Advanced Hepatocellular Carcinoma Tumor Stage at Diagnosis in the 1945-1965 Birth Cohort Reflects Poor Use of Hepatocellular Carcinoma Screening

Ann Robinson, Hesam Tavakoli, Benny Liu, Taft Bhuket, and Robert J. Wong

Individuals from the 1945-1965 birth cohort account for the majority of hepatocellular carcinoma (HCC) cases in the United States. Understanding trends in HCC among this birth cohort is vital given the increasing burden of chronic liver disease among this group. We retrospectively evaluated trends and disparities in HCC tumor stage at the time of diagnosis among the 1945-1965 birth cohort in the United States using the Surveillance, Epidemiology, and End Results (SEER) cancer registry. Tumor stage at the time of HCC diagnosis was assessed using Milan criteria and SEER HCC staging systems. Among 38,045 patients with HCC within the 1945-1965 birth cohort (81.6% male, 50.1% non-Hispanic white, 16.2% African American, 12.6% Asian, 19.8% Hispanic), 66.2% had Medicare or commercial insurance, 27.2% had Medicaid, and 6.6% were uninsured. During the period 2004-2006 to 2013-2014, the number of patients with HCC from the 1945-1965 birth cohort increased by 58.7% (5.9% increase per year). While the proportion of patients with HCC within the Milan criteria increased with time (36.4% in 2003-2006 to 46.3% in 2013-2014; $P < 0.01$), less than half were within the Milan criteria. On multivariate analysis within the Milan criteria, men were 12% less likely to have HCC compared to women, and African Americans were 27% less likely to have HCC compared to non-Hispanic whites (odds ratio, 0.73; 95% confidence interval, 0.68-0.78; $P < 0.01$). *Conclusion*: From 2004 to 2014, the burden of newly diagnosed HCC among the 1945-1965 birth cohort increased by 5.9% per year. While improvements in earlier staged HCC at diagnosis were observed, the majority of patients with HCC among the 1945-1965 birth cohort were beyond the Milan criteria at diagnosis; this may reflect poor utilization or suboptimal performance of HCC screening tests. (*Hepatology communications* 2018;2:1147-1155)

Worldwide, hepatocellular carcinoma (HCC) is the second most common cause of cancer-related deaths for men and women combined.[1] From 2003 to 2012, deaths from HCC increased at the highest rate of all cancer sites, with the greatest increase seen among individuals born between 1945 and 1965.[2] These observations are partly due to the higher risk of chronic hepatitis C virus (HCV) infection among this 1945-1965 birth cohort and the subsequent higher risk of developing HCV-associated HCC.[3]

Despite established guidelines for HCC screening and surveillance among at-risk individuals, overall persistence of poor utilization of HCC screening

Abbreviations: ALD, alcoholic liver disease; CI, confidence interval; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; OR, odds ratio; SEER, Surveillance Epidemiology and End Results.

Received March 19, 2018; accepted June 20, 2018.

This study was presented as an oral presentation at the 2017 American Association for the Study of Liver Disease Annual Liver Meeting in Washington, DC.

Supported by an AASLD Foundation Clinical and Translational Research Award in Liver Diseases (to R.W).

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep4.1236

Potential conflict of interest: Dr. Wong consults, advises, is on the speakers' bureau, and received grants from Gilead. He is on the speakers' bureau for Bayer and Salix.

and surveillance contributes to advanced-stage HCC beyond eligibility for potentially curative therapy.[4–9] However, given the increased awareness and emphasis on HCV screening among the 1945-1965 birth cohort, it is possible that this has also translated into improved rates of HCC screening and surveillance among this group. Furthermore, the 1945-1965 birth cohort represents a large majority of patients with chronic liver disease in the United States, and specifically understanding HCC epidemiology among this group will provide valuable data to improve HCC screening and surveillance programs. Thus, our current study aims to evaluate updated trends in HCC epidemiology among a large national population-based cancer registry, with a focus on tumor stage at diagnosis among the 1945-1965 birth cohort.

Patients and Methods

All adults (age 20 years and older) with HCC from 2004 to 2014 were identified using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) population-based cancer registry, with data obtained from participating state and regional cancer registries.[10] The 2004-2014 SEER includes data from 18 regions in the United States (San Francisco–Oakland, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose–Monterey, Los Angeles, Alaska Natives, Rural Georgia, California excluding San Francisco/San Jose–Monterey/Los Angeles, Kentucky, Louisiana, New Jersey, and Greater Georgia) and represents approximately 28% of the U.S. population. Data included in the national SEER registry are compiled based on state and regional cancer registries. Cancer data collected by the database registrars are based on available data provided by the clinical providers as well as the health systems and hospitals that are within each registrar's region.

