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Hepatocellular Carcinoma from Epidemiology to Prevention: Translating Knowledge into Practice

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Abstract

Hepatocellular carcinoma (HCC) is the 3rd leading cause of cancer-related death worldwide and one of the leading causes of death in patients with cirrhosis.¹ HCC incidence in the United States (US) has more than doubled over the past 2 decades and is anticipated to continue increasing over the next 20 y, due to the growing number of patients with advanced hepatitis C virus (HCV) and/or non-alcoholic steatohepatitis (NASH). At its current pace, HCC is projected to surpass breast and colorectal cancer to become the 3rd leading cause of cancer-related death in the US by 2030.² Currently only 46% of HCC cases are diagnosed at an early stage and most do not receive curative therapy.² Epidemiologic and clinical studies have identified many factors that affect risk for HCC and can be used to identify at-risk patients and implement prevention measures. Although several advances in HCC prevention, early detection, and diagnosis are efficacious and could reduce the incidence and mortality of HCC, widespread dissemination and successful implementation are essential for these strategies to be effective in clinical practice. Challenges include limited recognition of at-risk patients, availability of well-validated risk stratification measures, and surveillance in high-risk groups.

Efficacy vs Effectiveness

Efficacy means the degree to which an intervention produces an expected result under carefully controlled conditions chosen to maximize the likelihood of observing an effect if it exists, whereas effectiveness means the extent to which an intervention is beneficial in usual practice settings, among broader populations.³ Whereas efficacy of an intervention is primarily determined by its biological effects, its effectiveness can be influenced by external patient, provider, system, and societal factors, including the availability and accessibility of the intervention by the health system, identification of patients who are appropriate for the intervention by providers, recommendation of the intervention by providers, acceptance of

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the intervention and adherence by patients, and high-quality test performance when delivered by health systems in usual practice. Given these external factors, efficacy studies can overestimate the intervention's potential effect in clinical practice.

Models of effectiveness can be operationalized to evaluate therapeutic (e.g., HCV treatment) or diagnostic (e.g., HCC surveillance) interventions in large populations. For example, HCV therapy is highly efficacious, producing rates of sustained viral responses greater than 90% in patients with genotype 1 infection (Table 1). However, its effectiveness in usual practice could be substantially lower (17%), given relatively small decrements in rates of access to care, accurate diagnostic tests for HCV, proper treatment recommendations by providers, and acceptance or adherence to treatment by patients. Even if a new anti-viral regimen with 100% efficacy was developed, its overall effectiveness would be only slightly higher (i.e., 24%) if all other parameters were unchanged.⁴ Similarly, ultrasound is efficacious in surveillance for HCC, detecting the cancer with 63% sensitivity. However its effectiveness in clinical practice is substantially lower due to under-recognition of patients with cirrhosis, low utilization among patients with known cirrhosis, and its operator-dependent nature. Effectiveness data more accurately reflect an intervention's ability to decrease disease burden in clinical practice and therefore are equally, if not more, important than efficacy data.³ Therefore, it is imperative to evaluate and improve the effectiveness of HCC risk stratification, prevention, early detection, and diagnosis in usual practice settings.

A Model for Care

The Quality in the Continuum of Cancer Care (QCCC) model provides a framework for evaluating the HCC prevention processes, including potential failures that create a gap between efficacy and effectiveness.⁵ It outlines several steps within the cancer prevention (e.g., screening) process, including identification of at-risk patients, primary prevention, early detection, diagnosis, treatment, and survivorship (Figure 1). The QCCC considers the complexity of the environment in which cancer prevention occurs, highlighting the influence of patient-, provider- and organizational-level factors. As for breast, cervical, and colorectal cancers^{6,7}, the QCCC can help identify intervention targets and strategies to increase HCC prevention effectiveness in clinical practice.

For example, HCC screening is a complex process in clinical practice.⁸ First, providers must be knowledgeable about HCC risk factors and the target patient population for whom prevention and/or surveillance is recommended.⁹ Second, providers must accurately identify patients with cirrhosis and refer eligible patients for primary prevention or HCC surveillance. Third, the healthcare system must have sufficient capacity to schedule and deliver surveillance tests; patients must comply with provider recommendations. Finally, providers must follow up on surveillance results and refer any patients with abnormal results for diagnostic evaluation and treatment. Each of these steps is prone to failure, and the screening process also depends on the availability of surveillance and diagnostic tests. The effectiveness of HCC screening can therefore be reduced by factors at the patient level (e.g., lack of medical insurance), provider level (e.g., poor knowledge of guidelines), and system level (e.g., insensitive surveillance tests or insufficient capacity).

Identification of At-risk Patients, Based on Epidemiology Findings

Accurate identification of patients who are high risk for HCC is the first step for delivery of prevention and early detection programs. This responsibility lies with clinic providers, who depend on a combination of clinical exam, laboratory, and radiology findings. Epidemiology studies have established several important risk factors for HCC that can help providers identify at-risk patients.

