Screening for Hepatocellular Carcinoma in Chronic Liver Disease
A Systematic Review

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Background:
Guidelines recommend routine screening for hepatocellular carcinoma (HCC) in high-risk patients, but the strength of evidence supporting these recommendations is unclear.

Purpose:
To review the benefits and harms of HCC screening in patients with chronic liver disease.

Data Sources:
MEDLINE, PsycINFO, and ClinicalTrials.gov from inception to April 2014; Cochrane databases to June 2013; reference lists; and technical advisors.

Study Selection:
English-language trials and observational studies comparing screening versus no screening, studies of harms, and trials comparing different screening intervals.

Data Extraction:
Mortality and adverse events were the outcomes of interest. Individual-study quality and the overall strength of evidence were dual-reviewed using published criteria.

Data Synthesis:
Of 13,801 citations, 22 studies met inclusion criteria. The overall strength of evidence on the effects of screening was very low. One large trial of patients with hepatitis B found decreased HCC mortality with periodic ultrasonographic screening (rate ratio, 0.63 [95% CI, 0.41 to 0.98]), but the study was limited by methodological flaws. Another trial in patients with hepatitis B found no survival benefit with periodic α-fetoprotein screening. In 18 observational studies, screened patients had earlier-stage HCC than clinically diagnosed patients, but lead- and length-time biases confounded the effects on mortality. Two trials found no survival differences between shorter (3- to 4-month) and longer (6- to 12-month) screening intervals. Harms of screening were not well-studied.

Limitations:
Only English-language studies were included. The evidence base is limited by methodological issues and a paucity of trials.

Conclusion:
There is very-low-strength evidence about the effects of HCC screening on mortality in patients with chronic liver disease. Screening tests can identify early-stage HCC, but whether systematic screening leads to a survival advantage over clinical diagnosis is uncertain.

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Hepatocellular carcinoma (HCC) incidence and mortality have increased internationally over the past 4 decades (1, 2), with localized tumors accounting for most of the increase (3). The rationale for screening is that imaging tests, such as ultrasonography, may identify patients with early-stage HCC (4), and several potential options exist for treating patients with early-stage HCC, including liver transplantation, radiofrequency ablation, and liver resection (5). Several professional societies currently recommend HCC screening using imaging studies and tumor markers, primarily in patients at higher risk for HCC due to chronic hepatitis B or cirrhosis (5–7). However, recommendations for HCC screening remain controversial, in part because of concerns over the quality and paucity of existing evidence and because concerns about overdiagnosis and patient harms have been raised in other cancer screening programs (8–12).

We conducted a systematic review of the published literature to better understand the incremental benefits and harms of routine HCC screening compared with clinical diagnosis.

Methods
This manuscript is part of a larger report commissioned by the Veterans Health Administration (13). A protocol describing the review plan was posted to a public Web site before the study was initiated (14). The analytic framework that guided this review was developed in collaboration with a panel of technical experts and is provided in Figure 1 of Supplement 1 (available at www.annals.org).

Data Sources and Searches
We searched MEDLINE, PsycINFO, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and ClinicalTrials.gov from database inception to June 2013. We updated the MEDLINE, PsycINFO, and ClinicalTrials.gov searches in April 2014. The detailed search strategy is provided in Supplement 2 (available at www.annals.org). We obtained additional articles from systematic reviews, reference lists of pertinent studies, reviews, and editorials and by consulting technical advisors.
Study Selection

Detailed inclusion and exclusion criteria are provided in Supplement 3 (available at www.annals.org). We included English-language, controlled clinical trials and observational studies that assessed the effects of screening on HCC-specific and all-cause mortality in adult populations. We used the term “screening” to include any surveillance or screening program in which specific tests (ultrasonography, computed tomography, magnetic resonance imaging, or α-fetoprotein measurement) were performed explicitly to detect HCC in asymptomatic patients. Studies had to include a comparison group of patients who did not have routine screening. We excluded observational studies that did not consider important confounding factors, such as age, sex, and liver disease severity. Because we anticipated few clinical trials comparing screening versus no screening, we also included trials comparing frequencies of screening. We included studies of any population with chronic liver disease with or without cirrhosis but excluded studies of patients with prior HCC. We also searched for systematic reviews and primary studies that focused on potential harms of HCC screening.

