Disparities in Liver Cancer Occurrence in the United States by Race/Ethnicity and State

Farhad Islami, MD, PhD[1]; Kimberly D. Miller, MPH[2]; Rebecca L. Siegel, MPH[3]; Stacey A. Fedewa, PhD, MPH[4]; Elizabeth M. Ward, PhD[5]; Ahmedin Jemal, DVM, PhD[6]

[1]Strategic Director, Cancer Surveillance Research, Surveillance and Health Services Research, American Cancer Society, Atlanta, GA; [2]Epidemiologist, Surveillance and Health Services Research, American Cancer Society, Atlanta, GA; [3]Strategic Director, Surveillance Information Services, Surveillance and Health Services Research, American Cancer Society, Atlanta, GA; [4]Strategic Director, Risk Factors and Screening Surveillance, Surveillance and Health Services Research, American Cancer Society, Atlanta, GA; [5]Senior Vice President, Intramural Research, American Cancer Society, Atlanta, GA; [6]Vice President, Surveillance and Health Services Research, American Cancer Society, Atlanta, GA.

Corresponding author: Farhad Islami, MD, PhD, Strategic Director, Cancer Surveillance Research, American Cancer Society, 250 Williams Street, Atlanta, GA 30303; farhad.islami@cancer.org

The first 2 authors contributed equally to this article.

DISCLOSURES: The authors report no conflicts of interest.

doi: 10.3322/caac.21402. Available online at cacancerjournal.com

Abstract: Liver cancer is highly fatal, and death rates in the United States are increasing faster than for any other cancer, having doubled since the mid-1980s. In 2017, it is estimated that the disease will account for about 41,000 new cancer cases and 29,000 cancer deaths in the United States. In this article, data from the Surveillance, Epidemiology, and End Results (SEER) Program and the National Center for Health Statistics are used to provide an overview of liver cancer incidence, mortality, and survival rates and trends, including data by race/ethnicity and state. The prevalence of major risk factors for liver cancer is also reported based on national survey data from the Centers for Disease Control and Prevention. Despite the improvement in liver cancer survival in recent decades, only 1 in 5 patients survives 5 years after diagnosis. There is substantial disparity in liver cancer death rates by race/ethnicity (from 5.5 per 100,000 in non-Hispanic whites to 11.9 per 100,000 in American Indians/Alaska Natives) and state (from 3.8 per 100,000 in North Dakota to 9.6 per 100,000 in the District of Columbia) and by race/ethnicity within states. Differences in risk factor prevalence account for much of the observed variation in liver cancer rates. Thus, in contrast to the growing burden, a substantial proportion of liver cancer deaths could be averted, and existing disparities could be dramatically reduced, through the targeted application of existing knowledge in prevention, early detection, and treatment, including improvements in vaccination against hepatitis B virus, screening and treatment for chronic hepatitis C virus infections, maintaining a healthy body weight, access to high-quality diabetes care, preventing excessive alcohol drinking, and tobacco control, at both the state and national levels. **CA Cancer J Clin 2017;000:000-000. © 2017 American Cancer Society.**

Keywords: cancer stage, death rates, incidence, liver cancer, mortality, surveillance, survival, United States

Introduction

Liver and intrahepatic bile duct cancer (hereafter *liver cancer*) is the fifth and eighth leading cause of cancer death in men and women, respectively, accounting for approximately 41,000 cancer cases and 29,000 deaths in the United States in 2017.[1] Liver cancer death rates are increasing at a faster pace than any other cancer.[2,3] An average 19 years of life are lost per death because of a relatively young median age at diagnosis (63 years) and a high fatality rate.[2] Liver cancer incidence has been rising in the United States since at least the mid-1970s,[2,4] a trend that is projected to continue through at least 2030.[5] A major factor contributing to this increase is the comparatively high prevalence of hepatitis C virus (HCV) infection among those born during 1945 through 1965, also called "baby boomers."[2,6] The sustained rise in obesity and type II diabetes over the past several decades has also likely contributed to the increasing liver cancer trend.[7]

The incidence of liver cancer varies by race/ethnicity and state, mainly because of differences in the prevalence of major risk factors and, to some degree, because of disparities in access to high-quality care.[1,2,8] However, there is limited information on contemporary liver cancer mortality and survival rates in the United States,

particularly by race/ethnicity. Recently, the *Annual Report to the Nation on the Status of Cancer* series (hereafter the *Annual Report*) featured liver cancer incidence rates and trends but provided limited information on mortality.[2,3] A small number of other studies that examined liver cancer mortality and/or survival in the United States did not report death rates by either state[9,10] or race/ethnicity.[3,11]

In this report, we examine trends in liver cancer incidence, survival, and mortality in the United States and provide contemporary state-level death rates for 5 broad racial and ethnic groups. State-level statistics are particularly important, as they can inform state cancer-control planning, early detection, and prevention efforts. By using data from a population-based subset of the United States, we also describe disparities in survival rates and trends by race/ethnicity and stage. Prevalence and trends in major risk factors for liver cancer, as well as interventions to prevent or mitigate their burden, are also reviewed in detail.

Materials and Methods

US mortality data from 1990 through 2014 were obtained from the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC), as provided through the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program.[12] These data were the source for long-term death rate trends and cross-sectional 5-year rates.

Initially, we used long-term survival data (1975-2012) from the 9 oldest SEER registries (Connecticut, Hawaii, Iowa, New Mexico, and Utah, and the metropolitan areas of Atlanta, Detroit, San-Francisco/Oakland, and Seattle-Puget Sound [SEER 9]) to examine relative survival trends by stage at diagnosis and by race (white, black, and other races combined). However, because there was no substantial change in relative survival for any stage or race in the 1970s and 1980s (data not shown), we used data from SEER 13 (the SEER 9 registries plus rural Georgia, the Alaska Native Tumor Registry, and the metropolitan areas of Los Angeles and San Jose/Monterey) to examine trends in cause-specific survival (hereafter *cancer-specific* survival) from 1992 to 2012 by race/ethnicity.[13] Data from all 18 SEER registries (SEER 13 plus Louisiana, Kentucky, New Jersey, and the remainder of California and Georgia [SEER 18]) provide coverage for 28% of the US population and were used to calculate contemporary (2006-2012) stage distribution and 5-year cancer-specific survival.

Population-based liver cancer incidence data were also obtained to provide additional context for the select mortality statistics presented herein. The North American Association of Central Cancer Registries, which compiles data from registries participating in SEER and/or the CDC's National Program of Cancer Registries, was the source for 5-year incidence rates (2009-2013),[14] while the SEER 13 registries were the source for long-term incidence trends (1992-2013).[13]

Liver cancer cases and deaths were classified according to the *International Classification of Diseases for Oncology, third edition*, and the *International Classification of Diseases, 10th revision* (codes C22.0-C22.1), respectively.[15,16] Age-adjusted rates per 100,000 were calculated using SEER*Stat software, version 8.3.2.0.[17] SEER 13 incidence rates were adjusted for reporting delays using registry-specific factors available in SEER*Stat, with the exception of rates for American Indians/Alaska Natives (AIs/ANs), which were adjusted using combined US registry delay factors provided by the National Cancer Institute.[3] Delay adjustment, which has the greatest impact on the most recent data years, accounts for future corrections to currently available cancer incidence data, thus providing a more accurate depiction of contemporary incidence trends.[18] Joinpoint regression analysis was used to model and quantify trends in the observed death rates overall and by race/ethnicity.[19] Trends in incidence and death rates by race/ethnicity are shown with smoothed lines, which were fitted using locally weighted regression curves (the LOWESS command in Stata software, version 13),[20] in which 30% of the data were used in the smoothing.

The broad racial groups used throughout our analysis of cancer occurrence exclude Hispanic ethnicity for whites (hereafter *non-Hispanic [NH] whites*), blacks, Asian/Pacific Islanders (APIs), and AIs/ANs. Long-term death rate trends (1990-2014) by race/ethnicity exclude deaths from Louisiana, New Hampshire, and Oklahoma, because these states did not report data on Hispanic ethnicity for one or more years during the study period. To avoid underascertainment of AI/AN ethnicity in areas with a low percentage AI/AN population, results for AIs/ANs are based on data from Contract Health Service Delivery Area (CHSDA) counties.

