Hepatocellular carcinoma (HCC); aetiological considerations

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Abstract: Hepatocellular carcinoma (HCC) is a commonly occurring cancer worldwide. The aetiology of HCC, often associated with different molecular carcinogenic pathways, differs geographically; with chronic viral hepatitis being the main cause in most localities. Different driving mutations resulting from distinct carcinogenic pathways potentially impact the choice of effective therapies for HCC.

Keywords: HCC; aetiology; biology

Citation: Abdel-Rahman O. Hepatocellular carcinoma (HCC); aetiological considerations. Adv Mod Oncol Res 2015; 1(1): 18–19; http://dx.doi.org/10.18282/amor.v1.i1.8.

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, with approximately 600,000 new cases per year, and the third leading cause of cancer-related deaths[1,2]. According to data from GLOBOCAN 2012, wide geographic and socio-economic differences exist among different ethnic groups of the world with 83% of the estimated 782,000 new cancer cases worldwide prevailing in less developed countries, and 50% in China alone[3]. In men, the regions of high incidence are Eastern and South-Eastern Asia with age-standardized rates (ASRs) of 31.9% and 22.2% respectively. Intermediate rates occur in Southern Europe (9.5%) and Northern America (9.3%) and the lowest rates are in Northern Europe (4.6%) and South-Central Asia (3.7%). In women, the rates are generally much lower than men with an overall male:female ratio of 2.5, the highest incidence being in Eastern Asia and Western Africa (10.2% and 8.1% respectively), the lowest in Northern Europe (1.9%) and Micronesia (1.6%). These geographical differences in HCC incidence have been largely ascribed to differences in risk factor epidemiology in different areas of the world[4,5].

Aetiology/biology correlations in HCC

HCC usually develops in a liver already chronically damaged, often from cirrhosis. The aetiology of liver disease, and consequently that of HCC, differs geographically with consequent differences in the HCC genotype. In most areas, chronic viral hepatitis due to either hepatitis B virus (HBV) or hepatitis C virus (HCV) is the main cause of HCC[6].

HCV-related HCC

Approximately 195,000 cases of liver cancer (31.1% of cases globally) are attributed to HCV, with northern and middle Africa being the areas of highest prevalence[7,8]. Additionally, HCV is the most common viral aetiology of HCC in the western population (Europe/North America)[9]. It is difficult to determine the likelihood of the development of HCC among HCV infected persons due to the paucity of adequate long term cohort studies. However, the best estimate is from 1% to 3% after 30 years[10]. Lastly, alcohol is an important factor in patients with HCV infection, with HCV reported in 4.6%–55.5% of alcoholics. 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[11].

**HBV-related HCC**

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[12]. Risk is higher in those with HBeAg+, high ALT, high HBV DNA, cirrhosis and the elderly. Risk is markedly reduced with successful antiviral therapy[13]. Characteristically, HBV can cause HCC both in the presence and absence of cirrhosis due to its ability to integrate its DNA into host cells and act as a mutagenic agent, causing secondary chromosomal rearrangement and increasing genomic instability[14]. This is in contrast to HCV-related HCC which is found almost exclusively in patients with cirrhosis.

**Alcoholic liver disease**

The development of cirrhosis from alcohol consumption increases the risk of HCC. It has been suggested that heavy alcohol consumption of >80 g/d ethanol for at least five years increases the risk of HCC by nearly five-fold[15]. This mechanism of developing HCC is particularly prevalent in many Western countries[16].

**Non-alcoholic steatohepatitis (NASH)**

NASH, in association with multiple components of the metabolic syndrome is thought to increase the risk for developing chronic liver disease, cirrhosis, and HCC[17].

**Conclusion**

Paying proper attention to the diverse aetiologies that may be associated with developing HCC has a profound significance in terms of prevention as well as treatment of this disease. Different aetiologies may be associated with different molecular carcinogenic pathways, and consequently different driving mutations that may impact the choice of effective therapies for this disease.

**Conflict of interest**

The author declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

**References**


doi: 10.18282/amor.v1.i1.8