Seven investigators reviewed the titles and abstracts of citations identified from literature searches. If at least 1 reviewer indicated that a citation may be relevant, a second reviewer screened the citation for concordance. Two reviewers independently assessed the full-text articles for inclusion using the eligibility criteria in Supplement 3. Disagreements were resolved through consensus.

Data Extraction and Quality Assessment

From each study, we abstracted study design, objectives, setting, population characteristics (including sex, age, race or ethnicity, and liver disease cause and severity), patient eligibility and exclusion criteria, number of patients, years of enrollment, method and frequency of screening, adjusted and unadjusted mortality, and adverse events. A second author checked each entry for accuracy.

Two reviewers independently assessed the quality of each trial by using a tool developed by the Cochrane Collaboration (15). We resolved disagreements through discussion. Each trial was given an overall summary assessment of low, high, or unclear risk of bias. Two reviewers graded the strength of evidence for outcomes by using published criteria that consider the consistency, coherence, directness, and applicability of a body of evidence as well as the internal validity of individual studies (16).

We adapted existing tools to assess the quality of observational studies (17–19). We do not report an overall summary assessment for observational studies because there are no validated criteria for doing so.

Data Synthesis and Analysis

We qualitatively synthesized the evidence on the benefits and harms of HCC screening. Clinical heterogeneity and the small number of trials precluded a meta-analysis of the findings.

Role of the Funding Source

The U.S. Department of Veterans Affairs Quality Enhancement Research Initiative supported this review but had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

RESULTS

The electronic and manual searches yielded 13 801 total citations, from which we identified 286 potentially relevant full-text articles. Twenty-two primary studies contained primary data relevant to the efficacy of HCC screening and met our inclusion criteria (Figure).

Effects of Screening on Mortality

Two trials and 18 observational studies provided very-low-strength evidence from which to draw conclusions about the mortality effects of HCC screening compared with no screening. The trials had substantial methodological flaws that threatened their internal validity, and their findings have limited applicability beyond the patient population with hepatitis B. The observational studies, most of which included patients with cirrhosis and hepatitis B, hepatitis C, or alcoholic liver disease, showed that screening detects patients with earlier-stage disease, who more frequently receive curative therapy. However, it is impossible to say whether the longer survival in patients with screen-detected disease was a true effect of screening or reflects lead- and length-time biases inherent to all observational studies, as well as selection biases that were common in many of the studies.

Randomized, Controlled Trials

Two community-based trials compared the effects on mortality of screening versus no screening (20, 21). Both were conducted in China in areas with high prevalence of HCC, and most participants had hepatitis B with or without cirrhosis (Table 1 of Supplement 4, available at www.annals.org). One cluster randomized trial recruited screening group participants (n = 9757) from 1993 to 1995 and offered them serum α-fetoprotein testing and ultrasonography every 6 months. Participants in the control group (n = 9443) were not made aware of the study nor actively followed. Death from HCC occurred less frequently in the screening group (83.2 vs. 131.5 per 100 000 person-years; rate ratio, 0.63 [95% CI, 0.41 to 0.98]).

However, the trial had several serious methodological limitations that gave it a high risk of bias (Table 2 of Supplement 4). One major concern is whether patients in both groups had the same risk for HCC. There is no information about randomization technique or allocation concealment and very little information about the baseline characteristics of the 2 groups, which is especially important in cluster randomized trials. Another concern is that...
weak methods used to ascertain the outcome measure—death from HCC—could have introduced bias. If deaths were underreported in the control group, results could have been biased toward the null. On the other hand, if deaths covered HCC on imaging is higher.