Several notable, recent studies have used cross-sectional, nationally representative survey data to describe trends in and the current prevalence of major liver cancer risk factors. As such, these studies are summarized herein in lieu of replicating previous analyses. In brief, we included in our review studies that analyzed the CDC's National Health and Nutrition Examination Survey (NHANES) for prevalence estimates of obesity,[21] hepatitis B virus (HBV) and HCV infection,[6,22] diabetes,[23] and nonalcoholic fatty liver disease.[24] NHANES' estimates for several health-related factors are based on direct measurements gathered during in-person examinations and thus are less susceptible to bias from self-report. State-level estimates of obesity and alcohol intake were obtained from analyses of the Behavioral Risk Factor Surveillance System, a computer-assisted telephone

TABLE 1. Liver and Intrahepatic Bile Duct Cancer Average Annual Incidence and Death Rates and 5-Year Cancer-Specific Survival Ratios (95% CIs) in the United States by Sex and Race/Ethnicity*

	INCIDENCE RATE PER 100,000, 2009 TO 2013			DEATH RATE PER 100,000, 2010 TO 2014			5-YEAR SURVIVAL (%), 2006 TO 2012		
RACE/ ETHNICITY	ALL	MEN	WOMEN	ALL	MEN	WOMEN	ALL	MEN	WOMEN
All	7.7 (7.6-7.7)	11.8 (11.8-11.9)	4.0 (4.0-4.1)	6.3 (6.2-6.3)	9.2 (9.2-9.3)	3.7 (3.7-3.8)	21.0 (20.5-21.5)	20.9 (20.3-21.5)	21.3 (20.3-22.3)
NH white	6.3 (6.2-6.3)	9.7 (9.6-9.8)	3.3 (3.2-3.3)	5.5 (5.4-5.5)	8.0 (7.9-8.1)	3.3 (3.2-3.3)	20.1 (19.4-20.8)	20.2 (19.4-21.1)	19.8 (18.5-21.1)
Black	10.2 (10.0-10.3)†	16.8 (16.5-17.1)†	5.0 (4.8-5.1)†	8.4 (8.2-8.5)†	13.3 (13.0-13.6)†	4.6 (4.5-4.8)†	16.3 (15.0-17.7)†	15.5 (13.9-17.1)†	18.8 (15.9-21.8)
AI/AN	15.2 (14.2-16.3)†	21.3 (19.5-23.3)†	10.0 (8.8-11.2)†	11.9 (11.0-12.8)†	16.9 (15.3-18.6)†	7.8 (6.8-8.8)†	16.2 (12.0-20.9)	17.0 (12.1-22.7)	13.4 (6.2-23.5)
API	13.5 (13.3-13.8)†	20.8 (20.3-21.3)†	7.7 (7.4-8.0)†	9.8 (9.6-10.1)†	14.4 (14.0-14.8)†	6.2 (5.9-6.4)†	27.1 (25.8-28.5)†	27.2 (25.6-28.8)†	27.0 (24.7-29.5)†
Hispanic	13.0 (12.8-13.2)†	19.5 (19.2-19.9)†	7.5 (7.3-7.7)†	9.1 (8.9-9.2)†	13.1 (12.8-13.3)†	5.8 (5.6-5.9)†	20.7 (19.6-21.9)	20.5 (19.1-21.9)	21.5 (19.3-23.7)

95% CI indicates 95% confidence interval; AI/AN, American Indian/Alaska Native; API, Asian and Pacific Islander; NH, non-Hispanic.

*Incidence and death rates are age-adjusted to the 2000 US standard population. Five-year cancer-specific survival ratios are based on cases diagnosed from 2006 to 2012; all were followed through 2013.

†The *P* value for the difference between the individual racial/ethnic groups and NH whites (reference group) was $< .05$.

Sources: Incidence: North American Association of Central Cancer Registries, 2016. Survival: Surveillance, Epidemiology, and End Results (SEER) Program, SEER 18 registries, 2016. Mortality: National Center for Health Statistics, Centers for Disease Control and Prevention, 2016.

survey of adults 18 years and older. Additional studies we reviewed used data from the CDC's National Health Interview Survey (self-reported cigarette smoking prevalence)[25] and the Substance Abuse and Mental Health Services Administration's National Survey on Drug Use and Health (self-reported binge drinking among adults ages 50 years and older).[26]

Cancer Occurrence

National Level

Incidence and mortality

Average annual liver cancer incidence (2009-2013) and death (2010-2014) rates for the most recent 5 years of available data in the United States were 7.7 and 6.3 per 100,000, respectively. Both incidence and death rates were notably 2- to 3-fold higher in men than in women for each of the 5 major racial/ethnic groups (Table 1). Liver cancer incidence and death rates were highest for AIs/ANs (15.2 and 11.9 per 100,000, respectively) and were more than double those in NH whites (6.3 and 5.5 per 100,000, respectively), among whom the rates were lowest. Death rates increased with age up to ages 80 to 84 years in all racial/ethnic groups except blacks, among whom mortality peaked at ages 60 to 64 years (Fig. 1).

Liver cancer incidence and mortality patterns are similar, with rates overall increasing since at least 1975 for incidence and since 1980 for mortality.[4] Data by ethnicity are only available since 1992 for incidence (Fig. 2) and since 1990 for mortality (Fig. 3). From 1990 to 2014, death rates rose by 57% in blacks, 69% in Hispanics, and 82% in NH whites; in AIs/ANs, the death rate more than doubled, from 5.4 (per 100,000) to 11.9. In stark contrast, death rates declined slightly in APIs, from 10.8 (per 100,000) in 1990 to 9.6 in 2014. As a result of this divergent trend, a crossover between APIs and AIs/ANs occurred, in that death rates in AIs/ANs were about 40% lower than those in APIs in 1990 but were 10% higher in 2014 (Fig. 3). In all racial/ethnic groups, changes in liver cancer death rates were in the same direction among men and women (Table 2).

Overall, our findings confirm and expand upon results on liver cancer occurrence from the *Annual Report* series and other published results.[2,3,11,27] Despite rising death rates, however, liver cancer incidence rates in AIs/ANs did not show any increase after 2009 in our analysis. This is likely because AI/AN mortality data in our analysis were from CHSDA counties nationwide, whereas incidence trends were based only on cases from CHSDA counties in areas

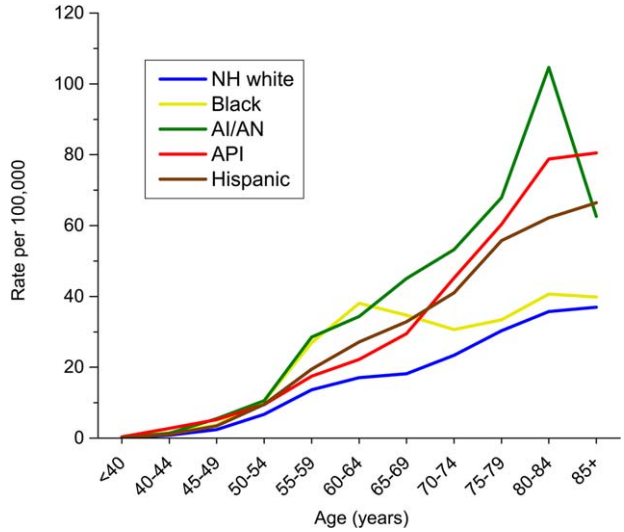

FIGURE 1. Liver and Intrahepatic Bile Duct Cancer Age-Specific Death Rates in the United States by Race/Ethnicity, Both Sexes Combined, 2010 to 2014.

AI/AN indicates American Indian/Alaska Native; API, Asian and Pacific Islander; NH, non-Hispanic. Rates for AIs/ANs are based on data from Contract Health Service Delivery Area counties.

Source: National Center for Health Statistics, Centers for Disease Control and Prevention, 2016.

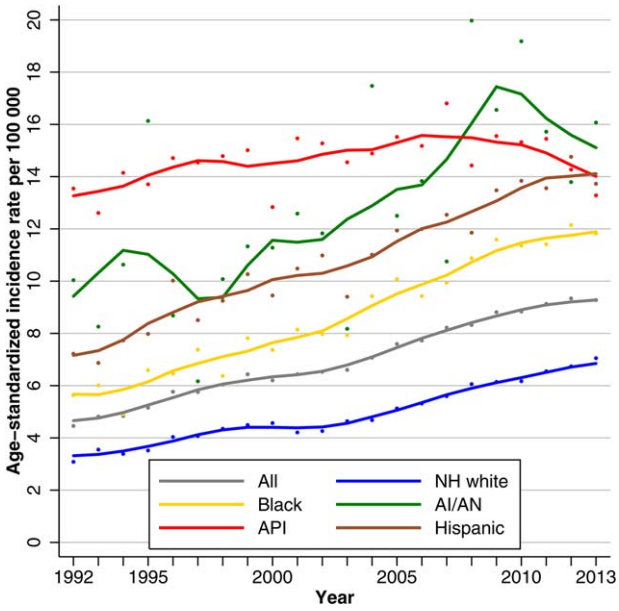

FIGURE 2. Trends in Liver and Intrahepatic Bile Duct Cancer Incidence Rates in the United States by Race/Ethnicity, Both Sexes Combined, 1992 to 2013.

AI/AN indicates American Indian/Alaska Native; API, Asian and Pacific Islander; NH, non-Hispanic. Rates are age-adjusted to the 2000 US standard population. Trends for AIs/ANs are based on data from Contract Health Service Delivery Area counties.

Source: Surveillance, Epidemiology, and End Results (SEER) Program, SEER 18 registries, 2016.

covered by SEER 13. Indeed, the *Annual Report*, which used nationwide CHSDA incidence data, reported a statistically significant, continuous increase in liver cancer incidence among AI/AN men from 2003 to 2012,[2] consistent with death rate trends in our analysis.

