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EPIDEMIOLOGY OF HEPATOCELLULAR CARCINOMA

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ABSTRACT: Hepatocellular carcinoma (HCC) is a major cause of cancer death. Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. It is the fifth most common cancer worldwide and the third most common cause of cancer mortality. Despite advances in prevention techniques and new technologies in both diagnosis and treatment incidence and mortality continue to rise. It is less common in most parts of the developed Western world but appears to be increasing substantially in incidence. This malignancy occurs more often among men and older person. Rates of HCC are particularly high in Eastern / Southeastern Asia and Africa, intermediate in Southern Europe and low in most high-income countries. The most prominent risk factors for this cancer are hepatitis B virus (HBV) and hepatitis C virus (HCV). Some other factors are participating in a high incidence of HCC such as cirrhosis, cigarette smoking, alcohol drinking, obesity, aflatoxin exposure, familial/genetic factors, and metabolic disorders. The present review has aimed an overview of worldwide incidence, determinants or risk factors and distribution of HCC.

INTRODUCTION: The liver is the largest glandular organ in the body has more functions than any other body organ. The liver plays a major role in the maintenance of metabolic functions and detoxification of the exogenous and endogenous challenges like xenobiotic, drugs, viral infections and chronic alcoholism [1]. Chronic liver diseases are common disorders characterized by bad sequels started with steatosis to chronic hepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) [2, 3]. Hepatocellular carcinoma (HCC) is the most common primary neoplasm of the liver. HCC is a significant cause of morbidity and mortality. It carries an unfavorable prognosis with aggressive growth behavior and a high rate of recurrence [4, 5].

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Hepatocellular carcinoma is the fifth most common cancer worldwide and the third leading cause of cancer-related deaths [6, 7, 8]. Hepatocellular carcinoma accounts for approximately 6% of all human cancers [9]. Since 1980, the incidence of liver cancer has tripled. Liver cancer death rates have increased by almost 3% per year since 2000 [10]. Overall survival for patients diagnosed with HCC is generally dismal (1 and five year survival rates of 20% and 6%, respectively) [11, 12].

For patients diagnosed with a small tumor and no distant spread, applying potentially curative therapy such as surgical resection, liver transplantation or local ablation significantly prolongs survival (40%-50% at five years) [13, 14]. It is often clinically silent until it is well advanced or tumor diameter exceeds 10 cm [15]. A large number of populations may remain asymptomatic. HCC patients may show jaundice, bloating from fluid in the abdomen, easy bruising from coagulopathy, loss of appetite, unintentional weight loss, nausea, vomiting or fatigue.

Patients usually complain about right upper quadrant pain, weight loss, and deterioration of liver function in cirrhotic cases. Most symptoms are unspecific such as abdominal pain, malaise, fever, jaundice, anorexia, ascites, hemorrhage, and encephalopathy [16]. In most of the cases, cancer occurred in liver but did not begin there, rather are metastasized from anywhere in the body; such type of liver cancer is called secondary liver cancer. In Europe and United States secondary liver cancers are more frequent than primary liver cancer, but in Asia and Africa, primary liver cancer is more common cancer [17]. The most relevant risk factors for HCC are chronic Hepatitis B and Hepatitis C virus infection [18, 19].

Advanced ages, being male, obesity, alcohol abuse, diabetic and family history are also increased risks for developing HCC [20]. 70% - 90% of patients have cirrhosis have HCC [21]. HCC screening includes radiologic tests such as ultrasound, computerized tomography, magnetic resonance imaging and serological markers such as α-fetoprotein at 6-month intervals. Multiple treatments available but only orthotopic liver transplantation (OLT) or surgical resection is curative. Additional treatment modalities include transarterial chemo-embolization, radiofrequency ablation, microwave ablation, percutaneous ethanol injection, cryo-ablation, radiation therapy, systemic chemotherapy, and molecularly targeted therapies [22]. This article focuses on the epidemiology of hepatocellular carcinoma (HCC). It contains briefly reviews the incidence, the major distribution, and global determinants or risk factors of HCC.

Incidence: Over the past 20 years, the incidence of HCC has become doubled from 2.6 to 5.2 per 100,000 populations [23]. The incidence of HCC in developing nations is over twice the incidence of that in developed countries. The major risk factors for hepatocellular carcinoma vary by region and degree of national development [24, 25].

