Published in final edited form as:
Clin Gastroenterol Hepatol. 2013 May ; 11(5): 472–477. doi:10.1016/j.cgh.2012.11.010.

Improving Hepatocellular Carcinoma Screening: Applying lessons from colorectal cancer screening

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Hepatocellular carcinoma (HCC) is one of the leading causes of death among patients with cirrhosis and has an increasing incidence in the United States[1]. The prognosis for patients with HCC depends on tumor stage at the time of diagnosis, with curative options only available for patients diagnosed at an early stage[2]. Patients with early HCC achieve 5-year survival rates near 70% with resection and transplantation, whereas those with advanced HCC have a median survival of less than one year[3, 4]. HCC screening strives to detect HCC at an early stage and is recommended for patients with cirrhosis[5].

HCC screening is a complex process, requiring several steps when implemented in clinical practice.[6] First, providers must be knowledgeable about the benefits of HCC screening and for whom screening is recommended. Second, providers must be able to accurately identify patients with cirrhosis and refer these patients for appropriate screening tests. Third, patients must comply with these provider recommendations. The healthcare system must have sufficient capacity to schedule and complete/deliver the screening tests, and finally, providers and patients must complete clinically-indicated follow-up on any abnormal screening test results[7]. In addition to each of the above steps in the screening process, screening tests must remain effective in usual practice settings[8, 9]. Thus, the effectiveness of HCC screening may be reduced due to factors at the patient-level (e.g. insurance), provider-level (e.g. knowledge of guidelines), and system-level (e.g. availability of screening tests).

The Quality in the Continuum of Cancer Care (QCCC) conceptual framework (Figure 1), which has been successfully used for understanding screening processes in breast, cervical, and colorectal cancer[10, 11], provides a useful model to highlight how aspects of the HCC screening process differ from other cancers and therefore may pose unique challenges to its effectiveness. While research on improving the HCC screening process is in its infancy

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Conflicts of Interest: None of the authors have any conflicts of interest to disclose.

Author Contributions:
Amit Singal was involved in study concept and design, drafting of the manuscript, critical revision of the manuscript, and study supervision.
Jasmin Tiro was involved in critical revision of the manuscript.
Samir Gupta was involved in drafting of the manuscript and critical revision of the manuscript.

stage, important lessons can be learned from prior colorectal (CRC) screening studies. Although CRC screening rates and outcomes still fall short of desirable levels, several successful interventions have led to substantial improvement over time[12, 13]. In fact, there has been a steady increase in CRC rates from 20–30% in 1997 to approximately 55% in 2008[14, 15]. This improvement in CRC screening rates is in part related to lessons learned from experiences in breast and cervical cancer screening programs[16]. In contrast, HCC screening rates among patients with cirrhosis remain below 30% nationally, and the majority of tumors are still diagnosed at an advanced stage when curative therapies are no longer available[17–20]. In this commentary, we compare and contrast several steps in the cancer screening processes for CRC and HCC to illustrate issues that need to be addressed in the promotion and delivery of HCC screening.

Step 1: Accurate provider identification of at-risk population

CRC screening requires providers to assess age- and family-related risk and recommend screening to at-risk patients. CRC screening is uniformly recommended to all average-risk patients at age 50 years. Early screening initiation is recommended in high-risk patients, such as those with a family history of colon cancer, which providers fail to adequately assess in up to one-third of patients[21]. However, given the relative ease of assessing age-related risk, identification of the at-risk population has not been regarded as a major barrier to effective CRC screening.

Risk assessment for HCC screening is likely to be more challenging compared to identification of those eligible for CRC screening based on age and family history. Providers must recognize the presence of underlying liver disease as well as the transition to cirrhosis, which can occur without overt clinical symptoms. Under-recognition of liver disease and cirrhosis substantially contributes to the underutilization of HCC screening; in fact, nearly 40% of patients present with HCC without having previously recognized liver disease and/or cirrhosis (Figure 2)[22, 23]. Although liver biopsy currently remains the gold standard for assessing stage of fibrosis, the increasing availability and accuracy of non-invasive markers of fibrosis may help improve the recognition of cirrhosis in the future[24]. Patients with non-alcoholic fatty liver disease (NAFLD) appear to be at the highest risk, with over 80% of patients having unrecognized liver disease at the time of HCC presentation. With the prevalence of NAFLD increasing and now approaching 50% of the population in the United States, this issue may become even more problematic in the future[25].