Chronic hepatitis B virus (HBV) infection affects 350 million persons worldwide and is the most common risk factor for HCC worldwide. Cohort studies estimate HCC incidence rates among subjects with chronic HBV infection to be 0.02–0.2 per 100 person-years in inactive carriers, 0.3–0.6 per 100 person-years for those with chronic HBV infection without cirrhosis, and 2.2–3.7 per 100 person-years for those with compensated cirrhosis.¹⁰ Several demographic (male sex, older age, Asian or African ancestry, family history of HCC), viral (higher levels of HBV DNA and HB surface antigen; HB e antigen [HBeAg] positivity; HBV genotype; duration of infection; and co-infection with HCV, HIV, or HDV), and environmental (heavy intake of alcohol and possibly tobacco, exposure to aflatoxin) factors increase HCC risk among individuals with chronic HBV infection.¹⁰

HCV infection is associated with a 15- to 20-fold increase in risk for HCC. Once HCV-related cirrhosis is established, HCC develops at an annual rate of 1%–8% (average, 3.5%). Among HCV-infected individuals, risk factors for HCC include male sex, genotype 3 infection¹¹, co-infection with HBV or HIV, diabetes, obesity, and high level of alcohol consumption.¹² Hispanics with HCV are at a significantly higher risk, whereas African Americans are at a considerably lower risk, of developing cirrhosis and HCC than non-Hispanic whites. HCV viremia of any level is a strong risk factor for HCC compared to no viremia. Although a few studies reported a correlation between HCV load and or HCC, most studies did not find such an association.

Several components of the metabolic syndrome have been associated with increased risk of HCC.¹³ Meta-analyses of cross sectional, case control, and cohort studies report pooled odds ratios of approximately 2.5 for the association between type 2 diabetes and HCC, independent of viral hepatitis or alcohol use.^{14;15} Most studies reported a modest increase in the relative risk of HCC in obese persons. A systematic review of 10 cohort studies found a positive association between obesity (measured as body mass index) and risk of HCC in 7 studies (relative risks ranging from 1.4 to 4.1), no association in 2 studies, and an inverse association in 1 study.¹⁶

The factors that affect risk of HCC among obese person are unclear and may include high waist to hip ratio¹⁷, altered levels of adipokines¹⁸, or development of NASH. There seems to be a synergistic interaction between obesity and hepatitis virus infection, with an increased risk of developing HCC at a young age in the absence of major HCC risk factors¹⁹. Epidemiologic studies support at least a modest association between non-alcoholic fatty liver disease (NAFLD) or NASH and HCC, but this association is mostly limited to those who develop cirrhosis. The few population-based cohort studies of patients with NAFLD have been limited by the low number of HCC cases and inability to identify high risk sub-

groups.²⁰ Several case-control studies have evaluated this association indirectly and reported the prevalence of diabetes and obesity to be greater among NAFLD-related cases of HCC than controls (patients with other chronic liver diseases).²⁰ A polymorphism in the patatin-like phospholipase domain-containing 3 gene (*PNPLA3*) has been associated with an increased risk of cirrhosis and possibly HCC.²¹ Studies have shown low risk of HCC among patients with primary sclerosing cholangitis²² or most liver disorders without cirrhosis.

Most risk factors for HCC in the US and Europe are associated with cirrhosis; patients with cirrhosis can therefore be identified and targeted for cancer prevention and surveillance. The risk of HCC among patients with cirrhosis is highest in those with HCV infection (5 y incidence, 17% in the West and 30% in Japan) or hemochromatosis (5 y incidence, 21%), followed by HBV (5 y incidence, 10% in the West and 15% in Asia)²³ and alcoholic cirrhosis (5 y incidence, 8%–12%²⁴). Among patients with NASH-related cirrhosis, the incidence of HCC ranges from 2.4% within 7 y to 12.8% within 3 y.

HCC rarely develops in patients with HCV infection without cirrhosis, and when it does it affects patients with bridging hepatic fibrosis. Although HBV infection can lead to HCC in patients without advanced fibrosis or cirrhosis, more than 85% of cases of HBV-related HCC in Western countries occurred in patients with cirrhosis.²⁵ There have also been reports of NASH-related HCC in patients with mild or no hepatic fibrosis^{26;27}, but it is not clear what factors might contribute to development of HCC in patients with NASH without cirrhosis.

