TURNING THE TIDE ON THE LIVER CANCER EPIDEMIC IN TEXAS

Amit G. Singal, MD, MS

This is to acknowledge that Amit Singal MD MS has disclosed that he has financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Singal will be discussing off-label uses in his presentation.

NAME: Amit G. Singal, MD, MS
Associate Professor of Medicine
David Bruton Jr. Professor in Clinical Cancer Research
Division of Digestive and Liver Disease
University of Texas Southwestern Medical Center

BRIEF BIO: Dr. Singal is a transplant hepatologist and health services researcher who completed his training at the University of Michigan and joined the UT Southwestern faculty in 2010. He is an expert in hepatocellular carcinoma (HCC), particularly in early tumor detection and screening process failures, and serves as Medical Director of the Liver Tumor Program. He is currently leading CPRIT- and NIH-funded grants to evaluate interventions to improve the effectiveness of early tumor detection efforts among patients with cirrhosis in the United States.

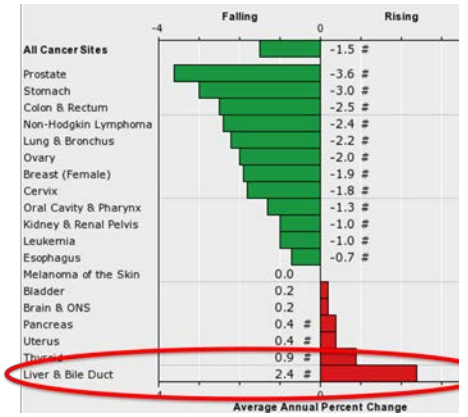
OVERVIEW: Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death worldwide. Although it has a lower incidence in the United States, its incidence is increasing due to a high burden of advanced hepatitis C virus infection and non-alcoholic fatty liver disease cases. Anti-viral treatment for chronic hepatitis B and C is effective for primary prevention and has the potential to reduce HCC incidence both globally and in the United States. Secondary prevention with HCC screening in at-risk patients is associated with improved early tumor detection, curative treatment receipt, and improved survival; however, it is underused in clinical practice with less than 20% of at-risk patients undergoing any screening.

OBJECTIVES:
1. Identify primary risk factors for hepatocellular carcinoma in the United States
2. Describe the role of hepatitis B and hepatitis C treatment in the primary prevention of hepatocellular carcinoma
3. Discuss the benefits (and limitations) of hepatocellular carcinoma screening in at-risk persons

EPIDEMIOLOGY

Hepatocellular carcinoma (HCC), the most common type of primary liver cancer, is an important and growing health problem globally and locally.[1] HCC is the fifth most common cancer and third leading cause of cancer-related death worldwide. However, there is considerable geographic variation in HCC incidence, with over 75% of cases occurring in Southeast Asia and sub-Saharan Africa. Although HCC incidence and morality rates are lower in the United States, both are rapidly rising. Over the past two decades assessed by SEER, HCC incidence doubled and mortality increased faster than every other solid tumor (**Figure 1**). However, a recent analysis using the US Cancer Statistics Registry found the increasing incidence may be reaching a plateau. Although HCC incidence increased by 4.5% annually between 2000 and 2009, it increased by only 0.7% annually between 2010 and 2012. Within the United States, there is variation in age-adjusted HCC incidence, with Texas having the highest rate at 9.7/100,000 persons.

Figure 1: HCC has fastest increasing mortality among solid tumors in the U.S



HCC disproportionately affects racial/ethnic minority and underserved populations, and disparities are widening.[2] Age-adjusted incidence rates are highest in Asians (10.8 per 100,000 person-years), followed by Hispanics (7.0 per 100,000 person-years), Blacks (6.3 per 100,000 person-years), and finally non-Hispanic Whites (2.4 per 100,000 person-years). Age-adjusted mortality rates are also significantly higher for Hispanics (7.0 per 100,000 persons) and non-Hispanic Blacks (6.4 per 100,000 persons) than non-Hispanic whites (3.6 per 100,000 persons). Similarly, HCC patients from low-income households have significantly higher mortality than high-income patients, with the greatest disparities in those with early stage HCC. HCC patients from the lowest census tract socioeconomic status (SES) have a 10.4% worse 5-year survival compared with the highest SES strata.

RISK FACTORS

Understanding risk factors for HCC is important to inform at-risk populations who can benefit from HCC screening. The primary HCC at-risk populations are detailed in Table 1.[3]

Regardless of etiology, cirrhosis – the end-result of any chronic liver injury – is the most important risk factor for HCC.[3] Over 90% of HCC in the U.S. occur in the presence of cirrhosis, and HCC is the leading cause of death in these patients.[4] The most common etiologies of cirrhosis associated with HCC include chronic hepatitis B, chronic hepatitis C, alcohol-related, and non-alcoholic steatohepatitis (NASH). Hemochromatosis, primary biliary cholangitis, autoimmune hepatitis and alpha-1 antitrypsin deficiency are less common causes and have prevalence rates of 1% - 8% among patients with HCC. Of note, patients with cirrhosis due to genetic hemochromatosis are at markedly increased risk of HCC, with a relative risk of ~20.

Chronic hepatitis B virus (HBV) infection is the most common etiology for HCC worldwide. HCC risk among HBV-infected persons is related to the mode of HBV acquisition.

