Review

Hepatitis C Virus Mediated Hepatocellular Carcinoma: A Focused Review for a Time of Changing Therapeutic Options

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Hepatocellular carcinoma (HCC) is a major cause of morbidity and mortality, accounting for approximately 600,000 deaths annually world-wide and 10,000 deaths annually in the United States. Chronic infection with the hepatitis C virus (HCV) is the leading risk factor for HCC in the United States, and the second leading risk factor for HCC world-wide. The addition to the anti-HCV treatment armamentarium of boceprevir and telaprevir in 2011, and of simeprevir and sofosbuvir in 2013, mark a transition to a new era. In this new era, treatment for HCV is becoming so highly effective and tolerable that for the first time eradication of chronic HCV on a population level is realistically foreseeable. A major reduction in the burden of chronic HCV is likely to translate into a substantial reduction in the incidence of HCC. Here, we review the epidemiology, pathogenesis, and treatment of HCC with a special focus on hepatocarcinogenesis associated with chronic HCV infection.
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INTRODUCTION

Hepatocellular carcinoma (HCC) is a leading cause of cancer mortality, accounting for an estimated 600,000 deaths worldwide and 10,000 deaths in the United States annually. Chronic infection with the hepatitis C virus (HCV) is the second most important risk factor for HCC worldwide, after chronic infection with the hepatitis B virus (HBV). This is a time of tremendous change in the clinical management of chronic HCV, since the FDA approval of boceprevir and telaprevir in 2011, simeprevir in November 2013, and sofosbuvir in December 2013. There is the expectation that additional anti-viral agents will be approved in the near future as well, and that in soon combinations of all-oral anti-viral medications will be available as an alternative to interferon-based regimens. This explosion of new options for the treatment of HCV holds the promise for more effective and also better tolerated therapy, which could significantly decrease the burden of chronic HCV in the United States.

We speculate that a significant reduction in the burden of chronic HCV in the United States could result in a significant decrease in the incidence of HCC, although due to the natural history of chronic HCV infection leading to HCC only after many years of infection, we anticipate this could take many years to manifest. We therefore offer this focused review on special considerations regarding HCC in the context of chronic HCV infection. We will address the epidemiology of HCC and HCV with attention to important clinical co-factors for HCV-mediated HCC, address the pathogenesis of HCC with attention to comparing and contrasting mechanisms of hepatocarcinogenesis in HCV versus of other etiologies including HBV, and finally address how treatment options may be tailored to HCV-mediated HCC.

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EPIDEMIOLOGY AND CLINICAL RISK FACTORS / CO-FACTORS

Primary liver cancer, of which hepatocellular carcinoma (HCC) is the most common form, is the 5th most frequently diagnosed cancer and the 2nd most common cause of cancer death worldwide.[1] World-wide, HCC accounts for approximately 600,000 deaths annually, with approximately half occurring in China.[1] In the United States, HCC accounts for approximately 10,000 deaths annually.[2]

Worldwide, HBV is the most common etiology of HCC accounting for approximately 50% of cases, and HCV accounts for a further 25% of cases.[3-5] Unlike in most of Africa and Asia where HBV is the single leading risk factor for HCC, in Japan and in the US it is HCV.[6]

Cirrhosis secondary to HCV is associated with the highest annual risk for developing HCC.[6] Annual incidence rates of HCC in patients with HCV-related cirrhosis range widely from 1% to 8%,[6,7] and this wide range may reflect important differences both in viral genome and host factors. The progression to hepatic fibrosis, cirrhosis, and HCC is thought to occur slowly in chronic HCV infection, with an interval of 20-30 years between infection and development of HCC.[8]

Although infection with either chronic HBV or chronic HCV alone account for a majority of HCC cases, a minority patients have co-infection with both viruses. Although the prevalence of co-infection with both chronic HBV and chronic HCV is not well characterized, a meta-analysis published by Donato et al in 1998 found a pooled incidence of approximately 2.5%.[9] They found a synergistic effect of co-infection with HBV and HCV, with an overall odd ratio of 17.3 for development of HCC with HCV alone, 22.5 for HBV alone, and 165 for HBV/HCV co-infection.[9] Even in the absence of detectable hepatitis B surface antigen (HBsAg), "occult" HBV co-infection with HCV carries a 2-fold increased risk for the development of HCC over chronic HCV infection alone.[10] The relevance of occult HBV infection in HCC is discussed in greater detail below.