Although cirrhosis is easy to identify in patients with jaundice or ascites, it can be more difficult to detect in patients with well-compensated cirrhosis. Patients can have compensated cirrhosis for several years and have a high risk for developing HCC. Under-recognition of cirrhosis is one of the main reasons for the underuse of HCC surveillance in the United States (US); more than 20% of patients who present with HCC have unrecognized cirrhosis.²⁸ Patients with NASH have the highest risk for unrecognized liver disease. In a study of 251 patients with NAFLD, 54 (21.5%) had NAFLD mentioned as a possible diagnosis, 37 (14.7%) were counseled regarding diet and exercise, and 26 (10.4%) were referred to a specialist.²⁹ With the prevalence of NAFLD increasing in the US and worldwide, unrecognized cirrhosis is likely to become a larger problem.³⁰

Men have a 2-fold to 4-fold greater risk for HCC than women, across almost all liver disease etiologies. Sex-based differences in behavior and environmental exposures such as alcohol use might account for some of this difference. However, male and female sex hormones may also have roles in HCC risk.

Translating Epidemiology into Risk Stratification in Clinical Practice

Scoring systems to estimate risk for HCC, based on risk factors such as cirrhosis, can be used to help identify high-risk patients most likely to benefit from prevention and early detection programs.³¹ They might also be used to identify low-risk patients (how have an annual incidence of HCC below 1.5%) for whom HCC surveillance is not cost-effective. However, these types of algorithms must be sufficiently accurate, validated in diverse patient populations, and based on available data to be widely useful.

Studies performed in Asia have derived and validated HCC risk scores for HBV-infected patients based on age, sex, level of alanine aminotransferase, viral load, HBeAg status, and the presence of cirrhosis. Generally, these scores have high negative predictive values (above 95%) for development of HCC over a 3–10 y period. For example, the REACH-B score identified patients who developed HCC with area under the receiver operating characteristic curve values greater than 0.80, but this system can only be applied to patients without cirrhosis. Other risk scoring systems, such as the GAG-HCC and CU-HCC, consider factors such as presence of cirrhosis and core promoter mutations and may be more accurate, particularly for non-Asian cohorts.³² HCC risk scoring systems for patients receiving antiviral therapy with adequate viral suppression, and/or in other racial/ethnic groups, including patients from the US and Europe, require further evaluation.³³

A multivariate analysis model was developed, using data from the using HALT-C trial, to determine the risk of HCC in patients with HCV infection based on older age, black race, lower platelet count, higher level of alkaline phosphatase, esophageal varices, and smoking.³⁴ The model allowed for risk stratification of patients, with 5 y HCC incidence rates of 0.4%, 4.2%, and 17.8% in the low-risk, intermediate-risk, and high-risk groups, respectively. However, this model had an area under the curve value of only 0.60 (95% confidence interval [CI], 0.50–0.70) when externally validated.³⁵

Genetic factors, such as the single nucleotide polymorphism 61*G (rs4444903) in the epidermal growth factor gene (*EGF*), may help identify which patients with HCV infection are at highest risk for HCC.³⁶ Longitudinal clinical, laboratory, and histologic data can also be used to predict clinical outcomes of patients, including development of HCC.³⁷ However, these models must be validated, particularly in patients with sustained responses to direct-acting antiviral (DAA) agents.

Irrespective of etiology of chronic liver disease, the degree of hepatic fibrosis seems to be associated with HCC risk. The degree of liver stiffness measured using elastography is associated with HCC risk.³⁸

Prevention

Preventing HCC is an important aspect in the care of any patient with chronic liver disease. Primary prevention focuses on preventing the occurrence of HCC risk factors, or treating them at an early stage. The best targets for prevention programs are usually identified using the population-attributable fraction (PAF)—the proportional reduction in disease that would occur if exposure to a risk factor were eliminated.

Worldwide, HBV infection contributes the largest PAF for HCC. However, in the US and several regions in Europe, obesity, diabetes, and NAFLD appear to contribute the largest PAF.³⁹ For example, the European Prospective Investigation into Cancer and Nutrition found obesity to account for approximately 16% of cases of HCC in Europe.⁴⁰ Similarly, based on data from a Surveillance, Epidemiology, and End Results (SEER) analysis of the Medicare population, diabetes and or obesity to contribute to 36.6% of cases of HCC.⁴¹ However, calculation of the PAF assumes that all cases of HCC that develop in patients with metabolic syndrome are etiologically related to this condition, which is unlikely to be true.

In cross-sectional studies of HCC, viral hepatitis accounted for most cases; there have been no convincing studies of temporal trends of increasing NASH- or obesity-related HCC. Among 1500 patients at Veterans Administration hospitals who developed HCC from 2005 through 2010, the annual proportion of NASH-related HCC remained relatively stable (7.5%–12.0%). In contrast, the proportion of HCC cases associated with HCV increased from 61.0% in 2005 to 74.9% in 2010. The proportion of HCC cases associated with alcohol abuse alone decreased from 21.9% in 2005 to 15.7% in 2010, and the annual proportion of HCC cases associated with hepatitis B remained relatively stable (1.4%–3.5%).⁴² Given that HBV and HCV appear to make the greatest contribution to HCC burden, the highest quality data for primary prevention support HBV vaccination and/or anti-viral treatment programs. However, some data support evaluation of chemoprevention agents for patients with non-viral liver disease.