The International Classification of Disease for Oncology, Third Edition, was used by the SEER database to identify HCC.[11] HCC tumor stage was evaluated using SEER historic summary staging as specified in the SEER Coding and Staging Manual; this staging is unique to SEER and is not used particularly for prognosis but to describe the extent of disease.[11] Tumors confined to only one lobe of the liver with or without vascular invasion at the time of diagnosis were defined as localized. Tumors involving more than one lobe through contiguous growth of a single lesion, extension to adjacent structures (gallbladder, diaphragm, or extrahepatic bile ducts), or spread to regional lymph nodes were defined as regional. Metastatic disease or extension of cancer to distant lymph nodes or nearby organs, such as the stomach, pleura, or pancreas, was defined as distant. In addition to SEER HCC staging, we also evaluated tumor characteristics, including size and number of tumors at the time of diagnosis, to determine whether a patient's tumor met Milan criteria (single lesion less than 5 cm or no more than three lesions each less than 3 cm) with no extrahepatic or vascular involvement.[12]

Insurance status was evaluated using SEER classifications, which included three categories: Medicare or commercial insurance, Medicaid, and uninsured/no insurance. Medicare or commercial insurance includes patients with private insurance (fee-for-service, managed care, Health Maintenance Organization, Preferred Provider Organization, Tricare) or Medicare (administered through a managed care plan, Medicare with private supplement, or Medicare with supplement, not otherwise specified, and military). Medicaid includes patients with Medicaid (including

ARTICLE INFORMATION:

From the Department of Medicine, Division of Gastroenterology and Hepatology, Alameda Health System – Highland Hospital, Oakland, CA.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Robert J. Wong, M.D., M.S.
Division of Gastroenterology and Hepatology
Alameda Health System – Highland Hospital Campus
1411 East 31st Street
Highland Hospital – Highland Care Pavilion 5th Floor
Endoscopy Unit, Oakland, CA 94602.

administered through managed care plans, Medicare with Medicaid eligibility, and Indian/Public Health Service). Uninsured is defined as those who were either not insured or self-paid at the time of HCC diagnosis. Race/ethnicity-specific comparisons used SEER categories of non-Hispanic white, African American, Asian and Pacific Islander, Native American and Alaskan Native, and Hispanic white (Hispanic). Time-specific trends used year of diagnoses as follows: 2004-2006, 2007-2008, 2009-2010, 2011-2012, and 2013-2014.

Demographic characteristics of the study cohort were presented as proportions and frequencies. Overall time-specific trends in number of newly diagnosed cases of HCC were stratified by sex and race/ethnicity. Proportion of patients with HCC SEER localized, HCC SEER advanced, HCC within Milan criteria, and HCC outside Milan criteria at diagnosis were also stratified by sex, race/ethnicity, and primary insurance status. Comparison of tumor stage at diagnosis between groups used χ^2 testing. Predictors of HCC tumor stage at diagnosis (probability of SEER localized versus distant and probability of HCC within Milan criteria versus outside Milan) were evaluated using multivariate logistic regression models. Variables selected for inclusion in the multivariate models were determined based on those hypothesized to be clinically significant in affecting tumor stage at diagnosis. Statistical significance was met with a 2-tailed *P* value of <0.05. All statistical analyses were performed with Stata version 14 (Stata Corp, College Station, TX). The study was reviewed and determined to be exempt by the Alameda Health System Institutional Review Board because human subjects were not involved (as per U.S. Department of Health and Human Services guidelines), and the SEER database is publicly available without individually identifiable private information.

Results

Among 38,045 patients within the 1945-1965 birth cohort diagnosed with HCC in the 2004-2014 SEER registry, 81.62% (n = 31,054) were male individuals. A majority of patients were non-Hispanic white (50.10%, n = 18,995), and 16.21% were African American (Table 1). At the time of diagnosis, 52.24% had SEER localized-stage HCC and 16.67% had SEER distant-stage HCC. Overall, only 42.79% were within Milan criteria at the time of diagnosis.

