Screening for Hepatocellular Carcinoma in Adults at Increased Risk

November 2023

U.S. Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development Service

Recommended citation: Landsteiner A, Ullman K, Langsetmo L, Zerzan N, Kalinowski C, Haglund J, Wilt TJ. Screening for Hepatocellular Carcinoma in Adults at Increased Risk: A Systematic Review. Washington, DC: Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs. VA ESP Project #09-009; 2023.

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PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to conduct timely, rigorous, and independent systematic reviews to support VA clinicians, program leadership, and policymakers improve the health of Veterans. ESP reviews have been used to develop evidence-informed clinical policies, practice guidelines, and performance measures; to guide implementation of programs and services that improve Veterans' health and wellbeing; and to set the direction of research to close important evidence gaps. Four ESP Centers are located across the USA. Centers are led by recognized experts in evidence synthesis, often with roles as practicing VA clinicians. The Coordinating Center, located in Portland, Oregon, manages program operations, ensures methodological consistency and quality of products, engages with stakeholders, and addresses urgent evidence synthesis needs.

Nominations of review topics are solicited several times each year and submitted via the ESP website. Topics are selected based on the availability of relevant evidence and the likelihood that a review on the topic would be feasible and have broad utility across the VA system. If selected, topics are refined with input from Operational Partners (below), ESP staff, and additional subject matter experts. Draft ESP reviews undergo external peer review to ensure they are methodologically sound, unbiased, and include all important evidence on the topic. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. In seeking broad expertise and perspectives during review development, conflicting viewpoints are common and often result in productive scientific discourse that improves the relevance and rigor of the review. The ESP works to balance divergent views and to manage or mitigate potential conflicts of interest.

ACKNOWLEDGMENTS

The authors are grateful to external peer reviewers, and the following individuals for their contributions to this project:

Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

Timothy Morgan, MD
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Technical Expert Panel

To ensure robust, scientifically relevant work, the technical expert panel (TEP) guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members included:

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Disclosures

This report was prepared by the Evidence Synthesis Program Center located at the **Minneapolis VA Health Care System,** directed by Timothy J. Wilt, MD, MPH and Wei Duan-Porter, MD, PhD and funded by the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development.

Executive Summary

KEY FINDINGS

- The evidence is very uncertain regarding the effectiveness and harms of hepatocellular carcinoma (HCC) screening in adults at increased risk.
- Evidence is generally very uncertain regarding comparative effects of different screening strategies including imaging modalities, intervals, and biomarkers.
- Most studies analyzed only individuals with an HCC diagnosis (HCC-cohorts), thus missing the target increased risk population. Major methodological issues that limit certainty include a combination of lead- and length-time bias and little controlling for confounders known to affect receipt of screening and survival.
- We found very little data from studies that could provide more reliable information (cohort, case-control, randomized controlled trials [RCTs]) regarding screening among individuals at risk for HCC. Among these studies, methodological concerns or inconsistent findings also severely limited conclusions.
- Evidence gaps could be closed with completion of RCTs, especially RCTs comparing screening with no screening, and higher methodological quality observational studies.
- Until methodologically higher quality studies are completed, the current uncertainty challenges HCC screening implementation and patient-clinician decision-making.

An estimated 41,210 Americans will be diagnosed with liver cancer in 2023 (approximately 9.5 per 100,000), with 29,380 expected to die from the disease. HCC is the sixth most common cancer and the most common form of liver bile duct cancer (accounting for approximately 75% of cases). HCC is the second leading cause of cancer-related deaths worldwide, though incidence and mortality vary by age, race or ethnicity, and sex. HCC occurs most frequently and is most deadly among males, Asians and Pacific Islanders, and older adults. Results of the Surveillance, Epidemiology, and End Results Program (SEER) show that age-adjusted rates of liver and intrahepatic bile duct cancer in the USA more than doubled between 1992 and 2012 (4.6 to 9.3 per 100,000) before leveling off over the last decade. Mortality from the disease has followed a similar trajectory (from 3.9 per 100,000 in 1992 to 6.7 per 100,000 in 2016). Shifting patterns of liver disease and cirrhosis etiology may partially account for HCC incidence and mortality trends. However, screening programs may have harms and be ineffective (*ie*, identifying individuals with HCC but not improving receipt of effective therapies).