A number of host and virus factors affect risk for development of HCC mediated by HCV. The most important host parameter is the degree of hepatic fibrosis. HCV results in HCC mediated through cirrhosis most of time, although HCC may occur in HCV patients in the absence of cirrhosis. Although some patients with HCC mediated by non-cirrhotic HCV may have occult HBV, cases of HCV-mediated HCC with negative HBV DNA assays for both tumor and non-tumor tissue have been documented, suggesting that chronic HCV alone in the patient with a non-cirrhotic liver truly is a sufficient condition for the development of HCC.[11] A systematic review of the data on HCC arising from HCV without cirrhosis found insufficient to report the prevalence of this phenomenon with any certainty, but the lower bound of the pooled estimated prevalence was reported at 6.7%.[12]

Important viral parameters include HCV genotype and IL-28B genotype. Genotype 1b HCV has been reported to carry higher risk for HCC than other genotypes,[13-15] although other data suggests that genotype 3 could confer higher risk than non-genotype 3 HCV for the development of HCC.[16] Of course, regional differences in prevalence of the various genotypes may introduce confounding into such analysis, and at minimum may limit the generalizability of these findings from studies in one part of the world to patient populations in other regions. IL-28B genotype, which has been demonstrated to predict response to IFN/ribavirin therapy for HCV, may also affect risk for HCC. In one Japanese study, although patients with HCC had IL-28B genotypes in a distribution reflecting the general population with chronic HCV, those with the IL-28B T/T genotype had higher rates of recurrent HCC after treatment with percutaneous radiofrequency ablation or resection.[17] Retrospective studies on the impact of HCV genotype and IL-28 genotype on risk for HCC should be interpreted with caution, because an apparent association between these parameters and incidence of HCC could be confounded by the known genotype-dependent differential response to interferon-based therapy, and therefore may be an indirect marker of anti-viral treatment failure rather than a more aggressive phenotype of HCC per se.

HBV infection is another important co-factor for HCC development in patients with HCV. High HBV viral load and hepatitis B e-antigen (HBeAg) positivity are known to increase the risk for HCC compared to patients with low viral loads and HBeAg negativity.[6,18] HBV genotype D is associated with increased risk of HCC in comparison to genotype A, and genotype C with increased risk of HCC in comparison to genotype B.[6,18] Hepatitis B infection can persist even in the absence of detectable HBsAg, a phenomenon termed "occult HBV". Patients with occult HBV may develop HCC, and in fact the highest rates of occult HBV have been reported in patients with HCC.[19] Occult hepatitis B may be indicated by the presence of anti-hepatitis B core antibody (anti-HBc) without accompanying HBsAg or anti-hepatitis B surface antibody (anti-HBs), or may occur even in the presence of anti-HBs, which is generally thought of as protective against HBV infection.[20] However, even anti-HBc is not a reliable marker of occult HBV, with up to 25% of patients with detectable HBV DNA being negative for anti-HBc.[21] In a prospective study of patients with HCV undergoing OLT, patients found to have occult HBV were significantly more likely to have HCC than those without occult HBV, implying that occult HBV co-infection superimposed on chronic HCV infection may be an important and under-appreciated risk factor for HCC, even in the United States.[22] There appears to be a particular association between chronic HCV infection and occult HBV infection. Estimates of the prevalence of occult HBV within a population of patients with chronic HCV has been reported at up to 38% in a study from Japan,[23] and prevalence of HCV within a population of patients with occult HBV reported at 27% in a German study.[24] There is evidence that occult HBV, and not just HBsAg-positive chronic HBV, is an important risk factor for the development of HCC.[25]

HIV is another apparent co-factor with HCV for the development of HCC. There is conflicting data on whether the clinical course of HCC in patients with HIV may be more aggressive than in HIV-negative controls.[26,27] There is data to suggest that since the advent of highly-active anti-retroviral therapy for HIV, patients with AIDS have benefited from increased longevity which has also been mirrored by an increasing incidence of HCC.[28] Furthermore, HCC has been observed to develop more rapidly in HIV/HCV co-infected patients than in patients with HCV alone, possibly due to more rapid progression to cirrhosis.[29] What direct role of the HIV virus may play in hepatocarcinogensis, other than mediated by accelerated hepatic fibrosis in the setting of HCV, is not known.