People who live in HBV-endemic areas, such as Southeast Asia or Africa, typically acquire HBV infection at the time of birth or during early childhood, and over 90% develop chronic HBV infection. HBV carriers without cirrhosis have an annual HCC incidence of approximately 0.5%, which increases to 1% in elderly patients. Patients from Africa are at particularly high risk, potentially related to a synergistic effect of aflatoxin exposure, and HCC can develop early in the 3rd to 4th decades of life. HBV-infected patients who are exposed to aflatoxin have a 60-fold increased relative risk of for HCC compared to those with neither exposure. In contrast, most people in the United States and Europe acquire HBV infection as adults via intravenous drug use or sexual transmission and most experience spontaneous resolution after an acute infection. Patients with chronic HBV in Europe and the United States are typically at low risk for HCC in the absence of cirrhosis. In fact, >90% of HBV-infected patients who develop HCC in the United States have underlying cirrhosis. Risk factors, including older age, co-infection with hepatitis C, family history of HCC, HBV genotype, and high viral replication (high DNA levels and HBV eAg positivity) may identify high-risk subgroups. However, risk models with these variables have not been externally validated in Western populations and are not ready for routine use in clinical practice.

Table 1: Populations in whom HCC screening is recommended

SCREENING RECOMMENDED
Asian male HBV carriers over age 40
Asian female HBV carriers over age 50
African Blacks with HBV
HBV carriers with family history of HCC
Cirrhosis related to HBV
Cirrhosis related to hepatitis C
Cirrhosis related to other etiologies
SCREENING BENEFITS UNCERTAIN
HBV carriers younger than 40 (males) or 50 (females)
HBV carriers who contacted HBV as an adult
Hepatitis C carriers without cirrhosis
NASH patients without cirrhosis

Chronic hepatitis C virus (HCV) infection is currently the most common etiology for HCC in the United States, Europe, and Japan. HCC can be attributed to hepatitis C infection in ~60% of patients in the United States and Europe. HCC risk is increased 17-fold in hepatitis C-infected patients compared to hepatitis C -negative patients. However, HCC risk is primarily limited to those with cirrhosis, with an annual incidence rate of 2-8%, and patients without cirrhosis are at a low risk (<1%) for developing HCC. Several factors can moderate HCC risk in hepatitis C-infected patients, including older age, male gender, alcohol use, and comorbid conditions such as HIV infection or diabetes. Although viral factors, such as genotype or viral load, do not correlate with HCC risk, successful treatment significantly reduces HCC risk among patients with hepatitis C cirrhosis.

Nonalcoholic steatohepatitis (NASH), the liver manifestation of the metabolic syndrome, is an increasingly common cause of HCC. Several studies have linked HCC to the metabolic syndrome and its components. An analysis of SEER-Medicare demonstrated patients with metabolic syndrome have 2.1-fold increased odds of HCC compared to those without metabolic syndrome. Similarly, a prospective study of >900,000 individuals found liver cancer mortality was 4.5-fold higher in men with BMI >35 and 1.7-fold higher in women with BMI >35 compared to normal weight individuals. A meta-analysis found a pooled risk estimate of 2.2 - 2.4 among case-control and cohort studies for the association between diabetes and HCC. The association between metabolic syndrome and HCC is likely driven by an increased risk of NASH as well as the direct carcinogenic potential of obesity. Although it is clear NASH is a risk factor for HCC, this risk is lower than hepatitis C-related cirrhosis. The highest HCC risk is seen

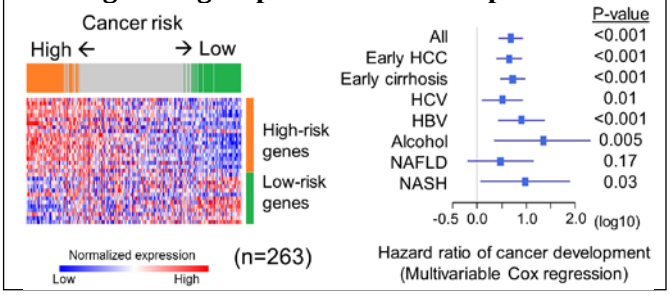
among the subset of NASH patients with cirrhosis, although there are increasing reports of HCC developing in NASH patients in the absence of cirrhosis. Patients with NASH cirrhosis have cumulative HCC incidence rates of 2.4-12.8%, while NASH patients without cirrhosis have cumulative HCC mortality rates below 1%. NASH cirrhosis is anticipated to be the major etiologic factor for HCC in the future as the prevalence of NASH continues increasing in parallel with the obesity and diabetes epidemics.

Alcohol-related cirrhosis is another common cause of HCC. Alcoholic liver disease has been reported as a contributing factor in nearly one-third of HCC cases. However, HCC incidence rates in alcoholic cirrhosis may be overestimated given early studies predated routine hepatitis C testing. A recent registry study from Denmark suggested HCC mortality rates may be less than 1% in alcoholic cirrhosis; however, these results require external validation. Although HCC risk increases with daily alcohol intake of 40-60 grams/day, it is unclear if lower alcohol levels increase HCC risk. An Italian case-control study with 464 HCC patients and 824 patients without liver disease found a linear increase in the odds of HCC with increasing alcohol intake, starting at 60 grams/day. This study also suggested a synergistic effect between alcohol and viral hepatitis, as patients with both risk factors had a 2-fold increased incidence of HCC compared to those with viral hepatitis alone. Outside of promoting the development of cirrhosis, there is little evidence for a direct carcinogenic effect of alcohol.

Beyond the presence of cirrhosis, there are several well-recognized demographic risk factors for HCC. In most countries, HCC rarely occurs before age 40 and the highest age-specific rates are seen in those older than 70 years. Male gender is also an independent risk factor for HCC, with 2-4 times higher rates in men than women. The higher incidence rates in men may be related to differential exposure to risk factors, including viral hepatitis, alcohol, and obesity; however, available data do not fully explain observed differences in HCC rates and a potential role for sex hormones has been suggested. There are also racial/ ethnic differences in the distribution of HCC as described above.

