Hepatocellular Carcinoma Screening Is Associated With Increased Survival of Patients With Cirrhosis

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BACKGROUND & AIMS: **Hepatocellular carcinoma (HCC) screening of patients with cirrhosis is recommended by professional societies to increase detection of early stage tumors and survival, but is underused in clinical practice.**

METHODS: **We conducted a retrospective cohort study of 13,714 patients diagnosed with HCC from 2003 through 2013 included in the Surveillance, Epidemiology, and End Results Program–Medicare database. We characterized receipt of HCC screening in the 3 years before HCC diagnosis using mutually exclusive categories (consistent vs inconsistent vs no screening) and the proportion of time covered with screening. Correlates for screening receipt were assessed using a multivariable 2-part regression model. We examined the association between screening receipt and early detection of tumors using multivariable logistic regression. We evaluated associations between screening receipt and overall survival using a Cox proportional hazards model, after adjustments for effects of lead-time bias and length-time bias on survival rate estimators.**

RESULTS: **Most patients with cirrhosis (51.1%) did not receive any screening in the 3 years before a diagnosis of HCC, and only 6.8% of patients underwent consistent annual screening. The proportion with consistent screening increased from 5.4% in 2003 to 2006 to 8.8% in 2011 to 2013 ($P < .001$). The mean proportion of time covered was 13.4% overall, which increased from 11.7% in 2003 to 2006 to 15.2% in 2011 to 2013. Receipt of consistent screening was associated with detection of early stage tumors (odds ratio, 1.98; 95% CI, 1.68–2.33) and a reduced risk of death after correction for lead-time bias (hazard ratio, 0.76; 95% CI, 0.70–0.83). Inconsistent screening was associated with a slightly smaller increase in early detection of HCC (odds ratio, 1.31; 95% CI, 1.20–1.43) and a reduced risk of death (hazard ratio, 0.86; 95% CI, 0.83–0.90). After correction for lead- and length-time biases, higher proportions of patients with consistent (23%; 95% CI, 21%–25%) and inconsistent screening (19%; 95% CI, 19%–20%) survived for 3 years compared with patients without screening (13%; 95% CI, 12%–14%).**

CONCLUSIONS: **In an analysis of the Surveillance, Epidemiology, and End Results Program–Medicare database, we found HCC screening to be underused for patients with cirrhosis. This contributes to detection of liver tumors at later stages and shorter times of survival. However, the proportion of patients screened for HCC has increased over time.**

Keywords: SEER Database Analysis; Screening; Liver Cancer; Ultrasound.

Liver cancer is the second leading cause of cancer-related death worldwide.[1] Hepatocellular carcinoma (HCC), the most common type of primary liver cancer, is the leading cause of death among patients with cirrhosis.[2] Although HCC is the sixth leading cause of cancer-related death in the United States, its incidence has tripled over the past 30 years.[3–6]

Abbreviations used in this paper: **HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; ICD-9, International Classification of Diseases, 9th revision; OR, odds ratio; PTC, proportion of time covered; SEER, Surveillance, Epidemiology and End Results.**

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HCC prognosis depends on tumor stage at the time of diagnosis, with curative treatment options only available for patients diagnosed at an early stage. Patients with early stage HCC can achieve 5-year survival rates of 70% if they undergo surgical resection or liver transplantation, compared with a median survival of 1 year for patients with advanced HCC.[7] Given data from a large randomized controlled trial and several cohort studies showing a potential survival benefit associated with early tumor detection, professional society guidelines from the American Association for the Study of Liver Diseases and National Comprehensive Cancer Network recommend HCC screening in high-risk patients, including those with cirrhosis.[8,9] The potential benefit of HCC screening has come into question recently, with a case-control study from the National Veterans Affairs health system showing no association between screening receipt and HCC-related mortality, highlighting the need for further studies in large populations.[10]

HCC screening is a complex, multifaceted process that poses many unique challenges. Prior studies have suggested that less than 20% of patients with cirrhosis receive HCC screening.[11,12] Therefore, many patients with HCC are diagnosed at an advanced stage, when they are no longer eligible for curative treatment. However, most studies were conducted at single centers and prior multicenter studies were published several years ago, which may no longer reflect current practice. Our study's aim was to characterize utilization of HCC screening receipt and its association with early tumor detection and improved survival in a nationally representative cohort of patients in the United States.

What You Need to Know

Background

Hepatocellular carcinoma (HCC) screening is recommended in patients with cirrhosis to improve early tumor detection and survival but is underused in clinical practice.

Findings

Consistent HCC screening is associated significantly with increased early detection and improved survival, but benefits are attenuated in those with inconsistent screening. However, HCC screening continues to be underused in the United States, with most patients not receiving any HCC screening before HCC diagnosis despite improvements over time. Fewer than 10% of patients receive consistent screening before HCC diagnosis, and the mean proportion of time covered by screening is less than 15% for all patients.

Implications for patient care

Efforts are needed to increase HCC screening to reverse high rates of late-stage tumor detection and poor HCC-related survival.

Methods

Data Source

We conducted a retrospective cohort study using the Surveillance, Epidemiology and End Results (SEER)–Medicare data linked to the American Medical Association Master File. Linked SEER–Medicare data combines clinical, demographic, and survival information for persons with cancer from the SEER program of cancer registries with Medicare claims information on covered health services from time of Medicare eligibility until death. The SEER program collects data on incident cancer cases from 20 cancer registries, including state, central, metropolitan, and the Alaska Native registries.[13–15] These areas account for approximately 28% of the population in the United States.[13,16] Medicare is the primary health insurer for approximately 97% of individuals ages 65 years and older, and roughly 95% of Medicare beneficiaries are covered by both Part A (inpatient hospitalizations) and Part B (outpatient visits and physician office visits/services) benefits.[17] The American Medical Association Master File includes current and historical data for more than 1.4 million physicians, residents, and medical students in the United States, Puerto Rico, Virgin Islands, and certain Pacific Islands. Data include information about education, training, and professional certification and credentialing.[18,19]

Study Population

We included all Medicare beneficiaries, ages 65 years and older, who have been diagnosed with HCC (International Classification of Diseases [ICD]-[Oncology] O code 8170) from 2003 to 2013.[20] Only patients with diagnostically confirmed HCC (positive histology, cytology, laboratory tests, positive radiology tests) were eligible for inclusion. We excluded patients with Medicare Part A and B enrollment fewer than 3 years before HCC diagnosis. We also excluded patients enrolled in Medicare health maintenance organizations because Medicare health maintenance organization plans were not required to submit individual claims information for services to the Centers for Medicare and Medicaid Services.[21] Although a majority of patients were covered by traditional Medicare, approximately 13% of people were enrolled in a Medicare Advantage plan in 2003 and this increased to 28% in 2013.[21] Missing patient and tumor characteristics were imputed using similar variables if available; otherwise, patients with missing characteristics that could not be imputed were excluded from the sample.[15,17]

We defined a subset of patients with known cirrhosis (n = 2972) based on ICD 9th revision (ICD-9) codes

(571.2, 571.5, or 571.6) from Medicare claims.[17,22] Patients with evidence of ascites or hepatic encephalopathy were included in the known cirrhosis sample even in the absence of other ICD-9 codes for cirrhosis (n = 405). The first claim for ascites or hepatic encephalopathy was used as a proxy date for the diagnosis of cirrhosis. For provider analyses, we excluded patients who exclusively saw emergency medicine providers or only saw providers 1 month before HCC diagnosis. Providers with no information regarding specialty, practice arrangement, or medical school graduation date also were excluded if missing characteristics could not be imputed.