HBV Vaccination

HBV vaccination programs are a prime example of primary prevention strategies for HCC, and have been the most successful in reducing its incidence, in specific areas. A large randomized controlled trial (RCT) in China demonstrated the efficacy of HBV vaccination in reducing liver-related mortality (hazard ratio, 0.30; 95% CI, 0.11–0.85) and primary liver cancer (hazard ratio, 0.16; 95% CI, 0.03–0.77) over a 25 y period.¹⁸ In practice, these programs greatly reduced the prevalence of HBV infection (from 16% to 1.4% in China, from 9.8% to 1.3% in Taiwan, and from 9.3% to 0.9% in Spain) along with the incidence of HCC. Since the implementation of universal HBV vaccination program for newborns in Taiwan in 1986, the average annual incidence of HCC in children from 6 to 14 y old has decreased 65%–75%.⁴³ The effectiveness of HBV vaccination programs are primarily limited by lack of diffusion into some rural parts of East Asia and Africa; continued effort is needed to increase implementation of HBV vaccination programs.

Treatment of HBV Infection

There are approximately 400 million persons with chronic HBV infection worldwide, with about 800,000 living in the US. These people cannot benefit from immunization and remain at increased risk for HCC. However, there is evidence from RCTs that antiviral agents strongly and durably reduce levels of HBV DNA levels and improve liver function and histology. However, there is limited robust evidence on patients' long-term clinical outcomes, and whether these agents prevent HCC.

In a study performed in Taiwan, patients with chronic HBV infection and cirrhosis or advanced fibrosis were randomly assigned to groups given 100 mg lamivudine/day or placebo for up to 5 y. This trial was terminated early because of a significant difference between treatment groups in the number of end points reached; the incidence of HCC was significantly reduced in the lamivudine group compared with the placebo group (3.9% vs 7.4%; hazard ratio, 0.49; $P=0.047$).⁴⁴

Papatheodoridis et al systematically reviewed data on HCC incidence from 21 studies, including 2881 patients with HBV who were treated with medium-term nucleos(t)ide analogues (19 studies of lamivudine, 1 of emtricitabine, and 1 of adefovir).⁴⁵ A total of 168

patients (4.3%) receiving nucleos(t)ide analogue therapy were diagnosed with HCC during a mean or median follow-up period of 40 months. In the 3 studies including untreated patients with HBV infection followed for at least 24 months, the rate of HCC was significantly lower among treated (22/779, 2.8%) than untreated patients (34/534, 6.4%; $P=.003$).

Although fewer data are available on the effects of anti-viral agents such as entecavir and tenofovir, a multi-national European cohort study reported clinical outcomes in patients treated with entecavir for a median of 20 months.⁴⁶ Patients with a virologic response (serum level of HBV DNA below 80 IU/ml) had a significantly lower probability of developing hepatic decompensation or HCC or death (hazard ratio, 0.29; 95% CI, 0.08–1.00; $P=.05$). In a subgroup analysis, this effect was statistically significant only among patients with cirrhosis (hazard ratio, 0.22; 95% CI, 0.05–0.99; $P=.04$). These encouraging findings were limited by a relatively small number of clinical events, but only 3 of 372 patients developed HCC. There have been reports of HBV treatment-related reductions in HCC risk in non-Asian US populations.⁴⁷ The effect of interferon on HCC incidence in patients with chronic HBV has also been evaluated in several studies and meta-analyses; most data indicate that interferon treatment decreases overall HCC incidence in sustained responders.^{48;49}

Patients receiving antiviral treatment, especially those in virologic remission, seem to develop HCC less frequently than untreated persons. However, the risk for development of HCC cannot be eliminated. Therefore, surveillance for the development of HCC in patients with chronic HBV infection must be life-long, or continue until treatments are available to completely eradicate HBV from the liver.

Treatment of HCV Infection

Successful HCV treatment has been reported to slow liver disease progression and reduce the risk of cirrhosis and HCC.⁵⁰ A systematic review of observational studies associated a⁵¹ sustained virologic response (SVR) with reduced risk for HCC in patients with all stages of liver disease (hazard ratio, 0.24, 95% CI, 0.18–0.31). Approximately 1.5% of patients with SVRs developed HCC, compared with 6.2% of those who did not respond. A SVR was associated with a similar reduction in the risk for HCC in patients with cirrhosis (hazard ratio, 0.23; 95% CI, 0.16–0.35; $P<.001$); approximately 4.2% of patients with an SVR developed HCC compared to 17.8% of those without SVR.