A serum molecular signature panel, derived from a validated tissue transcriptome signature, is a promising HCC risk stratification biomarker.[5] Dr. Hoshida and colleagues discovered a hepatic tissue transcriptome signature that is highly predictive of HCC development in patients with diverse cirrhosis etiologies including hepatitis C (**Figure 2**). In 216 Child Pugh A cirrhosis patients followed for a median of 10 years, the signature accurately classified patients as poor-, intermediate-, and good-prognosis. HCC annual incidences were 5.8%, 2.2%, and 1.5% for poor-, intermediate-, and good-prognosis signatures, respectively (p=0.009). The investigators have surrogated the tissue transcriptome signature as a serum assay, with high concordance in a small number of samples.

Figure 2: A tissue-based HCC risk signature can accurately stratify patients into low, intermediate, and high risk groups for HCC development

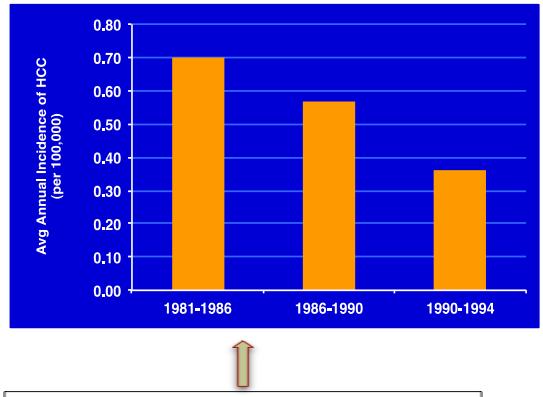


HCC PREVENTION

Hepatitis B Prevention

Given that the primary risk factors for HCC are HBV worldwide and hepatitis C in developed countries, most data on HCC primary prevention has focused on vaccines and anti-viral therapy. Less robust data exists on HCC prevention through modification of other known risk factors, such as alcohol cessation, weight loss, and control of diabetes. Despite its undoubted importance as a risk factor, there is limited evidence to support the effectiveness of alcohol reduction interventions at reducing HCC incidence. While dietary modifications and exercise are often recommended to achieve judicious weight loss in patients with NASH, it has not been shown to reduce the risk of HCC. While awaiting these data, it is prudent to counsel patients with regards to weight loss and smoking and alcohol cessation, which can still lead to health benefits outside of HCC prevention.

Figure 3: Implementation of HBV vaccination program associated with reduced HCC incidence



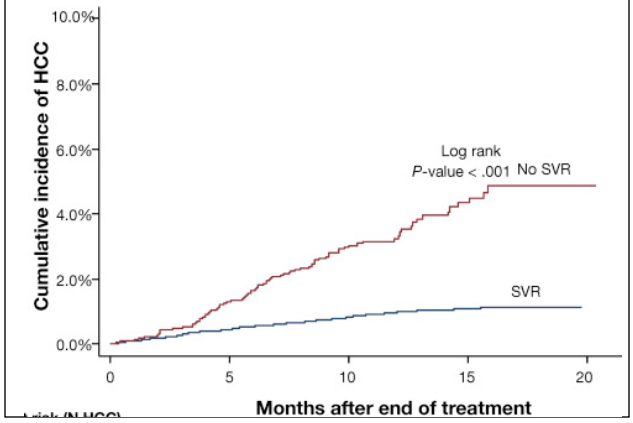
The most effective and cost-effective way to prevent HBV-related HCC is vaccination to prevent HBV infection.[6] A quasi-study from Taiwan demonstrated that the annual incidence of HCC steadily decreased after universal HBV vaccination of newborns began in 1986 (**Figure 3**). HCC risk decreased from 0.70 per 100,000 persons in 1981-1986 to 0.57 per 100,000 persons in 1986-1990 to 0.36 per 100,000 persons in 1990-1994 (p <0.0001). A subsequent study from Taiwan demonstrated that HCC incidence was statistically lower among vaccinated individuals than those who were not vaccinated. Furthermore, the risk of developing HCC among vaccinated individuals was significantly associated with incomplete HBV vaccination. It is anticipated that widespread implementation of HBV vaccination programs for all newborns globally can ultimately lead to a worldwide reduction, if not elimination, of HBV infection and HBV-related HCC. One modeling study suggested that routine HBV vaccination, with at least 90% coverage, could prevent 84% of global HBV-related deaths. The HBV vaccine has been incorporated into the Expanded Program of Immunization in over 180 countries, including most in Eastern and Southeastern Asia; however it will take decades for its impact to be observed among adults. Further, there are still low rates of HBV vaccination in other endemic parts of the world, such as parts of sub-Saharan Africa.

Antiviral therapy can significantly reduce HCC incidence in persons with chronic HBV infection.[7, 8] In a large randomized controlled trial evaluating HBV anti-viral therapy, 651 HBV-infected patients with advanced fibrosis or cirrhosis were randomized to receive lamivudine or placebo. After a median duration of 32 months, HCC was diagnosed in 7.4% of the placebo group compared to 3.9% of those receiving lamuvidine. Although there have not been similar randomized trials with entecavir or tenofovir, similar effects are expected with these newer antiviral agents. Propensity-matched analyses comparing entecavir-treated patients with untreated patients found treated patients were significantly less likely to develop HCC (HR 0.37, 95%CI 0.15 – 0.91). It is still unclear if treatment is only beneficial among patients with high viral loads or if a similar treatment benefit is present in those with lower DNA levels.

Hepatitis C Prevention

Despite considerable research, there is not a vaccine available for hepatitis C infection. Difficulties impeding the development of a vaccine include the variability of its genomic structure, the large number of quasispecies, and the lack of an effective neutralizing antibody against the virus. However, there are several other effective primary prevention measures. Screening of all donated blood has virtually eliminated transfusion-associated hepatitis C infections in industrialized countries, and similar measures should be implemented in developing countries. Universal precautions of using disposable needles and potentially needle-exchange programs can similarly reduce parenteral transmission of hepatitis C infection.

