EDITORIAL

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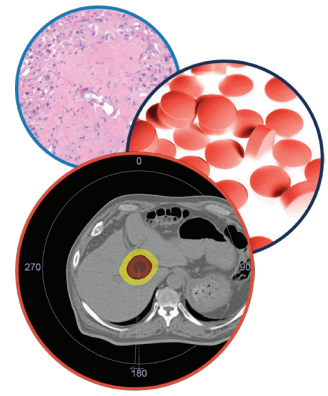

Hepatic Oncology

Preventing hepatocellular carcinoma: the crucial role of chronic hepatitis B monitoring and antiviral treatment



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"...achieving substantial population level health gains depends on the development of a comprehensive screening, monitoring and treatment program..."

Liver cancer is the second leading cause of cancer death worldwide, responsible for an estimated 746,000 deaths and 782,000 new cases in 2012 [1]. The countries in the Western Pacific region accounts for 64% and China alone accounts for 51% of the new liver cancer cases and deaths each year. Approximately 80% of hepatocellular carcinoma (HCC), the most common type of liver cancer, is associated with viral hepatitis [1]. In countries with high prevalence of hepatitis B virus (HBV) infection, such as China, up to 80% of HCC is associated with hepatitis B [2]. Liver cancer carries a poor prognosis with a global mortality to incidence ratio of 0.95 [1]. In the USA, the 1-year survival rate remains less than 50% [3]. Asians and Pacific Islanders have the highest incidence of HCC among the different racial/ethnic groups.

While every individual with chronic hepatitis B infection (CHB) or HBV carrier is at risk for developing HCC, disease progression leading to cirrhosis is associated with the greatest risk [2]. In an effort to improve survival through early detection of HCC, the American Association for the Study of Liver Diseases recommended HCC screening with abdominal ultrasound (US) at 6–12 month intervals of HBV carriers considered at increased risk for HCC, including those with cirrhosis, family history of liver cancer and Asian male HBV carriers above the age of 40 [4,5]. However, it remains controversial whether population-wide HCC screening of CHB patients results in a reduction in HCC mortality particularly in resource-constraint regions of the world that have the highest burden of HCC. The only two randomized trials available to date are both from China [6,7]. A population-based study in the city of Shanghai, conducted by the Liver Cancer Institute of Fudan University, reported 1-year HCC survival rates improved from 31.2% in the control group to 65.9% in the screened group among 18,816 CHB patients aged 35–59 years with or without cirrhosis, who were randomized into either a group using US and AFP screening every 6 months or a control group [6]. The second study from a rural setting in Qidong, using AFP screening every 6 months without US, did not show any improvement in survival [7]. According to the National Cancer Institute [8], screening for HCC

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of persons at elevated risk does not result in a decrease in mortality, based on fair evidence. The current recommended screening tool for HCC is abdominal US, which has a sensitivity and specificity of 60 and 90%, respectively [9]. However, the effectiveness of US screening depends on the experience of the examiner, technology used, body habitus, the presence of cirrhosis and the size of the tumor. Furthermore, lesions identified on US requires further evaluation with more sophisticated and costly computer tomography or MRI. The management of HCC is also complex and requires expertise in multidiscipline including liver surgery, local-regional therapies and transplantation, which many patients in the developing countries have either no access to or cannot afford [2]. Even after initial successful treatment, HCC is associated with a high recurrence rate and would require long-term surveillance with imaging studies and repeat treatments for recurrent disease.

Hepatitis B vaccine created the first breakthrough in HBV prevention and indirectly in HCC prevention. For that reason, it is also called the first anticancer vaccine. Antiviral therapy for CHB has the potential to prevent progression to cirrhosis, reverse the fibrosis caused by cirrhosis [10] and prevent HCC by slowing the progression of liver disease [2,5,11]. Screening and chronic disease management of CHB meets established public health criteria as formulated originally by Wilson and Junger [12]:

- It is a serious health disorder that can be diagnosed before symptoms develop;
- It can be detected by reliable, inexpensive and minimally invasive tests;
- Chronically infected patients have years of life to gain if medical evaluation, monitoring or treatment is initiated early;
- The cost of screening is acceptable in relation to the anticipated benefits.