The second trial used patient-level randomization stratified by township to assign patients with hepatitis B from 1989 to 1992 to the screening intervention (n = 3712), which consisted of serial α-fetoprotein tests followed by ultrasonography for high α-fetoprotein values, or the usual care group (n = 1869) (21). The population-based cancer registry used active case-finding techniques, and mortality was ascertained through the cancer registry and a population-based vital status registry. Cancer staging and cause of death were assessed by personnel blinded to intervention status. Only 28.8% of screening group participants completed all scheduled testing, but all participants completed at least 1 screening test. Fewer patients had stage III HCC in the screening group (19.8% vs. 41.0%; P value not reported). Hepatocellular carcinoma mortality was similar in both groups (1138 vs. 1114 per 100 000 person-years; P = 0.86), as was all-cause mortality.
(1843 vs. 1788 per 100 000 person-years; \( P \) value not significant). This trial had an unclear risk of bias because of poor reporting of randomization and allocation concealment techniques.

Two additional trials compared ultrasonography screening intervals (22, 23). One recent community-based cluster randomized trial in Taiwan compared 4- versus 12-month ultrasonography screening intervals in patients with serologic evidence of hepatitis B or C (22). Although more patients with HCC in the 4-month interval group had very-early-stage disease (37.5% vs. 6.7%; \( P = 0.017 \)), the 1-, 2-, and 4-year survival rates among patients with HCC were similar (95% vs. 80%, 78.8% vs. 64%, and 57.4% vs. 56%, respectively; \( P = 0.40 \)). The study had an unclear risk of bias because of poor reporting of outcome assessment and statistical analyses.

A trial with low risk of bias compared 3- versus 6-month ultrasonography screening intervals in 1278 patients with cirrhosis from alcohol use or viral hepatitis and found similar all-cause mortality rates in both groups (11.3% vs. 12.1%; \( P = 0.38 \)) (23). A similar number of patients were diagnosed with HCC in both groups (8.3% vs. 11.0%; \( P = 0.13 \)), and most met Milan criteria (79.2% vs. 71.4%; \( P = 0.40 \)).

**Observational Studies**

Eighteen observational studies compared survival in patients with screen-detected HCC versus those with HCC diagnosed incidentally as part of another work-up or because of symptoms (Table 3 of Supplement 4) (24–41). The studies represented a range of geographic settings, including Asia (6 studies), Europe (6 studies), Australia (1 study), and the United States (5 studies). Most patients included in these studies had hepatitis B or C with Child–Pugh class A or B cirrhosis, although patients in the nonscreening groups had more severe liver disease in many of the studies. Ultrasonography with or without \( \alpha \)-fetoprotein measurement was the screening method used in nearly all studies, except for 2 U.S. studies in which a small number of patients had computed tomography (26, 31).

In general, patients who had undergone screening had earlier-stage HCC than those who had HCC diagnosed incidentally or due to symptoms; in 12 studies, 60.0% to 100% of screened patients versus 19.6% to 56.5% of nonscreened patients met the equivalent of Milan criteria. More screened patients received potentially curative treatment, although only a small proportion had hepatic resection (range, 2.8% to 23.9% in 14 studies [24, 26, 28–31, 33–38, 40, 41]; 53.5% in 1 outlier study [39]) or liver transplantation (range, 1% to 15% in 5 studies [28, 31, 32, 36, 38, 41]; 23% and 30.1% in 2 other studies [24, 35, 40]).

Survival from the time of HCC diagnosis was generally higher among screened than nonscreened patients (Figure 2 of Supplement 1). However, several methodological considerations temper the confidence with which one can draw conclusions from this body of observational literature (Table 4 of Supplement 4). Most of the studies were single-center retrospective cohort studies in which all patients with diagnosed HCC were first identified and screening status was subsequently determined. Few studies reported data on loss to follow-up, and many did not report using a comprehensive method to assess mortality outcomes equally in screening and nonscreening groups. Only 4 of the studies reported objective and replicable methods for distinguishing screened from nonscreened patients (26, 27, 31, 41). Furthermore, selection bias is a concern for all but 3 of the studies (26, 27, 31). In most studies, the comparison group was drawn from a referral population and unmeasured patient, treatment, health care access, and other factors probably differed between groups.