Figure 4: DAA-based HCV therapy is associated with reduced HCC incidence



Guideline-concordant screening and treatment for hepatitis C can significantly reduce HCC incidence and mortality.[9, 10] In patients without cirrhosis, sustained viral response (i.e. virologic cure) after hepatitis C treatment can halt progression of fibrosis and virtually eliminate any risk of HCC. Among hepatitis C-infected patients who already have cirrhosis, sustained viral response with interferon-based therapy significantly reduces the risk of hepatic decompensation, liver-related mortality, and HCC incidence. In a meta-analysis of 26 cohort studies, patients with hepatitis C cirrhosis and sustained viral response after interferon-based therapy achieve a 73% relative risk reduction in HCC incidence. The mechanism for reduction in HCC recurrence is unclear – whether related to the sustained viral response or a direct IFN-related immune-mediated antitumor effect. This debate has become more relevant with the introduction of all oral, direct acting antiviral (DAA) therapy, which has replaced interferon -based therapy for HCV. Recent studies have demonstrated similar improvements in fibrosis and decreased risk of incident HCC in patients with HCV-related cirrhosis. In a retrospective cohort study of patients treated with DAA-based hepatitis C therapy, patients who achieved sustained viral response had a significantly reduced risk of HCC (0.90 vs. 3.45 HCC/100 person-years; adjusted HR 0.28, 95%CI 0.22 – 0.36) (**Figure 4**).

Statins or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have been evaluated as a potential chemopreventive agent for HCC.[11] Statins have been shown to have anti-proliferative, pro-apoptotic, and anti-angiogenic effects, supporting their potential role in this area. A meta-analysis found statins were associated with a 41% reduction (95% CI 30% - 50%) in HCC incidence; however, there was significant heterogeneity between studies. When limiting analyses to a high-risk population, it was estimated 57 people would need to be treated with statins to prevent one case of HCC. Given the number needed to treat and limitations of the data, the authors conclude it is not prudent to prescribe statins solely for purpose of chemoprevention at this time. Further large prospective cohort studies and randomized clinical trials are needed to better define any potential role of statin therapy in HCC prevention.

Similarly, coffee has been proposed as a potential chemopreventive agent for HCC.[12] Coffee ingestion has long been reported to have a beneficial effect on liver enzymes and the risk of fibrosis progression to cirrhosis. More recent studies suggest that the beneficial effects of coffee may extend to HCC prevention. Animal models have suggested that coffee compounds may modulate enzymes involved in carcinogenesis and have antioxidant effects. In a meta-analysis, coffee drinkers were found to have a 43% reduction in HCC risk compared to non-drinkers. There appeared to be a dose-dependent response with a 56% reduction in heavy drinkers, compared to a 31% reduction in low or moderate coffee drinkers. However, current studies are limited by confounders, and a clear causal relationship has yet to be established so the role of coffee ingestion in HCC prevention is still unclear.

CLINICAL PRESENTATION

Liver cell dysplasia is a premalignant lesion in patients with cirrhosis. Some dysplastic nodules have concurrent foci of HCC at the time of initial presentation, and one-third of high-grade dysplastic nodules will progress to HCC over a two-year follow-up period. Not all dysplastic nodules will progress to HCC, as 15% of nodules have been noted to disappear on follow-up.

There is variation between patients in terms of the natural history of HCC. Tumor doubling times have ranged from 1 month to 19 months, with a median doubling time of 4-6 months. Furthermore, tumor doubling times may not be stable within a patient, as tumors can transition from periods of slow growth to more accelerated exponential growth. There are currently no accurate methods to predict tumor biology and tumor growth rates.

The clinical presentation of HCC varies widely and is largely driven by the degree of hepatic reserve. In patients with underlying cirrhosis, HCC can present with hepatic decompensation, including hepatic encephalopathy, ascites, or jaundice. In patients with adequate hepatic reserve, particularly those without cirrhosis, HCC is more likely to present with tumor-related symptoms including abdominal pain, weight loss, weakness, anorexia, malaise, or a palpable mass on exam. Small tumors are often asymptomatic, and HCC typically becomes symptomatic when it reaches 5-8 cm in diameter. Outside of an elevated AFP level, laboratory findings are non-specific and are more often related to the underlying liver disease than HCC. Since nearly 40% of patients can have HCC as their first presentation of cirrhosis, identification of chronic liver disease and cirrhosis prior to the development of HCC is of paramount importance.

Extra-hepatic manifestations of HCC can result from distant metastases or a paraneoplastic syndrome. The most common sites of metastases are lung, bone, lymph nodes, and adjacent abdominal viscera. Osteoclastic destruction from bone metastases can present as pain, while other sites of metastases are often asymptomatic. Paraneoplastic symptoms, which can occur in advanced stage tumors and serve as a poor prognostic marker, are rare but include hyperlipidemia, hypoglycemia, and hypercalcemia.

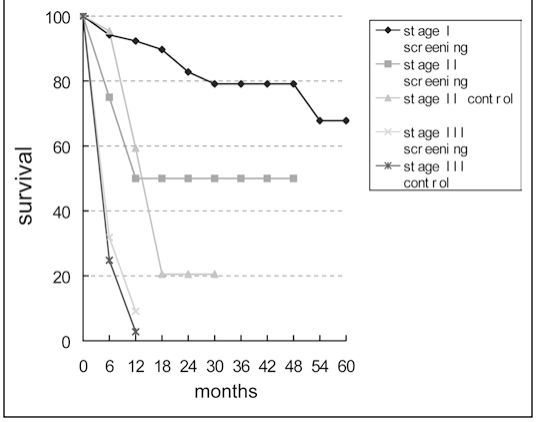
HCC SCREENING

Value of HCC Screening

Curative options are only available for early stage HCC, highlighting the importance of early tumor detection to improve prognosis. Patients with early stage HCC can undergo curative therapies such as surgical resection or liver transplantation, resulting in 5-year survival rates exceeding 70%. In contrast, patients with advanced stage HCC are only amenable to palliative therapies and have a median survival of less than 1 year.