Veterans have an unadjusted 5-fold higher HCC incidence compared with the general population. HCC incidence among Veterans receiving care in VA peaked in 2015 (31 per 100,000), then declined to 22 per 100,000 patients in 2018. This decline appears to be driven primarily by a reduction in hepatitis C-related HCC, but importantly, during the same period the incidence of non-hepatitis C-related HCC increased. Effective early HCC identification and treatment options are important. The 3-year payer costs in the VA related to cirrhosis are estimated to be $154,688 with $69,010 for HCC treatment. Early identification of liver cancers may reduce disease-specific and all-cause mortality by providing an opportunity for potentially curative therapies (surgical resection, ablative therapy, or liver transplantation). A recent systematic review highlighted that HCC treatment costs, harms, and limited mortality benefits may lead some patients to forgo treatment, underlining the importance of more effective detection and treatment options.

Screening for HCC among adults at increased risk (especially those with cirrhosis) has been recommended by several specialty societies (*eg,* American Association for the Study of Liver Diseases [AASLD], European Association for the Study of the Liver [EASL]) (typically through abdominal ultrasound imaging with AFP every 6 months) and is considered a quality metric for practice performance by AASLD. However, the National Cancer Institute's Physician Data Query concluded that based on fair evidence, screening of persons at elevated risk does not result in a decrease in mortality from HCC and would result in rare but serious side effects. The United States Preventive Services Task Force and other USA medical societies have not issued HCC screening guidelines. Questions surrounding screening include whether to conduct screening, the appropriate imaging technique if conducting screening (ultrasound, magnetic resonance imaging [MRI], computed tomography [CT]), use of AFP, screening intervals (*eg,* 3, 6, or 12 months), populations defined as increased or "at risk" and thus potential screening candidates, and when to discontinue screening.

CURRENT REVIEW

The Veterans Health Administration (VA) Evidence Synthesis Program (ESP) is responding to a request from the National Gastroenterology and Hepatology Program (NGHP) for an evidence review evaluating the data regarding screening for hepatocellular carcinoma (HCC) and, specifically, to identify the benefits and harms of HCC screening among adults at increased risk. We are updating a prior review the ESP conducted in 2014 synthesizing the evidence of screening for HCC in chronic liver disease. The current review updates the evidence with the intention that findings improve health and health care by informing clinical guidelines, VA directives, and implementation strategies related to HCC screening across the VA. We conducted the systematic review to identify and critically appraise the available evidence on the effects, comparative effects, and harms of HCC screening versus no screening and different screening strategies in populations at increased risk. We also assessed whether benefits and harms varied by patient or co-existing medical characteristics, presence of cirrhosis, liver disease etiology, screening intervals, or screening modality with or without alpha-fetoprotein (AFP).

Key Question

The following key question was the focus of this review: *What are the benefits and harms of HCC screening among adults at increased risk?* We were also interested in whether benefits and harms of HCC screening varied by the following factors:

- Patient or co-existing medical characteristics (*eg*, age, sex, race/ethnicity; comorbidities)
- Presence of cirrhosis
- Liver disease etiology (hepatitis, B, C, alcohol, metabolic liver disease), severity, or HCC risk
- Screening intervals (*eg*, semiannual, annual, biennial) or abdominal imaging technique
- Screening modality with or without AFP (ultrasound, MRI, CT)

METHODS

A preregistered protocol for this review can be found on the PROSPERO international prospective register of systematic reviews (CRD42023406164). Two previous reviews assessing the effectiveness of screening for HCC in chronic liver disease, Kansagara et al and Singal et al, were conducted in 2014

and 2022. We utilized and updated the published search strategy by Singal et al, searching in Embase and MEDLINE from July 1, 2020, through January 24, 2023.