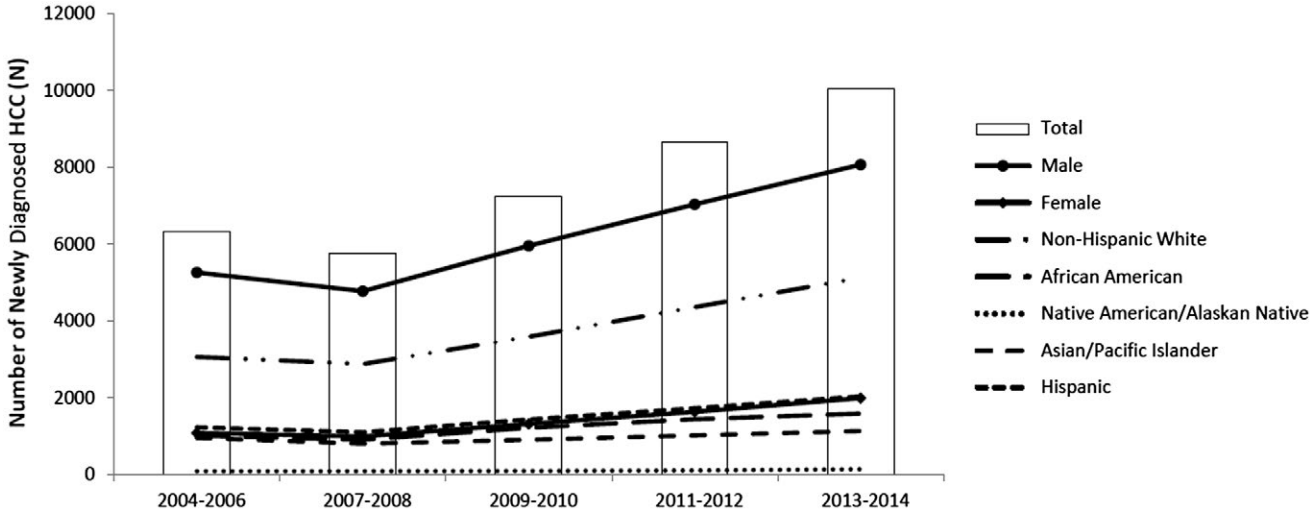
TABLE 1. CHARACTERISTICS OF THE 1945-1965 BIRTH COHORT PATIENTS WITH HCC

	Frequency (n)	Proportion (%)
Sex		
Female	6,991	18.38
Male	31,054	81.62
Race/ethnicity		
Non-Hispanic white	18,995	50.1
African American	6,146	16.21
Native American/Alaskan Native	480	1.27
Asian/Pacific Islander	4,790	12.63
Hispanic	7,506	19.8
Primary insurance		
Medicare/commercial	19,487	66.19
Medicaid	8,006	27.19
Uninsured	1,948	6.62
HCC stage at diagnosis		
SEER localized	17,343	52.24
SEER regional	10,318	31.08
SEER distant	5,535	16.67
Milan criteria		
HCC outside Milan criteria	21,764	57.21
HCC within Milan criteria	16,281	42.79

TRENDS IN HCC OVER TIME

During the period 2004-2006 to 2013-2014, there was an overall 58.7% increase (5.9% mean annual percentage increase) in newly diagnosed HCC among the 1945-1965 birth cohort (Fig. 1). Female individuals had significantly greater proportional increases in newly diagnosed HCC compared to male individuals in the 1945-1965 birth cohort (females 2004-2006 to 2013-2014, 84.5% increase, 8.5% mean annual percentage increase; males 2004-2006 to 2013-2014, 53.4% increase, 5.3% mean annual percentage increase). When stratified by race/ethnicity, the greatest proportional increase in new diagnosis of HCC was seen among non-Hispanic whites (for 2004-2006, 67.6% increase, 6.8% mean annual percentage increase), and the lowest was in Asian/Pacific Islanders (for 2004-2006, 18.6% increase, 1.9% mean annual percentage increase) (Fig. 1).

When evaluating tumor stage-specific trends in HCC diagnoses, the overall proportion of 1945-1965 birth cohort patients with HCC within Milan criteria increased from 36.43% in 2004-2006 to 46.33% in 2013-2014 (Fig. 2). Similar increases in HCC within Milan criteria at diagnosis were observed in all categories when stratified by sex and race/ethnicity; however, the smallest relative percentage increase was observed in male (27.18%) and Hispanic (19.06%) patients. Using SEER-specific HCC staging systems, the proportion of SEER localized-stage HCC at diagnosis among the 1945-1965 birth cohort increased



	Percent Increase in Newly Diagnosed HCC Per Year: 2004-2006 to 2013-2014	Annual Percent Increase in Newly Diagnosed HCC
Overall	58.7%	5.9%
Male	53.4%	5.3%
Female	84.5%	8.5%
Non-Hispanic White	67.6%	6.8%
African American	57.2%	5.7%
Native American/Alaskan Native	61.0%	6.1%
Asian/Pacific Islander	18.6%	1.9%
Hispanic	66.1%	6.6%