Since patients with HCC are asymptomatic when tumors are at an early stage, routine screening should be performed in at-risk individuals.[13] The best data supporting HCC surveillance are two large randomized controlled trials in patients with chronic HBV comparing screening every six months to no screening (i.e. Level I evidence). In one of the trials with 19,200 HBV carriers, 45% of 86 patients who developed HCC in the screening group were detected at an early stage, compared to none among the 67 no-screening group patients ($p< 0.01$). The HCC-related mortality rate of patients undergoing screening was also significantly lower than that of the no-screening group (83.2 vs. 131.5 per 100,000, $p< .01$), with a hazard ratio of 0.63 (95% CI 0.41 – 0.98) (**Figure 5**). However, it is unclear if data from HBV patients can be extrapolated to cirrhosis due to lower sensitivity of ultrasound in a cirrhotic nodular liver and higher competing risk of non-HCC mortality.

Figure 5: HCC screening reduces mortality in patients with chronic HBV



Although there is not a randomized controlled trial for HCC screening in cirrhosis, several prospective cohort studies have demonstrated an association between HCC screening and improved early detection and survival (i.e. Level II evidence**)**.[14] Among 47 studies with 15,158 patients, HCC screening was associated with improved early stage detection (OR 2.08, 95% CI 1.80–2.37) and curative treatment rates (OR 2.24, 95% CI 1.99–2.52). HCC screening was also associated with significantly prolonged 3-year survival (OR 1.90, 95% CI 1.67–2.17), including in the subset of studies adjusting for lead-time bias. In one prospective multi-center cohort study of 451 patients with cirrhosis and HCC, patients who underwent screening had a prolonged survival compared to those who did not undergo screening, after adjusting for lead-time bias. The most substantial benefit was seen in patients with Child Pugh A cirrhosis although patients with Child Pugh B cirrhosis still derived a statistically significant survival benefit. Given the competing risk of dying from liver related complications, there is not a benefit in performing HCC screening in patients with Child Pugh C cirrhosis who are not otherwise transplant candidates. Given these data, HCC screening is recommended by several professional studies including the American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), National Comprehensive Cancer Network (NCCN), and US Department of Veterans Affairs (VA).

HCC screening in patients with cirrhosis has been demonstrated to be cost effective in several cost effectiveness analyses.[15] The standard threshold for cost effectiveness has been determined to be a maximal of $50,000 per quality-adjusted life year (QALY). Screening with

biannual ultrasound and AFP in patients with Child Pugh A cirrhosis increases mean life expectancy with incremental cost effectiveness ratios (ICER) between $26,000 and $55,000 per QALY.

The value of cancer screening programs must weigh screening benefits with potential for screening harms. Screening harms can occur at several steps throughout the screening process and accumulate over time at the population-level. Although screening benefits directly correlate with cancer risk, with the greatest benefit among those at highest risk, harms occur independent of cancer risk and it is possible low-risk patients suffer an equal or greater burden of screening harms. Multiple types of harms must be considered when considering a cancer screening program: 1) *physical harms* can result from screening or follow-up testing and extends beyond medical complications to include factors such as discomfort; 2) *financial harms* can include anticipated or real costs of screening and diagnostic evaluation plus indirect costs such as missed work; and 3) *psychological harms* can include anticipation or fear of abnormal results, reactions of depression, anxiety, or cancer-specific worry after positive results, and psychological effects of being labeled with a diagnosis.

Screening strategies provide the best value when the balance between benefits and harms is optimal.[16] As screening intensity (determined by test modality and interval) initially increases, screening benefits increase and screening value transitions from low to high value. Further increases in screening intensity beyond an optimal level lead to increases in harms and costs, and screening value transitions back to low-value. Early data suggest HCC screening can be associated with some physical screening harm although these findings still require validation in other practice settings. In a retrospective cohort study among 680 cirrhosis patients undergoing HCC screening over a 3-year period at Parkland Health & Hospital System, we found screening-related physical harm in 187 (27.5%) patients, with 66 (9.7%) having multiple CT/MRI exams. Screening-related harm increased from 11.9% among those with 1 screening exam to 29.6% among those with ≥2 screening exams. The most common trigger was false positive screening tests (ultrasound 34% and AFP 27%), but 39% had harms due to indeterminate results.

HCC Screening Tests

Abdominal ultrasound is the recommended radiologic test for HCC screening.[17] Its advantages include being widely available, non-invasive, relatively inexpensive, and it poses no risk of contrast or radiation exposure. The efficacy of ultrasound for HCC screening has been evaluated primarily in cohort studies. Ultrasound's sensitivity and specificity for early stage HCC varied widely between studies, ranging between 29-100% and 94-100%, respectively. In a meta-analysis of cohort studies, the pooled sensitivity of ultrasound for early stage HCC was only 45% but had high pooled specificity of 91%. The authors found significant heterogeneity among studies and noted significant limitations, such as verification bias.

Two possible explanations for the lower effectiveness of ultrasound in clinical practice, as compared to clinical trials, are operator performance and patient characteristics. While well-trained technicians and/or physicians performed ultrasound in most clinical trials, radiology technicians with varied experience perform ultrasound in routine clinical practice. Alternatively, the sensitivity of ultrasound may be influenced by patient characteristics, as is the case for breast density with mammography. For HCC screening, the ability of ultrasound to accurately visualize the liver in patients with morbid obesity or a very nodular liver may be impaired.