In addition to the methodological issues specific to individual studies, the potential for length- and lead-time biases is inherent in any observational study of screening effects (42). Although there is no infallible way to circumvent the threat of lead-time bias other than to conduct a well-designed randomized, controlled trial, 5 studies used statistical techniques to adjust for lead-time bias (27, 33, 35, 38, 41). These studies used various assumptions about tumor doubling time to estimate the lead time of screening diagnosis. Three of the studies adjusted for lead time and found that the survival advantage for screened patients disappeared when the tumor doubling time was assumed to be 90 to 120 days or longer (Table 3 of Supplement 4) (27, 33, 38). A fourth study used serial ultrasonographic data from 13 patients to estimate a tumor doubling time of 216 days, although survival among screened patients remained higher even after adjustment for lead time (35). Finally, in a large multisite Italian cohort comparing patients with screen-detected versus symptomatically detected HCC (patients with incidental diagnoses were excluded), adjustment for lead time based on probabilistic estimates of tumor doubling time attenuated survival effects seen over 3 years but not over longer follow-up (41).

**Harms of Screening**

None of the included studies reported direct harms of screening, and no studies examined the psychological effects of screening.

Patients with positive screening results from ultrasonography or \( \alpha \)-fetoprotein testing usually have further confirmatory testing. In most of the studies, confirmatory testing was done with computed tomography and, less commonly, with magnetic resonance imaging or liver biopsy, although few studies reported rates of actual testing used for diagnosis. One meta-analysis of 8 studies found the risk for needle-track seeding from liver biopsy for suspected HCC to be 2.7% (43). One recent systematic review of the diagnostic accuracy of imaging for HCC screening and diagnosis found few studies reporting harms data: One study found that contrast-enhanced computed
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**Table 1. Summary of the Evidence on Screening for HCC in Patients With Chronic Liver Disease and Treatment in Patients With Early-Stage HCC**

<table>
<thead>
<tr>
<th>Outcome, by Comparison</th>
<th>Study Characteristics</th>
<th>Findings</th>
<th>Strength of Evidence*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening vs. no screening</td>
<td>2 RCTs of patients with HBV-related disease (total n = 19 200) 18 NRCSs (1 of patients with HBV-related disease, 3 of patients with HCV-related disease, 7 of patients with HBV/HCV-related disease, and 7 of patients with HBV/HCV/alcohol-related disease) (total n = 12 887) 1 meta-analysis of 36 NRCSs (total n = 13 361)</td>
<td>In 1 trial of ultrasonography with high risk of bias, the RR for death due to HCC was 0.63 (95% CI, 0.41–0.98). In 1 trial of α-fetoprotein with unclear risk of bias, all-cause mortality per 100 person-years was 1.84 vs. 1.79 (P = NS) in the intervention and usual care groups, respectively. The combined OR of 3-y survival in the meta-analysis of 36 observational studies was 1.90 (CI, 1.67–2.17).</td>
<td>Very low</td>
<td>Trials were limited by selective outcome reporting, allocation concealment, and other analytic issues. Observational studies were limited by selection, lead-time, and length-time biases. Screening consistently diagnosed HCC at an earlier stage, but the effect on overall mortality is unclear.</td>
</tr>
<tr>
<td>Harms</td>
<td>Needle-track seeding</td>
<td>1 meta-analysis of 8 NCSs (total n = 1340) 1 NCS (n = 3391)</td>
<td>Overall risk, 2.7% (range, 0%–5.8%)</td>
<td>Low</td>
</tr>
<tr>
<td>Other</td>
<td>1 systematic review of diagnostic accuracy studies, including harms of contrast-enhanced CT (1 RCT, n = 97) and gadoxetic acid-enhanced MRI (1 NRCS, n = 178)</td>
<td>Rate of adverse events in contrast-enhanced CT: 13–15% Rate of mild to moderate adverse events in contrast-enhanced MRI: 25%</td>
<td>Very few studies and the nature of the adverse events was not well-characterized.</td>
<td></td>
</tr>
<tr>
<td>Shorter vs. longer intervals</td>
<td>Mortality</td>
<td>2 RCTs (1 of patients with HCV/alcohol-related disease and 1 of patients with HBV/HCV-related disease) (total n = 2022)</td>
<td>Shorter screening intervals (3–4 mo) offered no advantage over longer intervals (6–12 mo).</td>
<td>Moderate</td>
</tr>
<tr>
<td>Harms</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