Asia: In India, the age-adjusted incidence rate of hepatocellular carcinoma (HCC) for men ranges from 0.7 to 7.5 and for women 0.2 to 2.2 per 100,000 of population per year. The age-standardized mortality rate for HCC in India for men is 6.8/100,000 and for women is 5.1/100,000. The incidence of HCC in cirrhotics in India is 1.6% per year. The incidence of HCC is increasing in India. The high incidence of HCC in India is related to cirrhosis of liver, chronic hepatitis B virus (HBV) infection, chronic hepatitis C virus (HCV) infection, alcohol consumption and aflatoxin exposure, diabetes mellitus, non-alcoholic fatty liver disease (NAFLD), smoking and tobacco use [26, 27]. More than half of HCCs occur in China alone wherein 2008 the age-standardized incidence rate was 37.4 per 100,000 individuals for males and 13.7 per 100,000 individuals for females. The incidence of HCC in Mongolia and Korea are also high with 99 and 49 cases per 100,000 persons respectively [28]. The high incidence of HCC in these areas is related to the high hepatitis B virus (HBV) infection rates in Asia and especially in China where HBV has traditionally been acquired via transmission from mother to child [29, 30]. Japan also has a high incidence of HCC with a case index of approximately 40 per 100,000 populations. Hepatitis C virus (HCV) is the dominant hepatitis virus in Japan, accounting for 80% of HCC cases. The prevalence of HCV increased in Japan after World War II due to intravenous (IV) drug use as well as contaminated blood transfusion [31, 32].

Africa: In Africa first case of HCC was reported in 1879. Lack of screening and access to medical care is a major cause of death in the black African population. Whites living in the subcontinent have a low incidence of HCC. Most of these cases are found in rural areas. The age-standardized incidence rate in Mozambique (Africa) has the highest, recorded 41.2/100,000 persons each year. Chronic HBV infection is the major cause of HCC in Africa. Cirrhosis coexists with HCC is about 60% of patients in this region [33, 34].

The United States and Europe: In the United States, the overall incidence of HCC is lower than in other parts of the world. The age-adjusted incidence rate tripled from 1975 to 2005 from 1.6/100,000 to 4.9/100,000. This increase is likely a result of the increasing prevalence of HCV from unscreened blood transfusions and IV drug use. The incidence of HCC in the United States is expected to continue to increase over the next decade, because of peak HCV infection rates. HBV accounts for only 10% to 15% of HCC cases in the United States because of widespread HBV vaccination programs [35].

Europe has a slightly higher incidence (2-4 times) of HCC than the United States. The Mediterranean countries (Italy, Spain, and Greece) have incidence rates ranging from 10-20 per 100,000 individuals. These countries also attribute approximately two-thirds of their cases to chronic HCV infection [36, 37].

The global burden of cancer in 2012 was an all-time high of 14 million cases and predicted to grow to 22 million over the next two decades [38]. Recently incidence in the United States has stabilized will little annual change in rate between 2009 and 2011. In contrast, incidence rates have declined in some Asian countries, Spain, and Italy. The decreasing incidence rates were seen China is likely due to programs to reduce aflatoxin B1 exposure and hepatitis B virus (HBV) transmission as well as other public health efforts [36]. In Japan, the decreasing incidence of HCC is related to declining rates of hepatitis C virus (HCV) infection in the population [39, 40].

Distribution of Hepatocellular Carcinoma:

1. Geographic Distribution: The incidence of HCC varies widely by geographic location. The geographic distribution of HCC is highly uneven. Three geographic areas with different incidence rates (low, intermediate and high) have been recognized [41]. Most HCC cases (>80%) occur in either sub-Saharan Africa or in Eastern Asia. China alone accounts for more than 50% of the world's cases [42]. High incidence regions (more than 15 cases per 100,000 populations per year) include sub-Saharan Africa, the People's Republic of China, Hong Kong, and Taiwan [43]. Intermediate incidence areas include Eastern and Western Europe, Thailand, Indonesia, Jamaica, Haiti, New Zealand, and Alaska. Low incidence areas (less than three cases per 100,000 per year) include North and South America, most of Europe, Australia and parts of the Middle East [44].

2. Age: The incidence of HCC increases with age [45]. HCC is considered a disease of older persons with a high incidence in people between 65 to 69 years old. However, the prevalence in young people has risen in recent years due to environmental risk factors at birth[46]. Various studies have also reported that age plays a contradictory role on the prognosis of HCC. Young patients had poorer survival rates than elderly patients. This reduction in survival resulted from a more advanced tumor stage at diagnosis even though they had a better liver function. Also, young patients tended to exhibit larger tumor sizes and poorer differentiation compared with older ones. Young patients have a better survival which is compensated by better liver function, more aggressive therapy, and faster recovery [47]. Fibrolamellar type of HCC typically occurs in young patients [48, 49, 50].