Other known co-factors for the development of HCC in patients with chronic HCV include heavy alcohol use[6,30] and diabetes mellitus / metabolic syndrome.[6]

PATHOGENESIS

The pathophysiology of hepatocellular carcinogenesis is a very complex process about which much has been learned,[3,5,19,31-36] but which remains incompletely understood. Many specific molecular, genetic, and epigenetic events have been documented along the pathway to development of HCC. However, it remains unclear which specific events might be critical for the development of HCC ("drivers"), and which

may be markers of HCC ("passengers"). Cirrhosis is the most important risk factor for HCC, and the great majority of HCC cases mediated by both HCV as well as by HBV do develop in the context of cirrhosis. Most of the key events in the progression to HCC are probably consequences of repeated cycles of cellular inflammation, injury, repair, death, and regeneration. Molecular events associated with such chronic inflammation are likely key to hepatocarcinogensis arising both from chronic HCV and HBV.[33] Important pathways common to hepatocarcinogenesis from any etiology include activation of the Raf/mitogen activated protein kinase (MAPK), wnt/beta-catenin, and transforming growth factor-β pathways.[37] Telomere shortening is another common event in HCC pathogenesis. Telomere shortening is an event which has been demonstrated in human cirrhotic liver tissue (including both viral and non-viral etiologies of cirrhosis) in comparison to human non-cirrhotic controls,[38] which suggests a "driver" rather than "passenger" role in the development of HCC. Other common pathways likely include accelerated inflammation due to maladaptive immune responses, and oxidative stress from an inflammatory micro-environment.

In addition to these common pathways, etiology-specific mechanisms have also been elucidated. Examples of these include chromosomal instability generated by HBV retroviral insertion into the host genome, and protein-protein interactions between products of both the HBV and HCV viral genomes with important regulators of tumor suppression and DNA repair such as the p53 protein. Special etiology-dependent considerations in HCC pathogenesis are discussed in greater detail below.

PATHWAYS TO HEPATOCARCINOGENESIS UNIQUE TOHCV

The HCV genome encodes a variety of proteins including "core" which is a structural protein, as well as "NS3" and "NS5A" which are non-structural proteins. These specific protein products of the viral genome have been implicated in the pathogenesis of HCC, through pathways unique to patients infected with the HCV virus.

As with other etiologies of cirrhosis, any driver of inflammation and oxidative stress is likely to contribute to hepatocarcinogenesis, and in the case of HCV nonstructural proteins NS3 and NS5A have been implicated in this role, as has the HCV core protein.[39-41] Another mechanism of HCC carcinogenesis unique to HCC involves inhibitional binding of the NS5A protein with the p53 protein, which has a critical role in tumor suppression and DNA repair.[42,43]

A similar mechanism mediated by physical interaction between NS3 and the p53 protein has been proposed.[44] The HCV core protein has also been implicated in inhibiting T-cell proliferation, implying a possible role in failure of immune system surveillance for HCC.[45] Yet another mechanism unique to HCV involves mutations of the core gene, certain of which have been associated with increased risk - up to 8-fold - in comparison to wild-type core gene, for HCC in human studies.[46,47]

MicroRNAs (miRNA) are short non-coding segment of RNA which have been shown to be dysregulated in a variety of cancer states, including HCC. Altered patterns of expression of specific miRNA are an epigenetic phenomenon associated with HCC. As with many specific events along the pathway to HCC, it remains not entirely clear whether dysregulation of these miRNA may represent "driver" or "passenger" events. Regardless, of the over 1000 miRNA which have been identified in humans, it appears that a subset of these are most relevant to HCC carcinogenesis, and further subsets of these may be specific to various etiologies of chronic liver disease. For example, distinct panels of dysregulated miRNA have been identified in patients with HCC arising from HCV as compared to HCC arising in patients with HBV.[48]

Interestingly, HCV may promote some of the pathways by which obesity and metabolic syndrome lead to HCC mediated by fatty liver disease.[49] From an epidemiological perspective, a particular association between chronic HCV infection and type-2 diabetes has been noted, with a higher prevalence of type-2 diabetes in a large population with chronic HCV than either a population with chronic HBV, or a population without viral hepatitis.[50] There is also data to suggest an association between insulin resistance and development of HCC in patients with chronic HCV, independent of the presence of diabetes.[51] The HCV core protein has been implicated in dysregulated glucose metabolism and insulin resistance,[52,53] although this is likely to be just one of several mechanisms by which chronic HCV infection may play a role.