Hepatocellular Carcinoma Screening Definition

The primary outcome of HCC screening receipt during the 3-year period before HCC diagnosis was defined using 2 measures. We first used 3 mutually exclusive categories: (1) consistent screening, (2) inconsistent screening, and (3) no screening. Consistent screening was defined as having 1 or more abdominal ultrasound per calendar year, and inconsistent screening was defined as having 1 or more abdominal ultrasound during the study period, but less than annually. Our second measure was the proportion of time covered (PTC) with screening. PTC was defined as the proportion of the 36-month study period in which patients had received screening, with each abdominal ultrasound providing 7 months of screening coverage. For both measures, receipt of an abdominal ultrasound was identified using the Current Procedural Terminology codes 76700 and 76705. In a sensitivity analysis, we characterized receipt of ultrasounds performed with screening intent, as determined by a validated algorithm.[17,23]

Patient and Provider Characteristics

We collected information on age at HCC diagnosis, sex, race/ethnicity, metropolitan area based on rural/urban continuum codes, census poverty level (as a proxy for socioeconomic status), and year of HCC diagnosis. Tumor characteristics from the SEER Patient Entitlement and Diagnosis Summary File[24,25] were used to construct the Milan Criteria (ie, a single tumor <5 cm or 2–3 tumors all <3 cm with no evidence of extrahepatic involvement or metastasis).[24,25] Liver disease etiology, per Medicare claims ICD-9 codes, was categorized as hepatitis B virus (HBV), hepatitis C virus, alcoholic liver disease, or other. To determine the degree of liver dysfunction, we collected Medicare claims information for ascites (ICD-9 codes 789.51 or 789.59) or hepatic encephalopathy (ICD-9 code 572.2) at least 6 months before HCC diagnosis, as well as pharmacy claims for spironolactone or furosemide (for the presence of ascites) and lactulose or rifaximin (for hepatic encephalopathy). We used diagnosis and procedure codes 1 year before the HCC diagnosis to calculate the National Cancer Institute Comorbidity Index as a measure of noncancer comorbidity.[26,27]

Provider-level characteristics were aggregated to the patient level. For each patient, we determined whether they visited each type of clinic provider (gastroenterology/hepatology, internal medicine/family practice, or other) during the 3-year screening period. We defined the principal provider as the one with the highest total reimbursement by each patient during the study period. If there was a tie in the highest total amount of reimbursements or this information was not available, then the most commonly visited provider was used. For the principal provider, we collected information on practice arrangement, year of graduation, and US training status.[17] Practice arrangement was categorized as solo practice, group practice, hospital-based, university-based, or other.

Statistical Analysis

We first characterized receipt of HCC screening and predictors for screening receipt. We used a multivariable 2-part regression model to identify patient and provider predictors of screening receipt, for which the outcome variable was defined as PTC. For the 2-part model, the first part used logistic regression to predict the probability of any HCC screening (PTC > 0), and the second part used a conditional ordinary least-squares regression to predict the level of PTC among patients with any screening.

Likelihood ratio tests were used to determine goodness-of-fit on both of the full models for our primary sample in which all explanatory variables were included against the reduced model. This model was obtained by omitting variables that were nonsignificant at the 5% level in the full model and re-estimating the remaining coefficients. We used Akaike Information Criterion to determine the best fit and identify the preferred model, which had the lowest Akaike Information Criterion among the reduced models for all regression analyses. Multicollinearity also was tested between pairs of coefficients to identify any collinearity issues using variance inflation factor scores.

We next evaluated the association between HCC screening receipt and clinical outcomes including early tumor detection (defined as within Milan Criteria) using simple and multivariable logistic regression, and overall survival using the Cox proportional hazards model, respectively. For these analyses, the categoric measure of HCC screening receipt (consistent screening vs inconsistent screening vs no screening) was used. We used Kaplan–Meier survival curves to calculate time until death after HCC diagnosis. Follow-up evaluation was recorded on the date of death or censored at the end of the study period (December 31, 2014). Crude and adjusted hazard ratios (HRs) with 95% CIs were estimated.

Lead- and length-time biases were corrected using the method proposed by Duffy et al.[28,29] Lead time is the time between early detection by screening and when cancer otherwise would present symptomatically, which can lead to perceived survival benefit even if the disease course was not changed. Length-biased time relates to slow-growing tumors, which are less likely to be fatal, also have a longer asymptomatic period, and therefore are more likely to be screen-detected. Statistical correction for lead-time bias is based on sojourn time, the period during which HCC is asymptomatic but screen-detectable (Supplementary Methods). We identified screen-detected patients by those who received screening imaging with intent[23] within 6 months before HCC diagnosis. We assumed an exponential distribution for the sojourn time with a mean of 6 months for our base-case analysis, based on prior studies[30–32]; however, we also performed sensitivity analyses with the mean sojourn times of 3 and 9 months.

Length-time bias was adjusted based on the proportion of patients with slow-growing tumors and the relative risk of death from slow-growing tumors vs aggressive tumors (Supplementary Material). We assumed that 20% of HCCs are slow-growing for our base-case analysis, and we performed sensitivity analyses with proportions of 10% and 30%. For this range of values, plausible values for the relative risk of death from slow-growing tumors vs aggressive tumors were 0.8 and 0.9. We used 0.9 as our base case, and 0.8 as a sensitivity analysis. Thus, in total we tested 6 scenarios for length-time bias adjustment.

All variables in our analyses were entered sequentially using forward selection. Our criterion for entry was $P < .05$, and remaining variables that did not meet criteria were removed. Analyses were conducted using STATA 14.0 (StataCorp, College Station, TX) and SAS 9.4 (SAS Institute, Inc, Cary, NC). The study protocol was approved by the Institutional Review Board of Texas A&M University. All authors had access to the study data and reviewed and approved the final version of the manuscript.

Results

Patient Characteristics

Between January 2003 and December 2013, there were 13,714 patients diagnosed with HCC. The number of patients diagnosed with HCC increased over time, from 868 patients in 2003 to 1531 patients in 2013. Patient characteristics are described in Table 1. The mean age of patients at HCC diagnosis was 73 years, and approximately 67% were men. The population was predominantly white, followed by Hispanics, blacks, and Asians. A majority of patients in our sample resided in metropolitan areas and nearly one third of the population were living 10% to 19% below the poverty level. The most common etiology of liver disease was chronic hepatitis C virus infection. Approximately 22% of patients were diagnosed with cirrhosis before the study period and 21% were diagnosed with cirrhosis during the study period; however, more than half of the patients did not have cirrhosis or had unrecognized cirrhosis at the time of HCC presentation. Few patients had hepatic decompensation, and only 12% had ascites and 10% had hepatic encephalopathy.

Characteristics of the providers are found in Supplementary Table 1. More than 40% of patients saw only internal medicine/family practice providers before the diagnosis, and only 14% previously had visited a gastroenterologist or hepatologist. More than three quarters of principal providers were in a group or solo practice, with less than 10% in a hospital- or university-based setting.

Receipt of Hepatocellular Cancer Screening

Most (51.1%) patients did not receive any screening in the 3 years before HCC diagnosis, whereas 42.1% underwent inconsistent screening and only 6.8% underwent consistent screening. After accounting for ultrasound screening intent, only 16.4% of patients underwent inconsistent screening and 2.0% received consistent screening.[23] Screening receipt was higher in the subset of patients with known cirrhosis, with 53.2% and 18.5% receiving inconsistent and consistent screening, respectively.

The proportion of patients receiving consistent screening steadily increased over time from 5.4% for patients diagnosed between 2003 and 2006, to 6.2% diagnosed between 2007 and 2010, and 8.8% diagnosed between 2011 and 2013. During this time period from 2003 to 2006 to 2011 to 2013, the number of patients with no screening decreased from 52.5% to 49.6%. Similarly, consistent screening increased from 16.4% to 21.2% over this time period in the subset of patients with known cirrhosis (Figure 1).

