JNCI J Natl Cancer Inst (2016) 108(4): djv359

doi:10.1093/jnci/djv359
First published online November 30, 2015
Commentary

COMMENTARY

Hepatitis-Associated Liver Cancer: Gaps and Opportunities to Improve Care

Brian McMahon, Joan Block, Timothy Block, Chari Cohen, Alison A. Evans, Anu Hosangadi, W. Thomas London, Morris Sherman; on behalf of the 2015 Princeton HCC Workshop participants

Affiliations of authors: Liver Disease and Hepatitis Program, Alaska Native Tribal Health Consortium, Anchorage, AK (BM); Hepatitis B Foundation, Doylestown, PA (JB); Baruch S. Blumberg Institute and Hepatitis B Foundation, Doylestown, PA (TB); Hepatitis B Foundation, Doylestown, PA (CC); Drexel University School of Public Health, Philadelphia, PA (AAE); Hepatitis B Foundation, Doylestown, PA (AH); Fox Chase Cancer Center, Philadelphia, PA (WTL); University of Toronto, Toronto, Canada (MS).

Correspondence to: Joan Block, RN, BSN, Hepatitis B Foundation, 3805 Old Easton Road, Doylestown, PA, 18902 (e-mail: joan.block@hepb.org).

Abstract

The global burden of hepatocellular carcinoma (HCC; primary liver cancer) is increasing. HCC is often unaccompanied by clear symptomatology, causing patients to be unaware of their disease. Moreover, effective treatment for those with advanced disease is lacking. As such, effective surveillance and early detection of HCC are essential. However, current screening and surveillance guidelines are not being fully implemented. Some at-risk populations fall outside of the guidelines, and patients who are screened are often not diagnosed at an early enough stage for treatment to be effective. From March 17 to 19, 2015, the Hepatitis B Foundation sponsored a workshop to identify gaps and limitations in current approaches to the detection and treatment of HCC and to define research priorities and opportunities for advocacy. In this Commentary, we summarize areas for further research and action that were discussed throughout the workshop to improve the recognition of liver disease generally, improve the recognition of liver cancer risk, and improve the recognition that screening for HCC makes a life-saving difference. Participants agreed that primary prevention of HCC relies on prevention and treatment of viral hepatitis and other underlying etiologies. Earlier diagnosis (secondary prevention) needs to be substantially improved. Areas for attention include increasing practitioner awareness, better definition of at-risk populations, and improved performance of screening approaches (ultrasound, biomarkers for detection, risk stratification, targeted therapies). The heterogeneous nature of HCC makes it unlikely that a single therapeutic agent will be universally effective. Medical management will benefit from the development of new, targeted treatment approaches.

Depending upon the methodology used, HCC is estimated to be the second (1) or third (2) most common cause of cancer mortality worldwide. Globally, the leading cause of HCC is chronic viral hepatitis, with 45% attributable to infection with hepatitis B virus (HBV) and 26% due to hepatitis C virus (HCV). In the United States, chronic HCV infection (40%) and alcohol abuse (29%) are the leading causes of HCC (2,3). A growing etiology of HCC is nonalcoholic fatty liver disease (NAFLD) as a result of the rising epidemic of obesity and diabetes worldwide (4,5). As part of its Princeton Workshop series, the Hepatitis B Foundation convened a group of nineteen leading HBV and HCC experts to consider gaps and opportunities to improve the detection and medical management of HBV-associated HCC.

HCC Incidence and Risk Factors

Gaps in Knowledge

The incidence of HCC is generally underestimated, regardless of geographic region, as many liver-related deaths are not identified as HCC and many known HCC-related deaths are miscoded in medical records and/or not noted on death certificates (6,7).

Received: August 10, 2015; **Accepted:** October 22, 2015

Tumor registries can be misleading with regard to actual incidence as the quality and completeness of registries vary. There have been several studies on the incidence of HBV-related HCC in Asia (especially China and Taiwan), the United States, and Europe, upon which we can base conclusions. These include population-based, prospective cohort studies, such as the Haimen City Cohort study and the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus study (REVEAL-HBV) (8,9), as well as clinic-based prospective and retrospective studies. In many middle- and low-income countries, the incidence of HCC is estimated based on limited data, and well-designed studies are lacking.

The population data for the United States increasingly reflects the impact of immigration of people who have early life exposure to HBV and who come from regions of the world where different HBV genotypes may be more prevalent than those in the United States. The authors are unaware of any comprehensive study of HBV genotypes in the United States, and changes in the risk groups that develop HCC in the United States often remain invisible. It is difficult to discern if the rates of HCC among immigrants from Asia to the United States are increasing, as country of origin and ethnic subgroup information are incomplete and not available population-wide (10). Risk factors of concern in the US population (including immigrants) include chronic viral hepatitis, alcohol abuse, diabetes, and metabolic syndrome as a result of obesity.