PATHWAYS TO HEPATOCARCINOGENESIS UNIQUE TO NON-HCV ETIOLOGIES

There are several mechanisms by which HBV may lead to HCC not shared with HCV. First, HBV is a hepadna virus and belongs to Group VII retroviridae. HBV, as a retrovirus, integrates into the host hepatocyte genome, which can lead to chromosomal instability.[4,54] In addition to inducing chromosomal instability in general, there is evidence that HBV is prone to insertion of its genome into "hotspots" in host hepatocyte DNA, including sites linked to specific genes including hTERT and MLL4.[55-60] Although shortening of telomeres has been observed in HCC in associated with a variety of etiologies of chronic liver diseases, HBV genome insertion into hTERT and disruption of this gene may accelerate this process particularly in HBV.

Accumulation of HBV surface antigen in the endoplasmic reticulum, which accounts for the classic "ground-glass" appearance of HBV-infected hepatocytes, can also promote oxidative stress promoting HCC development.[33]

Another mechanism unique to HBV involves the hepatitis B x-protein (HBx), which is thought to play a role in hepatocarcinogenesis, primarily through protein-protein interactions.[31] There is evidence from cell line experiments that HBx protein can inhibit the function of the p53 protein,[61] which as noted above has important tumor-suppressor and DNA repair functions. Animal models suggest an additional

role for HBx promoting HCC mediated through the c-myc pathway.[19] However, the relative importance of this HBx-mediated mechanism in the propensity of chronic HBV infection to result in hepatocarcinogenesis is unclear and a matter of some debate.[5]

TREATMENT

Generally accepted approaches of treatment of HCC are guided by, or at least reflected in, the Barcelona-Clinic Liver Cancer (BCLC) algorithm for the treatment of HCC, which is endorsed by the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL).[62-64] Patients with HCC without cirrhosis are best treated with resection. Patients with cirrhosis and early stage HCC (BCLC stage 0 or A), within the Milan Criteria, are generally offered liver transplant. Selected cirrhotic patients (especially those with good synthetic function, absent portal hypertension, and solitary tumors) may also be good candidates for resection. Patients with more advanced disease are offered loco-regional therapy including percutaneous chemical or thermal ablation, or trans-arterial chemo- or radio-embolization. In some patients, this therapy may be able to convert a patient who is not a candidate for curative intervention (resection or transplant) to one who is, i.e. "down-staging". For other patients who remain ineligible for curative therapy, these treatments can significantly retard progression of disease and improve survival. Patients with metastatic disease or macrovascular invasion are offered systemic treatment sorafenib, or may be candidates for experimental therapies in the setting of clinical trials. Patients with very end-stage disease, BCLC stage D, may only be candidates for palliative measures for symptom control. In the BCLC algorithm, no consideration is given to the underlying etiology of chronic liver disease, and patients with HCC arising from HCV are managed in the same fashion as patients with HCC arising from HBV or other etiologies.

However, etiology of chronic liver disease does impact screening strategies for HCC. In particular, the AASLD guidelines for screening for HCC identify specific populations of individuals at sufficiently high risk for developing HCC, so as to merit a protocolized screening strategy based on abdominal ultrasound every 6 months.[62] AASLD guidelines recommend screening specific sub-populations of patients with chronic HBV in the absence of cirrhosis (Asian males over age 40, Asian females over age 50, family history of HCC, North-African Blacks) but recommend screening patients with HCV only if cirrhosis is present, to the extent of explicitly stating that chronic HCV with stage 3/4 (i.e. bridging fibrosis) is not a clear indication for screening.[62] Although this is the only HCV-specific recommendation for the management of HCC, there is evidence that anti-viral medication for the treatment of HCV may play an important role not only in the prevention of HCC but also in its management.