CT = computed tomography; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; MRI = magnetic resonance imaging; NA = not applicable; NCS = noncomparative study; NRCS = nonrandomized comparative study; NS = not significant; OR = odds ratio; RCT = randomized, controlled trial; RR = rate ratio.

* Assessed using the Grading of Recommendations, Assessment, Development, and Evaluation criteria. “High” indicates that further research is very unlikely to change our confidence in the estimate of effect. “Moderate” indicates that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. “Low” indicates that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. “Very low” indicates that any estimate of effect is very uncertain.

tomography was associated with adverse events in 13% to 15% of patients, and another found mild to moderate adverse events in 25% of patients receiving gadoxetic acid–enhanced magnetic resonance imaging (44).

**DISCUSSION**

We systematically reviewed and critically appraised trials and observational studies examining the risks and benefits of HCC screening in patients with chronic liver disease. Periodic ultrasonography and α-fetoprotein testing have been the most commonly evaluated screening methods, and patients with viral hepatitis have been the most frequently studied population. Although screening identifies patients with early-stage HCC and some of these patients do well with curative therapy, there is very-low-strength evidence from which to draw conclusions about the balance of benefits and harms of screening for HCC (Table 1).

The body of evidence on which current recommendations for screening are based has substantial shortcomings. The large-scale trial conducted among hepatitis B–infected patients in China has serious methodological limitations that undermine the validity of its findings (5–7). The only other trial found that serial α-fetoprotein screening offered no survival advantage. The applicability of these studies to the United States, moreover, is limited because of more widespread imaging use, higher rates of incidental diagnosis, and a smaller proportion of patients whose primary risk is hepatitis B.

Although numerous, observational studies do not contribute substantially to the strength of evidence. Most studies included patients with viral hepatitis and cirrhosis and found that patients with screen-detected HCC were more likely to have earlier-stage disease and survived longer from the time of diagnosis. However, most were single-center studies that retrospectively evaluated patients with HCC and had lead- and length-time biases in addition to other design limitations.

Screening programs have the intended effect of identifying patients with early-stage disease, more of whom
undergo such potentially curative therapies as liver transplant or partial hepatic resection. Some cohort studies suggest that long-term survival of patients who have liver resection or transplantation for HCC can be high (40% to 70% for resection and 52% to 81% for transplant patients after 5 years [45]), although perioperative morbidity and mortality may be substantial [46]. In contrast, a large prospective screening study in patients with viral hepatitis found that 5- and 10-year survival was low (28% and 4%, respectively) among those who developed HCC and received curative treatment [47].

The natural history of early-stage or screen-detected HCC has not been well-characterized, and tumor growth patterns can differ markedly among patients, with some showing steady growth, others showing no growth followed by a period of rapid growth, and others with little or no long-term growth [48–51]. The net balance of benefits and harms might favor widespread screening if much of the HCC found as a result of routine screening were to progress and cause morbidity before patients’ underlying illness did. On the other hand, if screen-detected HCC were more indolent, the risks of treating disease that would not have otherwise been clinically relevant (that is, overdiagnosed HCC) might tip the balance away from routine screening. Unfortunately, we found no evidence examining rates of overdiagnosis.