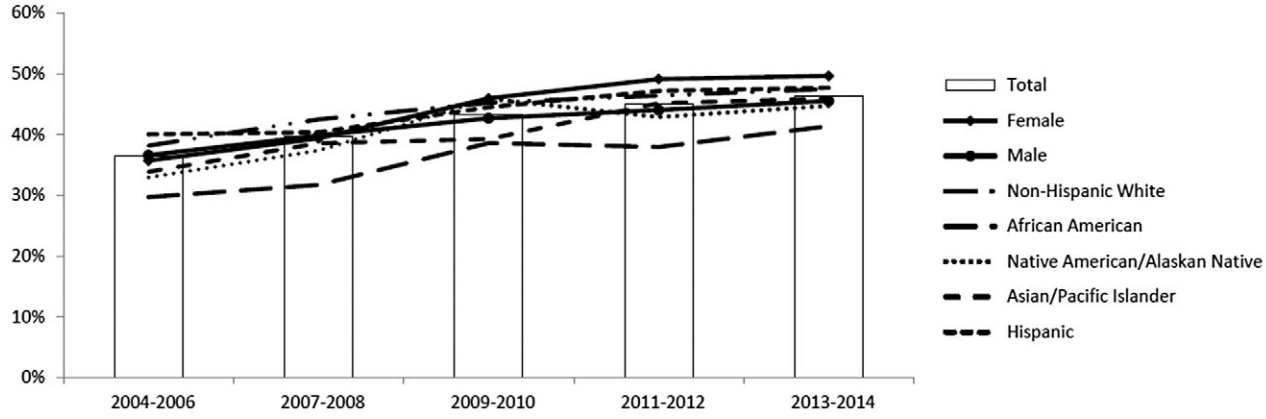
FIG. 1. Trends in newly diagnosed HCC among the 1945-1965 birth cohort.

from 49.71% in 2004-2006 to 53.99% in 2013-2014 (Fig. 3). The greatest relative percentage increase in SEER localized HCC during the period 2004-2006 to 2013-2014 was observed in male patients, Asian/Pacific Islanders, and Native American/Alaskan Natives (Fig. 3).

FACTORS ASSOCIATED WITH ADVANCED HCC AT DIAGNOSIS

Overall, African Americans had more advanced HCC at presentation compared to other race/ethnic groups. For example, compared to non-Hispanic whites, African Americans were more likely to have SEER distant-stage HCC at diagnosis (20.30% versus 16.15%, $P < 0.001$) and were more likely to have HCC outside of Milan criteria at diagnosis (63.31% versus 55.44%, $P < 0.001$) (Table 2). When stratified by insurance status, patients with HCC who were uninsured at the time of diagnosis were more likely to have SEER distant-stage HCC and HCC outside of Milan criteria compared to those with Medicare/commercial insurance and compared to those with Medicaid (Table 2).

On multivariate analyses among the 1945-1965 birth cohort, male individuals with HCC were significantly less likely to be within Milan criteria at diagnosis compared to female individuals (odds ratio [OR], 0.88; 95% confidence interval [CI], 0.83-0.93; $P < 0.001$) (Table 3). African Americans (OR, 0.73; 95% CI, 0.68-0.78; $P < 0.001$) and Asian/Pacific Islanders (OR, 0.85; 95% CI, 0.079-0.92; $P < 0.001$) were significantly less likely to be within Milan criteria compared to non-Hispanic whites with HCC. Patients with HCC diagnosed in the most recent 2013-2014 era were significantly more likely to be within Milan criteria compared to those diagnosed in 2004-2006 (OR, 1.12; 95% CI, 1.05-1.20; $P = 0.001$). Patients with HCC who were uninsured at the time of diagnosis had a significantly lower likelihood of being within Milan criteria compared to those with Medicare/commercial insurance (OR, 0.46; 95% CI, 0.41-0.51; $P < 0.001$).



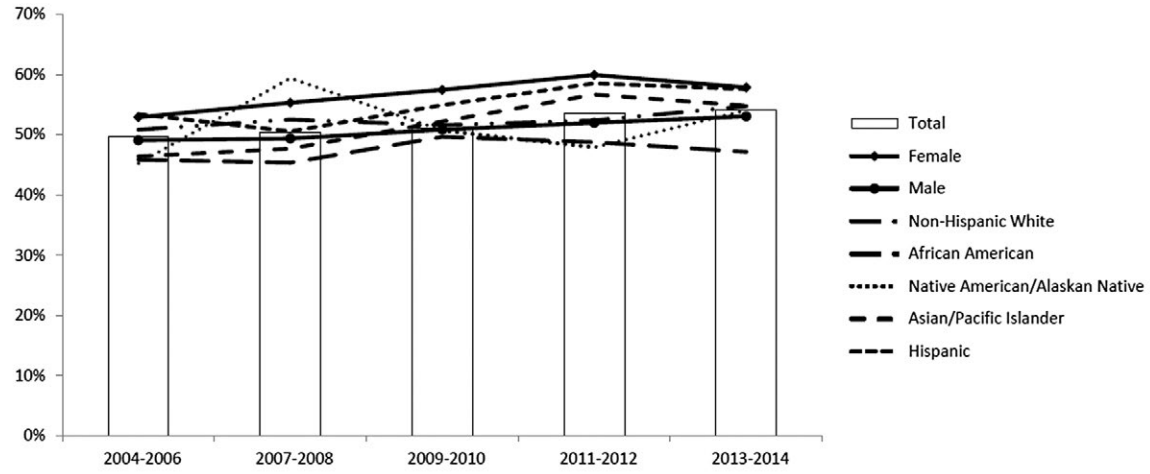
	2004-2006	2013-2014	Relative Percentage Increase in Proportion of HCC Patients Within Milan Criteria: 2004-2006 to 2013-2014
Overall	36.43%	46.33%	27.18%
Male	36.58%	49.62%	35.65%
Female	35.69%	45.52%	27.54%
Non-Hispanic White	38.16%	47.50%	24.48%
African American	29.69%	41.38%	39.37%
Native American/Alaskan Native	32.93%	44.70%	35.74%
Asian/Pacific Islander	33.86%	45.92%	35.62%
Hispanic	40.03%	47.66%	19.06%