The mean PTC was 13.4% (SE, 0.18%) for all patients and 27.6% (SE, 0.49%) for patients with known cirrhosis. Excluding patients without any screening, the mean PTC was still low at 32.0% (SE, 0.27%) among all patients. After accounting for screening intent, the mean PTC was only 5.0% (SE, 0.12%) among all patients and 13.8% (SE, 0.38%) among patients with known cirrhosis.

Predictors of Screening Receipt

Receipt of any screening was associated significantly with younger age, female sex, racial/ethnic minority status, known cirrhosis, presence of a documented liver disease etiology, hepatic decompensation including ascites or hepatic encephalopathy, higher comorbidity score, or prior visit with a

Table 1. Baseline Characteristics of HCC Patients (n = 13,714)

Variable	Consistent screening[a] (n = 937)	Inconsistent screening[b] (n = 5768)	No screening (n = 7009)	*P* value
Age at HCC diagnosis, *y*	69.8 (9.8)	71.7 (9.9)	74.5 (9.2)	<.001
Sex (% male)	583 (62.2)	3786 (65.6)	4815 (68.7)	<.001
Race/ethnicity				<.001
Non-Hispanic white	436 (46.5)	3390 (58.8)	4624 (66.0)	
Black	83 (8.9)	624 (10.8)	713 (10.2)	
Hispanic	168 (17.9)	864 (15.0)	773 (11.0)	
Asian	177 (19.0)	584 (10.1)	515 (7.4)	
Other	73 (7.8)	306 (5.3)	384 (5.5)	
Metropolitan area (%)	884 (94.3)	5360 (92.9)	6419 (91.6)	.001
Census poverty level				.002
0% to <5%	168 (17.9)	1095 (19.0)	1406 (20.1)	
5%–9%	204 (21.8)	1392 (24.1)	1683 (24.0)	
10%–19%	315 (33.6)	1739 (30.2)	2240 (32.0)	
20%–100%	250 (26.7)	1542 (26.7)	1680 (24.0)	
Year of HCC diagnosis				<.001
2003	47 (5.0)	358 (6.2)	463 (6.6)	
2004	50 (5.3)	367 (6.4)	492 (7.0)	
2005	47 (5.0)	435 (7.5)	495 (7.1)	
2006	62 (6.6)	452 (7.8)	558 (8.0)	
2007	80 (8.5)	504 (8.7)	607 (8.7)	
2008	66 (7.0)	562 (9.7)	706 (10.1)	
2009	71 (7.6)	607 (10.5)	706 (10.1)	
2010	113 (12.1)	578 (10.1)	711 (10.1)	
2011	107 (11.4)	612 (10.6)	714 (10.2)	
2012	122 (13.0)	690 (12.0)	801 (11.4)	
2013	172 (18.4)	603 (10.5)	756 (10.8)	
Cirrhosis duration				<.001
No prior diagnosis	117 (12.5)	2368 (41.1)	5391 (76.9)	
<3 y before HCC	270 (28.8)	1820 (31.6)	776 (11.1)	
>3 y before HCC	550 (58.7)	1580 (27.4)	842 (12.0)	
Liver disease etiology				<.001
Hepatitis B	37 (4.0)	163 (2.8)	124 (1.8)	
Hepatitis C	132 (14.1)	918 (15.9)	848 (12.1)	
Alcohol-related	21 (2.2)	249 (4.3)	218 (3.1)	
Other liver disease	69 (7.4)	565 (9.8)	418 (6.0)	
>1 liver disease	637 (68.0)	2061 (35.7)	668 (9.5)	
No known liver disease	41 (4.4)	1812 (31.4)	4733 (67.5)	
Milan criteria (% yes)	596 (63.6)	2443 (42.4)	1772 (25.3)	<.001
Ascites (%)	270 (28.8)	1011 (17.5)	328 (4.7)	<.001
Hepatic encephalopathy (%)	287 (30.6)	796 (13.8)	235 (3.4)	<.001
NCI comorbidity index				<.001
None	5 (.53)	186 (3.2)	763 (10.9)	
Low, 1–2	85 (9.1)	975 (16.9)	2100 (30.0)	
Moderate, 3–4	188 (20.1)	1476 (25.6)	1891 (27.0)	
High, ≥5	659 (70.3)	3131 (54.3)	2255 (32.2)	

HCC, hepatocellular carcinoma; NCI, National Cancer Institute.
[a]Receipt of ≥1 abdominal ultrasound per calendar year.
[b]Receipt of ≥1 abdominal ultrasound during the study period but less than annually.

gastroenterologist/hepatologist or internal medicine/family practice provider (Table 2). Among patients with screening, female sex, Asian race, known cirrhosis, presence of a documented liver disease etiology, presence of decompensated cirrhosis, high comorbidity score, and prior visit with a gastroenterologist/hepatologist were associated with a higher PTC (Table 2). Predictors of consistent and inconsistent HCC screening, compared with no screening, identified by logistic regression analysis were similar (Supplementary Table 2).

Association Between Screening Receipt and Early Tumor Detection

Approximately one third (35.1%; n = 4813) of HCC patients were diagnosed at an early stage within the Milan Criteria. In multivariable logistic regression analysis, patients with consistent screening (adjusted odds ratio [OR], 1.98; 95% CI, 1.68–2.33) and inconsistent screening (adjusted OR, 1.31; 95% CI, 1.20–1.43) were associated with early tumor detection compared with no screening (Table 3). Similar results were observed after

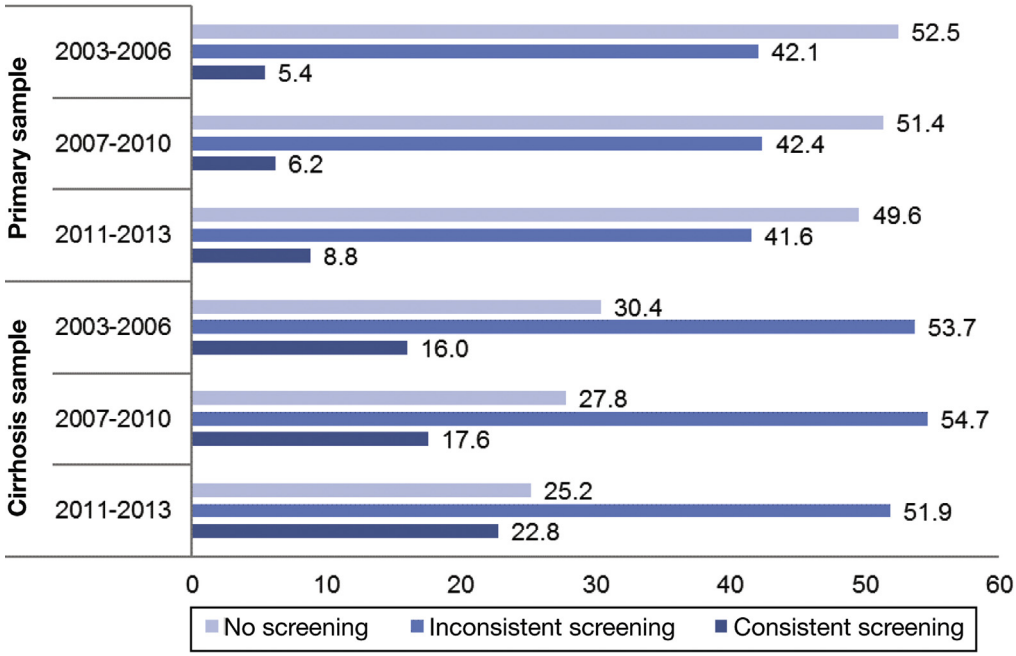


Figure 1. Percentage change in hepatocellular carcinoma (HCC) screening receipt over time (n = 13,714).

accounting for screening intent (data not shown). Of patients with known cirrhosis before HCC presentation, approximately half (56.2%) were detected at an early stage within the Milan Criteria. Receipt of consistent screening (adjusted OR, 2.56; 95% CI, 2.02–3.24) and inconsistent screening (adjusted OR, 1.70; 95% CI, 1.42–2.03) were associated similarly with early tumor detection.