Alpha fetoprotein (AFP) is the best-studied serologic test for HCC screening.[18] Assessment of serum AFP is easy to perform, inexpensive, and broadly available. Nonetheless, serum testing for AFP levels is not without its drawbacks. For instance, the optimal threshold for AFP positivity is under debate. Although a cutoff value of 20 ng/mL in HCC surveillance is the most commonly used, false-negative and false-positive findings occur in about 20 – 40% of patients. One third of patients with HCC have AFP levels that are considered normal and an equal fraction of individuals without HCC have abnormal AFP levels.

Although AFP has insufficient sensitive and specific when used alone, using AFP in combination with abdominal ultrasound significantly increases sensitivity for early tumor detection. In a meta-analysis of studies comparing ultrasound with vs. without AFP measurement, ultrasound detected any stage HCC with a lower level of sensitivity than ultrasound plus AFP measurement (RR 0.88, 95% CI, 0.83–0.93) and early-stage HCC with a lower level of sensitivity than ultrasound plus AFP measurement (RR, 0.81, 95% CI, 0.71–0.93). Ultrasound with vs. without AFP detected early-stage HCC with sensitivities of 63% and 45%, respectively (p=0.002).

Currently available data support the use of ultrasound and AFP as the screening tests of choice for HCC screening. However, several efforts are ongoing to identify better screening tools to improve sensitivity for early stage HCC detection.

Given ultrasound's poor performance as a radiologic screening test, dynamic contrast-enhanced imaging has been proposed as an alternative strategy.[19] However, contrast-enhanced CT is limited by radiation exposure and concerns for contrast nephropathy, particularly if performed every 6 months. Therefore, greater enthusiasm exists for MRI as an alternative strategy. In a prospective cohort of 407 cirrhosis patients undergoing MRI and ultrasound over 18 months (the PRIUS Study), MRI had higher sensitivity than ultrasound for early HCC detection (86% vs. 28%, p<0.001). However, MRI is time-consuming (~45 minutes) and costly, with prior cost-effectiveness analyses demonstrating MRI is not cost-effective for HCC screening in all patients with cirrhosis.

Abbreviated MRI has been recently proposed as a 15-minute truncated version of a diagnostic MRI, only including dynamic contrast enhanced sequences, to make it a more cost-effective screening strategy.[20] An abbreviated MRI only including the dynamic contrast enhanced portion is a rational design for HCC screening given diagnostic criteria for HCC are primarily based on a liver lesion's enhancement characteristics. The principle of abbreviated MRI has been shown to be effective for breast cancer screening in prior studies but has been relatively understudied for HCC screening. In a pilot study of 94 cirrhosis patients undergoing diagnostic MRI for liver lesion characterization, we found abbreviated MRI had comparable performance to standard diagnostic MRI for HCC detection (kappa >0.90), suggesting abbreviated MRI would likely be superior to ultrasound for HCC detection. The potential for abbreviated MRI as an alternative screening strategy was also demonstrated in a study among 174 patients who underwent MRI. In this study, abbreviated MRI had a sensitivity of 81% and specificity of 96%. In a subsequent pilot study among 19 patients at UC San Diego, abbreviated MRI had a sensitivity of 90% for early HCC and specificity of 89% compared to only 50% and 67% respectively for ultrasound. Although promising, abbreviated MRI still requires further comparative effectiveness evaluation in large cohorts of patients with cirrhosis.

Several novel serum biomarkers are also being evaluated as possible tools for early HCC detection. Two biomarkers with promising results in phase II biomarker studies include des-gamma carboxy-prothrombin (DCP) and the lens culinaris-agglutinin reactive fraction of AFP (APF-L3%). DCP is an abnormal prothrombin protein that is generated as a result of an acquired defect in the posttranslational carboxylation of the prothrombin precursor in malignant hepatic cells. In a nested case-control study, DCP and AFP had sensitivities of 74% and 61% respectively for HCC at any stage, which was increased to 91% by using the two markers in combination. Glypican 3, GP73, osteopontin, squamous cell carcinoma antigen, human hepatocyte growth factor, and insulin growth factor-1, are examples of other biomarkers that are currently being evaluated but data are preliminary and require validation in large cohorts. Proteomic approaches may also provide tools to identify other novel serum biomarkers in HCC in the future.

Increasing data support the potential use of longitudinal biomarkers instead of interpretation at a single threshold.[21] Most studies use a single threshold to evaluate biomarkers, without considering prior results; however, this is not how biomarkers are typically interpreted in clinical practice. Increasing AFP, even if <20 ng/mL, can be a sign of HCC and stable or decreasing levels, even if >20 ng/mL, are reassuring. Using longitudinal patterns can increase biomarker accuracy by improving both sensitivity and specificity. Data from all 1050 patients in the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) cohort demonstrated a parametric empirical Bayes (PEB) screening algorithm, which incorporates screening history, was more accurate for early HCC detection than a single threshold approach for interpreting AFP. PEB improved AUROC from 0.84 to 0.93 compared to the single threshold approach in cirrhosis patients. When the false positive rate was set at an acceptable rate of 10%, sensitivity for HCC detection increased from 60% to 77% ($p<0.001$).

Given the heterogeneity of HCC lesions, it is likely that no single biomarker will be sufficiently sensitive and specific in isolation and there has been increasing interest in biomarker panels combining multiple biomarkers.[22] GALAD is a biomarker panel incorporating AFP, AFP-L3% and DCP, with patient age and sex. GALAD has been primarily evaluated for early detection and has superior performance vs. each individual biomarker in diverse cirrhosis etiologies. In 6834 patients (2430 HCC and 4404 non-HCC patients), GALAD had an area under the ROC curve (AUROC) >0.90 for early HCC detection. GALAD is promising but still requires validation in phase III and phase IV biomarker studies prior to routine adoption in clinical practice.