Effect information and population, intervention, and comparator characteristics were abstracted from all included studies. The internal validity (risk of bias [RoB]) of each included study was rated using the Cochrane Risk of Bias Tool 2.0 (RoB-2) for RCTs and the Risk of Bias in non-Randomized Studies - of Interventions (ROBINS-I) tool for observational studies. All data abstraction and internal validity ratings were completed by 1 reviewer and then checked by another; disagreements were resolved by consensus or discussion with a third reviewer.

We anticipated with the inclusion of mostly large observational studies and with adjustment for confounders that clinical variability and statistical heterogeneity would remain high. Prior to analysis, we examined the clinical and methodological characteristics of the included studies to determine if appropriate for pooling (*ie,* screening modality and comparator, patient and disease factors including etiology and HCC risk in both the screening and control cohorts within and across studies, outcomes reported in each group, study design, country of origin). Due to the large variation in study methodology, results are summarized narratively first by study design, as it was found that the study methodology heavily impacted the risk of bias. Within each study design section, the outcomes are presented by screening method comparisons. Authors categorized the screening approach into uniquely defined groups; as such we have grouped reported outcomes by screening strategies that appeared to have the greatest similarity in protocol. We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology to rate overall certainty of evidence for critical outcomes as high, moderate, low, or very low.

RESULTS

Our search identified 171 potentially relevant articles after deduplication and title and abstract screening. Of these, 74 primary studies met eligibility criteria: 5 RCTs and 69 observational studies (5 cohort, 2 case-control, 62 HCC-cohort). We have differentiated cohort studies (which include the population at risk of HCC) from HCC cohort studies (which included only those diagnosed with HCC) because of the difference in target populations and potential biases. Of the 5 RCTs, 2 were rated some concerns RoB, while the other 3 were rated high RoB. Of the 5 cohort studies, 1 was rated serious RoB, and the other 4 rated critical RoB. Of the 62 HCC-cohort studies, 11 were rated serious RoB, and the remaining 51 were rated critical RoB. The large number of HCC cohort studies with critical RoB reflect possible lead time and length time bias that are intrinsic to this study design. Overall, we found very low strength evidence examining the effects of screening for HCC on all-cause and HCC mortality among patients at increased risk for HCC and thus are uncertain of the effects. A summary of the evidence for HCC and all-cause mortality outcomes by study design and screening modalities is provided below. Summary of the other identified outcomes (sensitivity, specificity, percent receiving treatment, percent receiving transplant, harms, *etc*) are provided in the main report. These outcomes were infrequently reported and were not assessed using GRADE.

CONCLUSIONS

Evidence is very uncertain whether screening for HCC in individuals at increased risk reduces all-cause or HCC mortality. Evidence is also very uncertain as to the comparative effectiveness of varying screening strategies including screening intervals, imaging modalities, additive value of AFP to imaging tests, and in what populations screening may be effective. Harms data were limited regarding psychological distress, liver biopsy complications, renal insufficiency, overdiagnosis, and financial

burden. However, all screening strategies have diagnostic- and treatment-induced harms, patient and clinician burden, and costs. Randomized trials evaluating screening versus no screening as well as different screening strategies are needed. More rigorous observational studies and use of target trial emulation as a framework for design could aid in designing observational studies to provide greater certainty. Until methodologically higher quality studies are available, the current state of the evidence provides serious challenges to HCC screening implementation and patient-clinician decision-making.