There are important gaps in the understanding about many of the risk factors for HBV-associated HCC (eg, the role of the metabolic syndrome, the synergism of aflatoxin with hepatitis viruses, reactivation of HBV in patients receiving chemotherapy or immunosuppressive therapy, the role of alcoholic cirrhosis). Specific HBV genotypes appear to be an underlying risk factor for HCC. Studies in Asia, such as the REVEAL-HBV study, have shown that the incidence of HCC is substantially higher in persons infected with genotype C than in those with genotype B (11). A prospective HCC surveillance study of Alaska Native people with chronic HBV infection found that the incidence of HCC was higher in those infected with genotype F, and the age at HCC diagnosis was younger in those with genotypes F and C compared with those infected with genotypes A, B, and D (12). There is also much to be elucidated about the impact of therapeutic intervention for HBV on HCC risk. Patients who received HBV antiviral therapy had a lower risk of HCC than those that did not (13), and even those with decompensated cirrhosis had improved outcomes with antiviral therapy (14). It is unclear if intervention earlier, or for longer, would increase benefit. That said, the positive effect of HBV antiviral therapy persisted in subgroup analysis after adjusting for serum markers of fibrosis, and antiviral therapy was protective throughout a range of fibrosis levels.

Gaps in Prevention of HCC

HBV vaccination status substantially impacts the incidence of HCC, as vaccination at birth and in early childhood reduces the risk of developing chronic HBV infection after exposure. Prospective studies in Taiwan, Alaska, and Thailand have shown a marked decrease in the incidence of HCC in association with universal infant and early childhood HBV vaccination (15,16). The birth dose of vaccine is critical for reducing perinatal transmission of HBV (17), but there are global barriers to administration because of limited infrastructure, current birthing practices (eg, difficulty reaching babies not born in hospitals) and lack of political will, necessity of cold chain for vaccine doses, birth dose if HBV vaccine is not routine in most countries in sub-Saharan Africa and many regions of Asia, and birth dose of HBV vaccine lacking in the GAVI-funded universal childhood vaccination programs (18).

Other areas of need for HCC prevention include the identification of HBV and HCV infections and appropriate treatment and effective treatment of NAFLD. As noted, the prevalence of NAFLD is increasing; current medical treatments are not particularly effective and nonmedical interventions are generally ineffective.

Detection of HCC

Limitations of the Current Guidelines for Screening and Surveillance of HCC

Currently, the American Association for the Study of Liver Diseases (AASLD) recommends surveillance for HCC with liver ultrasound every six months for at-risk populations of individuals chronically infected with HBV including: Asian men over age 40 years and Asian women over age 50 years, patients with a family history of HCC, patients with cirrhosis, and Africans over the age of 20 years (19,20). Surveillance is also recommended by AASLD for patients with non-HBV cirrhosis (eg, those with HCV or alcoholic cirrhosis). The World Health Organization (WHO) recommends surveillance for HCC with liver ultrasound and serum alpha fetoprotein (AFP) levels every six months for HBV-infected patients with cirrhosis or family history of HCC and conditionally for those over the age of 40 years. Importantly, WHO recommends that surveillance be done only where ablative and/or surgical therapies are available to treat early lesions. As such, screening to identify those at risk is not generally done in low-income countries where interventional therapies are not available. Ultrasound for screening is also not available in many low-income countries, highlighting the need for better serologic markers for HCC with higher sensitivity and specificity than AFP, which has a high rate of false-positive results.

One issue of much discussion at the workshop was the need for a more specific definition of "at-risk" individuals. The current screening and surveillance approach (semi-annual ultrasound, blood tests) is around 70% to 80% effective in detecting HCC, and 80% to 90% specific (20,21,22,23). Who are the other 20% to 30% that the guidelines miss, and how do we reach them? Applying current methods to these populations broadly (eg, HBV-positive without recognized cirrhosis or younger than age 40 years) would result in many false positives. There are now a variety of different ways to assess the risk of HCC for different categories of patients with liver disease (eg, patients with chronic HBV infection, patients with cirrhosis of different causes, patients awaiting transplant, the general population in high-incidence regions).