HCC Screening Interval

HCC screening in at-risk patients should be performed every 6 months, as this has been demonstrated to be superior to a 12-month screening interval and non-inferior to a 3-month interval for early tumor detection.[23] In a meta-analysis of prospective cohort studies evaluating the efficacy of screening tests for detecting HCC, ultrasound had a sensitivity of 70% in studies using a six-month interval compared to a sensitivity of 50% in those with screening intervals between 6 and 12 months. A retrospective analysis of a multi-center Italian database showed patients who received screening every six months had tumors detected at an earlier stage and significantly better overall survival than patients receiving annual screening, even after correcting for lead time bias. The median survival among the 510 patients in the six-month screening group was 40 months, compared to 30 months in the 139 patients in the twelve-month

screening group (p=0.03). A subsequent multi-center study among 1340 patients with cirrhosis evaluated whether further shortening the screening interval to three months results in better detection of early stage tumors and improves survival. The majority of patients in both groups were detected at an early stage (79% vs. 71%, p=0.40) and similar proportions received curative therapies (62% vs. 58%, p=0.88). Furthermore, the 3-month screening group had a higher incidence of non-malignant lesions, leading to a higher number of unnecessary recall procedures.

HCC Screening Underuse in Clinical Practice

Despite data showing improved survival with HCC screening and guideline recommendations from several professional societies, fewer than 20% of patients with cirrhosis undergo screening.[24] Screening rates are lower among non-Caucasians and those of low socioeconomic status. Although screening rates are higher among patients receiving subspecialty care, gastroenterologists or hepatologists only follow 20-40% of cirrhosis patients in the United States. Underuse of HCC screening is related to multiple failure points, including many patients having unrecognized liver disease and/or cirrhosis prior to HCC presentation; however, the most common reason for a lack of HCC screening is physicians failing to order HCC screening in patients with known cirrhosis. This deficit can be related to several issues including lack of knowledge about HCC surveillance benefits and clinic time constraints given the myriad of competing medical issues. Patients typically demonstrate high levels of knowledge about HCC surveillance and report high levels of acceptance and willingness to participate in HCC screening. A study conducted in a safety-net patient population suggested patient-reported barriers such as lack of transportation and difficulty with scheduling screening testing may be associated with lower rates of screening, but it is unclear if these data can be generalized to non safety-net settings. Downstream issues, such as radiologic capacity, do not appear to be major barriers to HCC screening at this time.

Despite literature demonstrating HCC screening underuse in cirrhosis patients, few studies have evaluated interventions to increase screening.[25] Two small studies suggested a benefit of nursing protocols and automated reminders, although both were conducted among selected patients followed by hepatologists. Another study suggested EMR clinical reminders may increase HCC screening participation among cirrhosis patients followed by primary care providers. Implementation of EMR clinical reminders significantly improved screening rates from 18% to 28% ($p< 0.001$) in a study including 2884 VA patients. We recently demonstrated an intervention including mailed outreach invitations and patient navigation could significantly increase repeat HCC screening every 6 months compared with usual care. In a large pragmatic randomized clinical trial, repeat screening was performed in 23.3% of outreach/navigation patients, 17.8% of outreach-alone patients, and 7.3% of usual care patients. Repeat screening was significantly higher in both outreach groups than usual care (p<0.001 for both) as well as for outreach/navigation compared to outreach-alone (p=0.02).

SUMMARY

HCC is the third most common cause of cancer-related death worldwide and one of the most common causes of death in patients with cirrhosis. The highest HCC incidence rates are in Southeast Asia and Africa, related to high rates of endemic HBV infection; however, these rates are declining with more widespread HBV vaccination and treatment programs. Its incidence in

the United States and Europe is rising due to the current epidemic of hepatitis C infection and NASH. The advent of highly effective direct acting antiviral treatment for hepatitis C serves as a chemopreventive agent and may reduce HCC incidence in the future. HCC screening using ultrasound and the serum biomarker, alpha fetoprotein, is recommended in high-risk populations, such as those with cirrhosis, to detect HCC at an early stage when curative options exist. These simple measures create a roadmap to improving HCC prognosis in the future.