CERTAINTY OF EVIDENCE RATINGS

Study Design	Screening Methodology	Follow-Up	Total N (# Studies)	Certainty	Summary Statement
All-Cause Mortality					
RCT	US at 3 months vs at 6 months	5 years	1278 (1)	⊕⊕◯◯ Low	There may be little to no difference in all-cause mortality when screening every 3 months compared to every 6 months.
Cohort	US every 6 months vs US alternating with CT every 6 months	10 years	992 (1)	⊕◯◯◯ Very low	The evidence is very uncertain on the effect of US screening every 6 months on all-cause mortality compared to US with alternating CT every 6 months.
HCC Cohort	Any imaging (+/- AFP) vs no screening	5-8 years	121,822 (6)	⊕◯◯◯ Very low	The evidence is very uncertain on the effect of screening on all-cause mortality.
	US at 3 months vs US at 6 months	50 months	1107 (1)	⊕◯◯◯ Very low	The evidence is very uncertain on the effect of screening at 3 months compared to 6 months on all-cause mortality.
	Biannual AFP + US HCC detected by positive US with negative AFP vs positive results on both US and AFP	5 years	1776 (1)	⊕◯◯◯ Very low	The evidence is very uncertain regarding all-cause mortality in adults with HCC detected by positive US with negative AFP vs HCC detected by positive results on both US and AFP.
	Biannual AFP + US: HCC detected by positive AFP with negative US vs positive results on both US and AFP	5 years	1776 (1)	⊕◯◯◯ Very low	The evidence is very uncertain regarding all-cause mortality in adults with HCC detected by positive results on Biannual AFP with negative US vs HCC detected by positive results on both US + AFP.
HCC-Specific Mortality					
RCT	US at 3 months vs at 6 months	5 years	1278 (1)	⊕⊕◯◯ Low	There may be little to no difference in HCC-specific mortality when screening every 3 months compared to every 6 months.
	US at 6 months vs CT at 12 months	31-35 months	163 (1)	⊕◯◯◯ Very low	The evidence is very uncertain on the effect of US screening every 6 months compared with CT screening every 12 months.
Case-Control	US +/- AFP vs no screening	4 years	814 (2)	⊕◯◯◯ Very low	The evidence is very uncertain on the effect of screening with ultrasound with or without AFP compared to no screening on HCC-specific mortality in adults at increased risk for HCC.
HCC Cohort	Biannual AFP + US: HCC detected based on US and AFP test results: 1) Both US & AFP positive;2) US positive but AFP negative; 3) US negative but AFP positive	5 years	1776	⊕◯◯◯ Very low	The evidence is very uncertain regarding HCC-specific mortality based on whether HCC is detected by 1) both US & AFP positive results; 2) US positive but AFP negative results or 3) US negative but AFP positive results.
Overall Survival					
RCT	US screening at 3 months vs at 6 months	5 years	1278 (1)	⊕⊕◯◯ Low	There may be little to no difference in overall survival when screening every 3 months compared to every 6 months.

Study Design	Screening Methodology	Follow-Up	Total N (# Studies)	Certainty	Summary Statement
Cohort	US at 6 months vs US alternating with CT at 6 months	10 years	992 (1)	⊕◯◯◯ Very low	The evidence is very uncertain on the effect of US screening at 6 months on overall survival compared to alternating US and CT screening at 6 months.
HCC Cohort	Any imaging (+/- AFP) vs no screening	5 years	3965 (5)	⊕◯◯◯ Very low	The evidence is very uncertain on the effect of screening on overall survival.
	US at 3 months vs US at 6 months	5 years	1107 (1)	⊕◯◯◯ Very low	The evidence is very uncertain on the effect of screening at 3 months compared to 6 months on overall survival.
	Biannual AFP + US: HCC detected by positive US with negative AFP vs HCC detected by positive results on both US and AFP	5 years	1776 (1)	⊕◯◯◯ Very low	The evidence is very uncertain regarding overall survival in adults with HCC detect by positive US with negative AFP vs positive results on both US and AFP.
	Biannual AFP + US HCC detected by positive AFP with negative US vs HCC detected by positive results on both US and AFP	5 years	1776 (1)	⊕◯◯◯ Very low	The evidence is very uncertain regarding overall survival in adults with HCC detected by positive AFP with negative US versus HCC detected by positive results on both US and AFP.

Abbreviations. AFP=alpha-fetoprotein; CT=computed tomography; HCC=hepatocellular carcinoma; RCT=randomized controlled trial; US=ultrasound.