There are also issues with the two main modes of detection of HCC for surveillance, ultrasound and serological biomarkers. Although ultrasound is generally inexpensive, noninvasive, and widely available, the quality is operator-dependent and highly variable, and obesity (a problem particularly in North America) impacts efficacy of ultrasound considerably. The AASLD guidelines discuss the need for ultrasonographers to undergo special training (similar to that done for mammograms) (19).

The advantages of biomarkers are that they are very inexpensive, very widely available, and generally require only a blood sample. The disadvantages of currently available biomarkers are that they can be insensitive (particularly for small tumors), are not highly specific (yielding false positives), and

some are also markers of advanced disease (and are therefore unsuitable for early detection). The most well-studied and commonly used biomarker is serum AFP; however, sensitivity and specificity are limited and AASLD does not recommend AFP as a stand-alone screening approach. In addition, some liver tumors do not express AFP.

Implementation of Screening and Surveillance Guidelines: Areas of Need

The majority of HCC cases diagnosed in the United States do not come through cancer screening and surveillance. For some, the diagnosis of chronic HBV infection first occurs when they are diagnosed with HCC, but many who have been diagnosed with HBV have not been followed. They are outside of the continuum of care (risk assessment, primary prevention, detection, diagnosis, cancer treatment, recurrence surveillance, and end-of-life care) that is in place for other types of cancer (24).

Several barriers to the implementation of guidelines for HCC surveillance were discussed at the workshop. High-quality evidence for the effectiveness of HCC surveillance is lacking, and it is unlikely that sufficient studies would ever be conducted to obtain what would be considered high-quality evidence. In addition, practitioners may fail to recognize the presence of liver disease or to initiate and maintain screening for HCC in those found to have liver disease or a chronic viral hepatitis infection (25). The authors are unaware of any studies showing that surveillance can be maintained every six months for more than a few years, and patient surveillance visits tend to drop off over time. A retrospective study of about 5000 insured, noncirrhotic HBV patients in the United States found that only 6.7% of patients were in full compliance (defined as one liver ultrasound every 6 months) over the time period assessed (2006–2010). About 60% had incomplete compliance (one or more ultrasounds over the observational period), and about 34% had no surveillance at all. Patients were less likely to be screened if they had HBV/HIV co-infection or lived in a rural area (26). One study demonstrated increased compliance by issuing reminders through the electronic health record (EHR) system. Providers were prompted to perform liver ultrasound for patients with cirrhosis who had not received surveillance in the preceding six months (27). Another barrier to implementation in many cases is the lack of reimbursement for screening.

Improving Early Detection

Hepatitis flares can occur in people with HBV infections in association with cancer chemotherapy and immunosuppressive treatment of nonmalignant diseases (eg, rheumatoid arthritis) (28,29). While some institutions are beginning to implement programs to screen patients for HBV prior to these treatments, this is not widespread.

New approaches to HCC screening being studied include assessment of noninvasive markers of liver fibrosis and a noninvasive transient elastography technique to assess liver stiffness (an indicator of fibrosis). The specificity of tests for noninvasive serologic markers of liver fibrosis is good for differentiating advanced from nonadvanced fibrosis, but sensitivity is low. Assessing liver stiffness is a bedside procedure that can be done in the clinic and provides immediate results with less sampling error (30,31). However, there is a higher failure rate in patients with a high body mass index (BMI).

Functional assays for liver enzymes could potentially be used to identify patients who are at risk for developing HCC. Researchers are looking at a variety of liver-associated proteins. One recent example is liver-type fatty acid-binding protein (L-FABP) that is decreased in HCC (32), although it would be better to have a functional marker that increases rather than decreases. Changes in the viral genome have been observed in association with HCC, for example, mutations in the HBV reverse transcriptase domain (33). It is not yet known when these types of changes occur. Could they be observed a year or two, or more, before diagnosis? There are also reports from genome-wide association studies (GWASs) of single-nucleotide polymorphism (SNP) associations with HCC. One example is MHC class I polypeptide-related sequence A (MICA), which is associated with progression from cirrhosis to HCC (34). However, GWAS studies of liver cancer, as well as other types of cancer and other diseases, have not been successfully reproduced.

A Focus on Biomarkers

A topic of much interest and discussion at the workshop was the role and potential of biomarkers for early detection and surveillance of both primary HCC and recurrences for detection of AFP-negative HCC and for risk stratification of patients for surveillance and potential intervention. Biomarkers could also have a use in precision medicine (personalized therapeutic strategies) and in predicting prognosis/response to treatment, as well as for enrichment of therapeutic clinical trial populations. Biomarkers could potentially play an important role in the developing world, where access to ultrasound is limited. Biomarker-based algorithms incorporating laboratory values and demographic data are being developed and evaluated for use in assessing risk of HCC (35).