The Centers for Disease Control and Prevention (CDC) recently recommended screening for hepatitis C virus (HCV) infection using a birth-cohort screening strategy (i.e. screening all patients born between 1945 and 1965) instead of the previously recommended risk-based strategy (i.e. screening only patients with known risk factors for HCV infection) to simplify risk assessment and increase HCV testing rates[26]. Although mass screening strategies are possible for certain liver diseases, such as viral hepatitis, this would not be possible for other etiologies, such as NAFLD given that it is a diagnosis of exclusion with no serologic markers. Therefore, education of primary care providers regarding the at-risk population for NAFLD and the necessity for high clinical suspicion is likely crucial.

There have not been any interventions to date that address the accurate identification of patients with cirrhosis for HCC screening. Liver biopsy remains the gold standard for assessing liver fibrosis but is often avoided given the potential for complications and lack of patient acceptance[27]. Despite significant advances in the accuracy of non-invasive markers for liver fibrosis, they have yet to be widely incorporated into routine clinical practice[28]. With the growing use of electronic medical records, incorporation of electronic prompts using applicable ICD-9 codes or non-invasive markers of fibrosis, such as AST to platelet

ratio index (APRI), could potentially help providers accurately identify at-risk patients in the future[23, 28–30]. Overall, we anticipate optimizing screening will required concerted efforts to develop and implement interventions for identifying individuals at risk for HCC in usual practice.

Step 2: Provider recommendation and referral for screening

Despite over ten years of consistent United States Preventive Services Task Force (USPTF) and American Cancer Society (ACS) guidelines recommending CRC screening[31, 32], providers are still not systematically referring all individuals eligible for screening[15]. In fact, lack of physician recommendation for screening remains the most powerful predictor for screening non-completion[33, 34]. In one analysis, 20% of patients not up-to-date with CRC screening reported lack of provider recommendation as a significant barrier[14]. Although CRC screening rates have consistently improved over this time period, there are still many missed opportunities for screening recommendations[35]. Physicians have reported multiple barriers to implementing cancer screening guidelines including inadequate levels of knowledge, provider forgetfulness, time constraints in clinic, provider fatigue, lack of financial incentive, and competing health problems[36, 37]

Successful strategies to bypass or increase provider recommendations for CRC screening rates have included organized screening efforts, patient-directed prompts, provider-focused reminders, and systematic mass screening programs[38]. Patient-directed prompts, such as postcards and one-on-one patient education, has been shown to be effective at improving CRC screening rates by 5% to 42% compared to usual care[15, 39]. Provider-focused intervention strategies, such as provider assessment and feedback or provider reminder and recall systems, are also effective and recommended by the Community Preventive Services Task Force[40, 41]. Interventions at the health system, such as public awareness campaigns and systematic mass screening programs which do not rely on provider-based referrals, may improve screening rates by 7% to 28%[15, 39, 42]

HCC screening has not been adopted into routine clinical practice and rates remain below 30% nationally, despite being standard of care in patients with cirrhosis[18–20]. Screening rates are higher among patients who receive subspecialty care; however, only 20–40% of cirrhotic patients are followed by gastroenterologists or hepatologists nationally[23]. Even among patients with recognized cirrhosis, providers fail to order HCC screening in nearly two-thirds of patients[22]. In a secondary analysis of the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial, nearly one-third of patients followed by expert hepatologists in academic centers had inconsistent screening[43]. The strongest predictor for receipt of consistent screening in this study was the provider, after adjusting for differences in patient characteristics.

There have yet to be any interventions to increase HCC screening referrals among patients with cirrhosis. Future interventions should likely focus on optimizing provider referrals for HCC screening given that physician factors appear to be more important than patient-level factors in determining HCC screening rates. Potential provider-based interventions include provider education, electronic reminder systems, and provider feedback of screening rates. Although system-based screening invitations to patients with known cirrhosis could also be considered, issues of potential overuse among patients with Child Pugh C or poor functional status would need to be addressed. Given HCC screening is only performed in a targeted population of patients with cirrhosis, interventions such as public awareness campaigns are unlikely to be cost-effective; however targeted patient education programs about the importance of HCC screening may increase rates of patient demand and self-referral.

Step 3: Patient adherence to recommendations for screening

Despite provider recommendations, many patients do not complete CRC screening. In fact, nearly one-fourth of patients failed to adhere to provider recommendations to endoscopic CRC screening and over one-half failed to adhere to FOBT testing[44, 45]. Patient factors associated with screening non-completion include younger age, minority background, recent immigration, limited knowledge regarding the importance and effectiveness of screening, and low socioeconomic status[15]. The type of CRC screening test offered may also play a role, with significantly lower rates of screening completion among patients who were only offered colonoscopy compared to those who were given a choice between colonoscopy and other screening modalities[46]. Provision of client reminders, small media, one-on-one patient education, and reducing structural barriers are all effective ways of overcoming patient barriers to screening completion once it is offered[40, 47–49].