Association Between Screening Receipt and Survival Without Adjusting for Lead and Length Time Biases

HCC patients who received consistent (HR, 0.73; 95% CI, 0.67–0.79) and inconsistent (HR, 0.85; 95% CI, 0.81–0.88) screening were associated with lower mortality rates compared with no screening (Figure 2, Table 4). The median survival was 17 months for patients with consistent screening, 10 months for inconsistent screening, and 5 months for no screening estimated from Kaplan–Meier curves. The 3-year survival rate was 25% (95% CI, 22%–28%), 20% (95% CI, 19%–21%), and 13% (95% CI, 12%–14%) for patients with consistent, inconsistent, and no screening, respectively (Supplementary Table 3).

Association Between Screening Receipt and Survival After Adjusting for Lead- and Length-Time Biases

Across sensitivity analyses with sojourn time ranging from 3 to 9 months, consistent and inconsistent screening continued to be associated with a survival benefit compared with no screening after adjusting for lead-time bias (Table 5). The difference in median survival time was estimated to be less than 1 month for patients with inconsistent screening and 1 to 3 months for those with consistent screening after adjusting for lead-time bias compared with the median survival time without adjustment, across the sensitivity analyses. One possible reason for the small impact of lead-time bias is that the proportion of screen-detected patients was low (Supplementary Tables 3 and 4). Further adjustment for length-time bias to screen-detected patients across all 6 assumptions had minimal impact on 1-, 3-, and 5-year survival rates (typically <1% difference in survival rates compared with the estimators adjusting for lead-time bias alone), therefore inconsistent and consistent screening continued to be associated with a survival benefit relative to the no-screening group (Supplementary Table 3).

Discussion

We found less than half of at-risk patients in a nationally representative cohort of patients in the United States underwent any HCC screening over the 3-year period before HCC diagnosis. HCC screening receipt was associated with early tumor detection and potentially improved overall survival, with attenuated benefits in those with inconsistent screening compared with those who had received consistent screening. Although HCC screening continues to be underused, screening receipt increased over time, suggesting HCC early detection and survival may be further improved in the future.

Prior studies have shown HCC screening underuse, with less than 20% of at-risk patients undergoing HCC screening.[11,12] Most patients are classified as undergoing inconsistent screening, although this category masks differences between patients, with some undergoing

Table 2. Correlates for Proportion of Time Covered by HCC Screening (n = 13,714)

	Probability of receiving any HCC screening			Level of HCC screening among those with screening		
Variable	Adjusted odds ratio	95% CI	*P* value	Adjusted coeffecient	95% CI	*P* value
Age at HCC diagnosis	0.99	0.98–0.99	.03	0.0004	-0.0002–0.001	.19
Sex						
Male	Ref	Ref	Ref	Ref	Ref	Ref
Female	1.33	1.21–1.45	<.001	0.01	0.003–0.02	.01
Race/ethnicity						
Non-Hispanic white	Ref	Ref	Ref	Ref	Ref	Ref
Black	1.18	1.03–1.36	.02	-0.002	-0.02 to 0.01	.80
Hispanic	1.44	1.27–1.64	<.001	0.01	-0.001 to 0.03	.07
Asian	1.65	1.42–1.92	<.001	0.07	0.05–0.08	<.001
Other	1.29	1.07–1.56	.01	0.05	0.03–0.07	<.001
Year of HCC diagnosis						
2003	Ref	Ref	Ref	Ref	Ref	Ref
2004	0.84	0.67–1.06	.15	-0.003	-0.03 to 0.02	.83
2005	0.94	0.75–1.18	.62	-0.03	-0.05 to -0.0002	.05
2006	0.77	0.62–0.96	.02	-0.01	-0.03 to 0.02	.56
2007	0.78	0.63–0.97	.03	-0.01	-0.03 to 0.02	.70
2008	0.81	0.65–0.99	.05	-0.01	-0.04 to 0.01	.25
2009	0.68	0.55–0.85	<.001	-0.03	-0.05 to -0.003	.03
2010	0.77	0.62–0.96	.02	-0.004	-0.03 to 0.02	.73
2011	0.70	0.57–0.87	.001	-0.01	-0.03 to 0.02	.65
2012	0.72	0.58–0.88	.002	-0.002	-0.03 to 0.02	.90
2013	0.75	0.61–0.93	.01	0.02	-0.002 to 0.05	.07
Cirrhosis duration						
No prior diagnosis	Ref	Ref	Ref	Ref	Ref	Ref
<3 y before HCC	1.93	1.71–2.18	<.001	0.02	0.004–0.03	.01
>3 y before HCC	1.42	1.24–1.63	<.001	0.07	0.06–0.09	<.001
Liver disease etiology						
No known liver disease	Ref	Ref	Ref	Ref	Ref	Ref
Hepatitis B	2.96	2.28–3.83	<.001	0.08	0.05–0.11	<.001
Hepatitis C	2.39	2.10–2.72	<.001	0.06	0.04–0.08	<.001
Alcohol-related	1.30	1.04–1.62	.02	0.03	-0.003 to 0.05	.08
Other liver disease	2.38	2.05–2.78	<.001	0.05	0.03–0.07	<.001
>1 liver disease	4.76	4.15–5.46	<.001	0.10	0.09–0.12	<.001
Presence of ascites	1.27	1.09–1.47	.002	0.02	0.004–0.03	.01
Hepatic encephalopathy	1.41	1.19–1.66	<.001	0.04	0.03–0.06	<.001
NCI comorbidity index						
None	Ref	Ref	Ref	Ref	Ref	Ref
Low, 1–2	1.31	1.05–1.63	.02	0.01	-0.02 to 0.05	.54
Moderate, 3–4	1.64	1.32–2.05	<.001	0.02	-0.01 to 0.05	.25
High, ≥5	2.30	1.84–2.86	<.001	0.04	0.003–0.07	.04
Provider specialty						
Other[a]	Ref	Ref	Ref	Ref	Ref	Ref
Gastroenterology	10.09	7.35–13.9	<.001	0.06	0.01–0.12	.03
Internal medicine	3.28	2.39–4.52	<.001	0.01	-0.05 to 0.06	.83
Practice setting						
Solo practice	Ref	Ref	Ref	Ref	Ref	Ref
Group practice	.97	0.88–1.07	.56	-0.01	-0.02 to 0.001	.08
Hospital-based	.86	0.72–1.02	.08	0.001	-0.02 to 0.02	.93
University-based	.93	0.60–1.44	.74	0.02	-0.03 to 0.06	.45
Other	.97	0.83–1.13	.67	0.01	-0.01 to 0.03	.27
Training location						
Outside United States	Ref	Ref	Ref	Ref	Ref	Ref
Within United States	.92	0.84–1.01	.09	-0.002	-0.01 to 0.01	.78
Unknown	1.06	0.79–1.43	.69	-0.01	-0.05 to 0.02	.44

HCC, hepatocellular carcinoma; NCI, National Cancer Institute.
[a]Providers other than gastroenterologist or primary care provider.