Stage distribution and survival

Figure 4 shows liver cancer stage distribution by race/ethnicity. The proportion of liver cancers diagnosed at the localized stage ranged from 40% in AIs/ANs to 45% in APIs (approximately 15% of cases were unknown stage). The 5-year liver cancer-specific survival rate was 21% overall for patients diagnosed during 2006 through 2012, ranging from 4% for distant stage disease to 37% for localized disease (Fig. 5). There was little difference in 5-year survival between men and women. Compared with NH whites (20%), survival was statistically significantly lower in blacks (16%) and higher in APIs (27%) (Table 1). Absolute differences in stage-specific survival by race/ethnicity were largest for localized disease, for which survival was highest in APIs (46%) and lowest in blacks (30%) and AIs/ANs (28%) (Fig. 5). Notably, although there was little difference in stage distribution between NH whites and blacks, the 5-year survival rate in blacks was approximately 5% lower for all stages combined (Table 1).

The 5-year survival rate for liver cancer has been increasing since at least 1992 in all races except for AIs/ANs, in whom the trend is inconsistent, in part because of sparse data (Fig. 6). Compared with NH whites, 5-year survival has increased more rapidly in APIs and has lagged in blacks, whereas trends in Hispanics have been similar. By stage, the most significant increase occurred for localized disease, for which the 5-year survival rate increased from 17% for patients diagnosed in the early 1990s to 39% for those diagnosed during 2006 through 2012 in the SEER 13 areas (Fig. 6). A more modest increase in survival was observed for regional-stage liver cancers, which rose from 8% to 14% over the same period. No improvement has been observed for distant-stage disease.

Consistent with our results, earlier studies found a lower 5-year survival rate in blacks than in whites[27] and an increase in 5-year relative survival in all races combined and in studied races (whites, blacks), largely limited to localized-stage and regional-stage liver cancer.[3]

State-Level Mortality

Similar to national patterns, liver cancer death rates in most states were 2- to 3-fold higher in men than in women (Table 3). Racial/ethnic disparities in liver cancer mortality were present in most states, including those with relatively less poverty and low liver cancer death rates, in which low rates among whites masked markedly higher rates among racial/ethnic minority groups (eg, Minnesota and Utah). Among states with available data, liver cancer death rates

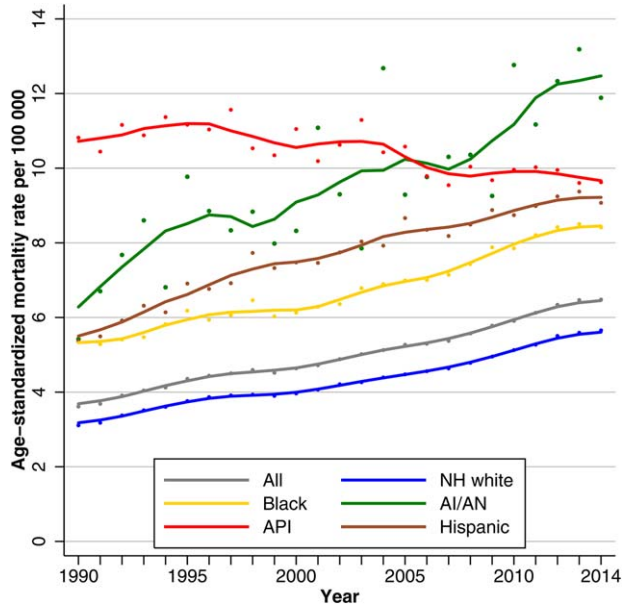

FIGURE 3. Trends in Liver and Intrahepatic Bile Duct Cancer Death Rates in the United States by Race/Ethnicity, Both Sexes Combined, 1990 to 2014.

AI/AN indicates American Indian/Alaska Native; API, Asian and Pacific Islander; NH, non-Hispanic. Rates are age-adjusted to the 2000 US standard population. Trends for AIs/ANs are based on data from Contract Health Service Delivery Area counties.

Source: National Center for Health Statistics, Centers for Disease Control and Prevention, 2016.

TABLE 2. Liver and Intrahepatic Bile Duct Cancer Mortality Trends* by Race/Ethnicity, 1990 to 2014

	TREND 1		TREND 2		TREND 3		TREND 4		TREND 5		2010 TO 2014 AAPC (95% CI)	2010 TO 2014 AVG ANNUAL DEATHS
	YEARS	APC	YEARS	APC	YEARS	APC	YEARS	APC	YEARS	APC		
All												
Both sexes	1990-1996	3.7†	1996-1999	0.6	1999-2008	2.2†	2008-2012	3.3†	2012-2014	1.2	2.3 (1.1-3.4)	22,723
Male	1990-1996	3.7†	1996-1999	0.5	1999-2014	2.6†					2.6 (2.4-2.8)	15,354
Female	1990-1995	3.7†	1995-2001	0.4	2001-2004	2.7	2004-2008	0.7	2008-2014	3.1†	3.1 (2.6-3.5)	7,369
NH white												
Both sexes	1990-1996	3.9†	1996-1999	0.1	1999-2008	2.2†	2008-2012	3.6†	2012-2014	1.5	2.5 (1.7-3.4)	15,123
Male	1990-1996	3.8†	1996-1999	0.5	1999-2007	2.3†	2007-2012	3.4†	2012-2014	1.1	2.3 (1.1-3.5)	10,156
Female	1990-1996	3.3†	1996-2001	−0.6	2001-2014	2.2†					2.2 (1.9-2.6)	4,967
Black												
Both sexes	1990-2014	2.1†									2.1 (1.9-2.2)	3,140
Male	1990-2014	2.4†									2.4 (2.1-2.6)	2,207
Female	1990-2014	1.2†									1.2 (0.9-1.5)	933
AI/AN												
Both sexes	1990-2014	2.3†									2.3 (1.6-3.1)	150
Male	1990-2014	2.7†									2.7 (1.7-3.7)	99
Female	1990-2014	1.7†									1.7 (0.3-3.0)	51
API												
Both sexes	1990-2014	−0.7†									−0.7 (−0.9-−0.5)	1,469
Male	1990-2014	−0.7†									−0.7 (−1.0-−0.5)	975
Female	1990-2014	−0.4									−0.4 (−0.9-0.0)	493
Hispanic												
Both sexes	1990-1998	3.9†	1998-2014	1.5†							1.5 (1.2-1.8)	2,739
Male	1990-1995	6.1†	1995-2014	1.6†							1.6 (1.3-1.9)	1,843
Female	1990-1998	3.4†	1998-2014	1.3†							1.3 (0.9-1.6)	896

95% CI indicates 95% confidence interval; AAPC, average annual percent change; AI/AN, American Indian/Alaska Native; APC, annual percent change; API, Asian and Pacific Islander; AVG, average; NH, non-Hispanic.

*APCs were based on trends from 1990 through 2014 and were calculated using Joinpoint regression (version 4.3.1.0), allowing up to 4 joinpoints.

†The APC is significantly different from zero ($P < .05$).

Source: National Center for Health Statistics, Centers for Disease Control and Prevention, 2016.

were statistically significantly higher in black men than in NH white men in all states except Mississippi, New Mexico, Arkansas, and South Carolina. The black-white racial disparity was the highest in the District of Columbia, in which the black rate for both sexes combined (13.3 per 100,000) was more than 4 times higher than that for NH whites (3.2 per 100,000). Liver cancer death rates were generally higher in APIs than in NH whites across states, although in some states with fewer liver cancer deaths among APIs, the difference was not statistically significant. Disparity patterns for Hispanics were less consistent than those for other minority groups, in that liver cancer death rates were higher than in NH whites in only about one-half of states with available data.

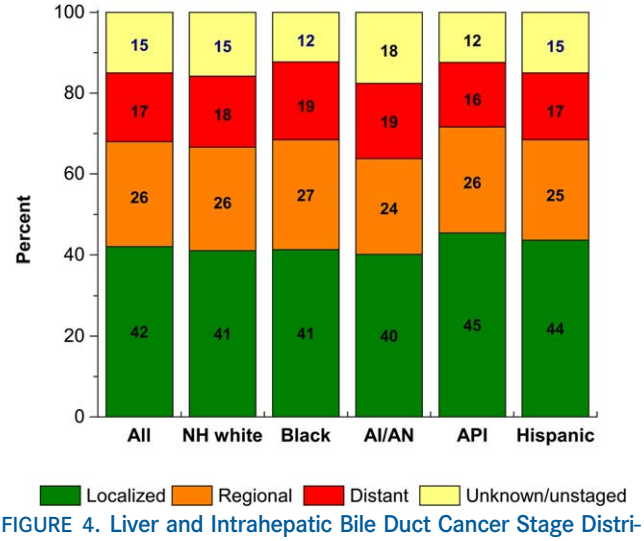

FIGURE 4. Liver and Intrahepatic Bile Duct Cancer Stage Distribution (%) in the United States by Race/Ethnicity, 2006 to 2012.
AI/AN indicates American Indian/Alaska Native; API, Asian and Pacific Islander; NH, non-Hispanic. For AIs/ANs, stage distribution is based on patients diagnosed in Contract Health Service Delivery Area counties.
Source: Surveillance, Epidemiology, and End Results (SEER) Program, SEER 18 registries, 2016.