"...access to diagnostics, treatment and monitoring is still limited in developing countries with the highest burden of hepatitis B virus-infection due to resource constraints."

Despite the fact that CHB infection is consistent with these criteria, access to diagnostics, treatment and monitoring is still limited in developing countries with the highest burden of HBV-infection due to resource constraints.

In 2010, the Institute of Medicine report [13] on viral hepatitis highlighted the lack of awareness about HBV and HCV infections and insufficient understanding about the extent and seriousness of their public health impact. As evidence to this inadequacy, a recent study [14] on whether provider knowledge of HBV management guidelines influence disease monitoring within the primary care settings, concluded that the majority of HBV-infected patients in the study received only periodic disease monitoring with ALT measurements, and testing for HBV DNA level and hepatitis B antigen in the primary care setting was limited. In addition, the study also concluded that there was suboptimal utilization of imaging to screen for HCC in the at-risk Asian population.

Recently, the United States Preventive Task Force found convincing evidence that antiviral treatment of chronic HBV infection is effective in improving intermediate outcomes (i.e., virologic or histologic improvement of clearance of hepatitis B antigen and adequate evidence that antiviral regimens improve health outcomes, such as reduced risk for HCC) [15]. Given the accuracy of the screening test and the effectiveness of antiviral treatment, the United States Preventive Services Task Force concluded that screening is of moderate benefit for populations at high risk for HBV infection, such as foreign born individuals from endemic countries, and this recommendation applies to screening for HBV in nonpregnant adolescents and adults who have not been vaccinated as well as other individuals at high risk for HBV infection [15]. The largest group of CHB-infected patients are inactive carriers without cirrhosis. Although treatment is not indicated for this group, both the United States and international professional practice guidelines recommend that inactive CHB should be monitored with serum ALT and HBV DNA levels at least once a year following diagnosis [5]. The reason is that inactive patients are still at risk for developing HCC with a rate of 0.2–0.5% per year, and also can develop active disease which is associated with an increased risk of HCC at 0.9–2.8% per year [16]. Despite these recommendations and the risk of disease progression, long-term monitoring of ALT and HBV DNA in patients who had inactive disease at the time of initial diagnosis is not a common practice. According to the findings from a recent study [17], where we assessed the health impact and cost–effectiveness of a strategy of monitoring patients with inactive CHB and treatment of patients who developed active disease with highly potent oral antiviral drugs, such as entercavir or tenofovir, an estimated 73% of HCC cases is preventable when this strategy of monitoring inactive and treating active patients

is implemented. Although the potential gains are high, achieving substantial population level health gains depends on the development of a comprehensive screening, monitoring and treatment program that would increase the number of CHB-infected persons in the population identified, monitored and treated. HCC prevention by screening the at-risk population for chronic HBV, long-term monitoring of those with inactive disease and oral antiviral suppressive treatment for those who meet the treatment criteria has the potential to be the first innovative, effective cancer prevention strategy that many countries can adopt. According to the new report from the International Agency for Research on Cancer (IARC), the global battle against cancer will not be won with cancer treatment alone but will require increased commitment to prevention and early detection. In accordance with our findings, a cost–effectiveness study [18] from Australia concluded that CHB monitoring and treatment coupled with a HCC surveillance strategy, was a cost-effective public health strategy and was preferable to HCC surveillance alone as a cancer control strategy.

Until there are more effective tools available for the early detection of HCC, and more effective curative therapies, prevention of hepatitis B by vaccinating all newborns and those at risk, as well as long-term monitoring of inactive and treatment of active CHB, will remain the most effective and cost-effective approach towards reducing the global burden of HCC.

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