Furthermore, data indicate that the effectiveness of anti-HCV agents (in real-world clinical settings) is considerably lower than their efficacy (reported from clinical trials), with an approximate 15%–20% difference in rates of SVR among patients receiving pegylated interferon and ribavirin, as well as boceprevir and telaprevir.⁴ Clinical trials have stringent inclusion criteria, and the results cannot always be generalized to patients in routine clinical care. For example, patients with anemia, thrombocytopenia, or decompensated cirrhosis were excluded from clinical trials, whereas about 10% of patients in clinical care have one of these. Differences in compliance with the treatment regimen as well as patients' ability to tolerate side effects could also account for differences in rates of SVR in clinical trials vs the real world. Although sofosbuvir-containing regimens are better tolerated and have shorter

treatment duration, patients with advanced cirrhosis and comorbidities are excluded from most clinical trials of DAAs, but continue to be treated in clinical practice.

Most importantly, the proportion of patients who receive treatment and achieve SVR continues to be small compared with the vast number of individuals infected with HCV. Data from the US and Europe show that fewer than 20% of HCV-infected patients are ever treated. In the US, the leading barriers to effective antiviral treatment remains at the basic levels of low rates of HCV case identification and inadequate health insurance coverage with limited access to regular health care. However, the estimated cohort frequency with HCV is a virtual cohort, in that these numbers are based on extrapolation of prevalence data (1%–2%) from relatively small epidemiology studies. However, most epidemiology studies that examined HCV prevalence reported that up to 50% of the subjects tested positive for HCV infection had no prior knowledge of their infection status.

At the current level of treatment penetrance, and assuming that rates of SVRs to DAAs are 80% in routine clinical practice, the number of cirrhosis cases will decrease by only 5%–10% by 2020. The biggest gain in the effectiveness of antiviral treatment is tied to increasing the number of patients treated with these drugs. Modeling studies found that treatment of half vs all infected persons would reduce the number cases by 30.2% vs 60.4%, respectively, over the next decade.⁵² The recent recommendation from the Centers for Disease Control for one-time screening of all adults born between 1945 and 1965 for HCV is a potential major advance toward increasing case identification.⁵³ Although the mental and physical health comorbidities that have been major barriers to antiviral treatment are less of an issue with DAA agents, these comorbidities could affect retention in care, adherence to treatment, and overall mortality.

Finally, although active HCV can hypothetically eradicated be eradicated from all infected persons, with a consequent reduction in HCC, the risk is unlikely to return to baseline for the growing number of patients who already have advanced hepatic fibrosis or cirrhosis. Patients with cirrhosis who achieve SVRs continue to be at risk for HCC, although their risk is lower than without treatment. However, persons with cirrhosis or those of older age, or persons with high levels of α -fetoprotein, low platelet counts, high stages of fibrosis, or diabetes, are still at risk for HCC.^{50;54} Therefore, we anticipate the risk of HCV-related HCC to continue for several years after the active infection is gone.

Treatment of NASH

There is no direct evidence that treatment of NAFLD or NASH by any modality (including bariatric surgery) can reduce HCC risk. Although weight loss can reduce the severity of NASH, no studies have shown weight loss to affect its outcomes, including HCC risk. Although bariatric surgery was associated with reduced risk for HCC among patients with a specific polymorphism in *PNPLA3*,⁵⁵ these data require validation.

Chemopreventive Agents

Some agents could have chemopreventive effects that reduce risk for HCC. However, further high-quality data are required before these agents can be used in clinical practice.

Several studies have reported that metformin therapy of patients with diabetes reduces the risk of HCC.^{56–58} In a meta-analysis of these observational studies, metformin use was associated with a 70% reduction in the odds of HCC in patients with diabetes (odds ratio, 0.30; 95% CI, 0.17–0.52; $P<.001$).⁵⁷

Data from epidemiology studies have indicated the potential chemo-preventive effects of statins specific to HCC.⁵⁹ In a large nested case–control study of patients with diabetes, statin use was associated with a 54% reduction in the odds of HCC (odds ratio, 0.46; 95% CI, 0.40–0.52).⁵⁸ A meta-analysis of observational studies and randomized trials with 4298 HCC cases among 1,459,417 patients found a 41% overall reduction in HCC risk with the use of statins⁶⁰. However, this finding was based mostly on analysis of observational studies, which are subject to several types of biases. Most importantly, physicians might be hesitant to give statins to patients with liver disease, leading to confounding by indication. In addition, differences between groups are sometimes reported after short times of statin therapy, which might be related to healthy-patient bias. Statins were not shown to provide any benefit in randomized trials, although most of these trials were conducted in low-risk patients without liver disease, and none were powered to detect differences in development of HCC. A better understanding of who will benefit, appropriate durations of treatment, and relevant biomarkers will be crucial to design of larger trials.

Several studies have reported an inverse relation between coffee drinking and risk of HCC. A meta-analysis of 16 studies (8 case–cohort and 8 case–control)⁶¹ reported a summary relative risk for developing HCC of 0.60 among coffee drinkers compared to those who do not drink coffee (95% CI, 0.50–0.71). The calculated summary relative risk was 0.72 (95% CI, 0.61–0.84) for low vs no coffee consumption and 0.80 (95% CI, 0.77–0.84) for each extra cup of coffee consumed daily. Consumption of other beverages such as tea or decaffeinated coffee is generally not associated with reduced levels of liver enzymes, fibrosis, or HCC. In addition to caffeine, coffee contains phytochemicals and antioxidants, this multiplicity of potentially important ingredients coupled with its varying amounts of caffeine, has prevented its operationalization as a chemopreventive agent.