Table 3. Multivariable Logistic Regression Model for Association Between HCC Screening Receipt and Early Tumor Detection (n = 13,714)

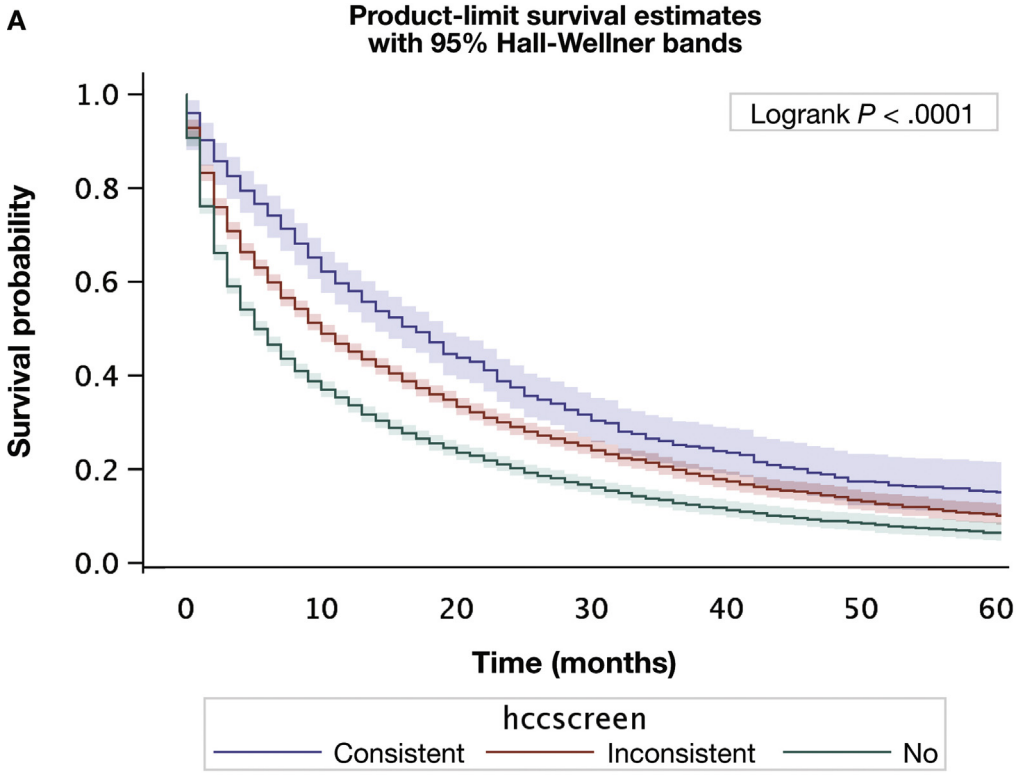
Variable	Adjusted OR	95% CI	*P* value
Screening group			
No screening	Ref	Ref	Ref
Consistent screening[a]	1.98	1.68–2.33	<.001
Inconsistent screening[b]	1.31	1.20–1.43	<.001
Age at HCC diagnosis	.99	0.98–0.99	<.001
Sex			
Male	Ref	Ref	Ref
Female	1.15	1.06–1.25	.001
Year of HCC diagnosis			
2003	Ref	Ref	Ref
2004	1.80	1.44–2.26	<.001
2005	1.68	1.34–2.10	<.001
2006	1.68	1.35–2.09	<.001
2007	1.57	1.27–1.94	<.001
2008	1.69	1.37–2.08	<.001
2009	1.65	1.34–2.03	<.001
2010	2.08	1.69–2.56	<.001
2011	1.88	1.53–2.31	<.001
2012	1.90	1.56–2.33	<.001
2013	2.08	1.70–2.56	<.001
Cirrhosis duration			
No prior diagnosis	Ref	Ref	Ref
<3 y before HCC	1.80	1.61–2.01	<.001
>3 y before HCC	1.88	1.67–2.13	<.001
Liver disease etiology			
No known liver disease	Ref	Ref	Ref
Hepatitis B	1.67	1.31–2.12	<.001
Hepatitis C	1.81	1.60–2.04	<.001
Alcohol-related	1.45	1.18–1.79	.001
Other liver disease	1.36	1.17–1.58	<.001
>1 liver disease	1.84	1.62–2.09	<.001
Hepatic encephalopathy	1.28	1.12–1.46	<.001
Provider specialty			
Other[c]	Ref	Ref	Ref
Gastroenterology	0.98	0.82–1.19	.87
Internal medicine	0.76	0.64–0.91	.003
Practice setting			
Solo practice	Ref	Ref	Ref
Group practice	1.06	0.97–1.15	.19
Hospital-based	1.12	0.96–1.30	.16
University-based	1.41	0.96–2.07	.08
Other	1.04	0.90–1.20	.59
Training location			
Outside United States	Ref	Ref	Ref
Within United States	1.15	1.05–1.25	.001
Unknown	1.25	0.96–1.64	.19

HCC, hepatocellular carcinoma; OR, odds ratio.
[a]Receipt of ≥1 abdominal ultrasound per calendar year.
[b]Receipt of ≥1 abdominal ultrasound during the study period but less than annually.
[c]Providers other than gastroenterologist or primary care provider.

screening infrequently (eg, 1 of 4 years) and others undergoing screening frequently (eg, 3 of 4 years). There are fewer data evaluating screening receipt as a continuous measure, such as PTC, which more accurately can capture and distinguish degrees of inconsistent, nonadherent screening.[33] Although we found that nearly half of all patients and roughly 70% of patients with known cirrhosis underwent some screening, the PTC reflected substantially lower adherent screening utilization. We found the mean PTC was less than 15% for all patients and remained less than 33% among those with screening.

This study reports a PTC measure among a large population-based sample. These findings help to better understand patterns of HCC screening adherence and characterize patterns of underuse in screening. Interventions to improve screening adherence to individuals at high risk of HCC are clearly needed to increase rates of early tumor detection and improve HCC-related survival.[34] We emphasize that future researchers should use a continuous measure such as PTC because they can better identify screening gaps and how often these gaps are occurring.

We found several patient- and provider-level characteristics that were associated with HCC screening receipt. The association between younger age and any HCC screening receipt may be related to provider perceptions of decreased benefit in elderly patients. However, prior studies have suggested HCC screening continues to be of benefit in older patients with preserved liver function and low comorbidity.[9,35,36] In contrast, the association between female sex and HCC screening receipt is unlikely to be related to differential perceived benefits. Studies have suggested females may be more likely to adhere to screening recommendations; however, patient adherence is not a common barrier to HCC screening completion and therefore it is unclear if this is the sole driver of this association.[37] Asian race was also a prominent and steady predictor for HCC screening, which was consistent with findings from prior literature.[17,38,39] This association may be attributed to high patient knowledge regarding HBV infection as a risk factor of HCC and the importance of HCC screening, given the high prevalence of HBV infection in Asian populations.[38–42] Documented liver disease, the presence of known cirrhosis, and receipt of gastroenterology care were 3 of the strongest predictors for HCC screening receipt in our study, with all being reported consistently in prior studies.[11,17,43–45] Although gastroenterology care is associated with increased screening receipt and survival, only a minority of patients received gastroenterology care before HCC diagnosis in our study. A prior survey study among primary care providers highlighted a lack of knowledge about screening benefits and society guideline recommendations as one of the most common barriers to HCC screening, underlining the importance of educational efforts among these providers.[46] Finally, many patients without screening had unrecognized liver disease and/or cirrhosis, which has been shown to be an important mediating factor for screening underuse.[43,47] This may be particularly problematic in the future as HCC epidemiology shifts from viral-mediated