FIG. 2. Trends in the proportion of newly diagnosed HCC among the 1945-1965 birth cohort who have HCC within the Milan criteria at diagnosis.

Similar trends were observed when evaluating the probability of having SEER localized-stage HCC at diagnosis among the 1945-1965 birth cohort (Table 3). Male patients were less likely to have SEER localized lesions in comparison to female patients (OR, 0.79; 95% CI, 0.72-0.86; P < 0.001). African Americans were significantly less likely to have SEER localized HCC at diagnosis compared to non-Hispanic whites (OR, 0.77; 95% CI, 0.70-0.85; P < 0.001), whereas Hispanics were more likely to have SEER localized HCC (OR, 1.17; 95% CI, 1.06-1.29; P = 0.002) (Table 3). Patients with HCC who were uninsured at the time of diagnosis were significantly less likely to have SEER localized HCC compared to those with Medicare/commercial insurance (OR, 0.40; 95% CI, 0.35-0.46; P < 0.001).

Discussion

Rates of HCC among the 1945-1965 birth cohort have increased in incidence by 58.7% over the past decade and are expected to continue growing over time.[13] Using data from the Centers for Disease Control and Prevention, the National Cancer Institute, and the North American Association of Central Cancer Registries, Ryerson et al.[2] reported that while overall U.S. cancer deaths for men and women combined declined by 1.5% per year from 2003 to 2012, liver cancer incidence rates overall increased sharply, and deaths from liver cancer increased at the highest rates of all cancer sites (mean annual percentage increase of 3.4%). The authors did not specifically evaluate trends in HCC diagnosed among the 1945-1965 birth cohort, and few studies have focused on the national burden of HCC among the 1945-1965 birth cohort. In our current study focusing specifically on the 1945-1965 birth cohort, we report concerning trends in newly diagnosed HCC, with a 5.9% annual increase from 2004 to 2014. However, it is important to note that while the Ryerson study focused on the incidence of HCC deaths, our study focused specifically on the 1945-1965 birth cohort, and our study design did not specifically allow for calculation of HCC incidence. Thus, our measurements are more reflective of changes in HCC prevalence among this group. Our observation



	2004-2006	2013-2014	Relative Percentage Increase in Proportion of Patients With SEER Localized Stage HCC: 2004-2006 to 2013-2014
Overall	49.71%	53.99%	8.61%
Male	49.07%	57.84%	17.87%
Female	52.90%	53.05%	0.28%
Non-Hispanic White	50.81%	54.71%	7.68%
African American	45.84%	47.13%	2.81%
Native American/Alaskan Native	45.21%	54.05%	19.55%
Asian/Pacific Islander	46.37%	54.79%	18.16%
Hispanic	53.38%	57.54%	7.79%

FIG. 3. Trends in the proportion of newly diagnosed HCC among the 1945-1965 birth cohort who have SEER localized-stage HCC at diagnosis.

of the increasing HCC burden among this 1945-1965 birth cohort likely also reflects the known increasing HCC incidence in the United States as well as the overall aging population of the 1945-1965 cohort, which increases the risk of disease progression to cirrhosis and HCC among those with chronic liver disease. This highlights the continued increasing burden of HCC among this cohort and emphasizes the importance of timely implementation of HCC screening and surveillance among 1945-1965 birth cohort patients at high risk of developing HCC.[13,14]

