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No Association Between Screening for Hepatocellular Carcinoma and Reduced Cancer-Related Mortality in Patients With Cirrhosis

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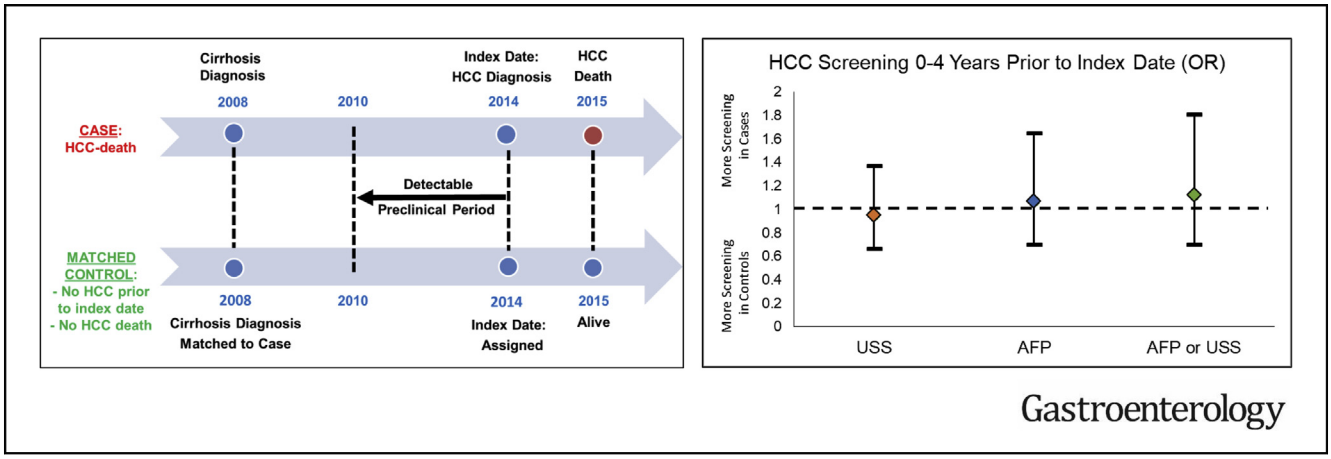
This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e17. Learning Objective: Upon completion of this CME activity, successful learners will be able to recognize current screening and treatment guidelines for hepatocellular carcinoma (HCC), describe gaps in existing evidence supporting HCC screening, and explain how unique research methodologies, including the case-control study design, addresses these voids.



See editorial on page 972.

BACKGROUND & AIMS: Screening patients with cirrhosis for hepatocellular carcinoma (HCC) has been recommended. We conducted a matched case–control study within the US Veterans Affairs (VA) health care system to determine whether screening by abdominal ultrasonography (USS) and/or by measuring serum level of α-fetoprotein (AFP) was associated with decreased cancer-related mortality in patients with cirrhosis. **METHODS:** We defined cases (n = 238) as patients with cirrhosis who died of HCC from January 1, 2013 through August 31, 2015 and had been in VA care with a diagnosis of cirrhosis for at least 4 years before the diagnosis of HCC. We matched each case to 1 control (n = 238), defined as a patient with cirrhosis who did not die of HCC and had been in VA care for at least 4 years before the date of the matched case's HCC diagnosis. Controls were matched to cases by year of cirrhosis diagnosis, race and ethnicity, age, sex, etiology of cirrhosis, Model for End-Stage Liver Disease score, and VA medical center. We identified all USS and serum AFP tests performed within 4 years before the date of HCC diagnosis in cases or the equivalent index date in controls and determined by chart extraction (blinded to case or control status) whether these tests were performed for screening. **RESULTS:** There were no significant differences between cases and controls in the proportions of patients who underwent screening USS (52.9% vs 54.2%), screening measurement of serum AFP (74.8% vs 73.5%), screening USS or measurement of serum AFP (81.1% vs 79.4%), or screening USS and measurement of serum AFP (46.6% vs 48.3%) within 4 years before the index date, with or without adjusting for potential confounders. There also was no difference in receipt of these screening tests within 1, 2, or 3 years before the index date. **CONCLUSIONS:** In a matched case–control study of the VA health care system, we found that screening patients with cirrhosis for HCC by USS, measurement of serum AFP, either test, or both tests was not associated with decreased HCC-related mortality. We encourage additional case–control studies to evaluate the efficacy of screening for HCC in other health care systems, in which available records

are sufficiently detailed to enable identification of the indication for USS and AFP tests.

Keywords: Surveillance; Survival; Liver Cancer; Liver Transplantation.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

The matched case-control study design is the best observational study design for determining whether screening reduces cancer-related mortality. A case-control study of HCC screening in patients with cirrhosis has not yet been performed.