Surveillance

Secondary prevention is typically performed through HCC surveillance, which aims to detect tumors at an early stage when they are amenable to curative therapy. The best evidence supporting HCC surveillance comes from a large RCT of patients in China with chronic HBV.⁶² In this study, more than 19,000 HBV carriers were randomly assigned to undergo surveillance ($n=9757$) or no surveillance ($n=9443$). HCC was detected at an early stage in a higher proportion of patients in the surveillance group than the control group (61% vs none, $P<.001$). Patients in the surveillance group also had a higher rate of curative therapy (47% vs 8%, $P<.001$) and lower mortality (83.2 vs 131.5/100,000 persons; $P<.001$). However, these data may be less applicable to North America and Europe, where most at-risk patients have cirrhosis. Data from patients with HBV infection cannot be directly extrapolated to patients with cirrhosis for several reasons, including the lower sensitivity for detection of cancer in cirrhotic nodular liver, fewer curative treatments, and higher competing risk of non-HCC mortality.⁶³

Given the lack of Level 1 data from patients with cirrhosis, efficacy of HCC surveillance in these patients is based on observational cohort studies, which have limitations, including lead-time bias, length-time bias, and potential selection bias.²¹ The best, if not only, way to address these concerns would be to perform an RCT of patients with cirrhosis, which has proven to be difficult. An RCT in Australia of patients with cirrhosis was terminated after 18 months due to poor enrollment—patients did not want to participate in a study in which they might be assigned to the group that received no HCC surveillance.⁶⁴ Similarly, many healthcare providers may refuse to support an RCT, given ethical concerns of withholding surveillance from some patients.⁶⁵

A lack of RCT data supporting HCC surveillance for patients with cirrhosis does not mean that surveillance is ineffective. For example, colonoscopy is widely accepted for colorectal cancer screening without data from randomized trials, but based on level 2 evidence and extrapolation of results from fecal occult blood test studies.⁶⁶ Data from cohort studies indicate that HCC surveillance increases early tumor detection and overall survival in patients with cirrhosis. A meta-analysis of 47 studies, comprising more than 15,000 patients, found that HCCs detected by surveillance of patients with cirrhosis were more likely to be early stage (odds ratio, 2.08; 95% CI, 1.80–2.37), and patients were more likely to receive curative treatments (odds ratio, 2.24; 95% CI, 1.99–2.52) and survive for 3 y (odds ratio, 1.90; 95% CI, 1.67–2.17), than in patients who had not undergone surveillance.⁶⁷ The survival benefit associated with HCC surveillance remained significant in the subset of studies that adjusted for lead-time bias (Table 2)^{68–73}

Abdominal ultrasound is recommended as the backbone of HCC surveillance testing, because it is efficacious for early tumor detection, safe, and inexpensive. Ultrasound's sensitivity for detection of early-stage tumors ranges from 29% to 100%; a meta-analysis reported a pooled sensitivity value of 63% (95% CI, 49%–76%) in patients with cirrhosis.⁷⁴ In subgroup analysis, a 6 month surveillance interval maximized ultrasound sensitivity for early detection of HCC, compared with intervals of 6–12 months (70% vs 50%). A retrospective analysis of a multicenter database in Italy also associated a 6 month interval with higher sensitivity for detection of early HCC than a 12 month interval.⁷⁵ A large randomized trial in France found that reducing the surveillance interval from 6 months to 3 months did not increase the proportion of tumors detected at an early stage (79% vs 71%; $P=.40$) or that of patients that received curative treatment (62% vs 58%; $P=.88$).⁷⁶ Several decision-analysis models have demonstrated that semiannual surveillance with ultrasound can be cost effective in patients with compensated cirrhosis.^{77–80}

Computed tomography (CT) and magnetic resonance imaging (MRI) have been proposed as alternative imaging approaches to increase the sensitivity of detection of early-stage HCC. However, optimizing value requires finding the screening intensity that best balances benefits with harms and costs. Few studies have evaluated CT or MRI in surveillance—they have been primarily studied as diagnostic technologies. The only study comparing ultrasound and CT surveillance found that biannual ultrasound detected a similar proportion of early-stage HCCs as annual CT (6.0% vs 6.3%), but at lower costs per HCC detected (\$17,000 vs \$57,000).⁸¹ Furthermore, cross-sectional imaging has adverse effects such as radiation exposure, which limit its utility in surveillance.