The liver cancer death rate in both sexes combined during 2010 through 2014 was highest (≥8 per 100,000) in the District of Columbia, Hawaii, Louisiana, and Texas and lowest (<5 per 100,000) in Iowa, Montana, South Dakota, Nebraska, Utah, Vermont, and North Dakota (Fig. 7). Consistent with a lower liver cancer death rate in NH whites, the death rate was generally higher in states with a lower proportion of NH whites. Among states with comparable proportions of NH whites, those with higher poverty levels tended to have higher liver cancer death rates. For example, the rate was higher in Kentucky (6.1 per 100,000; population, 87% NH whites) than in North Dakota (3.8 per 100,000; 89% NH whites).

The geographic patterns of incidence described in the *Annual Report* were generally comparable to the mortality

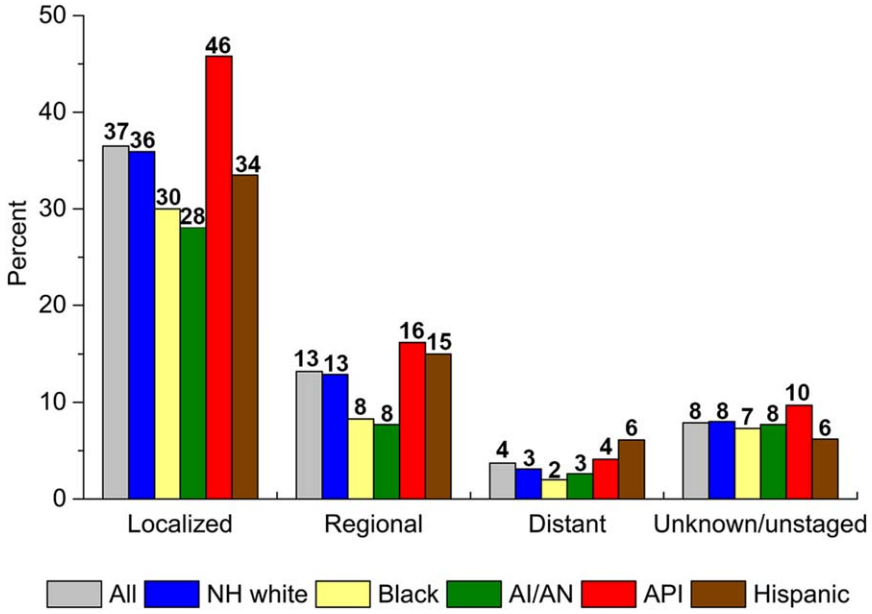

FIGURE 5. Liver and Intrahepatic Bile Duct Cancer 5-Year Cancer-Specific Survival (%) in the United States by Race/Ethnicity, Both Sexes Combined, 2006 to 2012.

AI/AN indicates American Indian/Alaska Native; API, Asian and Pacific Islander; NH, non-Hispanic. Survival is for patients diagnosed from 2006 to 2012; all were followed through 2013. For AIs/ANs, survival is based on patients diagnosed in Contract Health Service Delivery Area counties.
Source: Surveillance, Epidemiology, and End Results (SEER) Program, SEER 18 registries, 2016.

patterns in our study, with some differences. For example, in the *Annual Report*, Alabama and Louisiana ranked among the second and third quartile of states, respectively, in terms of liver cancer incidence rates[2] but were among the 10 states with highest liver cancer death rates in our analysis. These differences may be related to variation in access to care across states.

Risk Factors

Current Status and Trends

The majority (approximately 60%) of liver cancers in the United States are attributed to potentially modifiable risk factors, although these proportions vary somewhat because of differences in data sources, study periods, and methodology.[28–30] Makarova-Rusher et al estimated that, among US Medicare recipients during 2000 through 2011, metabolic disorders (including excess body weight, diabetes, impaired glucose tolerance, nonalcoholic fatty liver disease, and metabolic syndrome) accounted for the largest proportion of hepatocellular carcinomas (HCCs) (32%), followed by chronic HCV infection (21%), excessive alcohol drinking (13%), smoking (9%), and chronic HBV infection (4%).[28] HCC is the major histologic type of primary liver cancer, accounting for greater than 70% of all liver cancers in the

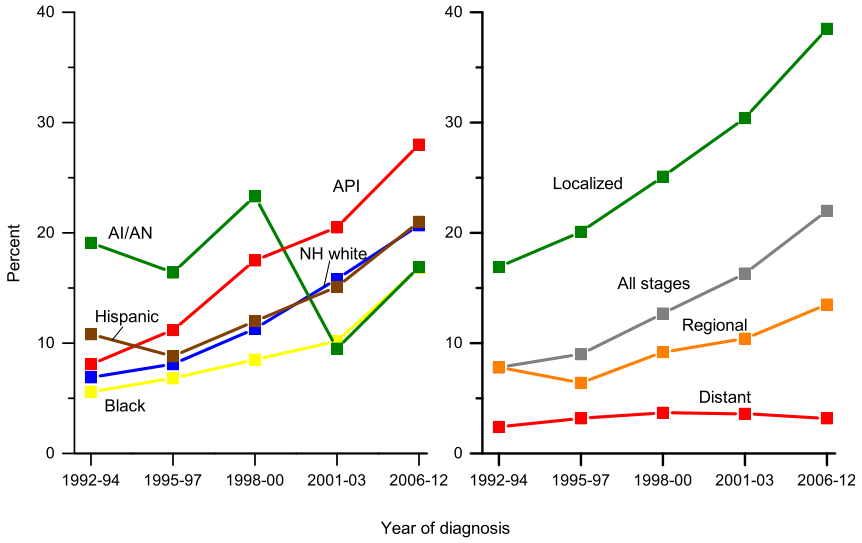

FIGURE 6. Trends in Liver and Intrahepatic Bile Duct Cancer 5-Year Cancer-Specific Survival (%) in the United States by Race/Ethnicity or Cancer Stage, Both Sexes Combined, 1992 to 2012.

AI/AN indicates American Indian/Alaska Native, API, Asian and Pacific Islander; NH, non-Hispanic. All patients were followed through 2013. Survival for AIs/ANs is based on patients diagnosed in Contract Health Service Delivery Area counties.
Source: Surveillance, Epidemiology, and End Results (SEER) Program, SEER 13 registries, 2016.

TABLE 3. Liver and Intrahepatic Bile Duct Cancer Death Rates in the United States by State, Sex, and Race/Ethnicity, 2010 to 2014*