Patient adherence does not currently appear to be a major barrier to HCC screening. Overall, over 95% of patients complete HCC screening once ordered by their provider[22]. At-risk patients have also demonstrated high levels of knowledge and reported high rates of acceptance for HCC screening, although this study was conducted among well-insured, highly-educated patients in a tertiary care setting[50]. In contrast to colonoscopy, whose uptake is limited by prep tolerance and patient perceptions, HCC screening primarily consists of an ultrasound, which is easy, painless, and without significant complications. Although younger age, minority race, and lower socioeconomic status are associated with lower HCC screening rates[20], it is unknown if these associations are due to lack of access to medical care, providers not ordering HCC screening in these subgroups, or patient non-adherence. This will be crucial to understand in the future, given the populations at highest risk for HCC tend to be socially disadvantaged, such as immigrants and those of low socioeconomic status[51].

Although interventions to increase patient adherence, such as patient education and nurse navigation programs, have been useful for increasing CRC screening rates, no studies have evaluated these intervention strategies for HCC screening interventions. However, the current high rates of patient adherence with HCC screening may simply reflect experiences with early adopters of screening or the “worried well”. Therefore, patient adherence will need to be monitored closely as HCC screening becomes more widely adopted. We anticipate that patient adherence rates may become suboptimal in the future, as broader populations are offered HCC screening, potentially requiring us to draw from lessons from interventions used to optimize CRC screening adherence at that time.

Step 4: Capacity of the health system to schedule tests

Although there are sufficient providers and resources to perform universal CRC screening with fecal occult blood testing, there is insufficient capacity for widespread CRC screening through colonoscopy. A study performed by the CDC reported 14.2 million colonoscopies were performed in 2002[52]; given the current underuse of CRC screening, endoscopic capacity is not an issue at this time. In fact, endoscopic output could be increased by 8.2 million without requiring an increase in resources or personnel. This increase would provide sufficient endoscopic capacity for expanding FOBT testing to the 41.8 million unscreened portion of the US population. However, using flexible sigmoidoscopy and colonoscopy as initial CRC screening tests among the unscreened portion of the population would quickly overwhelm endoscopic capacity. Furthermore, this analysis did not account for repeat routine or post-polypectomy surveillance, which would even further limit endoscopic capacity. Overall, it is clear that providing screening and diagnostic colonoscopy for all patients eligible for screening remains a challenge[14].

It is unknown if radiologic capacity is a significant barrier to HCC screening. In a single-center study, over 95% of patients were appropriately scheduled for HCC screening testing once ordered by their provider[22]. However, it is unknown if these results are generalizable, and radiologic capacity must still be assessed on a national level. Furthermore, radiologic capacity could become an issue if HCC screening rates improved and created a larger burden on the radiology scheduling system. This may be particularly difficult for community hospitals in rural areas and safety net hospitals, which often have limited resources[53].

One key difference between HCC and CRC screening comes in the separation between screening and diagnostic tools. In CRC screening, colonoscopy is often used as both the screening and diagnostic tool. In HCC screening, ultrasound is used as the screening tool, requiring CT or MRI to confirm the diagnosis in any patients with a suspicious mass. Therefore, future studies of ability to deliver HCC screening should assess the national radiologic capacity for ultrasonography as well as CT and MRI.

Step 5: Appropriate and timely follow-up of abnormal screening tests

Evidence-based follow-up of abnormal screening results is critical for the effectiveness of any screening program. Nonetheless, in CRC screening, high variability in diagnostic colonoscopy completion rates after abnormal fecal occult blood test screening has challenged screening effectiveness. Indeed, diagnostic colonoscopy completion rates after abnormal fecal occult blood testing as low as 22% have been reported in the literature[54–61]. Importantly, focused attention to quality improvement has been shown to significantly improve clinically indicated follow up after abnormal CRC screening tests[62].

Follow up after an abnormal US or AFP screening requires diagnostic imaging with contrast-enhanced CT or MRI to confirm the diagnosis. A secondary analysis of data from the HALT-C Trial suggests that follow-up of abnormal screening tests could be delayed more than six months in nearly one-fourth of patients[43]. These delays in follow-up are concerning given an approximate tumor doubling time of three months for HCC[63]. In fact, patients with tumors larger than 2 cm in diameter were significantly more likely to not have prior HCC screening and/or timely follow-up of abnormal tests than patients found with very early stage tumors. These screening process failures contributed to more advanced tumor stage in over one-third of HCC patients in HALT-C[43]. Further studies assessing the impact of delayed or lack of follow-up on HCC outcomes in clinical practice are still needed. If confirmed, several interventions that have been effective in CRC, including patient navigation, could potentially be applied to HCC screening.