Potential genetic markers of HCC (eg, HBV genotype variations, DNA mutations, methylation, HBV-host DNA junction sites) are also being studied. For example, retrospective analysis in archived liver tissue of an HCC gene signature was used to stratify patients into high-, intermediate-, and low-risk groups. The results show that the patients in the high-risk group had an annual HCC incidence of about four times that of those who were predicted to have a low risk (36). Although there are many potential genetic biomarkers described in the literature, none have been implemented clinically to improve care (37). In bringing a biomarker to the clinic, the detection platform is very important, and the ability to use a noninvasive (eg, blood, urine, saliva) test at the point-of-care would be desirable (vs laboratory diagnosis).

A biomarker for HCC should: be a robust surrogate for a particular clinical stage, have a low false-positive rate, be noninvasive/less invasive, improve clinical performance of the tools already available in routine practice, and be biologically relevant with functional pertinence to an outcome (38). Specific areas for further attention relevant to biomarker research could include: promising genes/biomarkers for characterizing HCC, consensus tumor subtypes and molecular classification, biomarker-guided interventions, using treatment-specific biomarkers to predict patient response to treatment, circulating biomarkers, the role of the microbiome in HCC (especially intestinal flora), and the development of biobanks and information commons.

HCC is not a single disease, and different etiologic factors contribute to tumor biology including demographics, environmental factors, and lifestyle. The biologic and genetic heterogeneity of tumors adds to the challenges of treatment (including differences between patients with the same cancer type, as well as differences within a patient's tumor). A systems biology strategy to address tumor heterogeneity and improve outcomes for liver cancer patients includes a robust biobanking system

Table 1. Workshop highlights*

Understanding the incidence of HCC

- More detailed/accurate incidence data are needed.
  - Accurate incidence data are lacking in some parts of the world (sub-Saharan Africa, parts of Asia, the Middle East).
  - The biology of HCC may be different for different etiologies. Look at the effectiveness of surveillance by etiology.
  - More information is needed on the role/impact of HBV genotype on incidence.
  - HCC in younger individuals is being observed (persons under the age currently recommended for screening by AASLD). This may be associated with specific genotypes.

Detection of HCC: bringing patients into care

- For many other cancers, early diagnosis does not necessarily require screening; however, for HCC screening it is essential. The evidence of the value of HCC screening is strongest for viral etiologies but is much less robust for other etiologies (alcoholism, NAFLD).
- Most patients have unresectable HCC at the time of diagnosis (had not been in screening programs, were not aware of their risk status).
- There is poor compliance with current HCC screening guidelines among both patients and providers. Creative ways to improve compliance are needed.
  - Incorporate prompts/reminders for providers into EHR systems; send reminders to patients every 6 months.
  - Task shifting to enhance compliance. Train midlevel practitioners (eg, nurse practitioners, physician assistants) in HCC screening and surveillance. (Could the Patient-Centered Outcomes Research Institute [PCORI] study the impact of task shifting on compliance?)
- Even if current screening and surveillance guidelines were followed faithfully, it is estimated that 20% to 30% of cases will be missed. Current approaches are 70% to 80% sensitive, and 80% to 90% specific in detecting HCC.
  - Need to identify HCC in low-incidence populations (those who fall outside of the current surveillance guidelines).
  - How to address the high potential for false positives in screening lower-risk populations?
- Need better use of biomarkers and algorithms in HCC screening and risk stratification.
  - Is there a need for different biomarkers/algorithms for different subpopulations (eg, those with low AFP; young age; female; genotype-associated, HBV-positive without recognized cirrhosis)?
- Collect biospecimens as part of surveillance (blood, serum, plasma, urine, and tissue) for use in future studies.

Medical management of HCC

- Reduction in HCC mortality will come from preventing viral hepatitis, finding and treating cases of chronic viral hepatitis, finding tumors early, and treating those early tumors.
- Need to emphasize the prevention of chronic viral hepatitis.
  - Many clinics that treat underserved populations, many of which are at high risk for chronic viral hepatitis, do not follow the guidelines for HBV screening and treatment.
  - Propose a PCORI study using the Hepatitis B Foundation HBV screening and management algorithm (49) in some of these clinics.
  - Promote the timely administration of the birth dose of HBV vaccine; encourage funders of global vaccine initiatives to provide the birth dose in resource-constrained countries that are disproportionately impacted.
- The heterogeneous nature of HCC makes it unlikely that a single therapeutic agent will be universally effective.
- Develop the potential of biomarkers for management of HCC:
  - Molecular-targeted therapies for subtypes of HCC.
  - Need efficient, rapid, cost-effective systems to assess hypothetical molecular targets. (eg, new tissue explant methods).
  - Predict prognosis/treatment outcome.
  - Enrich preventive and therapeutic clinical trial populations.
- Spontaneous immune responses are frequently observed in patients with HCC. Study the potential of immune checkpoint disrupters, alone or in combination with other therapies.
- Employ case review by a multidisciplinary tumor board to determine treatment strategy.

