus

Diabetes mellitus has been associated with increased risk of several cancers[42]. Diabetes mellitus was also shown to increase the risk of primary liver cancers only in the presence of other risk factors such as hepatitis C or B or alcoholic cirrhosis[43].

Metabolic and hereditary diseases

Other hepatic disease as autoimmune hepatitis, hemochromatosis, Wilson disease, alpha-1 antitrypsin deficiency and primary biliary cirrhosis may be associated with HCC development when in cirrhosis stage[44].

Risk factors and pathogenesis

Although the major risk factors have been identified, the molecular pathogenesis of HCC remains largely unknown. It is presumed that the progression of HCC is the consequence of cumulative genetic and epigenetic events similar to those described inother solid tumors[45]. This initiates chronic liver injury, increased liver cell turnover, triggering oxidative DNA damage and inflammatory events. This leads to the formation of dysplastic and macroregenerative nodules that are considered neoplastic nodules[20].

Finally, HCC is the most common primary liver cancer that has varous risk factors, however its molecular pathogenesis is still unknown.

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