The effectiveness of HCC surveillance in clinical practice is determined primarily by use of surveillance and the sensitivity of surveillance tests for early detection. A modeling study found that percentages of surveillance utilization and sensitivity must exceed 34% and 42%, respectively, for HCC surveillance to be associated with a survival benefit.⁸² HCC surveillance is performed in less than 20% of patients with cirrhosis in the US.⁸³ For example, underuse of surveillance may be prevalent in the Veterans Health Administration, safety net, and community health systems, where many patients with cirrhosis receive care from primary care providers, given limited capacity of subspecialty clinics.^{84;85} Underuse of HCC surveillance is associated with higher rates of advanced tumor presentation, when treatment options are limited and survival is significantly worse⁸⁶.

Equally problematic is the variable effectiveness of surveillance tests, given the operator-dependent nature of ultrasound. Although ultrasound is efficacious for early tumor detection, its effectiveness is substantially lower in clinical practice; one study reported that it detected early-stage HCC with as little as 32% sensitivity⁸⁷. Ultrasound is even less likely to detect early-stage HCC in male patients and those with Child B or Child C cirrhosis.⁸⁸ Inadequate sensitivity of surveillance tools is a common reason for late-stage tumor detection among patients followed in tertiary-care centers⁴⁵. Given that low annual incidence rate, the cost-effectiveness of HCC surveillance programs in NAFLD or NASH without cirrhosis still requires further evaluation.

Although HCC surveillance seems to be an accepted default⁸⁹, there is a clear and urgent need for interventions to address its shortcomings. Studies have suggested that interventions should be aimed at the provider or system level. Patients report high levels of acceptance and willingness to participate in HCC surveillance.⁹⁰ In contrast, providers report several barriers to effective HCC surveillance, including difficulty identifying at-risk patients with cirrhosis, suboptimal levels of knowledge about HCC surveillance guidelines, and time constraints, given competing clinical concerns.⁶⁵ A quasi-study evaluating HCC surveillance within the Veterans Health Administration system found that sending patients a reminder increased the proportion that underwent surveillance, from 18.2% to 27.6%. However, this rate still falls below the minimum cut-off at which HCC surveillance becomes beneficial⁴⁷. Inreach and outreach interventions might improve rates of HCC surveillance (Table 3).⁹¹ Preliminary data from an ongoing randomized study indicate that mailed outreach invitations can significantly increase the proportion of patients that schedule HCC surveillance, compared with visit-based surveillance (34.0% vs 11.5%, $P<.001$).

Similarly, tests for HCC biomarkers might increase rates of early tumor detection in clinical practice.⁹² Use of assays for α -fetoprotein (AFP), in combination with surveillance ultrasound, increased the sensitivity of early detection of HCC in clinical practice, from 32% without the combination vs 63% with the combination ($P<.001$).⁸⁷ Incorporating longitudinal data or adjusting for patient characteristics, such as etiology of liver disease or degree of hepatic inflammation, may further improve the accuracy of HCC detection by tests for AFP.^{93–95} For example, El-Serag et al. constructed an AFP-adjusted model incorporating age, platelet count, and ALT for the prediction of HCC. In that model, the probability of HCC increases from 3.5% to 8.1% with an AFP level of 20 ng/mL in a hypothetical 70 y old patient with a level of alanine aminotransferase of 40 IU/mL and platelet count of

100,000.⁹⁵ New biomarkers, including AFPL3, DCP, GP73, and osteopontin, are being evaluated for early HCC detection in phase 3 studies, including the Early Detection Research Network.⁹⁶ Johnson et al demonstrated the potential of a multi-biomarker approach in a study that combined data on patient sex, age, levels of AFP-L3, AFP, and des carboxy prothrombin (DCP) to derive a model for HCC detection.⁹⁷ The GALAD model detected HCC with 93%–95% sensitivity in discovery and internal validation cohorts; prospective studies are needed to externally validate its accuracy for early detection of HCC.

Diagnosis

Patients with an abnormal results from surveillance tests require timely diagnostic evaluation to determine the presence or absence of HCC. Radiologic imaging has priority in the diagnostic evaluation of patients with suspected HCC since it can facilitate HCC diagnosis, without a need for biopsy, and provides a determination of overall tumor burden. Patients with an ultrasound mass ≥ 1 cm or level of AFP ≥ 20 ng/mL should be evaluated with 4-phase CT or dynamic contrast-enhanced MRI. A meta-analysis found MRI and CT to detect lesions with similar levels of sensitivity (79% vs 72%, $P=.61$). However, in 11 studies that performed head to head comparisons, MRI detected HCC with a higher level of sensitivity (80%) than CT (68%) ($P=.002$).⁹⁸ MRI and CT detected HCC lesions smaller than 2 cm with significantly lower levels of sensitivity (55% and 42%, respectively).