Areas for further study/action

- Treatment of chronic viral hepatitis:
  - What is the impact of therapeutic intervention for HBV on HCC risk?
  - Does antiviral treatment (polymerase inhibitors) of those with low viral load but strong family history of HCC reduce their risk?
  - Should patients who have had ablation for HCC and have very low viral loads receive antivirals treatment?
  - Are biomarkers of HCC affected by treatment of chronic HBV infection?
- Link studies to proper biosample repositories.
- How to detect (and treat) the fastest growing tumors?
- Link validation type studies to outcome (not just a comparative marker result but actual outcome).
- Need large cohort studies of comparative effectiveness in treated populations.
  - Need biomarkers and other intermediate outcomes measures.
  - Build outcomes studies into screening and surveillance initiatives.
- Need data on the progression and regression of fibrosis (eg, regression in HCV patients who have been treated and cured or HBV patients who have been virally suppressed). If fibrosis regresses below a certain level, is surveillance still needed?
- Investigate further the reported association between statin use and reduced risk of HCC.
- Ask the National Cancer Institute to review HCC under the Recalcitrant Cancer Research Act of 2012.
- Survey current insurance coverage/reimbursement of HCC surveillances tests recommended by the guidelines (ie, ultrasound).

* AASLD = American Association for the Study of Liver Diseases; AFP = alpha fetoprotein; EHR = electronic health record; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; NAFLD = nonalcoholic fatty liver disease; PCORI = Patient-Centered Outcomes Research Institute.

(blood, serum, plasma, urine, and tissue) that can be used for omics-based classification and clinical and histopathology classifications (39). These integrated data can then inform the implementation of biomarker-guided interventions (eg, screening for/predicting diagnosis, prognosis, treatment response, drug toxicity) with the goal of improving patient outcome.

Treatment of HCC

Limitations of Current Staging and Treatment Guidelines

Many liver cancer staging systems are used around the world, each with strengths and weaknesses. Prominent systems discussed at the workshop included the Barcelona Clinic Liver Cancer (BCLC) Staging System (19,20) and the Hong Kong Liver Cancer (HKLC) Staging System (40). Per BCLC, for example, the curative treatments recommended for very-early-stage (0) and early-stage (A) "curable" small tumors have been transplantation, radiofrequency ablation (RFA), and resection (depending on number and size of nodules and suitability of the patient for transplant). For intermediate-stage (B) multinodular HCC, the BCLC-recommended palliative treatment is transcatheter arterial chemoembolization (TACE), and for advanced-stage (C) HCC with portal invasion the only palliative treatment is the multikinase inhibitor sorafenib. Per BCLC, patients with terminal-stage (D) HCC receive symptomatic treatment and supportive care. Participants discussed that there are differences among the many staging systems that can lead to differences in treatment. There are variations in staging systems relative to, for example, the definitions of early, intermediate, and locally advanced tumors, and the criteria for when a patient would be considered to be resectable, would be considered transplant eligible, or would receive only supportive care. A variety of retrospective studies have sought to compare survival for patients theoretically triaged based on different systems. However, it is important to recognize the differences in how the systems were developed when comparing outcomes. For example, BCLC was developed using data from untreated patients, while HKLC was developed using data from treated patients.

In the United States, HCC treatment triage varies from center to center. Despite the guidelines, day-to-day practice is often institution specific and based on resources (eg, whether the institution is a transplant center or not). A better approach for the patient would be case review by a multidisciplinary tumor board to determine appropriate treatment strategy.

Methods of Treatment: Areas of Need

Concerns were raised by workshop participants about patients waiting on a transplant list when they could be treated by a nontransplant method. Many institutions argue that patients should be bridged by ablation or resection and not listed on the transplant list. Then, if HCC recurs, it generally recurs at a stage that qualifies them for placement on a transplant list.

There are a host of other treatment-related issues that merit further consideration, such as: the HCC recurrence rate following ablation; the best therapeutic approach for early, small lesions (~2 cm tumor); the value of HBV antiviral therapy after resection (regardless of viral load); the high cost, limited life extension, and often use-limiting side effects of sorafenib (41,42,43); and the potential of statins in reducing the risk of HCC (44). Better definition of the indications for and limits of TACE are also needed. There are not sufficient data on which category of tumor responds best to TACE or to define TACE failure/stopping points.