NEW FINDINGS

HCC screening with ultrasonography, AFP, or both was not associated with decreased HCC-related mortality. This contrasts with many "cohort studies" of HCC screening, which are susceptible to lead-time and length-time bias.

LIMITATIONS

The main limitation of case-control studies of screening effectiveness is misclassification of tests performed among cases for suspected cancer as screening tests.

IMPACT

Current strategies for HCC screening have been based on ultrasonography ± AFP for more than 25 years. The authors hope that this study will lead to renewed efforts to develop and validate better screening tests.

Patients with cirrhosis have a high risk of hepatocellular carcinoma (HCC), ranging from 1% to 8% per year.[1] Most professional liver societies recommend screening patients with cirrhosis with abdominal ultrasonography (USS) with or without concomitant serum α-fetoprotein (AFP) testing every 6 months,[2–4] but many non-liver societies do not endorse HCC screening.[5,6] The rationale for HCC screening in patients with cirrhosis is that screening tests such as USS or serum AFP could identify patients with HCC at an early stage when they have potentially curative or life-prolonging treatment options, including liver transplantation, radiofrequency ablation, or surgical resection. However, it remains unclear whether HCC screening decreases cancer-related mortality in patients with cirrhosis, which should be the primary end point of HCC screening, rather than early-stage migration or increased frequency of receipt of potentially curative treatments.

Two randomized controlled trials (RCTs) of HCC screening have been performed.[7,8] However, these trials reached conflicting conclusions about screening effectiveness, and their methodology has been criticized.[9] Also, their results do not necessarily apply to North American and European patients with cirrhosis in the current era, because the trials were conducted in China from 1989 to 1997 in patients with chronic hepatitis B virus infection. HCC related to hepatitis B virus can occur in the absence of cirrhosis and important advances in the treatment of HCC have occurred since these studies were conducted.

Many observational studies have compared survival in patients diagnosed with HCC by screening with those who presented with symptomatic HCC. These studies were summarized in 2 systematic reviews,[9,10] which concluded that the interpretation of these observational studies was limited because of selection, verification, and lead-time and length-time biases.

Ideally, the effectiveness of HCC screening would be evaluated by a study that randomizes patients with cirrhosis to screening vs no screening. However, as concluded by the authors of the American Association for the Study of Liver Diseases (AASLD) HCC guidelines[11] and demonstrated by problems in patient recruitment encountered in a pilot study,[12] it is unlikely that such randomized trials of HCC screening will be feasible in the United States, where HCC screening has become the de facto standard of care. Nonetheless, concerns have been raised that HCC surveillance has been adopted in the United States without sufficient data to demonstrate its efficacy.[13,14]

As an alternative to RCTs, case–control studies have the potential to evaluate the effectiveness of cancer screening in an efficient manner.[15–17] To test for an effect of screening on cancer-related mortality, previous receipt of the screening test (eg, abdominal USS or serum AFP testing) was compared in patients with cirrhosis who died of HCC (cases) and in a matched sample of patients with cirrhosis who did not die of HCC (controls). A lower likelihood of screening before diagnosis during the time when the malignancy is occult but potentially detectable by the screening modality in those who die of cancer would provide evidence in support of a protective effect of screening on mortality. Thus, if HCC screening were effective, then we would expect patients who died of HCC to be less likely to have been screened than patients with cirrhosis who did not die of HCC. By selecting patients with fatal, rather than incident, cancers as case subjects, this case–control paradigm addresses the impact of screening on cancer-related mortality and is not susceptible to length-time or lead-time bias. The odds ratio (OR) in a bias-free case–control study of screening would be a valid estimate of the risk ratio that might be obtained from an RCT.[15]

The case–control study design has been used previously to evaluate screening effectiveness for malignancies other than HCC, such as colorectal cancer,[18,19] breast cancer,[20] esophageal cancer,[21] cervical cancer,[22] prostate cancer,[23]

Abbreviations used in this paper: **AASLD, American Association for the Study of Liver Diseases; AFP, α-fetoprotein; CAPRI, Compensation and Pension Record Interchange; CI, confidence interval; CDW, Corporate Data Warehouse (Veterans Affairs); CT, computed tomography; DPP, detectable preclinical phase; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; *ICD-9*, *International Statistical Classification of Diseases, Injuries and Causes of Death, Ninth Edition*; MELD, Model for End-Stage Liver Disease; MRI, magnetic resonance imaging; OR, odds ratio; RCT, randomized controlled trial; USS, ultrasound scan; VA, Veterans Affairs.**

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