Imaging characteristics such as arterial enhancement or delayed washout, observed by either MRI or CT, are sufficient for a diagnosis of HCC; no further investigation is necessary. Liver biopsy is typically reserved for patients with indeterminate lesions on cross-sectional imaging. However, an analysis of the SEER Medicare database found 32.4% of patients with HCC to have undergone 1 or more biopsies analyses; 47.8% of patients underwent a diagnostic sequence inconsistent with guideline recommendations.⁹⁹

Delays in diagnostic testing after patients present with a positive result from a screening test are barriers to effective colon and breast-cancer screening.^{100;101} However, there are few data on the prevalence of diagnostic delays among HCC patients. SEER analysis of the Medicare database found that median time from diagnosis to first consultation¹⁰² of 28 days for consultation with a hepatologist, 37 days for a surgeon, 41 days for a medical oncologist, 49 days for a radiation oncologist, and 55 days for an interventional radiologist. In a single-center study from a safety net health system, median time from presentation to diagnosis was 0.6 months; diagnosis was delayed by 3 months or more for 39% of patients. However, it is unclear whether these results can be generalized to other practice settings.¹⁰³ Furthermore, the optimal time of HCC diagnostic evaluation is unclear. Studies are needed to determine what interval for diagnostic evaluation is associated with clinically significant tumor growth or differential rates of curative treatment in clinical practice. While we await these data, 3 months may be a reasonable initial cut-off, based on tumor-doubling time.¹⁰⁴

Recommendations for Practice

Provider education may improve awareness and identification of at-risk patients and methods of HCC surveillance. However, system-level interventions such as incorporation of risk calculators into electronic medical records are much more likely to increase timely,

accurate and complete performance of HCC prevention measures. While awaiting more accurate risk calculators, use of ICD-9 codes and non-invasive markers of fibrosis e.g., AST to platelet ratio index (APRI), can be a simple method to identify at-risk patients with recognized and unrecognized cirrhosis who could benefit from HCC prevention and/or early detection efforts.^{105;106} System-level enrollment of these patients in prevention and/or surveillance programs can then be used to supplement visit-based opportunities. For example, through the Texas Hepatocellular Carcinoma Consortium (THCC), we are investigating the efficacy of a mailed outreach strategy to increase HCC screening process completion among patients with cirrhosis. Finally, tumor boards and multidisciplinary HCC clinics have been shown to reduce diagnostic delays, improve curative treatment receipt, and increase survival of patients with HCC.¹⁰⁷ Efforts such as these may serve as models to narrow the gap between HCC screening process efficacy and effectiveness.

Summary

Epidemiology and clinical studies have generated actionable information that can be used for HCC prevention and early detection. The resulting preventive and diagnostic efforts are efficacious with the potential to reduce incidence and mortality of HCC. However, diffusion of knowledge and practices into usual care can be difficult and the effectiveness of these interventions can be limited by a combination of patient-, provider-, and system-level factors. Overall, the QCCC conceptual framework can be used to identify challenges to clinical effectiveness of the HCC screening process and thereby inform intervention studies to improve outcomes. Efforts must continue to translate HCC-related knowledge into clinical practice and thereby reduce the gap between screening process efficacy and effectiveness.

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Figure 1.
The QCCC Model

Table 1
Factors Related to the Healthcare System and Human Behavior That Affect Translation of Efficacy into Effectiveness

	Efficacy	Access	Diagnosis	Recommendation	Acceptance	Adherence	Effectiveness
Therapy A	50%	80%	85%	85%	85%	70%	17%
Therapy B	70%	80%	85%	85%	85%	70%	24%

Table 2

Studies Assessing Survival Benefits of HCC Surveillance

Tumor Doubling Time	Estimated Lead Time	Survival (surveillance vs not)	Risk Estimate and or Statistical Significance	Author and Year
70 days	70 days	Median survival 298 vs 130 days	OR 0.81 (95% CI, 0.70–0.94)	El-Serag 2011
216 days	118 days	3 y survival 62.5% vs 36.6%	$P=.007$	Tong 2010
90 days	236 days	2 y survival 49.4% vs 28.6%	$P=.03$	Wong 2008
90 days	238 days	Median survival 6.3 vs 5.3 y	$P=.02$	Tanaka 2006
Not reported	Not reported	3 y survival 49.0% vs. 41.2%	odds ratio, 0.35 (95% CI, 0.24–0.49)	Yu 2004
Not reported	98–239 days	Median survival 30 vs 20 months	$P<.001$	Trevisani 2002

Note: Results reported after adjustments for lead-time bias

Table 3

Interventions to Increase Rates of HCC Surveillance

Number of Patients	Intervention	Provider Target	Effect Size (Intervention vs none)	Study
515	Quasi-study of nurse based protocol	Gastroenterologists	74% vs 93%	Aberra 2013
60	Randomized controlled trial of automated reminders	Gastroenterologists	89% vs 100%	Wigg 2013
790	Quasi-study of point-of-care reminders	Primary care providers	18% vs 28%	Beste 2014
600	Randomized controlled trial of mailed outreach interventions	Primary care providers	12% vs 34%	Singal 2015