HCV remains a major driver in the increasing number of registrants and recipients for liver transplantation in the 1945-1965 birth cohort.[14–17] An estimated 3.3% of the 1945-1965 birth cohort have the HCV antibody and account for nearly 75% of all U.S. HCV infections.[18] The availability of highly effective direct-acting antivirals for the treatment of chronic HCV will likely translate into reductions in HCV-associated HCC; however, overall trends in HCC may not necessarily peak, given the emergence of nonalcoholic steatohepatitis (NASH)-related HCC.[19–21] Cholankeril et al.[13] performed a retrospective analysis using the United Network for Organ Sharing/Organ Procurement Transplant Network database from 2003 to 2014 to compare HCC-related liver transplant trends between 1945 and 1965 and non-1945-1965 birth cohorts. They reported that 80.1% of all HCC-related liver transplants were of the 1945-1965 birth cohort alone. Furthermore, among this 1945-1965 birth cohort, NASH, as an indication for liver transplant, rose 1,327% compared to a 382% rise for HCV and a 286% rise for alcoholic liver disease (ALD) over the past decade, emphasizing the burden of not only HCV-associated HCC but also NASH-associated and ALD-associated HCC among the 1945-1965 birth cohort.[13]

Overall, the percentage of new HCC diagnoses within the 1945-1965 birth cohort within Milan criteria has increased over time. Yan et al.[14] reported that only 38.7% of the 1945-1965 birth cohort were within Milan criteria at diagnosis when using SEER data recorded from 2003 to 2011. Although rates are increasing over time, it remains concerning that, even in the most recent 2013-2014 era, only 46% of

TABLE 2. HCC TUMOR STAGE AT DIAGNOSIS AMONG THE 1945-1965 BIRTH COHORT

	SEER Localized		SEER Distant			HCC Outside Milan		HCC Within Milan		
	Frequency (n)	Proportion (%)	Frequency (n)	Proportion (%)	*P* Value	Frequency (n)	Proportion (%)	Frequency (N)	Proportion (%)	*P* Value
Sex					<0.001					<0.001
Male	1,384	51.15%	4,624	17.04%		17,934	57.75%	13,120	42.25%	
Female	3,459	57.15%	911	15.05%		3,830	54.78%	3,161	45.22%	
Race/ethnicity					<0.001					<0.001
Non-Hispanic white	8,644	52.63%	2,652	16.15%		10,530	55.44%	8,465	44.56%	
African American	2,586	47.52%	1,090	20.30%		3,891	63.31%	2,255	36.69%	
Native American/Alaskan Native	213	51.33%	61	14.70%		282	58.75%	198	41.25%	
Asian/Pacific Islander	2,250	51.82%	747	17.20%		2,832	59.12%	1958	40.88%	
Hispanic	3,590	55.50%	972	15.03%		4,156	55.37%	3350	44.63%	
Primary insurance					<0.001					<0.001
Medicare/commercial	9,960	55.27%	2,652	14.72%		9,932	50.97%	9555	49.03%	
Medicaid	3,718	50.74%	1,249	17.05%		4,431	55.35%	3575	44.65%	
Uninsured	658	37.73%	460	26.38%		1,367	70.17%	581	29.83%	

TABLE 3. EVALUATING PREDICTORS OF HCC TUMOR STAGE AT DIAGNOSIS

	Predictors of HCC Within Milan Criteria at Diagnosis			Predictors of SEER Localized HCC at Diagnosis		
	Odds Ratio	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value
Male (vs. female)	0.88	0.83-0.93	<0.001	0.79	0.72-0.86	<0.001
Age	1.00	0.99-1.00	0.313	1.00	0.99-1.01	0.89
Race/ethnicity						
Non-Hispanic white	1.00	Reference	—			
African American	0.73	0.68-0.78	<0.001	0.77	0.70-0.85	<0.001
Native American/Alaskan Native	0.91	0.72-1.13	0.384	1.21	0.85-1.73	0.289
Asian/Pacific Islander	0.85	0.79-0.92	<0.001	0.96	0.86-1.07	0.434
Hispanic	1.02	0.96-1.09	0.478	1.17	1.06-1.29	0.002
Year of diagnosis						
2004-2006	1.00	Reference	—			
2007-2008	0.87	0.81-0.94	<0.001	0.86	0.77-0.95	0.005
2011-2012	1.07	1.00-1.15	0.042	1.02	0.93-1.13	0.641
2013-2014	1.12	1.05-1.20	0.001	1.07	0.97-1.19	0.162
Primary insurance						
Medicare/commercial insurance	1.00	Reference	—			
Medicaid	0.86	0.81-0.90	<0.001	0.80	0.73-0.87	<0.001
Uninsured	0.46	0.41-0.51	<0.001	0.40	0.35-0.46	<0.001

2009-2010 dropped due to collinearity.