Better treatments for HCC are needed for both early- and advanced-stage tumors. Spontaneous immune responses are frequently observed in patients with HCC (45), including tumor-specific immune responses to ablative tumor therapies (46). Immunotherapy trials are needed to study antitumor immune responses induced by the combination of local tumor treatments and immune checkpoint inhibitors (which block the immune response–dampening effects of the immune checkpoint, thereby potentially enhancing the immune response to the tumor).

Another investigational treatment approach is molecular-targeted therapies for subtypes of HCC. Further study is needed to understand the true mechanisms of action of a product that appears to have a therapeutic effect for only a subgroup of patients. An efficient, rapid, cost-effective system to assess hypothetical molecular targets would help to advance identification of new investigational products. One early-stage/conceptual approach to link responsiveness to specific compounds with specific tumor subtypes is histological assessment of surgical tissue specimens (including phenotypic assessment after tissue culture with a targeted therapeutic compound, as well as molecular profiling to define tumor molecular subclass) (47,48). Predicting molecular subclass based on clinical histological features could also help to enrich the patient population in targeted clinical trials or to rescue shelved investigational drugs for use in specific subtypes of HCC.

Moving Forward

Reduction in liver cancer mortality is not going to come from treating advanced-stage (BCLC-C) HCC. It will come from preventing chronic viral hepatitis, finding and treating cases of chronic viral hepatitis, finding tumors early, and treating those early tumors. For prevention, there is an effective vaccine for HBV. An approved vaccine for HCV, however, is likely to be a long way off. Prevention of transmission of disease is difficult for HCV, and the populations most at risk are hard to reach (eg, IV drug users, aboriginal populations in Canada). Participants agreed that case review by a multidisciplinary tumor board is the best approach for the management of patients who have already developed HCC. The tendency is to apply the tool most readily available to the provider or the facility (eg, a patient referred to a surgeon tends to get surgery, while a patient referred to an interventional radiologist tends to get treatments that fall under their purview). Although the treatments may be effective, they might not necessarily be the best treatment for that particular individual. There is also a need to better understand the nature of the US-based HBV population. Research for HBV lags behind other diseases in having a systemic way of identifying patients at risk of progression and implementing prevention and therapeutics. Better use of existing systems (eg, automated datasets, electronic health records, state databases for mandatory reporting of HBV) could help to address this gap and connect people to care. Areas for further research and action that were discussed throughout the workshop are summarized in Table 1.

Funding

This work was supported by general operating funds of the Hepatitis B Foundation and an educational grant from Onyx Pharmaceuticals.

COMMENTARY

Notes

In addition to the authors, the following individuals participated in the 2015 Princeton HCC Workshop and contributed to the discussions of the findings and recommendations: Hashem El-Serag, Stuart Gordon, Tim Greten, Yujin Hoshida, Anand Mehta, Edith Mitchell, Jo Ann Rinaudo, Kirti Shetty, Michael Soulen, Ying-Hsiu Su, Xin Wei Wang. Independent science writer Theresa M. Wizemann was engaged under contract with the Hepatitis B Foundation to assist the authors with preparation of the draft as needed.