	MEN						WOMEN					
STATE	ALL	NH WHITE	BLACK	AI/AN	API	HISPANIC	ALL	NH WHITE	BLACK	AI/AN	API	HISPANIC
District of Columbia	15.3	4.3	22.9†	–	–	–	5.2	2.1	6.6†	–	–	–
Hawaii	12.0	10.4	–	–	12.0	22.3†	5.0	3.2	–	–	5.5†	–
Louisiana	12.3	10.6	16.6†	–	21.7†	8.2	4.6	4.1	5.9†	–	–	3.8
Texas	11.8	9.3	16.8†	–	15.3†	16.5†	4.7	3.5	5.2†	–	6.6†	7.7†
California	11.0	8.4	14.0†	16.4†	16.0†	14.2†	4.6	3.3	5.4†	8.3†	6.7†	6.4†
Mississippi	10.8	10.9	10.3	–	–	–	4.6	4.4	4.6	–	24.3†	–
New Mexico	10.3	5.5	11.2	11.1†	24.5†	17.5†	4.2	2.9	–	7.6†	–	5.9†
Rhode Island	11.1	10.1	20.9†	–	24.7†	17.7†	3.4	3.2	–	–	–	–
Alabama	9.6	9.1	11.8†	–	–	–	4.0	3.9	4.4	–	–	–
Arkansas	9.9	9.7	10.9	–	24.3†	7.2	3.8	3.5	5.5†	–	11.9†	–
Delaware	10.0	9.1	14.0†	–	–	12.9	3.7	3.3	6.3†	–	–	–
Washington	9.5	8.4	16.5†	27.3†	17.4†	10.5	4.0	3.6	6.9†	4.7	8.2†	5.6†
Alaska	9.2	7.7	–	12.4	17.0†	–	3.7	3.1	–	–	–	–
Maryland	9.9	8.3	13.8†	–	14.1†	6.6	3.8	3.3	4.6†	–	5.5†	3.3
Massachusetts	10.1	9.1	14.0†	–	22.1†	12.9†	3.6	3.4	3.8	–	6.7†	4.7
Tennessee	9.8	9.1	14.9†	–	17.9†	6.6	3.7	3.4	5.8†	–	–	–
Oregon	9.3	8.5	26.1†	10.6	19.8†	13.4†	3.7	3.5	–	–	8.1†	3.8
Arizona	8.8	7.1	13.0†	17.2†	14.8†	13.8†	3.9	3.3	4.2†	10.6†	4.9	6.3†
Illinois	8.7	7.5	12.6†	–	12.3†	13.2†	3.9	3.5	4.8†	–	4.5	6.7†
Kentucky	8.8	8.5	12.1†	–	–	10.0	3.8	3.7	4.4	–	–	–
Missouri	9.2	8.3	18.2†	–	13.3	9.4	3.6	3.3	5.6†	–	9.1†	–
New York	9.1	7.3	12.5†	27.2†	13.3†	12.6†	3.6	3.0	4.4†	–	5.2†	5.3†
Georgia	9.0	8.3	11.5†	–	12.7†	5.1†	3.6	3.4	4.0†	–	4.8	3.3
North Carolina	9.2	8.6	11.4†	–	11.6	6.6	3.3	3.1	3.8†	–	3.9	4.6
Oklahoma	8.9	8.2	12.4†	15.5†	9.3	7.9	3.6	3.4	3.6	6.0†	9.4†	3.9
Florida	8.8	8.7	9.7†	–	8.5	9.0	3.4	3.2	3.5	–	5.8†	3.9†
Pennsylvania	8.7	7.6	18.1†	–	14.1†	13.4†	3.5	3.2	5.5†	–	6.7†	5.2†
South Carolina	9.1	8.9	9.4	–	–	7.3	3.3	3.1	3.6	–	12.4†	–
Michigan	8.4	7.2	16.1†	22.4†	10.7†	13.4†	3.6	3.4	4.8†	–	5.9†	4.0
New Jersey	8.7	8.3	11.2†	–	8.9	8.9	3.4	3.2	3.9	–	3.9	4.0
Nevada	7.7	7.5	11.5†	–	8.7	7.1	3.8	3.6	5.0	–	3.9	4.1
Connecticut	8.7	7.8	13.5†	–	11.9	14.4†	3.2	2.8	4.8†	–	6.6†	4.2†
Indiana	8.1	7.6	14.6†	–	15.3†	10.7	3.5	3.3	5.3†	–	6.1	5.9†
Ohio	8.3	7.6	13.4†	–	11.1	11.2†	3.4	3.2	4.9†	–	3.8	3.4
Virginia	8.4	7.3	11.2†	–	13.7†	10.5†	3.3	2.9	4.1†	–	6.3†	5.8†
West Virginia	8.0	7.8	17.7†	–	–	–	3.3	3.2	–	–	–	–
Wisconsin	7.7	7.0	16.7†	32.2†	16.3†	15.7†	3.5	3.3	4.9†	15.1†	9.5†	3.3
Kansas	7.6	7.1	12.4†	–	19.2†	9.3	3.5	3.2	6.5†	–	–	6.0†
Colorado	7.5	6.1	11.2†	–	13.9†	15.5†	3.2	2.8	2.9	–	4.4	6.0†
Maine	7.4	7.2	–	–	–	–	3.4	3.4	–	–	–	–
Minnesota	7.2	6.3	24.3†	16.4†	23.2†	9.6	3.2	2.8	8.5†	–	10.4†	4.6
Wyoming	6.7	6.3	–	–	–	–	3.6	3.2	–	–	–	–
Idaho	7.0	6.4	–	–	–	18.0†	3.2	2.9	–	–	–	–
New Hampshire	7.9	7.9	–	–	–	–	2.4	2.3	–	–	–	–
Iowa	7.1	6.7	19.2†	–	30.0†	9.9	2.9	2.9	–	–	–	–
Montana	6.7	6.3	–	21.8†	–	–	3.2	3.0	–	–	–	–
South Dakota	6.5	5.8	–	19.3†	–	–	3.5	3.1	–	11.1†	–	–
Nebraska	7.1	6.5	12.6†	–	24.2†	10.2	3.0	2.8	–	–	–	–
Utah	6.2	5.3	18.7†	–	17.7†	12.2†	3.4	3.1	–	–	8.5†	6.1†
Vermont	7.0	7.0	–	–	–	–	2.3	2.3	–	–	–	–
North Dakota	5.5	5.2	–	–	–	–	2.2	2.1	–	–	–	–

AI/AN indicates American Indian/Alaska Native; API, Asian and Pacific Islander; NH, non-Hispanic.

*States are shown in descending order based on the overall rate (Fig. 7). Rates are per 100,000 and are age-adjusted to the 2000 US standard population. Data for AI/ANs are based on data from Contract Health Service Delivery Area counties. A dash (–) indicates that the rate is not shown because there were less than 10 deaths.

†The liver cancer death rate is statistically significantly different from the rate in NH whites: the 95% confidence interval for the rate ratio (vs NH whites) does not include unity (rate ratios are not shown).

Source: National Center for Health Statistics, Centers for Disease Control and Prevention, 2016.

United States.[11] However, another recent study indicated that 24% of all liver cancer deaths in adults ages 35 years and older in 2011 were caused by smoking.[30] Although the magnitude of association between HBV/HCV infection and HCC is much greater (relative risk [RR], 22-60) than that of excessive alcohol drinking (RR, 7.3), metabolic

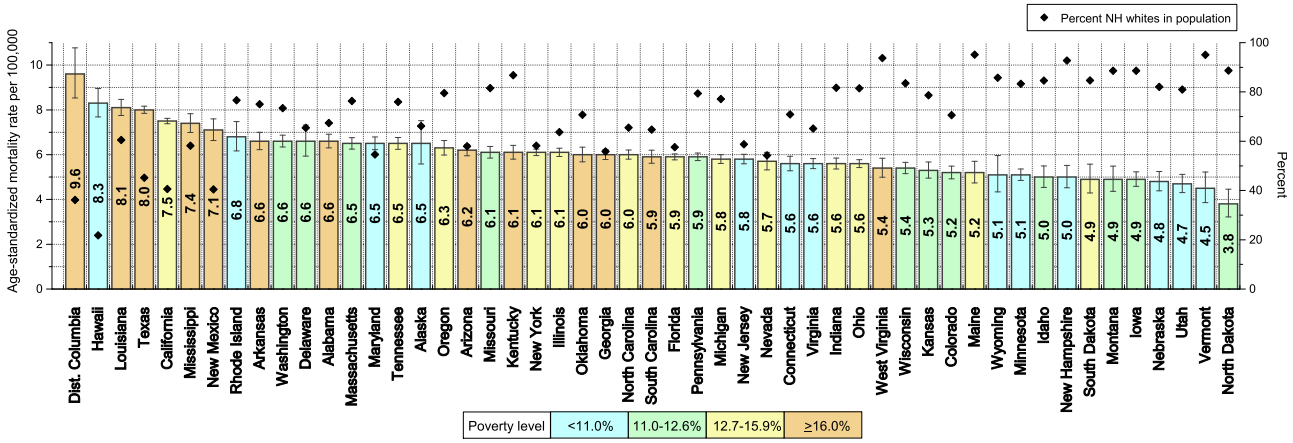

FIGURE 7. Liver and Intrahepatic Bile Duct Cancer Death Rates in the United States by State, 2010 to 2014, and Poverty Level and Proportion of Non-Hispanic Whites in the Population.

Rates are for both sexes and all races/ethnicities combined and are age-adjusted to the 2000 US standard population. The numbers inside bars represent liver cancer death rates. Bar colors represent categories of poverty level during 2013 through 2015. Poverty thresholds, as defined by the US Census Bureau, are available online (census.gov/data/tables/time-series/demo/income-poverty/historical-poverty-thresholds.html). The proportions of non-Hispanic (NH) whites in the population during 2010 through 2014 were based on US Census Bureau 2015 vintage population estimates available through the Surveillance, Epidemiology, and End Results (SEER) Program.

disorders (RR, 3.8),[28] or smoking (RR, 1.5),[31] these factors account for a substantial number of HCCs in the United States because of their higher population prevalence. Rare genetic disorders account for only 2% to 3% of HCCs.[28,29]

Differences in risk factor prevalence accounts for much of the variation in liver cancer rates by sex, age group, state, and race/ethnicity. For example, higher liver cancer death rates in Texan Hispanics (predominantly of Mexican origin) than in Floridian Hispanics (mostly of Cuban or Puerto Rican origin) may reflect higher prevalence of chronic HCV infection, excess body weight, and nonalcoholic fatty liver disease in Mexican Americans than in Hispanics of Cuban or Puerto Rican origin, as well as differences in immigration history.[32,33] Among populations with a large proportion of recent immigrants (APIs and Hispanics), aggregated liver cancer rates are influenced by high background HCV/HBV prevalence in some countries of origin.[34,35] Conversely, acculturation across generations in these populations also increases liver cancer risk, as several lifestyle risk factors are more common in the United States (eg, obesity, alcohol consumption, and smoking) than in many parts of Asia and Latin America.