Although management decisions guiding treatment of HCC, once established, are not guided by underlying etiology of chronic liver disease, there is evidence to suggest that patients with chronic HCV may have worse outcomes. An observational studies comparing long-term outcomes between patients with HCC arising from HCV, alcohol, and NASH found worse overall survival in patients with HCV or alcoholic liver disease in comparison to those with NASH.[65] However, this observation may be primarily a reflection on the long-term consequence of recurrent HCV infection after liver transplant, because no difference in recurrence-free survival was detected.[65]

CONSEQUENCE OF ANTI-VIRAL THERAPY FOR HCV

It is clear that successful treatment of HCV early in its natural history greatly improves long-term outcome by halting progression of fibrosis to cirrhosis and thereby preventing complications of cirrhosis including HCC. There is also evidence to suggest that even after HCV has resulted in cirrhosis, there is still an opportunity to reduce the risk for development of HCC through anti-viral therapy.

One meta-analysis based on 11 published studies[13,66-75] found an overall risk-reduction for the development of HCC of 3.7-fold in HCV patients treated with interferon and achieving sustained virological response (SVR).[76] This meta-analysis also detected a benefit for treatment with interferon even in those patients treated but not achieved SVR, in comparison to those who were untreated.[76]

A systematic review by Ng and Saab on the effects of SVR on long-term outcomes for patients with chronic HCV infection found that eradication of the virus resulted in a 1.7- to 4.2- fold decrease in risk for HCC.[77] This review analyzed findings from 6 studies including patients with chronic HCV and all stages of fibrosis,[78-83] in addition to 3 studies including patients only with HCV and advanced fibrosis.[84-86] Of these 9 studies, the highest relative risk reduction, although not the highest absolute risk reduction, was noted in studies including patients with all stages of hepatic fibrosis.[80,83]

A subsequent meta-analysis on the effect of SVR on HCC risk in HCV patients by Morgan et al similarly found an overall 4-fold risk reduction.[87] This meta-analysis was based on 20 studies (2 in abstract form) of which 12 included patients with all stages of fibrosis[74,88-98] and 8 included patients with advanced fibrosis only,[79,81,85,99-103] with minimal overlap of studies included in comparison to the work by Ng and Saab referenced above. In this meta-analysis, the overall relative risk reduction for HCC associated with HCV eradication was the same in the studies including only patients with advanced fibrosis, compared to the studies including patients with all stages of fibrosis. Again, the studies finding the highest relative risk reduction, of up to 10- or 20-fold, were those including patients with all stages of hepatic fibrosis.[95,97]

On a population level, a study by Chang et al reported a decrease in HCC-related mortality in Taiwan that occurred in relationship to a nation-wide program of treatment for chronic HCV.[104]

A randomized trial by Shiratori et al examined the benefit of treating HCV after HCC is established. A group of patients with HCC on a background of HCV were treated with percutaneous ablation and then randomized to either interferon or no additional treatment, and a superior 5-year survival was seen in the group treated with interferon.[105]

CONSEQUENCE OF ANTI-VIRAL THERAPY FOR OCCULT HBV IN SETTING OF HCV

As noted above, there has been increased recognition over recent years of occult HBV as a co-factor for the development of HCC in patients with chronic HBV. There is a large body of data to support the role for anti-viral therapy for chronic, HBsAg positive, HBV to improve survival of patient being treated for HCC.[106-114] A logical question that arises in this context is whether anti-viral therapy for occult HBV may offer any protection again the development of HCC, or whether such treatment could influence the clinical course of HCC in patients with chronic HCV and occult HBV. Shi et al conducted a meta-analysis[10] of studies investigating the risk of developing HCC in patients with occult HBV, including in their eight prospective studies[22,115-121] and eight retrospective studies.[21,122-128] They found that patients with both occult HBV and chronic HCV had an over two-fold increased risk for HCC in comparison to patients with chronic HCV alone. In addition to being associated with increased risk for HCC, there was an association reported by Chang et al between occult HBV and worse disease-free survival after treatment for HCC with resection.[129] These data suggest a possible role for treatment of occult HBV especially in patients with chronic HCV, to reduce the risk of HCC. One report supports the efficacy of this strategy,[130] although additional data are needed. It is quite possible that the increased risk for HCC associated with occult HBV may be associated with molecular/genetic events early in the course, i.e. viral genome insertion into host hepatocytes at the time of prior acute infection when viremia had been high, and viral genome insertion events would have been most likely.