References

1. Ferlay J, Soerjomataram I, Ervik M, et al. *GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11*. Lyon, France: International Agency for Research on Cancer. 2013. http://globocan.iarc.fr. Accessed June 15, 2015.
2. Fitzmaurice C, Dicker D, Pain A, et al., and the Global Burden of Disease Cancer Collaboration. The global burden of cancer 2013. *JAMA Oncol*. 2015;1(4):505–527.
3. Stewart BW, Wild CP, editors. *World Cancer Report 2014*. Lyon, France: International Agency for Research on Cancer; 2014.
4. Bodzin AS, Busuttil RW. Hepatocellular carcinoma: Advances in diagnosis, management, and long term outcome. *World J Hepatol*. 2015;7(9):1157–1167.
5. Noureddin M, Rinella ME. Nonalcoholic Fatty Liver Disease, Diabetes, Obesity, and Hepatocellular Carcinoma. *Clin Liver Dis*. 2015;19(2):361–379.
6. Asrani SK, Larson JJ, Yawn B, Therneau TM, Kim WR. Underestimation of Liver-Related Mortality in the United States. *Gastroenterology*. 2013;145(2):375–382, e1-e2.
7. Sartorius K, Sartorius B, Aldous C, Govender PS, Madiba TE. Global and country underestimation of hepatocellular carcinoma (HCC) in 2012 and its implications. *Cancer Epidemiol*. 2015;39(3):284–290.
8. Chen G, Lin W, Shen F, Iloeje UH, London WT, Evans AA. Past HBV viral load as predictor of mortality and morbidity from HCC and chronic liver disease in a prospective study. *Am J Gastroenterol*. 2006;101(8):1797–1803.
9. Iloeje UH, Yang HI, Chen CJ. Natural history of chronic hepatitis B: what exactly has REVEAL revealed? *Liver Int*. 2012;32(9):1333–1341.
10. Chu KC, Chu KT. 1999–2001 Cancer mortality rates for Asian and Pacific Islander ethnic groups with comparisons to their 1988–1992 rates. *Cancer*. 2005;104(12 Suppl):2989–2998.
11. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA*. 2006;295:65–73.
12. Livingston SE, Simonetti JP, McMahon BJ, et al. Hepatitis B virus genotypes in Alaska Native people with hepatocellular carcinoma: preponderance of genotype F. *J Infect Dis*. 2007;195(1):5–11.
13. Gordon SC, Lamerato LE, Rupp LB, et al., and the CHeCS Investigators. Antiviral therapy for chronic hepatitis B virus infection and development of hepatocellular carcinoma in a U.S. population. *Clin Gastroenterol Hepatol*. 2014;12(5):885–893.
14. Jang JW, Choi JY, Kim YS, et al. Long-term effect of antiviral therapy on disease course after decompensation in patients with hepatitis B virus-related cirrhosis. *Hepatology*. 2015;61(6):1809–1820.
15. McMahon BJ, Bulkow LR, Singleton RJ, et al. Elimination of hepatocellular carcinoma and acute hepatitis B in children 25 years after a hepatitis B newborn and catch-up immunization program. *Hepatology*. 2011;54:801–807.
16. Chiang CJ, Yang YW, You SL, Lai MS, Chen CJ. Thirty-year outcomes of the national hepatitis B immunization program in Taiwan. *JAMA*. 2013;310(9):974–976.
17. CDC. Implementation of newborn hepatitis B vaccination--worldwide, 2006. *MMWR Morb Mortal Wkly Rep*. 2008;57:1249–1252.
18. Komatsu H. Hepatitis B virus: where do we stand and what is the next step for eradication? *World J Gastroenterol*. 2014;20(27):8998–9016.
19. Bruix J, Sherman M. Management of hepatocellular carcinoma. AASLD Practice Guideline. *Hepatology*. 2005;42:1208–1236.
20. Bruix J, Sherman M. Management of hepatocellular carcinoma: And update. AASLD Practice Guideline. *Hepatology*. 2011;53:1020–1022.
21. Khalili K, Menezes R, Kim TK, et al. The effectiveness of ultrasound surveillance for hepatocellular carcinoma in a Canadian centre and determinants of its success. *Can J Gastroenterol Hepatol*. 2015;29(5):267–273.
22. Singal AG, Conjeevaram HS, Volk ML, et al. Effectiveness of hepatocellular carcinoma surveillance in patients with cirrhosis. *Cancer Epidemiol Biomarkers Prev*. 2012;21(5):793–799.
23. Yu NC, Chaudhari V, Raman SS, et al. CT and MRI improve detection of hepatocellular carcinoma, compared with ultrasound alone, in patients with cirrhosis. *Clin Gastroenterol Hepatol*. 2011;9(2):161–167.
24. Singal AG, Tiro JA, Gupta S. Improving hepatocellular carcinoma screening: applying lessons from colorectal cancer screening. *Clin Gastroenterol Hepatol*. 2013;11(5):472–477.
25. Davila JA, Morgan RO, Richardson PA, Du XL, McGlynn KA, El-Serag HB. Use of surveillance for hepatocellular carcinoma among patients with cirrhosis in the United States. *Hepatology*. 2010;52(1):132–141.