Hepatitis C virus

HCV infection accounts for approximately 20% of liver cancers worldwide,[36] with prevalence ranging from 3.5% or more in many countries in Central, East, and Western Asia and North Africa to less than 1% in several higher income countries in Western Europe.[37] According to NHANES, the prevalence of chronic HCV infection (defined as positive HCV RNA testing) in the United States was 1% during 2003 through 2010, representing approximately 2.7 million people.[6,38] However, this number is likely an underestimate, because populations with very high infection prevalence (eg, heavy drug users and incarcerated or homeless people) are not represented in NHANES.[37,38] A study incorporating these populations estimated that at least 3.5 million adults were infected with HCV as of 2010.[38] People born between 1945 and 1965 ("baby boomers") have an HCV prevalence of approximately 2.6% and account for about 80% of HCV-infected cases,[6] which explains the increased age-specific death rates for individuals ages 50 to 64 years in the current study. Major risk factors for chronic HCV infection in the United States are injection drug use and receipt of a transfusion before 1992.[6] Other factors that increase risk include being born to an HCV-infected mother, receiving high-risk tattoos or body piercing, needle-stick injuries, having sexual contact with infected people, and some medical conditions (eg, transplantation, hemodialysis, and human immunodeficiency virus infection).[39] HCV infection prevalence in the United States is higher among those with lower education or income and among ages 20–59 years is nearly twice as high among men as among women.[2,6]

According to NHANES, blacks in the United States are more likely than other races/ethnicities combined to have chronic HCV infection, although the prevalence for other individual minority groups is not available because of sparse data.[6] Some surveys and reports from state health departments indicate that HCV infection is generally more common in AIs/ANs, APIs, and Hispanics than in NH whites but may vary by geographic location.[34,35,40–43] Overall, the proportion of all HCCs during 2000 through 2011 attributable to HCV was 17% in whites, 21% in Hispanics, 30% in Asians, and 36% in blacks.[28]

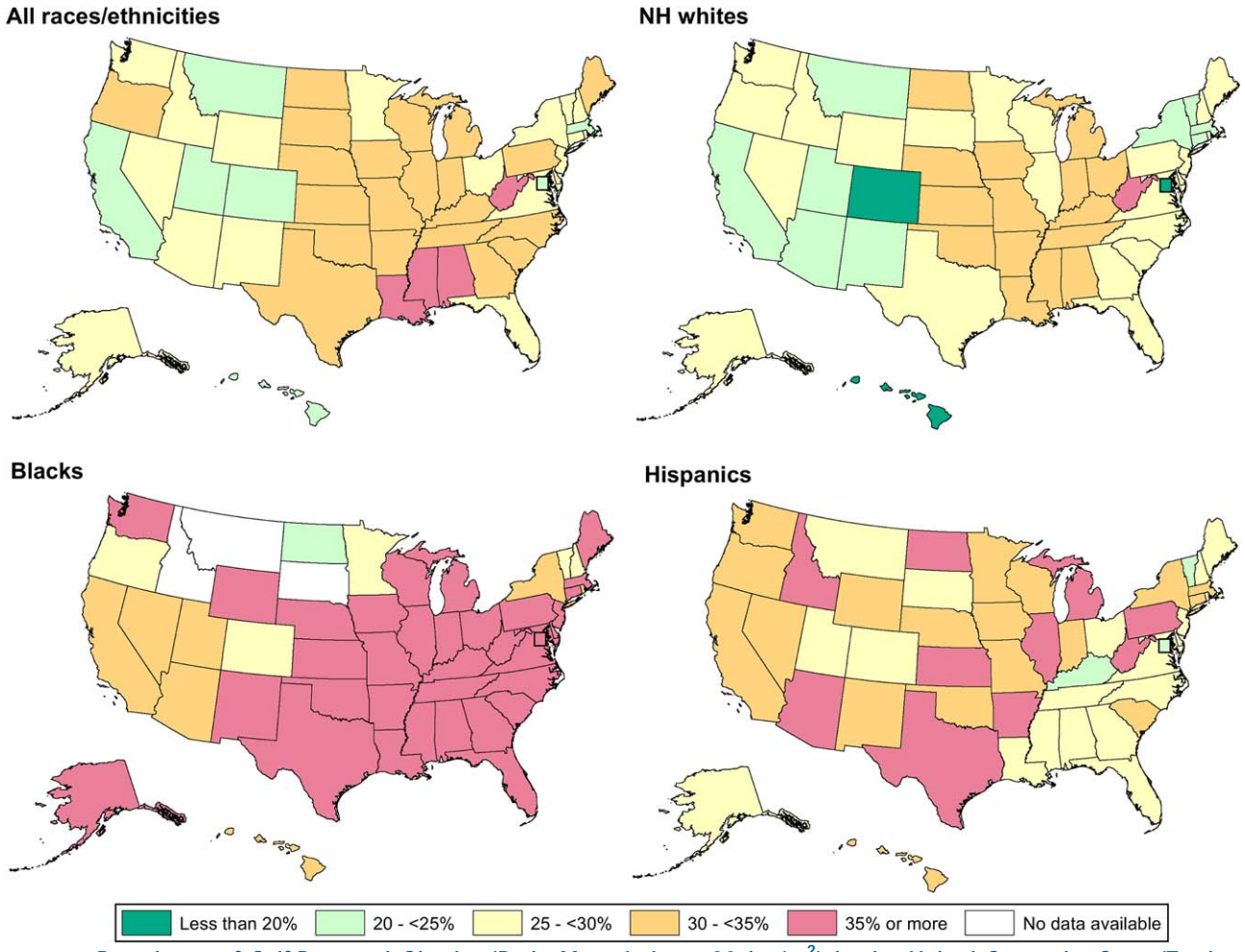

FIGURE 8. Prevalence of Self-Reported Obesity (Body Mass Index $\geq$30 kg/m^2) in the United States by State/Territory and Race/Ethnicity, Both Sexes Combined, 2013 to 2015.
Source: Behavioral Risk Factor Surveillance System, Centers for Disease Control and Prevention (cdc.gov/obesity/data/prevalence-maps.html).

Although representative information on HCV prevalence across states is not available, states with higher liver cancer incidence rates have generally reported higher HCV infection prevalence.[40,42,43] Higher prevalence of HCV infection in nonwhites and those with lower income is consistent with higher liver cancer death rates in states with both a higher proportion of nonwhites and high poverty.

Hepatitis B virus

Although HBV infection is the most common cause of liver cancer globally, accounting for over one-half of liver cancer cases worldwide, it accounts for less than 5% of liver cancers in the United States.[36] HBV infection prevalence is 5% or greater in many low- and middle-income countries in sub-Saharan Africa, Central and East Asia, and the Western Pacific, as well as a small number of countries in other regions, but it is generally low (<2%) in high-income countries.[44,45] Transmission of HBV infection in endemic countries is most common from mother to infant (vertical transmission), whereas in other countries, it mainly occurs through direct contact with body fluids, such as sharing syringes for drug use, needle-stick injuries, and sexual contact (horizontal transmission).[44]

Since the 1990s, the overall prevalence of chronic HBV infection (defined as positive for hepatitis B surface antigen) in the United States has been stable at 0.3% to 0.4% in individuals ages 20 years and older but has declined substantially (from 0.2% to 0.03%) in those ages 6 to 19 years, largely reflecting the influence of HBV vaccination uptake among children.[22] During 2011 to 2012, an estimated 850,000 people in the United States had chronic HBV infection.[22] However, prevalence varies greatly by race/ethnicity, ranging from 0.1% in NH whites and Mexican Americans to 0.6% in blacks and 3.1% in Asians.[22] Prevalence is also higher among foreign-born individuals (1.1%) compared with those born in the United States (0.1%),[22] with those born in China and other highly endemic countries having substantially higher prevalence (≥9%).[46] Consequently, 93% of Asians with chronic HBV infection are foreign-born,[22] and the proportion of all HCCs during 2000

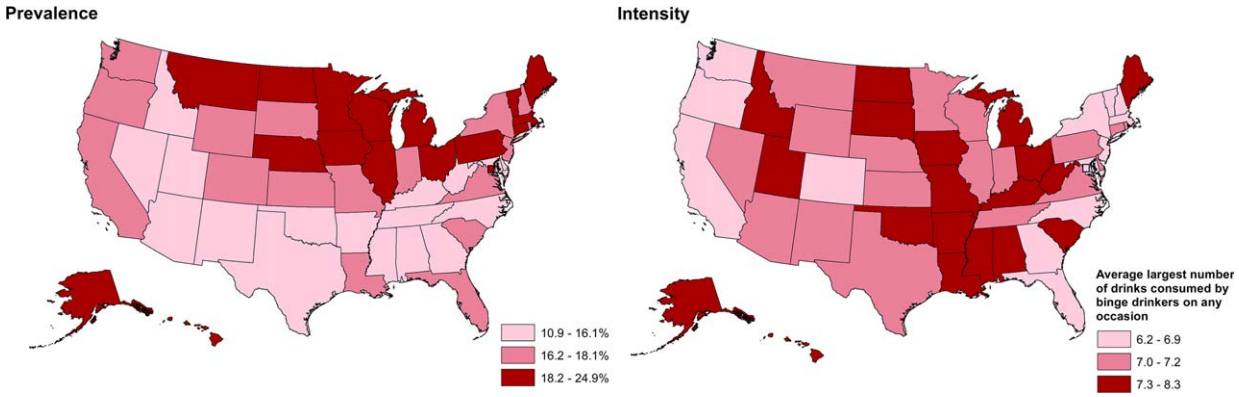

FIGURE 9. Prevalence and Intensity of Binge Alcohol Drinking Among Adults in the United States by State, Both Sexes Combined, 2015, Age-Adjusted to the 2000 US Standard Population.
Binge drinking is defined as ≥4 drinks for a woman or ≥5 drinks for a man on an occasion during the past 30 days.
Source: Behavioral Risk Factor Surveillance System, Centers for Disease Control and Prevention (cdc.gov/alcohol/data-stats.htm).

through 2011 attributable to HBV was 18% in Asians, compared with <3% in whites, blacks, and Hispanics.[28] A considerable proportion of liver cancers among Pacific Islander and AI/AN adults may also be attributable to HBV infection because of their high prevalence of HBV infection, although these data are unavailable.[47,48]