IMPLICATIONS OF NEW ANTI-VIRAL AGENTS FOR HCV

An estimated 3.2 million individuals in the United States are infected with chronic viral hepatitis C, many of whom are undiagnosed.[131] A recent cost-effectiveness analysis of boceprevir- or telaprevir-based triple therapy found an anticipated life-time risk reduction for HCC from 13.2% to 9.5% for patients with advanced fibrosis and from 4.7% to 2.9% for patients without advanced fibrosis, in comparison to interferon with ribavirin alone. If one were to imagine, as a thought-exercise, that all 3.2 million individuals with HCV were treated with triple therapy, this would therefore result in the prevention of between 57,000 and 118,000 cases of HCC depending on the relative prevalence of limited versus advanced fibrosis in the overall population. Rates of sustained virological response are expected to be higher with the newer anti-viral agents, translating to an even high theoretical maximum number of cases of HCC which could be prevented in the hypothetical scenario in which 100% of patients with chronic HCV were treated. Of course, this hypothetical scenario would depend on 100% of all patients being diagnosed, having access to anti-viral therapy, and adhering with therapy. Of course, the real-world anticipated benefit in terms of preventable cases of HCC would be much smaller. Nonetheless these new medications do hold the promise of significantly decreasing the burden of chronic HCV in the United States, with the anticipated downstream effect of reduced incidence of HCC attributable to HCV.

It is hard to predict how many patients will be successfully treated in the coming years. However, we do speculate that the improved tolerability and acceptability to patients of interferon-free, all oral, regimens will result in a larger number of patients successfully completing treatment. In addition, a recent recommendation for one-time testing for HCV of all patients in the "baby boomer" generation, together with what we anticipate will be a major marketing campaign on the part of pharmaceutical companies which have invested an enormous amount of resources in the research and development of these new drugs, will also result in increased patient awareness and interest in therapy. Unfortunately, it is possible that the rising incidence of obesity, metabolic syndrome, and NASH/NAFLD may result in a counter-balancing increase in the incidence of NASH-related HCC.

Importantly, although relevant to a smaller cohort of patients, the advent of newer anti-viral medications is likely to result in increased rates of cure of HCV post-transplant. This can be reasonably speculated to result in improved long-term survival of patients undergoing liver transplant for HCV cirrhosis complicated by HCC, even if rates of post-transplant HCC recurrence do not change. Similarly, we speculate that improved rates of SVR in patients with recurrent HCV who underwent liver transplant for HCV cirrhosis without HCC will be less likely to develop recurrent post-transplant cirrhosis and therefore be at lower risk for de-novo HCC in the transplanted liver.

For the research community, the availability of these new anti-viral agents on the market, and their incorporation into the clinical standard of care, will signal a shift in research energies and resources to other etiologies of HCC. One area of renewed focus will be the ongoing search for a cure for HBV. Currently, anti-viral HBV therapies such as tenofovir and entecavir offer potent viral suppression, but not cure. Two particularly interesting areas of research in this regard are therapies targeting covalently closed circular DNA (cccDNA) and targeting the putative HBV receptor on hepatocytes. Finally, it seems likely that the molecular mechanisms by which HCC arises mediated by NASH will be studied in greater detail. A greater understanding of hepatocarcinogenesis mediated by NASH may lead to new targeted therapies for this group of patients, which due to the anticipated decrease in the burden of chronic HCV, will comprise a larger proportion of HCC patients over time.

CONCLUSIONS

HCC is a devastating cancer with a fascinating pathogenesis. In this dawning era of proliferating new anti-viral

medications, clinicians have an opportunity to materially reduce the burden of HCC in this country over the next several decades. This involves screening patients for HCV, and offering treatment for HCV when appropriate. There is evidence that screening for occult HBV may be indicated in HCV patients, possibly by HBV PCR for patients with anti-HBc positivity regardless of anti-HBs status, and treatment with anti-viral medications for occult HBV when identified. As additional direct-acting anti-viral medications are developed, we may learn more about the specific events in HCV-mediated HCC carcinogenesis, which hopefully could lead to the development of new tests for HCC screening or possibly even new molecular targeted therapies for HCV-medicated HCC.

CONFLICT OF INTEREST

None.

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