patients with HCC overall were within Milan criteria at diagnosis. Effective screening and surveillance is critical to achieve early detection in HCC.[9,22] However, HCC screening rates among at-risk patients (such as cirrhosis) are poor, with some studies reporting less than 20% of patients with cirrhosis receiving appropriate HCC surveillance.[4,23] While the contributing factors to poor utilization of HCC surveillance are likely complex and multifactorial, suboptimal knowledge and awareness among providers and system-level barriers have been recently studied. Dalton-Fitzgerald et al.[24] conducted a web-based survey of 131 primary care providers at a large urban hospital. They reported that only 65% of providers surveyed reported annual surveillance and only 15% reported biannual surveillance for HCC in patients

with cirrhosis. Many providers believed that clinical examination (45%), levels of liver enzymes (59%), or alpha-fetoprotein alone (89%) were effective screening tools for HCC.[24,25]

In a recently published prospective study, Singal et al.[26] evaluated patients with diagnosed or suspected cirrhosis and randomly (1:1:1, n = 1,800) assigned patients to groups receiving different modalities for screening reminders. One group received mailed invitations for an ultrasound screening examination; the second had mailed invitations for an ultrasound screening exam as well as patient navigation for patients who declined (including motivational interviewing and barrier assessment); and the third received standard visit-based screening. They found that screening rates in the mailed invitation with navigation were 47.2%, mailed invitation alone 44.5%, and usual care 24.3% ($P < 0.001$ for both), with screening rates not differing significantly between each of the outreach groups ($P = 0.25$). This study highlights the potential impact of visual reminders and system navigators to improve HCC screening, particularly among underserved safety-net populations.

While insurance-specific and race/ethnicity-specific disparities in HCC tumor stage at diagnoses have been reported,[27,28] our current study emphasizes that these disparities persist even among the select group of 1945-1965 birth cohort patients. As mentioned above, these disparities likely reflect multifactorial barriers to effective HCC surveillance that span across providers, patients, and system-level factors. Our current observational study design is limited in establishing causation and can only demonstrate associations with HCC stage at diagnosis.

The current study uses a national population-based cancer registry that represents a large proportion of the U.S. population. The SEER registry allows for a comprehensive analysis of HCC epidemiology and outcomes. Despite this, the current study has several limitations that should be acknowledged. The SEER registry does not include etiology of HCC (e.g., chronic hepatitis B virus, chronic HCV, ALD, NASH), which may have affected rates of disease progression or rates of timely HCC screening and surveillance. Treatment data (e.g., antiviral therapies) were not available for inclusion in our study, and thus it was not possible to adjust for treatment in our analysis of HCC trends over time. Our study found significant disparities in disease severity among patients who were uninsured; however, this does not account for complex issues affecting this patient population, including access to care, language barriers, and socioeconomic needs, all of which may affect access or adherence to HCC screening and surveillance. Additionally, the SEER database groups Medicare and commercially insured patients into one category, and demographic and clinical differences between those with Medicare and commercial insurance could not be separately analyzed. Specific details about surveillance, such as whether surveillance imaging was ordered, appropriate intervals were followed, and patients attended appointments, were not available in the SEER registry, thus limiting our ability to evaluate this factor in affecting disease severity at the time of diagnosis. Furthermore, as mentioned above, the data collected in the SEER database are limited by what data are available and provided to the cancer registrars by the clinical providers and health and hospital systems within each network. Thus, there exists the possibility of potential errors in coding or data ascertainment as well as potential misclassification bias.

From 2004 to 2014, the burden of newly diagnosed HCC among the 1945-1965 birth cohort rose significantly at nearly 6% per year. However, the majority of HCC diagnosed among the 1945-1965 birth cohort was beyond Milan criteria. Despite advances in treatment of chronic hepatitis B virus and chronic HCV, the United States is still experiencing high HCC mortality rates due to the underutilization of HCC screening. More focus is needed on developing novel programs to improve HCC screening and surveillance among at-risk patients, including opportunities to incorporate health care technology to assist and improve providers' knowledge and awareness of timely implementation of HCC screening and surveillance.

REFERENCES

1) Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-E386.
2) Ryerson AB, Eheman CR, Altekruse SF, Ward JW, Jemal A, Sherman RL, et al. Annual Report to the Nation on the Status of Cancer, 1975-2012, featuring the increasing incidence of liver cancer. Cancer 2016;122:1312-1337.
3) Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med 2006;144:705-714.
4) Singal AG, Li X, Tiro J, Kandunoori P, Adams-Huet B, Nehra MS, et al. Racial, social, and clinical determinants of hepatocellular carcinoma surveillance. Am J Med 2015;128:e91-e97.
5) Davila JA, Henderson L, Kramer JR, Kanwal F, Richardson PA, Duan Z, et al. Utilization of surveillance for hepatocellular carcinoma among hepatitis C virus-infected veterans in the United States. Ann Intern Med 2011;154:85-93.