SELECTED REFERENCES

1. White DL, Thrift AP, Kanwal F, Davila J, El-Serag HB. Incidence of Hepatocellular Carcinoma in All 50 United States, From 2000 Through 2012. Gastroenterology 2017;152:812-820 e5.
2. Altekruse SF, Henley SJ, Cucinelli JE, McGlynn KA. Changing hepatocellular carcinoma incidence and liver cancer mortality rates in the United States. Am J Gastroenterol 2014;109:542-53.
3. Bruix J, Sherman M. Management of Hepatocellular Carcinoma: An Update. Hepatology 2010;53:1-35.
4. Yang JD, Kim WR, Coelho R, Mettler TA, Benson JT, Sanderson SO, Therneau TM, Kim B, Roberts LR. Cirrhosis is present in most patients with hepatitis B and hepatocellular carcinoma. Clin Gastroenterol Hepatol 2011;9:64-70.
5. Hoshida Y, Villanueva A, Kobayashi M, Peix J, Chiang DY, Camargo A, Gupta S, Moore J, Wrobel MJ, Lerner J, Reich M, Chan JA, Glickman JN, Ikeda K, Hashimoto M, Watanabe G, Daidone MG, Roayaie S, Schwartz M, Thung S, Salvesen HB, Gabriel S, Mazzaferro V, Bruix J, Friedman SL, Kumada H, Llovet JM, Golub TR. Gene expression in fixed tissues and outcome in hepatocellular carcinoma. N Engl J Med 2008;359:1995-2004.
6. Chang MH, You SL, Chen CJ, Liu CJ, Lee CM, Lin SM, Chu HC, Wu TC, Yang SS, Kuo HS, Chen DS. Decreased incidence of hepatocellular carcinoma in hepatitis B vaccinees: a 20-year follow-up study. J Natl Cancer Inst 2009;101:1348-55.
7. Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, Tanwandee T, Tao QM, Shue K, Keene ON, Dixon JS, Gray DF, Sabbat J. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 2004;351:1521-31.
8. Hosaka T, Suzuki F, Kobayashi M, Seko Y, Kawamura Y, Sezaki H, Akuta N, Suzuki Y, Saitoh S, Arase Y, Ikeda K, Kumada H. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. Hepatology 2013;58:98-107.
9. Singal AG, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. Clin Gastroenterol Hepatol 2010;8:280-8, 288 e1.
10. Kanwal F, Kramer J, Asch SM, Chayanupatkul M, Cao Y, El-Serag HB. Risk of Hepatocellular Cancer in HCV Patients Treated With Direct-Acting Antiviral Agents. Gastroenterology 2017;153:996-1005 e1.
11. Singh S, Singh PP, Singh AG, Murad MH, Sanchez W. Statins Are Associated With a Reduced Risk of Hepatocellular Cancer: A Systematic Review and Meta-analysis. Gastroenterology 2012.
12. Bravi F, Bosetti C, Tavani A, La Vecchia C. Coffee drinking and hepatocellular carcinoma: an update. Hepatology 2009;50:1317-8.
13. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol 2004;130:417-22.
14. Singal AG, Pillai A, Tiro J. Early Detection, Curative Treatment, and Survival Rates for Hepatocellular Carcinoma Surveillance in Patients with Cirrhosis: A Meta-analysis. PLoS Med 2014;11:e1001624.

15. Andersson KL, Salomon JA, Goldie SJ, Chung RT. Cost effectiveness of alternative surveillance strategies for hepatocellular carcinoma in patients with cirrhosis. Clin Gastroenterol Hepatol 2008;6:1418-24.
16. Atiq O, Tiro J, Yopp AC, Muffler A, Marrero JA, Parikh ND, Murphy C, McCallister K, Singal AG. An assessment of benefits and harms of hepatocellular carcinoma surveillance in patients with cirrhosis. Hepatology 2017;65:1196-1205.
17. Singal A, Volk ML, Waljee A, Salgia R, Higgins P, Rogers MA, Marrero JA. Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. Aliment Pharmacol Ther 2009;30:37-47.
18. Marrero JA, Feng Z, Wang Y, Nguyen MH, Befeler AS, Roberts LR, Reddy KR, Harnois D, Llovet JM, Normolle D, Dalhgren J, Chia D, Lok AS, Wagner PD, Srivastava S, Schwartz M. Alpha-fetoprotein, des-gamma carboxyprothrombin, and lectin-bound alpha-fetoprotein in early hepatocellular carcinoma. Gastroenterology 2009;137:110-8.
19. Kim SY, An J, Lim YS, Han S, Lee JY, Byun JH, Won HJ, Lee SJ, Lee HC, Lee YS. MRI With Liver-Specific Contrast for Surveillance of Patients With Cirrhosis at High Risk of Hepatocellular Carcinoma. JAMA Oncol 2017;3:456-463.
20. Besa C, Lewis S, Pandharipande PV, Chhatwal J, Kamath A, Cooper N, Knight-Greenfield A, Babb JS, Boffetta P, Padron N, Sirlin CB, Taouli B. Hepatocellular carcinoma detection: diagnostic performance of a simulated abbreviated MRI protocol combining diffusion-weighted and T1-weighted imaging at the delayed phase post gadoxetic acid. Abdom Radiol (NY) 2017;42:179-190.
21. Lee E, Edward S, Singal AG, Lavieri MS, Volk M. Improving screening for hepatocellular carcinoma by incorporating data on levels of alpha-fetoprotein, over time. Clin Gastroenterol Hepatol 2013;11:437-40.
22. Berhane S, Toyoda H, Tada T, Kumada T, Kagebayashi C, Satomura S, Schweitzer N, Vogel A, Manns MP, Benckert J, Berg T, Ebker M, Best J, Dechene A, Gerken G, Schlaak JF, Weinmann A, Worns MA, Galle P, Yeo W, Mo F, Chan SL, Reeves H, Cox T, Johnson P. Role of the GALAD and BALAD-2 Serologic Models in Diagnosis of Hepatocellular Carcinoma and Prediction of Survival in Patients. Clin Gastroenterol Hepatol 2016;14:875-886 e6.
23. Trinchet JC, Chaffaut C, Bourcier V, Degos F, Henrion J, Fontaine H, Roulot D, Mallat A, Hillaire S, Cales P, Ollivier I, Vinel JP, Mathurin P, Bronowicki JP, Vilgrain V, N'Kontchou G, Beaugrand M, Chevret S. Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis: a randomized trial comparing 3- and 6-month periodicities. Hepatology 2011;54:1987-97.
24. Singal AG, Yopp A, C SS, Packer M, Lee WM, Tiro JA. Utilization of hepatocellular carcinoma surveillance among American patients: a systematic review. J Gen Intern Med 2012;27:861-7.
25. Singal AG, Tiro JA, Marrero JA, McCallister K, Mejias C, Adamson B, Bishop WP, Santini NO, Halm EA. Mailed Outreach Program Increases Ultrasound Screening of Patients With Cirrhosis for Hepatocellular Carcinoma. Gastroenterology 2017;152:608-615 e4.