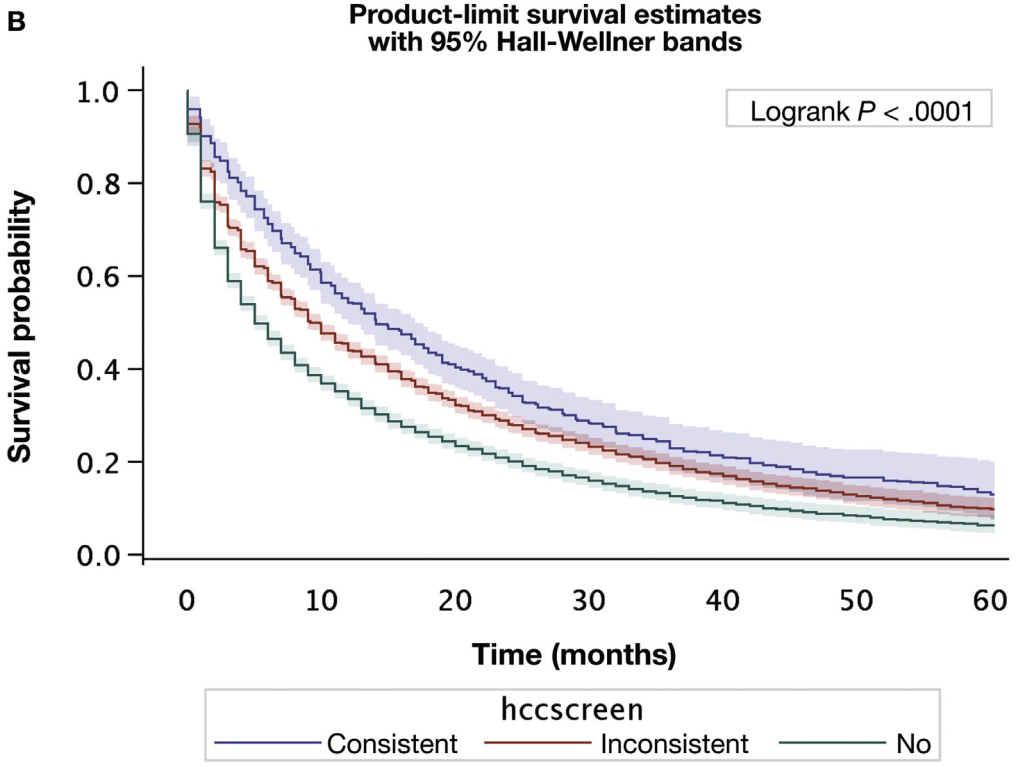


Figure 2. (*A*) Kaplan–Meier survival estimates by receipt of hepatocellular carcinoma (HCC) screening for all patients, unadjusted (n = 13,714). (*B*) Kaplan–Meier survival estimates by receipt of HCC screening for all patients, adjusted for lead-time bias with a mean sojourn time of 6 months (n = 13,714).

to nonalcoholic steatohepatitis, for which laboratory tests are not available to diagnose liver disease and transition to cirrhosis also can be difficult to recognize.

Our study reinforces prior data about the importance of consistent HCC screening among high-risk individuals, with significantly improved early detection and survival after adjusting for lead- and length-time bias.[32,48] Our study shows that this benefit also is shown in clinical practice, although benefits were attenuated with inconsistent screening compared with consistent screening. This attenuated association between inconsistent screening and survival may partly explain prior studies

Table 4. Multivariable Cox Proportional Hazards Model for Association Between HCC Screening Receipt and Overall Unadjusted Survival (n = 13,714)

Variable	Adjusted HR	95% CI	*P* value
Screening group			
No screening	Ref	Ref	Ref
Consistent screening[a]	0.73	0.67–0.79	<.001
Inconsistent screening[b]	0.85	0.81–0.88	<.001
Age at HCC diagnosis	1.15	1.13–1.18	<.001
Race/ethnicity			
Non-Hispanic white	Ref	Ref	Ref
Black	1.07	1.01–1.14	.03
Hispanic	0.99	0.94–1.05	.76
Asian	0.82	0.77–0.88	<.001
Other	0.81	0.75–0.88	<.001
Census poverty level			
0% to <5%	Ref	Ref	Ref
5%–9%	1.06	1.00–1.12	.04
10%–19%	1.07	1.02–1.13	.01
20%–100%	1.19	1.13–1.26	<.001
Year of HCC diagnosis			
2003	Ref	Ref	Ref
2004	0.92	0.84–1.02	.10
2005	0.91	0.83–0.99	.04
2006	0.85	0.77–0.93	<.001
2007	0.84	0.77–0.92	<.001
2008	0.87	0.79–0.95	<.001
2009	0.83	0.76–0.91	<.001
2010	0.78	0.71–0.85	<.001
2011	0.78	0.71–0.85	<.001
2012	0.84	0.77–0.92	<.001
2013	0.90	0.82–0.98	.02
Cirrhosis duration			
No prior diagnosis	Ref	Ref	Ref
<3 y before HCC	1.04	0.98–1.10	.24
>3 y before HCC	1.01	0.95–1.08	.77
Liver disease etiology			
No known liver disease	Ref	Ref	Ref
Hepatitis B	0.80	0.70–0.91	<.001
Hepatitis C	0.89	0.84–0.95	<.001
Alcohol-related	0.97	0.88–1.08	.62
Other liver disease	0.87	0.81–0.94	<.001
>1 liver disease	0.84	0.79–0.90	<.001
Presence of ascites	1.34	1.25–1.43	<.001
NCI comorbidity index			
None	Ref	Ref	Ref
Low, 1–2	1.06	0.98–1.15	.13
Moderate, 3–4	1.08	1.00–1.17	.06
High, ≥5	1.34	1.24–1.45	<.001
Provider specialty			
Other[c]	Ref	Ref	Ref
Gastroenterology	0.73	0.67–0.79	<.001
Internal medicine	0.92	0.85–1.00	.06
Practice setting			
Solo practice	Ref	Ref	Ref
Group practice	1.00	0.96–1.04	.98
Hospital-based	0.95	0.88–1.02	.15
University-based	0.86	0.71–1.04	.13
Other	1.02	0.96–1.09	.54

HCC, hepatocellular carcinoma; HR, hazard ratio; NCI, National Cancer Institute.
[a]Receipt of ≥1 abdominal ultrasound per calendar year.
[b]Receipt of ≥1 abdominal ultrasound during the study period but less than annually.
[c]Providers other than gastroenterologist or primary care provider.

Table 5. Multivariable Cox Proportional Hazards Model for Association Between HCC Screening Receipt and Overall Survival, Adjusted for Lead-Time Bias (n = 13,714)

Screening group	Adjusted HR	95% CI	*P* value
Unadjusted			
No screening	Ref	Ref	Ref
Consistent screening[a]	0.73	0.67–0.79	<.001
Inconsistent screening[b]	0.85	0.81–0.88	<.001
Adjusted for lead-time bias			
Mean sojourn time, 3 mo			
No screening	Ref	Ref	Ref
Consistent screening[a]	0.75	0.69–0.82	<.001
Inconsistent screening[b]	0.86	0.82–0.89	<.001
Mean sojourn time, 6 mo			
No screening	Ref	Ref	Ref
Consistent screening[a]	0.76	0.70–0.83	<.001
Inconsistent screening[b]	0.86	0.83–0.90	<.001
Mean sojourn time, 9 mo			
No screening	Ref	Ref	Ref
Consistent screening[a]	0.77	0.71–0.84	<.001
Inconsistent screening[b]	0.86	0.83–0.90	<.001

HCC, hepatocellular carcinoma; HR, hazard ratio.
[a]Receipt of ≥1 abdominal ultrasound per calendar year.
[b]Receipt of ≥1 abdominal ultrasound during the study period but less than annually.

that have shown a smaller benefit of screening. Of note, there has been increasing recognition that HCC screening benefits must be weighed against screening harms, which could not be evaluated in our study.[49] Further studies evaluating the balance of benefits and harms, including in subgroups such as those with nonalcoholic steatohepatitis, are needed to further inform the importance of HCC screening in patients with cirrhosis.