Several studies suggest that HCC may have variable rates of progression. In 1 trial comparing screening intervals, long-term survival was similar even though more patients undergoing frequent screening had small, early-stage HCC and received potentially curative therapy compared with patients assigned to a less intensive screening program [22]. A recent study found that the length of the waiting period for transplantation results in selection of patients with more indolent HCC because those with more aggressive disease lose candidacy while awaiting a transplant [52]. Another study of a mixed sample of patients with early- and late-stage disease who were randomly assigned to no treatment in 2 trials found 2 different survival patterns depending on the presence of an invasive tumor pattern and poor performance status (3-year survival of 8% vs. 50%; \( P = 0.0001 \)) [53].

We searched for systematic reviews through April 2014 and found several that examined HCC screening studies. A recent review of observational studies found that HCC screening was associated with detection of earlier-stage HCC and improved survival [54]. A Cochrane review found insufficient evidence for screening but focused only on studies of patients with hepatitis B and did not examine observational studies [11]. Several widely disseminated guidelines recommend HCC screening in high-risk patients with liver disease [5–7], but none used a systematic review that critically appraised included studies as a basis for the recommendations. Finally, a systematic review of cost-effectiveness modeling studies, most of which were based on assumptions from the literature, concluded that periodic surveillance with ultrasonography was probably cost-effective when the annual incidence of HCC was higher than 1.5%, although annual surveillance may be more cost-effective than semiannual surveillance in populations with annual HCC risk of 1.5% to 3.5% [55]. The only modeling study using data from a prospective cohort found that surveillance was probably not cost-effective [24].

Our findings neither support nor refute current clinical policy recommendations for HCC screening. Transparency about the strength of the evidence on which these recommendations are based is important, but policy rec-

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Table 2. Evidence Gaps and Recommendations for Future Research

<table>
<thead>
<tr>
<th>Evidence Gap</th>
<th>Potential Future Research</th>
</tr>
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<tbody>
<tr>
<td>No methodologically sound trials have examined the effects of screening on health outcomes in patients with chronic liver disease.</td>
<td>Trials examining the effects on health outcomes of screening in patients with hepatitis B, hepatitis C, and other forms of chronic liver disease.</td>
</tr>
<tr>
<td>The feasibility of conducting randomized trials of screening in patients with chronic liver disease has been questioned.</td>
<td>Studies evaluating the willingness of at-risk patients to participate in screening studies, including patients with hepatitis C.</td>
</tr>
<tr>
<td>Observational studies are limited by selection bias, limited generalizability, retrospective design, and inability to identify time at risk for HCC.</td>
<td>Studies of large registries of patients with chronic liver disease, with such prospective data as cirrhosis diagnosis date, receipt of screening, imaging findings, HCC diagnosis, and treatment received.</td>
</tr>
<tr>
<td>The contemporary natural history of early-stage HCC detected by imaging tests is not well-understood.</td>
<td>Prospective cohort studies examining the growth patterns of small (≤2 cm) liver lesions suspicious for HCC.</td>
</tr>
<tr>
<td>The harms of screening have not been well-explored.</td>
<td>Studies of the psychological effects of screening.</td>
</tr>
<tr>
<td>Current guidelines recommend 6-mo screening intervals. Two trials found no benefit comparing 3- or 4-mo screening intervals with 12-mo intervals. No trials have compared 6- vs. 12-mo screening intervals.</td>
<td>Trials comparing 6- vs. 12-mo screening intervals.</td>
</tr>
</tbody>
</table>

HCC = hepatocellular carcinoma.
opportunities are summarized in the context of benefits and harms of screening. The key evidence gaps and suggestions for corresponding future research opportunities are summarized in Table 2.

One limitation of our review was the exclusion of non–English-language articles. However, we mitigated the risk of missing relevant studies by searching multiple databases, bibliographies, and trial registries and by consulting experts. Moreover, evidence suggests that language restrictions do not bias results of reviews of conventional therapies (57).

In conclusion, there is very-low-strength evidence from which to draw conclusions about the effects of HCC screening on mortality in high-risk patients with chronic liver disease. Screening can identify more patients with earlier-stage disease who are candidates for potentially curative treatments, but there is limited evidence from which to draw firm conclusions about the balance of health outcomes and harms of using routine screening to identify HCC.

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