Oncogenic Viruses and Hepatocellular Carcinoma

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KEYWORDS

• Hepatocellular carcinoma • Oncogenic viruses • Hepatitis B • Hepatitis C

KEY POINTS

- Cirrhosis in patients with chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection is not a prerequisite step for hepatic tumorigenesis.
- The role of HCV and HBV in promoting hepatocellular carcinoma (HCC) development by either direct or indirect effects is still speculative, yet there is compelling evidence that both mechanisms exist.
- Vaccination plays a central role in the prevention of HBV-related HCC.
- Current antiviral therapies for HBV and HCV, if successful, can reduce but not completely eliminate the risk of HCC.
- The introduction of the new HCV direct-acting antiviral agents has not been in practice long enough to permit an estimate of their likelihood of reducing HCC incidence.

INTRODUCTION

Worldwide, approximately 80% of hepatocellular carcinoma (HCC) is caused by hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infection, especially in the setting of established cirrhosis or advanced fibrosis. There are more than half a million new cases of HCC globally and almost the same number of deaths caused by this disease annually[1] because of the very high case-fatality rate.

The risk of developing HCC among carriers of HBV infection ranges from 10- to 100-fold greater compared with the rates in uninfected people, depending on the markers and populations that are evaluated.[2] In HCV infection, the relative risk for developing HCC in patients with serologically confirmed HCV infection is estimated to be 17-fold.[3] The age-adjusted incidence of HCC is increasing in many countries,

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including the United States, and has been widely attributed to the spread of HCV infection in industrialized countries.[4] The geographic distribution of HCC coincides with the distribution of HBV and HCV infections in those areas. In the United States, Europe, Egypt, and Japan, more than 60% of HCC is associated with HCV and about 20% is related to HBV, whereas nonalcoholic fatty liver disease and other causes contribute to the remainder. In Africa and Asia, where HBV is endemic, 60% of HCC is associated with HBV, 20% is related to HCV, and the remainder is distributed among other risk factors (for example aflatoxin).[1,5] Men are more susceptible to HCC than women; older age, family history of HCC, and advanced disease are also associated with its development. Other risk factors for HCC, apart from viral hepatitis B and C, include alcohol consumption and nonalcoholic fatty liver disease. Although recent clinical observations and translational research have enhanced our understanding of the molecular mechanisms driving the initiation and progression of HCC, much remains unknown. The role of HCV and HBV in promoting HCC development either directly or indirectly is still speculative.[6,7] The indirect pathways include the development of HCC on a background of chronic inflammation and the associated regenerative wound-healing response that is linked to the development of fibrosis and cirrhosis. The more direct pathways refer to alteration in cellular homeostasis caused by integration of the virus (notably HBV DNA) into the host's genome or modifications in cell signaling by specific HBV or HCV viral-encoded proteins.[6,7] The evidence, as described later, is compelling that molecular derangements that are hepatocarcinogenic exist in viral infection; but the cause-and-effect relationships have yet to be confirmed.

In Taiwan, HBV vaccination has decreased the incidence of new infections and HCC; however, there is no vaccine for HCV. Suppression of HBV replication and a sustained viral response (SVR) in the treatment of HCV are associated with a reduction in HCC incidence among treated populations. There is an ongoing controversy regarding the role of antiviral therapy in reducing HCC incidence in cirrhotic patients with HBV.[8–12] Also a small subset of patients with HCV with advanced fibrosis or cirrhosis who achieve SVR remain at a heightened risk for HCC development.[13–18] None of the new HCV direct-acting antiviral agents have been in use long enough to evaluate their effect in reducing HCC incidence.

PATHOGENESIS

Current data indicate that HCC tumors are highly complex and heterogeneous resulting from the aberrant function of multiple molecular pathways. The role of HCV or HBV in promoting HCC development by either direct or indirect activity and their relative importance to the pathogenesis of HCC have not been clearly defined.[6,7]

Hepatitis B Virus

Although HBV integration into the host's genome is not essential for viral replication, there is substantial evidence showing that such HBV DNA genomic integration occurs.[19–22] Since the development of new whole-genome sequencing methods, several studies have been done to evaluate the relative extent and the functional impact of such integrations on the development of HCC. Whole-genome sequencing analysis of HCC in patients with HBV revealed that, although HBV sequences were present in both the tumor and their adjacent nontumorous liver tissue, HBV signals were more frequent in the tumor than in the nontumorous tissue.[23,24] Furthermore, although HBV integration in the nontumorous tissue occurs in many sites, in the tumor, most of the insertions are at major integration sites.[23] These findings suggest that, although in the nontumorous tissue hepatocytes are heterogeneous, HCC tumors are more likely