Given our study's strengths, we acknowledge it also had several limitations. Despite applying an algorithm to determine screening intent, this method is imperfect and prone to misclassification bias. We also did not capture alternative screening strategies (such as computed tomography or magnetic resonance imaging) that may be used in some practices and we did not account for the healthy adherer effect, which potentially could have influenced patient screening utilization and subsequent health outcomes.[50] Furthermore, we also attempted to construct Milan Criteria using available tumor characteristics, but this was limited by missing data. Similarly, there was a possibility of missing ICD-9 codes for cirrhosis, leading to ascertainment bias for this subgroup analysis. We also did not have laboratory data to assess liver dysfunction or data on performance status, which can influence HCC screening utilization and observed benefits. Moreover, evaluating survival benefit of HCC screening from observational studies such as this one may be subject to various biases. Although we adjusted for lead-time and length-time biases, reliable model parameters are not readily available. Therefore, we conducted sensitivity analyses to assess the impact of these

biases on estimated survival benefit across a range of plausible means of sojourn times, proportions of slow-growing tumors, and other required inputs.[28] Selection bias and the potential for residual confounding are difficult to correct in nonrandomized studies; individuals who receive screen examinations for HCC may be different from those who do not. Results of this study may not be generalizable to a wider population beyond a Medicare population.[51] Finally, migration of patients in and out of SEER registry geographic areas could potentially cause loss to follow-up evaluation, affecting the reliability of the data.[52]

In summary, we found HCC screening continues to be underused in the United States, with most patients not receiving any HCC screening before HCC diagnosis. Despite improvements over time, fewer than 10% of patients received consistent screening before HCC diagnosis, and the mean PTC with screening was less than 15% for all patients. Given the demonstrated benefits of HCC screening, it is clear that increasing HCC screening utilization is an important step to reversing the high rates of late-stage diagnosis and poor survival.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2018.10.031.

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Conflicts of interest
This author discloses the following: Amit Singal has been on advisory boards or served as a consultant for Wako Diagostics, Roche, Exact Sciences, and Glycotest. The remaining authors disclose no conflicts.

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Supplemental Methods

Lead- and Length-Time Bias Sensitivity Analysis

Following the parametric model by Duffy et al,[28] correction for lead-time bias involves estimation of the additional follow-up time owing to lead time in the case of screen-detected cancer. The expected additional follow-up time, s, is determined as follows: $E(s) = \frac{1-e^{-\lambda t}-\lambda t e^{-\lambda t}}{\lambda(1-e^{-\lambda t})}$ for a patient with screen-detected cancer known to be dead at time t after diagnosis, and $E(s) = \frac{1-e^{-\lambda t}}{\lambda}$ for a patient with screen-detected cancer known to be alive at time t after diagnosis. To correct for lead-time bias, $E(s)$ was subtracted from the observed survival time of screen-detected patients, which were defined as patients who received screening ultrasound within 6 months before HCC diagnosis.[28]

After the lead time was adjusted among screen-detected patients, we further adjusted for length time bias following the method proposed by Duffy et al.[28] The relative risk of death from screen-detected vs symptomatic tumors, φ, was estimated by the observed probability of death from screen-detected, p_1, and symptomatic tumors, p_2, and the observed probability of screen-detected tumors, p_3, by giving plausible values for a proportion of patients with slow-growing tumors, $1-q$, and the relative risk of death from slow-growing tumors vs aggressive tumors, θ, that is: $\widehat{\varphi} = \frac{p_2\{(\theta q+1-q)(\theta+q(1-\theta))-p_3\theta\}}{p_1\theta(1-p_3)}$. By multiplying $\widehat{\varphi}$ and the survival rate for patients with symptomatic tumors, in this section, we estimated the survival rate for screen-detected tumors correcting for length-time bias under various plausible data inputs.[28]

Supplementary Table 1. Baseline Characteristics for Providers of HCC Patients (n = 13,714)

Variable	Consistent screening[a] (%)	Inconsistent screening[b] (%)	No screening (%)	*P* value
Provider specialty				<.001
Gastroenterology	840 (89.7)	3895 (67.5)	2295 (32.7)	
Internal medicine	97 (10.4)	1792 (31.1)	4075 (58.1)	
Other[c]	0 (0)	81 (1.4)	639 (9.1)	
Practice setting				<.001
Solo practice	347 (37.0)	2076 (36.0)	2284 (32.6)	
Group practice	400 (42.7)	2720 (47.2)	3468 (49.5)	
Hospital-based	76 (8.1)	394 (6.8)	530 (7.6)	
University-based	17 (1.8)	52 (.9)	58 (.8)	
Other	97 (10.4)	526 (9.1)	669 (9.5)	
Medical school graduation				.058
Before 1968	84 (9.0)	534 (9.3)	727 (10.4)	
1969–1984	414 (44.2)	2654 (46.0)	3276 (46.7)	
1985–2000	405 (43.2)	2416 (41.9)	2794 (39.9)	
After 2001	34 (3.6)	164 (2.8)	212 (3.0)	
Training location				<.001
Within United States	601 (64.1)	3750 (65.0)	4923 (70.2)	
Outside United States	319 (34.0)	1894 (32.8)	1927 (27.5)	
Unknown	17 (1.8)	124 (2.2)	159 (2.3)	

HCC, hepatocellular carcinoma.
[a]Receipt of ≥1 abdominal ultrasound per calendar year.
[b]Receipt of ≥1 abdominal ultrasound during the study period but less than annually.
[c]Providers other than gastroenterologist or primary care provider.

Supplementary Table 2. Correlates of Consistent and Inconsistent HCC Screening Receipt (n = 13,714)

Variable	Consistent screening[a]			Inconsistent screening[b]		
	Adjusted OR	95% CI	*P* value	Adjusted OR	95% CI	*P* value
Age at HCC diagnosis	1.00	1.00–1.01	.07	1.00	0.99–1.00	.07
Sex						
Male	Ref	Ref	Ref	Ref	Ref	Ref
Female	1.29	1.09–1.53	.003	1.21	1.11–1.32	<.001
Race/ethnicity						
Non-Hispanic white	Ref	Ref	Ref	Ref	Ref	Ref
Black	0.98	0.74–1.29	.87	1.01	0.88–1.16	.87
Hispanic	1.51	1.20–1.89	<.001	1.24	1.09–1.41	.001
Asian	3.24	2.52–4.16	<.001	1.33	1.15–1.55	<.001
Other	2.11	1.54–2.91	<.001	1.12	0.93–1.34	.23
Year of HCC diagnosis						
2003	Ref	Ref	Ref	Ref	Ref	Ref
2004	0.91	0.57–1.47	.71	0.98	0.78–1.22	.83
2005	0.70	0.44–1.13	.15	1.04	0.84–1.29	.72
2006	0.65	0.41–1.02	.06	0.86	0.69–1.06	.16
2007	0.77	0.50–1.19	.25	0.89	0.72–1.10	.27
2008	0.54	0.35–0.85	.007	0.81	0.66–0.99	.04
2009	0.43	0.28–0.67	<.001	0.74	0.60–0.90	.003
2010	0.82	0.54–1.24	.34	0.78	0.64–0.96	.02
2011	0.64	0.42–0.97	.04	0.74	0.60–0.90	.003
2012	0.72	0.48–1.10	.13	0.79	0.65–0.97	.02
2013	0.94	0.563–1.41	.77	0.67	0.55–0.82	<.001
Cirrhosis duration						
No prior diagnosis	Ref	Ref	Ref	Ref	Ref	Ref
<3 years before HCC	3.31	2.53–4.34	<.001	2.12	1.88–2.40	<.001
>3 years before HCC	3.13	2.38–4.12	<.001	1.14	0.99–1.31	.07
Liver disease etiology						
No known liver disease	Ref	Ref	Ref	Ref	Ref	Ref
Hepatitis B	12.36	7.26–20.7	<.001	2.47	1.90–3.22	<.001
Hepatitis C	7.43	5.07–10.91	<.001	1.91	1.68–2.16	<.001
Alcohol-related	2.40	1.35–4.27	.003	1.35	1.08–1.68	.008
Other liver disease	6.66	4.37–10.16	<.001	2.18	1.88–2.54	<.001
>1 liver disease	18.98	13.11–27.50	<.001	3.62	3.14–4.16	<.001
Presence of ascites	1.63	1.29–2.05	<.001	1.67	1.43–1.96	<.001
Hepatic encephalopathy	1.70	1.35–2.15	<.001	1.20	1.01–1.43	.04
NCI comorbidity index						
None	Ref	Ref	Ref	Ref	Ref	Ref
Low (1–2)	1.96	0.19–1.21	.16	1.22	1.01–1.48	.04
Moderate (3–4)	2.21	0.19–1.17	.10	1.45	1.20–1.76	<.001
High (≥5)	3.72	0.14–0.87	.005	1.99	1.65–2.41	<.001
Provider specialty						
Other[c]	Ref	Ref	Ref	Ref	Ref	Ref
Gastroenterology	>999.99	>999.99	<.001	6.47	5.04–8.30	<.001
Internal medicine	>999.99	>999.99	<.001	2.89	2.25–3.70	<.001
Practice setting						
Solo practice	Ref	Ref	Ref	Ref	Ref	Ref
Group practice	0.89	0.74–1.06	.19	0.94	0.86–1.03	.19
Hospital-based	0.94	0.69–1.27	.67	0.81	0.69–0.96	.02
University-based	1.40	0.72–2.72	.32	0.79	0.51–1.24	.31
Other	0.99	0.75–1.31	.93	0.91	0.78–1.05	.20
Training location						
Outside United States	Ref	Ref	Ref	Ref	Ref	Ref
Within United States	0.95	0.80–1.13	.59	0.91	0.83–0.99	.03
Unknown	1.12	0.63–2.02	.70	1.01	0.76–1.33	.96