3. Race / Ethnicity: Racial / ethnic differences within multi-ethnic populations are also remarkable. In the United States between 2006 and 2010 incidence rate per 100,000 had highest in Asians / Pacific Islanders (11.7) followed by Hispanics (9.5), blacks (7.5), and finally whites (4.2). Rates of liver cancer among the same ethnicity also vary by geographic location. For example, liver cancer rates among Chinese populations outside China are lower than the rates reported by Chinese registries [51]. One study found that the age-adjusted incidence of HCC was highest among Asians (8.4 per 100,000) followed by blacks (4.2 per 100,000) and whites (2.2 per 100,000) [52].

Another study reported a greater age-adjusted incidence of HCC among Hispanic men (3.29 per 100,000) and women (1.23 per 100,000) compared with white men (1.82 per 100,000) and women (0.60 per 100,000) [53]. Racial/ethnic differences are likely due to variability in the prevalence of risk factors between racial/ethnic groups and between geographic locations.

4. Sex: This malignancy occurs more often among men than women. Men have an incidence of 11.5 per 100,000 compared to 3.9 in women. Hepato-cellular carcinoma death rates have also increased by 2.8% for males and 3.4% for females per year [54]. The explanation for this sex difference might be threefold: firstly, men could have higher rates of environmental exposure to liver carcinogens (such as smoking or alcohol) and hepatitis virus infections; secondly estrogen effects might suppress interleukin (Il)-6-mediated inflammation in women reducing both liver injury and compensatory proliferation; thirdly testosterone effects could increase androgen receptor signaling in men promoting liver cell proliferation [55, 56]. Experiments show a 2 to 8-fold increase in HCC

development in male mice. These data support the hypothesis that androgens influence HCC progression rather than sex-specific exposure to risk factors. No endogenous environmental factors that may affect male risk adversely include higher body mass index and higher levels of androgenic hormones [57, 58, 59].

Determinants (Risk Factors) of Hepatocellular Carcinoma: Fibrosis and cirrhosis are typically precursors of HCC [60]. Furthermore, HCV and HBV are the major etiological agents that lead to the development of HCC [61]. Other risk factors include environmental toxins, hereditary hemochromatosis and cirrhosis [62]. Coexistence of etiologies such as hepatitis B virus (HBV) and HCV infection, HBV infection and aflatoxin B1, HBV/HCV infection and alcohol or diabetes mellitus, HCV infection and liver steatosis increases the relative risk of HCC development [63].

1. Viral Infection:

Hepatitis B Virus (HBV): HBV is a DNA virus with a circular genome that encodes structural and replicative viral proteins. Association of chronic HBV infection and HCC was first elucidated in 1981 by Beasely and colleague [64]. There are eight genotypes of HBV classified using the letters A to H. Most studies have shown an association between genotype C and an increased risk of liver fibrosis and HCC [65, 66]. Approximately 340,000 cases of liver cancer (54.4% of cases globally) are attributed to HBV with the majority of these in Africa, Asia, and the Western Pacific region [67].

Worldwide chronic hepatitis B contributes to the greatest number of HCC. Individuals that have chronic hepatitis B may develop HCC without evidence of cirrhosis [68]. The association between HBV and cancer varies greatly depending on the country and the types of laboratory tests used to diagnose the disease [69, 70, 71]. In West Africa, HBV infection is generally acquired between the ages of 1 and five years and viral replication declines rapidly after adolescence. In East Asia, HBV infection is acquired before the age of 1 year in the majority of cases, and active HBV replication continues until an advanced age; therefore the incidence of HCC continues to increase with age without reaching a plateau [72]. In western countries, HBV is mostly transmitted in adolescence and adulthood through high-risk behaviors such as intravenous drug use, sexual exposure or iatrogenic causes including blood transfusion, unsafe needle practices, invasive procedures, hemodialysis or organ transplantation [73, 74, 75].