Metabolic disorders and excess body weight

Prospective studies have demonstrated that liver cancer risk increases by 26% per 5 kg/m^2 increase in body mass index (BMI) in the United States,[7] where 69% of people ages 20 years and older have excess body weight (BMI ≥25 kg/m^2).[49] From the 1960s to 2013-2014, the prevalence of overweight (BMI 25.0-29.9 kg/m^2) among adults remained high but stable at 32% to 34%,[50] while obesity (BMI ≥30 kg/m^2) tripled from 13% to 38%, and class 3 obesity (BMI ≥40 kg/m^2) increased 8-fold, from 1% to 8%.[21] These increases occurred in both men and women until the late 1990s, but since have been mainly confined to women.[21,50] Currently, overweight prevalence is higher in men (38%) than in women (30%), but more women than men are obese (40% vs 35%) and class 3 obese (10% vs 6%).[21] The prevalence of obesity has substantially increased in all races/ethnicities with available historical information.[50] Among women, obesity prevalence ranges about 3-fold to 5-fold, from a low of 12% in Asians to 38% in NH whites, 47% in Hispanics, and 57% in blacks.[21] Among men, obesity prevalence in NH whites (35%), blacks (38%), and Hispanics (38%) is similar but is nearly 3-fold the prevalence in Asians (13%).[21]

Prevalence of obesity by state and race/ethnicity is shown in Figure 8. In most cases, patterns of obesity prevalence in each racial/ethnic group correspond to liver cancer death rates. For example, both obesity prevalence and liver cancer mortality in the District of Columbia are among the lowest in the country in NH whites but are very high in blacks. Obesity may also contribute to substantially higher liver cancer death rates in blacks and Hispanics than in NH whites in Texas. In some other instances, however, this pattern is more equivocal. For example, although NH whites in Hawaii have lower obesity prevalence than NH whites in the continental United States, their liver cancer death rate is higher. These inconsistencies likely reflect differences in the prevalence of other major contributors to liver cancer, notably viral hepatitis infection.

A large-scale, prospective study in the United States has demonstrated that diabetes increases the risk of liver cancer by 2.3-fold in men and 1.4-fold in women.[7] Consistent with the increase in excess body weight, the prevalence of diabetes has increased from 9.8% in the late 1980s to 12.4% in 2011-2012, and it is estimated that an additional 36.5% are prediabetic.[23] The increase in diabetes over 2 decades has been more modest in NH whites (from 8.6% to 9.5%) than in blacks and Mexican Americans (from approximately 17% to 21%). Although trend data are not available for other minority groups, the contemporary prevalence of diabetes was relatively high in all Hispanics combined (18.7%) and in Asians (16.5%),[23] despite lower BMIs in the latter.[21] Diabetes prevalence is also high and increasing rapidly in those with low education and income.[23,51]

More than 20% of patients with nonalcoholic fatty liver disease, a condition highly associated with excess body weight and diabetes, will develop nonalcoholic steatohepatitis, a more serious type of nonalcoholic fatty liver disease in which fat accumulation in the liver causes inflammation and cell damage, thereby increasing the risk of liver cancer.[52] There is little information on trends in nonalcoholic steatohepatitis prevalence from population studies, partly because diagnosis may require invasive procedures. However, a few studies have reported a rising trend in the prevalence of nonalcoholic fatty liver disease in the United States, consistent with the increases in excess body weight and diabetes

prevalence, although there may be variations in reported prevalence based on diagnostic criteria used in those studies.[24,53] An analysis of NHANES data reported an increase in the prevalence of nonalcoholic fatty liver disease from 18% during 1988 through 1991, to 29% during 1999 and 2000, and to 31% during 2011 and 2012.[24] Among the 3 racial/ethnic groups in that analysis, Mexican Americans had the highest prevalence, followed by NH whites and blacks. An analysis of data from more than 1.3 million veterans using different diagnostic criteria also demonstrated an increase, although the reported prevalence was lower (an increase from 6% in 2003 to 18% in 2011); racial patterns were similar to those in NHANES.[52]

Alcohol drinking and tobacco smoking

Alcohol consumption increases liver cancer risk by approximately 10% per drink per day (eg, a 3-fold increased risk for someone consuming 8 drinks per day).[54] Excessive drinking includes binge drinking (≥4 drinks per occasion for a woman or ≥5 drinks per occasion for a man) and heavy drinking (≥8 drinks per week for a woman or ≥15 drinks per week for a man).[55] Binge drinking is the most common type of excessive alcohol drinking in the United States—17% of adults (or 38 million people) binge drink.[55] On the basis of the National Survey on Drug Use and Health, binge drinking prevalence among individuals aged 50 years and older has increased by approximately 20% in the last decade.[26] Men, those with a higher income, and tobacco and illicit drug users are most likely to binge drink. Compared with NH whites, the self-reported prevalence of binge drinking is similar in blacks, lower in Asians, and slightly higher in Hispanics.[26] As illustrated in Figure 9, states with the highest prevalence of binge drinking are in the North and Midwest, whereas the intensity of binge drinking is highest in the central South and parts of the Midwest.

Smoking increases liver cancer risk by approximately 50%.[31] Smoking prevalence among men is highest in AIs/ANs (38%), followed by blacks (21%), NH whites (17%), and APIs and Hispanics (12% to 13%). Prevalence in women is generally much lower than in men within the same racial/ethnic group (24% in AIs/ANs, 13% in blacks, 7% in Hispanics, and 3% in APIs), with the exception of NH white women (16%).[25] Despite overall reductions in smoking in the United States, prevalence is highest and declines are weakest among individuals with lower education levels and incomes,[25] who have a higher likelihood of other liver cancer risk factors. States with the highest smoking prevalence are in the Southern region among NH whites, in Southern states and the Midwest in black men, and in the Midwest in black women.[56]

Interventions

Many liver cancer cases could potentially be prevented by alleviating exposure to risk factors or mitigating the risk among those exposed. The following is a broad summary of current strategies along with their limitations and includes interventions intended for low-income individuals, minorities, and other high-risk groups. Tailored, culturally appropriate application of these interventions for different subpopulations at the state and local level is essential but remains a challenge, particularly considering the disparities in health care access and limitations in public health resources.

Hepatitis virus infection

The Institute of Medicine has established 4 general groups of recommendations for the prevention and control of HBV and HCV, including improvements in infection surveillance, awareness, infection care and services, and HBV vaccination.[57] More representative data are required on HBV and HCV prevalence among subpopulations in the United States, including data by state and from high-risk populations (eg, the homeless). Increasing awareness among policy makers, health care providers, and the general population is an essential part of any strategy to control HBV and HCV infection. Awareness is even more important for those at risk and the individuals/organizations that serve them, because many are unaware of viral hepatitis infection screening, HBV vaccination, or the availability of treatment to cure HCV infection. Currently, the CDC recommends one-time HCV testing for people born from 1945 to 1965.[39] However, only 14% of this cohort has reported HCV testing, with little variation between Asians, NH whites, blacks, and Hispanics.[58] In contrast, a recent assessment indicated that HCV testing among the AI/AN 1945 to 1965 birth cohort served by the Indian Health Service increased 4-fold during 2012 through 2015, from 8% to 33%, likely due in part to the implementation of integrated electronic clinical decision-support tools at Indian Health Service facilities as well as other provider-based initiatives.[59] Some professional organizations also recommend screening for high-risk individuals,[39] including the incarcerated population, which may be one of the cost-effective ways to reduce transmission of HCV infection.[60]

Although interferon and/or ribavirin have been used with some success to treat HCV infection, the introduction of oral direct-acting antivirals in 2014 represented major progress, resulting in very high cure rates with shorter term treatment and substantially fewer adverse side effects.[61,62] Although future studies are needed to determine the long-term effects of these new drugs, they are likely to reduce HCV complications, including HCC. However, underdiagnoses of HCV cases, in addition to obstacles to care and the high cost of direct-acting antivirals, are major barriers. For example, only slightly more than one-third of those with known HCV

infection receive follow-up care, and less than 10% are successfully treated.[39] The variation in reimbursement of direct-acting antivirals because of their high cost further contributes to suboptimal access in states with more restricted coverage.[39]

Unlike HCV, treatments for HBV infection, including pegylated α-interferon and nucleos(t)ide analogues, may halt the progression of active liver disease but do not cure the infection.[62,63] Thus, although these treatments have been able to reduce the risk of HBV-related HCC, they require long-term administration.[64] HBV vaccination is the most effective means of preventing HBV infection and liver cancer and has been part of routine childhood vaccinations in the United States since 1982.[65–67] In 2014, HBV vaccination coverage in children ages 19 to 35 months in the United States was 91% to 93% in NH whites, blacks, Hispanics, and Asians, and it was slightly higher in Pacific Islanders (95%) and AIs/ANs (99%).[68] Despite historically high HBV infection prevalence among Pacific Islanders and Alaska natives, comprehensive universal infant vaccination has been very successful in lowering the childhood infection rate in these populations.[47,48] For example, HBV prevalence in children ages 2 to 11 years in the US-affiliated Pacific Island countries decreased from 8.4% in the 1980s to 0.2% in the 2000s.[48] Although greater than 90% of adolescents in the United States received the HBV vaccine in 2015, coverage varied across states, ranging from 83% in Idaho to 98% in New Hampshire.[69] HBV vaccination of high-risk adults is also recommended, but coverage remains low at only 50% in the United States.[57] Both HBV and HCV infection can be prevented through the expansion of comprehensive programs to reduce transmission through high-risk behaviors (eg, using shared syringes).[57]