HCC, hepatocellular carcinoma; NCI, National Cancer Institute; OR, odds ratio.
[a]Receipt of ≥1 abdominal ultrasound per calendar year.
[b]Receipt of ≥1 abdominal ultrasound during the study period but less than annually.
[c]Providers other than gastroenterologist or primary care provider.

Supplementary Table 3. Kaplan–Meier Survival Estimates by Receipt of HCC Screening for All Patients, Unadjusted and Adjusted for Lead- and Length-Time Biases (n = 13,714)

Screening group	Median survival, *mo* (95% CI)	1-year survival, % (95% CI)[a]	3-year survival, % (95% CI)[a]	5-year survival, % (95% CI)[a]	Log-rank test
Unadjusted					
Consistent screening[b]	17.00 (15.00–19.00)	58 (55–61)	25 (22–28)	15 (12–18)	<.001
Inconsistent screening[c]	10.00 (10.00–11.00)	45 (44–46)	20 (19–21)	10 (9–11)	
No screening	5.00 (5.00–6.00)	34 (33–35)	13 (12–14)	6 (6–7)	
Adjusted for lead-time bias					
Mean sojourn time, 3 mo					
Consistent screening[b]	16.00 (13.09–18.00)	56 (53–59)	24 (22–27)	14 (12–17)	<.001
Inconsistent screening[c]	10.00 (9.00–10.00)	45 (43–46)	19 (18–21)	10 (9–11)	
Mean sojourn time, 6 mo					
Consistent screening[b]	14.05 (13.00–16.72)	54 (51–57)	24 (21–27)	13 (11–16)	<.001
Inconsistent screening[c]	9.94 (9.00–10.00)	44 (43–45)	19 (18–20)	10 (9–11)	
Mean sojourn time, 9 mo					
Consistent screening[b]	14.00 (12.65–16.00)	54 (51–57)	22 (19–25)	13 (11–16)	<.001
Inconsistent screening[c]	9.86 (9.00–10.00)	44 (43–45)	19 (18–20)	10 (9–11)	
Adjusted for lead- and length-time biases					
Mean sojourn time, 3 mo					
Consistent screening[b]		55 (53–58)	24 (22–26)	14 (13–16)	
Inconsistent screening[c]		44 (44–45)	19 (19–20)	10 (10–10)	
Mean sojourn time, 6 mo					
Consistent screening[b]		54 (52–56)	23 (21–25)	13 (11–15)	
Inconsistent screening[c]		44 (44–45)	19 (19–20)	10 (10–10)	
Mean sojourn time, 9 mo					
Consistent screening[b]		54 (52–56)	22 (20–24)	13 (11–15)	
Inconsistent screening[c]		44 (44–44)	19 (19–19)	10 (10–10)	

HCC, hepatocellular carcinoma.

[a]For lead- and length-time bias adjustment, the weighted average of screen-detected and symptomatic cancer was calculated assuming $1 - q = 20\%$ and $\theta = 0.9$.

[b]Receipt of ≥1 abdominal ultrasound per calendar year.

[c]Receipt of ≥1 abdominal ultrasound during the study period but less than annually.

Supplementary Table 4. Survival Estimates by Receipt of HCC Screening for Patients With Screen-Detected and Symptomatic Tumors, Unadjusted (n = 13,714) and Adjusted for Lead- and Length-Time Biases for Only the Screen-Detected Patients (n = 1136)

Screening group		N (%)	1-year survival, % (95% CI)[a]	3-year survival, % (95% CI)[a]	5-year survival, % (95% CI)[a]
Unadjusted for lead-time bias					
Consistent screening[b]	Screen-detected	390 (2.8)	63 (58–68)	31 (26–36)	19 (15–24)
	Symptomatic	547 (4.0)	54 (50–59)	21 (17–25)	12 (9–15)
Inconsistent screening[c]	Screen-detected	746 (5.4)	59 (55–62)	29 (26–33)	17 (14–20)
	Symptomatic	5022 (36.6)	43 (42–44)	18 (17–20)	9 (8–10)
No screening	Symptomatic	7009 (51.1)	34 (33–35)	13 (12–14)	6 (6–7)
Adjusted for lead-time bias					
Mean sojourn time, 3 mo					
Consistent screening[b]	Screen-detected	390 (2.8)	57 (52–62)	29 (24–34)	18 (14–22)
Inconsistent screening[c]	Screen-detected	746 (5.4)	54 (50–57)	26 (23–30)	16 (13–19)
Mean sojourn time, 6 mo					
Consistent screening[b]	Screen-detected	390 (2.8)	54 (49–59)	26 (21–31)	15 (11–20)
Inconsistent screening[c]	Screen-detected	746 (5.4)	51 (47–55)	24 (21–27)	15 (13–18)
Mean sojourn time, 9 mo					
Consistent screening[b]	Screen-detected	390 (2.8)	54 (48–58)	24 (19–29)	15 (11–19)
Inconsistent screening[c]	Screen-detected	746 (5.4)	51 (47–54)	23 (20–26)	14 (12–17)
Adjusted for lead- and length-time biases					
Mean sojourn time, 3 mo					
Consistent screening[b]	Screen-detected	390 (2.8)	57 (56–57)	28 (28–29)	17 (16–18)
Inconsistent screening[c]	Screen-detected	746 (5.4)	53 (53–53)	26 (25–26)	16 (15–16)
Mean sojourn time, 6 mo					
Consistent screening[b]	Screen-detected	390 (2.8)	54 (53–54)	25 (25–26)	15 (14–15)
Inconsistent screening[c]	Screen-detected	746 (5.4)	51 (50–51)	24 (23–24)	15 (14–15)
Mean sojourn time, 9 mo					
Consistent screening[b]	Screen-detected	390 (2.8)	54 (53–54)	23 (22–23)	14 (13–15)
Inconsistent screening[c]	Screen-detected	746 (5.4)	50 (50–50)	22 (22–23)	13 (13–14)

HCC, hepatocellular carcinoma.

[a]For length-time bias adjustment, the survival rates were estimated by $1 - q = 20\%$ and $\theta = 0.9$.

[b]Receipt of ≥1 abdominal ultrasound per calendar year.

[c]Receipt of ≥1 abdominal ultrasound during the study period but less than annually.