6) Davila JA, Kramer JR, Duan Z, Richardson PA, Tyson GL, Sada YH, et al. Referral and receipt of treatment for hepatocellular carcinoma in United States veterans: effect of patient and nonpatient factors. Hepatology 2013;57:1858-1868.
7) Davila JA, Morgan RO, Richardson PA, Du XL, McGlynn KA, El-Serag HB. Use of surveillance for hepatocellular carcinoma among patients with cirrhosis in the United States. Hepatology 2010;52:132-141.
8) Cadier B, Bulsei J, Nahon P, Seror O, Laurent A, Rosa I, et al.; ANRS CO12 CirVir and CHANGH groups. Early detection and curative treatment of hepatocellular carcinoma: a cost-effectiveness analysis in France and in the United States. Hepatology 2017;65:1237-1248.
9) van Meer S, de Man RA, Coenraad MJ, Sprengers D, van Nieuwkerk KM, Klumpen HJ, et al. Surveillance for hepatocellular carcinoma is associated with increased survival: results from a large cohort in the Netherlands. J Hepatol 2015;63:1156-1163.
10) National Cancer Institute. Surveillance Epidemiology, and End Results (SEER) Program. www.seer.cancer.gov. Published April 2017. Accessed July 1, 2017. SEER*Stat Database: Incidence - SEER 9 Regs Research Data, Nov 2016 Sub (1973-2014).
11) Adamo M, Dickie L, Ruhl J. 2014 SEER Program Coding and Staging Manual. Bethesda, MD: National Cancer Institute; May 2014.
12) Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693-699.
13) Cholankeril G, Yoo ER, Perumpail RB, Liu A, Sandhu JS, Nair S, et al. Rising rates of hepatocellular carcinoma leading to liver transplantation in baby boomer generation with chronic hepatitis C, alcohol liver disease, and nonalcoholic steatohepatitis-related liver disease. Diseases 2017;5,E20.
14) Yan M, Ha J, Aguilar M, Bhuket T, Liu B, Gish RG, et al. Birth cohort-specific disparities in hepatocellular carcinoma stage at diagnosis, treatment, and long-term survival. J Hepatol 2016;64:326-332.
15) Wong RJ, Aguilar M, Cheung R, Perumpail RB, Harrison SA, Younossi ZM, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology 2015;148:547-555.
16) Wong RJ, Cheung R, Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. Hepatology 2014;59:2188-2195.
17) Charlton MR, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. Gastroenterology 2011;141:1249-1253.
18) Smith BD, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Ward JW. Hepatitis C virus testing of persons born during 1945-1965: recommendations from the Centers for Disease Control and Prevention. Ann Intern Med 2012;157: 817-822.
19) Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology2010;138:513-521, 521.e1-e6.
20) El-Serag HB, Kanwal F. Epidemiology of hepatocellular carcinoma in the United States: where are we? Where do we go? Hepatology 2014;60:1767-1775.
21) Volk ML, Tocco R, Saini S, Lok AS. Public health impact of antiviral therapy for hepatitis C in the United States. Hepatology 2009;50:1750-1755.
22) Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. Hepatology 2002;35:519-524.
23) Beste LA, Ioannou GN, Yang Y, Chang MF, Ross D, Dominitz JA. Improved surveillance for hepatocellular carcinoma with a primary care-oriented clinical reminder. Clin Gastroenterol Hepatol 2015;13:172-179.
24) Dalton-Fitzgerald E, Tiro J, Kandunoori P, Halm EA, Yopp A, Singal AG. Practice patterns and attitudes of primary care providers and barriers to surveillance of hepatocellular carcinoma in patients with cirrhosis. Clin Gastroenterol Hepatol 2015;13:791-798.e791.
25) McGowan CE, Edwards TP, Luong MU, Hayashi PH. Suboptimal surveillance for and knowledge of hepatocellular carcinoma among primary care providers. Clin Gastroenterol Hepatol 2015;13:799-804.
26) Singal AG, Tiro JA, Marrero JA, McCallister K, Mejias C, Adamson B, et al. Mailed outreach program increases ultrasound screening of patients with cirrhosis for hepatocellular carcinoma. Gastroenterology 2017;152:608-615.e604.
27) Ha J, Yan M, Aguilar M, Tana M, Liu B, Frenette CT, et al. Race/ethnicity-specific disparities in hepatocellular carcinoma stage at diagnosis and its impact on receipt of curative therapies. J Clin Gastroenterol 2016;50:423-430.
28) Wang J, Ha J, Lopez A, Bhuket T, Liu B, Wong RJ. Medicaid and uninsured hepatocellular carcinoma patients have more advanced tumor stage and are less likely to receive treatment. J Clin Gastroenterol 2018;52:437-443.