Summary

In this commentary, the Quality in the Continuum of Cancer Care conceptual framework was used to highlight differences between the HCC and CRC screening processes and identify how HCC screening may pose unique challenges to its effectiveness. Although lack of provider recommendations is a significant barrier for both CRC and HCC screening, HCC screening appears to be limited by under-recognition of at-risk individuals with liver disease and cirrhosis. Future HCC screening interventions must help providers accurately identify at-risk patients as well as promote ordering of HCC screening among those with cirrhosis. On the other hand, patient adherence, a well-recognized barrier to CRC screening, does not appear to be a major issue in HCC screening at this time. However, adherence may become a more significant issue in the future, with expanded adoption of HCC screening, and must be monitored closely. Other steps in the screening process, including radiology capacity and timely follow-up, have been demonstrated as barriers for CRC screening, but further studies assessing their impact on HCC screening outcomes are still needed. Overall, many lessons learned from challenges to CRC screening can be applied to rapidly optimize HCC

screening in usual practice. The QCCC framework can continue to be used as a guide for monitoring progress as well as to identify new barriers to HCC screening in the future.

Acknowledgments

Financial disclosures: This work was conducted with support from UT-STAR, NIH/NCATS Grant Number KL2 TR000453 and the ACG Junior Faculty Development Award awarded to Dr. Singal. The content is solely the responsibility of the authors and does not necessarily represent the official views of UT-STAR, UT Southwestern Medical Center and its affiliated academic and health care centers, the National Center for Advancing Translational Sciences, or the National Institutes of Health.

Abbreviations

ACS	American Cancer Society
APRI	AST to platelet ratio index
CDC	Centers for Disease Control and Prevention
CRC	colorectal cancer
HALT-C	Hepatitis C Antiviral Long-term Treatment against Cirrhosis
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
NAFLD	nonalcoholic fatty liver disease
QCCC	Quality in the Continuum of Cancer Care
USPTF	United States Preventive Services Task Force

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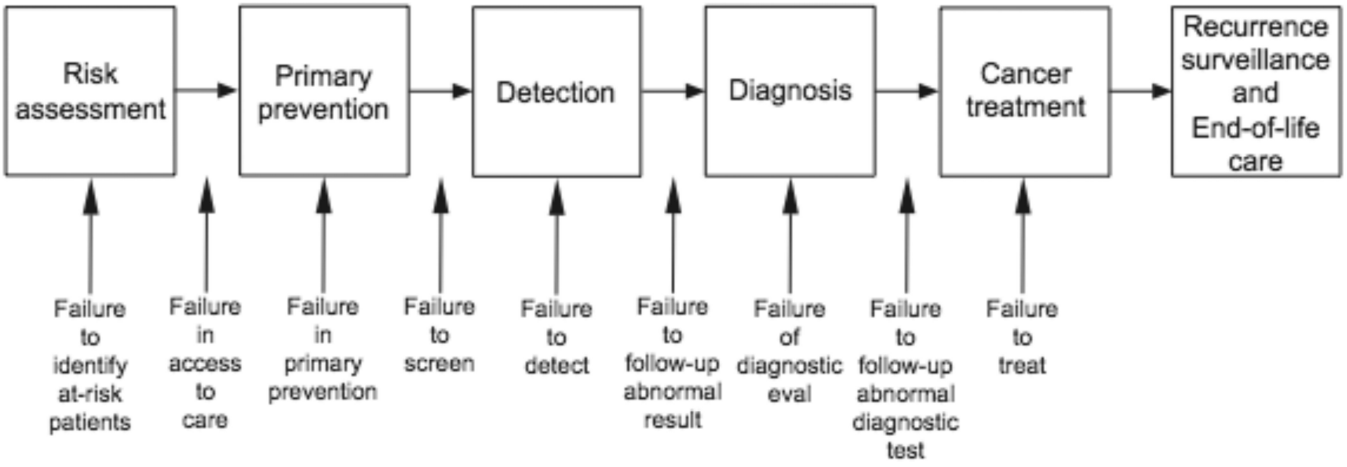

Figure 1.
The Quality in the Continuum of Cancer Care (QCCC) conceptual framework