

MINI-REVIEW

Burden of Hepatocellular Carcinoma in Asia

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Abstract

Hepatocellular carcinoma (HCC), the sixth most prevalent cancer worldwide, continues to have high prevalence in many countries of Asia. The main challenge is the high prevalence of chronic hepatitis and aflatoxin, for example in China. HBV vaccination should be the major preventive tactic in Asian countries. The burden of HCC is low in Iran because most cases are due to HBV and this infection was less common. Although in Iran, a mass vaccination program started in 1993, its impact on decreasing the burden of HCC due to HBV can only be expected in future decades.

Keywords: Hepatocellular carcinoma - burden - Asia

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Introduction

Hepatocellular carcinoma (HCC) is the primary malignancy of the liver. Most cases of HCC are secondary to either a viral hepatite infection (hepatitis B or C) or cirrhosis (alcoholism being the most common cause of hepatic cirrhosis) (Kumar et al., 2003). It represents approximately the sixth most prevalent cancer worldwide and due to the poor prognosis, it is also the fourth fatal cancer in the world. Also, HCC is the third most frequent cause of cancer deaths among men worldwide (Parkin et al., 2005). Males are affected more than females usually and it is most common between the age of 30-50 (Kumar et al., 2003).

Asia is the most populous continent in the world. It covers approximately 4 billion people and it hosts 60% of the world's current human population. The distribution of HCC is heterogeneous with a high prevalence seen in Asia (Teo and Fock, 2001) and eighty percent of the burden is borne by countries in Asia and sub-Saharan Africa (McGlynn and London, 2005).

The incidence ranges from <10 cases per 100,000 population in North America and Western Europe to 50-150 cases per 100,000 population in parts of Africa and Asia where (Taylor-Robinson et al., 1997; Deuffic et al., 1998; El Serag and Mason, 1999; Law et al., 2000) and it varies across different countries in Asia with the highest age-adjusted incidence rate exceeding 27.6-36.6 cases/100,000 men/year in the east Asian countries to 15 cases/100,000/year in developed countries such as

Japan (Okuda, 1992) and 5 cases/100,000/year in Iran (Gomaa et al., 2008) and this cancer causes 662,000 deaths worldwide per year, about half of them in China (World Health Organization., 2007). The highest liver cancer rate in the world is in China, according to the cancer registry reporting (Chen and Zhang, 2011).

Role of HBV

The most important risk factor for HCC is cirrhosis. So, HCV and HBV are the major etiological agents that lead to the development of HCC (Colombo et al., 1989). HBV and HCV infections together account for the majority of HCC and cirrhosis worldwide. Areas of the world with high HCC rates have high prevalence of chronic HBV Infection (CDC, 2003).

The majority of infected people with HBV reside in the HCC high-risk regions of Asia and Africa. In most such regions, HBV infection is associated with most cases of cirrhosis and HCC (Fallot et al., 2012). Although the anti-HCV positivity was the most frequent risk factor in both blacks and whites in western countries, HBsAg positivity was the most frequent etiological factor in Asians with HCC (Di Bisceglie et al., 2003).

In high-rate HCC and HBV areas, roughly 70% of HBV infections are acquired either in the prenatal period or in early childhood (CDC, 2003).

In the Asian eastern countries, HBV is the first cause of HCC. 80-90% of chronic liver diseases and HCC are caused by HBV in Taiwan (Chen, 1993). In Japan HBsAg-

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positive cases of HCC constituted 42% in 1977-1978, but reduced to 15.5% in 2000-2001, reported by the Liver Cancer Study Group of Japan (Kim et al., 2008). In Korea approximately 65-75% of HCC patients are positive for HBsAg and the high incidence rate of HCC in this country is related to the high carrier rate of HBV in the general population (Sin et al., 1996; Han and Ahn, 2005; Park and Kim, 2008).

A study in Taiwan concluded the importance of prenatal transmission of HBV and maternal virus load as a risk factor in HBV carcinogenesis in a familial clustering of HCC (Chen et al., 2004).

In Iran, 80% of HCC cases are positive for at least one of the markers of Hepatitis B virus and this virus appears to be the most common cause of HCC in Iran (Shamszad and Farzadgan, 1982; Merat et al., 2000) and a recent study in southern Iran indicated that the predominant cause for HCC was hepatitis B (Hajiani et al., 2005).

Additional analysis indicated that the cumulative HCC risk from age 30-70 years is estimated to be 87% for those persistently positive for both HBsAg and HBeAg, 12% for those persistently positive for HBsAg only, and 1% for those negative for HBsAg (You et al., 2004). So prolonged duration of HBeAg positivity or high HBV DNA level may be associated with an increased risk of HCC (Kao and Chen, 2005).

The Role of HCV

Anti-HCV positives are significantly associated with the development of HCC, (Kao et al., 1994). Unlike HBV, HCV infection is usually acquired in adulthood and acute HCV infections are usually silent (McGlynn and London, 2005). Unlike patients with hepatitis B infection, patients with HCC due to hepatitis C are invariably cirrhotic (Teo and Fock, 2001).

Besides, among HCV carriers, infection with genotype 1b increases the risk of HCC twofold compared to others without this genotype (Huang et al., 2011).