Hepatitis C Virus (HCV): HCV is a member of the Flaviviridae family of hepatotropic RNA viruses. Chronic HCV infection is a major cause of HCC in humans [76]. Approximately 195,000 cases of liver cancer (31.1% of cases globally) are attributed to HCV [77]. It is a leading cause of chronic hepatitis, liver cirrhosis, and HCC worldwide. The combination of HCV and HBV infection appears to increase the risk of HCC [78]. There have been six major genotypes identified (genotypes HCV-1 to HCV-6) each with multiple subtypes (distinguished by lowercase letters). Genotype 1 (a and b) is the most common worldwide [79]. Some studies identified genotype 1b with a high risk for HCC development [80].

Patients with HCV infection and who have been alcohol abusers prove to develop more severe fibrosis and have higher rates of cirrhosis and HCC than non-drinkers [81]. 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%). In Asia, the HCV infection rate is highest in Mongolia [82]. Hepatitis C virus is more commonly found in blacks and non-Hispanic whites [83, 84].

Having chronic hepatitis B infection increases the risk of developing liver cancer by 100-fold and having chronic hepatitis C infection increases the risk by 17-fold. Coinfection with HBV and HCV further increases the risk of HCC. HBV can cause liver cancer directly without causing cirrhosis. The hepatitis virus can mix its DNA with the DNA of a liver cell and cause mutations in its genes; thus mutations can lead a cell to lose control over its common function, reproduction and natural cell death, at last, it causes HCC. The risk of liver cancer is higher in heavy drinkers [85, 86].

2. Toxins:

Aflatoxin: Aflatoxin is a mycotoxin produced by the *Aspergillus fungus*. This fungus grows readily on foodstuffs such as corn and peanuts stored in warm, damp conditions [87]. There are four

aflatoxins: B1, B2, G1, and G2. Aflatoxin B1 (AFB1) has been shown to be the most potent hepatic carcinogen. AF also appears to have a synergistic effect on HCV-induced liver cancer [88]. It causes alterations in the hepatocyte DNA [89]. Aflatoxins can induce mutations of the p53tumor suppressor gene [90]. Individuals exposed to chronic HBV infection and AF has up to 30 times greater than the risk in individuals exposed to AF only [91]. The main site of metabolism of AFB1 is the liver but absorbed in the enterocytes of the small intestinal epithelium through the cytochrome p450 enzymes that activate AFB1 into aflatoxin-8, 9-exo-epoxide that is highly reactive with the p53 tumor suppressor gene, generating mutation at codon 249 (R249S; 249ser mutation) in more than 50% of cases of HCC that were exposed to AFB1 [92, 93].

Vinyl Chloride: A recent study reported long-term exposure to vinyl chloride is the identifiable risk factor for developing HCC. Angiosarcoma, hepato-carcinoma, and hepatoadenoma nodules were found in a worker who had been exposed to high doses of vinyl chloride for several years. An experimental study in rats shows angiosarcomas and hepato-carcinomas, the two types tumor found in the same animal after exposure to vinyl chloride [94].

Contaminated Drinking Water: Several studies in rural China have noted a higher mortality rate from HCC among people who drink pond-ditch water compared to those who drink well water. The blue-green algal toxin microcystin commonly contaminates these ponds and is thought to be a strong promoter of HCC [95].

Arsenic: Effects of arsenic on the liver have been suggested in a few case reports like noncirrhotic portal hypertension, hepatic enlargement, hepatocellular carcinoma, and liver angiosarcoma. Epidemiologic studies have not confirmed the association between arsenic exposure and hepatocellular carcinoma [96].

3. Personal Habits:

Alcohol Drinking: The annual incidence of HCC in alcohol-related cirrhosis is 1-4%. Alcoholic liver disease is the second most common risk factor for HCC in the USA after hepatitis C [97]. Heavy alcohol intake (more than 50-70 g/day) for prolonged periods is a well-established HCC risk factor. Heavy intake is associated strongly with the development of cirrhosis.

Women are more susceptible than men to liver injury from alcohol intake [98, 99]. Once alcoholic cirrhosis is established several factors further increase the risk of HCC; these include older age, male gender, and active infection with HBV or HCV. Its first metabolite (acetaldehyde) is a local carcinogen in humans [100]. The main mechanisms of alcohol-induced HCC are acetaldehyde formation, cytochrome P4502E1 induction, reduced anti-oxidants, reduced retinoic acid, hypomethylation, iron overload, immune surveillance, neoangiogenesis, and inflammation [101, 102].