26. Goldberg DS, Valderrama A, Kamalakar R, Sansgiry SS, Babajanyan S, Lewis JD. Hepatocellular carcinoma surveillance rates in commercially insured patients with noncirrhotic chronic hepatitis B. *J Viral Hepat*. 2015;22(9):727–736.
27. Beste LA, Ioannou GN, Yang Y, Chang MF, Ross D, Dominitz JA. Improved surveillance for hepatocellular carcinoma with a primary care-oriented clinical reminder. *Clin Gastroenterol Hepatol*. 2015;13(1):172–179.
28. Lok AS, Ward JW, Perrillo RP, McMahon BJ, Liang JT. Reactivation of hepatitis B during immunosuppressive therapy: Potentially fatal yet preventable. *Ann Intern Med*. 2012;156:743–745.
29. Pattullo V. Hepatitis B reactivation in the setting of chemotherapy and immunosuppression - prevention is better than cure. *World J Hepatol*. 2015;7(7):954–967.
30. Castéra L, Le Bail B, Roudot-Thoraval F, et al. Early detection in routine clinical practice of cirrhosis and oesophageal varices in chronic hepatitis C: comparison of transient elastography (FibroScan) with standard laboratory tests and non-invasive scores. *J Hepatol*. 2009;50(1):59–68.
31. Degos F, Perez P, Roche B, et al., and the FIBROSTIC study group. Diagnostic accuracy of FibroScan and comparison to liver fibrosis biomarkers in chronic viral hepatitis: a multicenter prospective study (the FIBROSTIC study). *J Hepatol*. 2010;53(6):1013–1021.
32. Wang B, Tao X, Huang CZ, Liu JF, Ye YB, Huang AM. Decreased expression of liver-type fatty acid-binding protein is associated with poor prognosis in hepatocellular carcinoma. *Hepatogastroenterology*. 2014;61(133):1321–1326.
33. Wu Y, Gan Y, Gao F, et al. Novel natural mutations in the hepatitis B virus reverse transcriptase domain associated with hepatocellular carcinoma. *PLoS One*. 2014;9(5):e94864.
34. Goto K, Kato N. MICA SNPs and the NKG2D system in virus-induced HCC. *J Gastroenterol*. 2015;50(3):261–272.
35. El-Serag, HB, Kanwal F, Davila JA, Kramer J, Richardson P. A new laboratory-based algorithm to predict development of hepatocellular carcinoma in patients with hepatitis C and cirrhosis. *Gastroenterology*. 2014;146(5):1249–1255, e1.
36. Hoshida, Y, Villanueva A, Sangiovanni A, et al. Prognostic gene expression signature for patients with hepatitis C-related early-stage cirrhosis. *Gastroenterology*. 2013;144(5):1024–1030.
37. Su YH, Lin SY, Song W, Jain S. DNA markers in molecular diagnostics for hepatocellular carcinoma. *Expert Rev Mol Diagn*. 2014;14(7):803–817.
38. Block TM, Marrero J, Gish RG, et al. The degree of readiness of selected biomarkers for the early detection of hepatocellular carcinoma: notes from a recent workshop. *Cancer Biomark*. 2008;4(1):19–33.
39. Wang XW, Thorgeirsson SS. The biological and clinical challenge of liver cancer heterogeneity. *Hepatic Oncology*. 2014;1(4):349–353.
40. Yau, T, Tang VY, Yao TJ, Fan ST, Lo CM, Poon RT. Development of Hong Kong Liver Cancer staging system with treatment stratification for patients with hepatocellular carcinoma. *Gastroenterology*. 2014;146(7):1691–1700, e3.
41. Carr BI, Carroll S, Muszbek N, Gondek K. Economic evaluation of sorafenib in unresectable hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2010;25(11):1739–1746.
42. McGlynn KA, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma: an emphasis on demographic and regional variability. *Clin Liver Dis*. 2015;19(2):223–238.
43. Robert C, Soria JC, Spatz A, et al. Cutaneous side-effects of kinase inhibitors and blocking antibodies. *Lancet Oncol*. 2005;6(7):491–500.
44. Mansourian PG, Yoneda M, Rao MK, Martinez FJ, Thomas E, Schiff ER. Effects of Statins on the Risk of Hepatocellular Carcinoma. *Gastroenterol Hepatol*. 2014;10(7):417–426.
45. Epstein RJ, Leung WT. Reversing hepatocellular carcinoma progression by using networked biological therapies. *Clin Cancer Res*. 2007;13(1):11–17.
46. Greten TF, Duffy AG, Korangy F. Hepatocellular carcinoma from an immunologic perspective. *Clin Cancer Res*. 2013;19(24):6678–6685.
47. Goossens N, Sun X, Hoshida Y. Molecular classification of hepatocellular carcinoma: potential therapeutic implications. *Hepatic Oncology*. 2015; In press.
48. Tan PS, Nakagawa S, Goossens N, et al. Clinicopathological indices to predict hepatocellular carcinoma molecular classification. *Liver Int*. 2015; In press.
49. McHugh JA, Cullison S, Apuzzio J, et al. Chronic Hepatitis B Infection: A Workshop Consensus Statement and Algorithm. *J Fam Pract*. 2011;60(9):E1–E8.