Assays for antibody to HCV (anti-HCV) as well as for the viral genome (HCV-RNA) have documented HCV as the next most common cause of these diseases after HBV in Taiwan (Kao and Chen, 1999; Kao and Chen, 2005). Also studies indicated that HCV still plays a significant role in hepatocarcinogenesis in areas endemic for HBV infection (Chen, 1995; Sun et al., 2003; Kao and Chen, 2005).

In Japan, anti-HCV-positive cases of HCC accounted for more than 70% of cases diagnosed over 10 years. HCC of unknown origin and other causes increased gradually and constituted 12.7% of cases reported in 2000-2001. Whereas; In Korea approximately 10-20% of HCC patients are positive for anti-HCV (Kim et al., 2008).

The co-infection of hepatitis B and C is associated with a further increased risk of HCC. It is believed that the two hepatotropic viruses accelerate liver disease (Chen et al., 1997).

Aflatoxin

In 1987 IARC classified aflatoxin as a human carcinogen (IARC, 1987). Ecological studies have shown

that the incidence of HCC correlates with contamination of foodstuff with aflatoxins (Anand, 2002). Aflatoxin is prevalent in particular in Africa, South-East Asia and China (Chuang et al., 2009) and most HCC cases due to aflatoxin occur in sub-Saharan Africa, Southeast Asia, and China, where populations suffer from both high HBV prevalence and largely uncontrolled exposure to aflatoxin in the food (Liu and Wu, 2010). In high exposure areas, aflatoxin multiplicatively interacts with HBV to induce HCC (Liu et al., 2012). An interaction of aflatoxin and HBV infection on HCC risk was revealed in short-term prospective studies in Shanghai, China. It was estimated that aflatoxin increased the risk of HCC four-fold, HBV increased the risk seven-fold, and the combination of aflatoxin and HBV increased the risk 60-fold (Qian et al., 1994). Recent studies in the high- aflatoxin contamination area of China have reported similar results (Yu et al., 2000; Ming et al., 2002).

Alcohol

Alcohol use varies between countries and within countries. Per capita alcohol intake is higher in Western Europe than in the US, and higher in the US than in Asia (Drinking in the United States, 1998). Studies of HCC found alcohol to be a more significant risk factor in low incidence areas than in high incidence areas, due to lower mean alcohol consumption in high-risk populations (McGlynn and London, 2005), however some studies in HBV-endemic populations have shown a positive association between alcohol consumption and HCC (Oshima et al., 1984).

A Japanese study indicated that alcohol consumption is more important than HCV as a major cause of liver cancer death among men (Makimoto and Higuchi, 1999). But a study conducted in the south of Iran suggested less than three percents of HCC patients was associated with alcohol consumption (Hajiani et al., 2005).

Mortality

Survival rates of primary liver cancer are uniformly poor in both high-rate and low rate areas (McGlynn and London, 2005).

In the past two decades, operative mortality and surgical outcome of liver resection and liver transplantation for HCC have improved (Lai and Lau, 2005).

In China an increasing trend was seen for liver cancer in recent years (Yang., 2005; Cai et al., 2008) and its mortality had been decreasing in Korea and Japan (Bae et al., 2002; Yoshimi and Sobue, 2003), however the mortality rates in these two Asian countries were much higher than Western countries (Matsuda and Saika, 2012).

The rate of HCC mortality moderately increased in Iran but reaching a plateau (Pourhoseingholi et al., 2010).

Conclusion

The prevalence of HCC is still high in Asia (Teo and Fock, 2001), however, recently declining trends in HCC incidence have been seen in some high-rate areas like as Hong Kong, Shanghai and Singapore (McGlynn et al., 2001; Parkin et al., 2002).

In some Asian countries like South Korea, National Cancer Screening program for liver cancer was initiated but the participation of general population is still low (Noh et al., 2012). The main challenge which still present in Asia, is the high prevalence of chronic hepatitis. So prevention of infection with hepatitis B and C virus is the key strategy to reduce the incidence of HCC in Asia (Lai and Lau, 2005). Prevention of infection with HBV reduces the risk of subsequent HCC. For example, following universal vaccination of neonates in Taiwan, the incidence of HCC among children declined from 0.7-0.36 per 100,000 (Chang et al., 1997). Also in most areas of the world where aflatoxin exposure is widespread, chronic HBV infection is highly prevalent. A Meta-Analysis showed that, reducing aflatoxin exposure to non-detectable levels could reduce HCC cases in high-risk areas by about 23% (Liu et al., 2012). Though HBV vaccination in these areas like China should be the major preventive tactic (McGlynn and London, 2005; Blumberg., 2010; Chen and Zhang, 2011). In Korea, the national vaccination program has contributed to the reduction of liver cancer mortality beyond just a natural decrease in Korean children and adolescents (Gwack et al., 2011).

Iran is located in Middle East, a region where majority of HCC cases presents with intermediate or advanced stages of the disease (Siddique et al., 2004). The high relative frequency of liver carcinoma in Middle East is related to endemicity of hepatitis B infection (Koriech and Al-Kuhaymi, 1994). Although in Iran, the mass vaccination program started in 1993 and reached 94% coverage in 2005 (Alavian et al., 2007), its impact on decreasing the burden of HCC due to HBV suppose to be in future decades (Pourhoseingholi et al., 2010). Therefore it is expected to see a changing epidemiology as similar changes in Japan (Kim et al., 2008) in which, the main cause of HCC shifted from HBV to HCV.

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