Smoking: Cigarette carries over 4000 toxic substances which cause hazardous adverse effects on almost every organ in the body. Several constituents of cigarette smoke are known liver carcinogens in humans and animal models, *e.g.* 4-aminobiphenyl, arsenic, and vinyl chloride, *etc*. [103] It is causally associated with liver cancer [104]. A meta-analysis reviewed the association between smoking and liver cancer demonstrated an odds ratio (OR) of 1.6 for current smokers and 1.5 for former smokers [105]. An Italian study reported that an interaction between tobacco smoking and infection with HBV and HCV could increase the risk of HCC [106, 107].

Betel Nut Chewing: Case-control trials have suggested that betel nut chewing, widespread in certain regions of Asia, may be an independent risk factor for cirrhosis and HCC [108].

4. Hereditary Diseases:

Hereditary Hemochromatosis: Hereditary hemochromatosis (HH) is an autosomic recessive disease in which an alteration in iron absorption, inducing deposition in the liver and other organs occur. Iron toxicity in the liver is produced by free radical formation, lipid peroxidation of cell organs causing cell death with fibrosis and cirrhosis [109].

***α*-1-antitrypsin Deficiency:** *α*-1-antitrypsin deficiency is an autosomic recessive disease with mutations in the gene A1AT causes an abnormal accumulation of *α*-1-antitrypsin in the hepatocyte endoplasmic reticulum resulting in hepatic cells dysplasia and cirrhosis[110].

Wilson's Disease: Wilson's disease is a heritable disease with mutations in the gene ATP7B and alteration in plasma copper circulation and its bile excretion. Excessive free copper can provoke cytoplasmic injury, cirrhosis and sometimes HCC [111].

5. Hormone:

Oral Contraceptive: A recent review of six studies showed a significant increase in HCC risk with a longer duration (>5 years) of exposure to oral contraceptives [112]. Estrogen and progesterone components of oral contraceptive have been shown to induce and promote liver tumors in animals [113]. Estrogens are thought to cause liver neoplasia by increasing proliferation rates, thereby increasing rates of spontaneous mutations [114]. A series of case reports documented the occurrence of HCC in relatively young men who had been long-term users of androgenic steroids [115, 116, 117].

Anabolic Steroids: Continuous use of anabolic androgenic steroid in high-doses is associated with substantial health risks, including hepatocellular adenoma. The malignant transformation from hepato-cellular adenoma to hepatocellular carcinoma [118].

6. Diseases Related to Life Style:

Obesity: Obesity is closely associated with hepatocellular carcinoma (HCC) as well as other malignancies. Obesity is an important risk factor for cancer development and overall mortality in HCC. Molecular mechanisms of hepato-carcinogenesis in obesity are adipose tissue remodeling, dysregulation of adipokines, increased reactive oxygen species, insulin resistance or hyperinsulinemia, alteration of gut microbiota, and dysregulation of microRNA. Obesity is the most common cause of non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH). NAFLD or NASH leads to HCC as well as liver cirrhosis [119, 120].

Diabetes: Diabetes mellitus directly affects the liver because the liver plays an essential role in glucose metabolism. Diabetes is an independent risk factor for HCC [121, 122]. Diabetes increases the risk of non-alcoholic fatty liver disease (NAFLD), a condition characterized by excess fat accumulation in the liver which ranges from isolated hepatic steatosis to more aggressive non-alcoholic steatohepatitis (NASH) and may progress then to fibrosis, cirrhosis, and eventually HCC [123, 124].

7. Cirrhosis of Liver: Cirrhosis occurs in 80-90% of HCC patients [125]. Cirrhosis is characterized by fibrous septae and nodule formation as well as alterations in blood flow. Hepatocellular carcinoma (HCC) can develop at any stage of cirrhosis[126]. The presence of cirrhosis of any cause increases the risk of HCC [127]. Main causes of liver cirrhosis are alcohol use, chronic hepatitis B, C and non-alcoholic steatohepatitis [128]. A high rate of HCC has also been reported in patients with cirrhosis due to genetic hemochromatosis [129] and primary biliary cirrhosis [130]. Different risk of HCC causes different rates of incidence: HCV>HBV>hemochromatosis. The stage of cirrhosis is also significant in determining the risk of HCC development [131, 132].

CONCLUSION: HCC is a common malignancy worldwide. The principal causal factors for carcinogenesis are viral infections, hereditary diseases, chronic medical conditions like diabetes and personal habits like alcohol drinking, smoking, *etc*. A detailed understanding of these risk factors and distribution is necessary to improve the screening, prevention, early identification, and management of HCC.

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