Excess body weight

Consistent with a substantial increase in the number of people with excess body weight and associated metabolic disorders in the United States, the estimated proportion of HCCs attributable to these factors increased from 26% during 2000 through 2003 to 36% during 2008 through 2011.[28] Excess body weight in childhood is a major contributor to the obesity epidemic, because, for many children, it extends into adulthood; it is also a risk factor for type II diabetes and other metabolic disorders associated with liver cancer in adults.[70,71] Therefore, preventing excess body weight in children should be a major focus of any weight-control intervention at the population level. Among children and adolescents ages 2 to 19 years, approximately one-third have excess body weight and 17% are obese, although there is substantial variation by race/ethnicity and across states.[49,72,73]

The etiology of childhood obesity is complex and is influenced by multiple behavioral, cultural/environmental (eg, family, school), socioeconomic, and genetic factors, which can lead to unhealthy diet, physical inactivity, and adverse changes in metabolism.[70,74–77] The relative effect of these factors may vary across subpopulations, including by race/ethnicity.[75–77] Because children generally spend a considerable amount of time in school (including preschool), school-based interventions can provide a great opportunity for weight control, such as education about healthy lifestyles and increasing physical activity and access to affordable, healthy food while reducing access to unhealthier foods at school.[74] However, the effects of school-based interventions may be difficult to sustain long term, and studies have shown that additional environmental strategies could improve outcomes. For example, family-based interventions may help to improve diet, increase physical activity, and reduce screen time at home.[74–76]

Among adults, intensive lifestyle interventions (including diet, physical activity, and behavior therapy) to promote healthier diet and physical activity have been shown to be successful in maintaining or reducing body weight and diabetes risk among participants in several studies.[78–80] However, these interventions have not been as successful at the population level, including when offered through primary care providers.[81–83] This inconsistency may be due in part to participation bias, but it may also reflect primary care providers' time constraints and insufficient training for delivering effective behavioral counseling, which could be remedied through appropriate instruction or referrals.[81–84] When lifestyle interventions are not successful for adequate weight loss, individuals with obesity may be eligible for pharmacotherapy, and those with class 3 obesity may benefit from bariatric surgery.[85]

The use of modern communication technologies, such as social and mobile tools, may have the potential to increase the efficiency and accessibility of behavioral interventions, but studies to date have produced mixed results.[86–88] Some regulations and policies may also help weight-control strategies in both children and adults, including mass media campaigns (increasing awareness and education to change unhealthy behaviors), food labeling and advertising regulation, taxation of nonessential high-calorie foods and sugary beverages, and improvements in urban structure (eg, increasing public transportation).[89–92] Overall, maintaining normal weight may be more challenging for minorities and individuals with low income, because they often live in neighborhoods with more limited access to healthier foods and appropriate environments for physical activity.[75,76] For example, poor neighborhoods usually have limited sports facilities and programs (in schools and outside) and fewer or unsafe sidewalks.[75,76]

Increased awareness, the availability of multiple recommendations and guidelines for maintaining a healthy body weight, and the implementation of some community-level interventions and regulations may have contributed to a modest decrease in obesity in children ages 2 to 5 years and stable trends in children ages 6 to 11 years as well as adult

men in the United States during the last decade.[21,49,72] However, to adequately address the obesity epidemic and associated metabolic disorders, comprehensive implementation of successful interventions and additional research to identify more efficient strategies at the population level, especially in racial/ethnic minorities, are needed.[72]

Other risk factors

In addition to reducing weight and increasing physical activity, appropriate diabetes care can prevent or delay complications like nonalcoholic fatty liver disease. However, undiagnosed diabetes remains a substantial challenge in the United States; one-third of patients with diabetes in the most recent NHANES survey were diagnosed by laboratory tests used in the survey and had not been previously diagnosed.[23] Undiagnosed diabetes was more common in Asians and Hispanics (50%) than in blacks (37%) and NH whites (32%). This highlights the importance of access to preventive medicine and routine blood sugar tests. However, disparities in access to high-quality diabetes care persist even among those diagnosed with the disease, largely driven by lack of insurance coverage,[93] particularly among Hispanics overall and lower income groups.[94,95]

For preventing excessive alcohol drinking, the Community Preventive Services Task Force recommends increasing alcohol excise taxes; regulating alcohol outlet density and the days and hours of alcohol sale; maintaining government controls over alcohol sales; using computers, mobile phones, and other electronic devices for interventions; and holding retailers accountable for harms when they illegally sell/serve alcohol.[55] Effective policies for reducing tobacco control have been discussed comprehensively in several publications.[31] Briefly, the policies recommended by the World Health Organization's Framework Convention on Tobacco Control include tobacco taxation, smoke-free laws, warning about the dangers of tobacco (warning labels and media campaigns), marketing bans, and assistance with smoking cessation.[96] Smoking prevalence across states is highly correlated with tobacco-control policies in states.[56,97] Although smoking may play a smaller role than some other risk factors in the burden of liver cancer, reducing tobacco use will also prevent numerous deaths from many other cancers and chronic diseases.[30,97]

Treatment and Survival

HCC has a very poor prognosis. The overall median survival for patients with untreated disease is 4 months, ranging from 2 months for late-stage cancers to 14 months for very early stage cancers.[98] Potentially curative treatments are available for early stage liver cancers, including surgical resection, ablation, and liver transplantation.[99–102] Currently, HCC is the leading diagnosis among liver transplant recipients (27% in 2015), and the number of liver transplants because of liver cancer continues to increase.[103] Transarterial embolization and transcatheter arterial chemoembolization are usually used to treat patients with intermediate-stage liver cancer who do not have tumor-related symptoms, vascular invasion, or metastasis and may increase survival.[100–102,104] Improvements in and access to treatments are the likely reasons for a substantial increase in localized-stage liver cancer survival and, to a lesser degree, regional-stage survival, as demonstrated in our analysis. Systemic treatment with sorafenib (an oral multikinase inhibitor) is used for more advanced HCCs, except for end-stage cancers, which are generally considered for palliative care only. However, sorafenib can increase survival for only a few months.[100–102] This, along with the lack of any specific treatment for end-stage HCC, explains the little improvement in 5-year survival for advanced cancers over the entire study period in our analysis.

Variation in treatment may account in part for differential stage-specific survival by race and ethnicity. Disparities in treatment for patients diagnosed with potentially curable, early stage disease have been documented in several studies. A study of patients diagnosed from 1998 to 2011 with clinical stage I/II HCC indicated that slightly less than 40% underwent surgery. A lower probability of undergoing surgery was observed for black and uninsured or Medicaid-insured patients in multivariate models that included stage and comorbidity score. In that study, the median survival of patients who underwent surgery was 48.3 months compared with 8.4 months for those who did not undergo surgery.[105] Other studies have noted pronounced disparities in the receipt of liver transplantation among patients who were eligible for this treatment. One such study of patients with early stage HCC reported to SEER registries from 1998 to 2010 who were eligible for liver transplantation based on the Milan criteria indicated that black, Asian, and Hispanic patients were substantially less likely to receive this treatment than NH whites.[106] A study in California by race and ethnicity examined HCC treatment and survival patterns in greater detail for Asian subpopulations. Consistent with previous studies, that study indicated that the probability of receiving surgical treatment was lower for black and Hispanic patients than for NH white patients. In addition, the study found considerable variations in surgical treatment among Asian subpopulations, with the lowest rates reported for Laotian/Hmong and Cambodian patients and the highest rates reported for Chinese, Korean, Japanese, and Vietnamese patients.[107] Those studies suggested that considerable progress in reducing liver cancer mortality could be achieved by ensuring equitable access to high-quality treatment, especially for patients with early stage disease for whom surgery potentially can be curative.

Part of the improvement in survival for localized-stage cancers may also be related to earlier detection. The American Association for the Study of Liver Diseases has developed

guidelines for the surveillance of high-risk individuals, such as certain patients with cirrhosis, HBV- or HCV-related chronic active hepatitis, or other chronic liver diseases that meet certain criteria.[100,101] However, although studies have suggested that such surveillance is cost-effective and could lead to a greater percentage of liver cancers diagnosed at earlier stages, it remains controversial.[100,101,108–110] Because of a lack of high-quality data from clinical trials, it is unclear whether liver cancer surveillance could translate into lower mortality from the disease,[100,101,110] demonstrating the need for further research.

Limitations

Population-based cancer data in the United States are generally available only for the 5 broad groups presented herein. However, liver cancer rates can vary substantially by subgroup within these large, heterogeneous populations. For example, as pointed out by the Office of Management and Budget in 1997, the broad category of Asian and Pacific Islander is problematic because it includes subpopulations with vastly disparate cultural, socioeconomic, and health profiles, which lead to substantial variations in cancer occurrence. In addition, caution is warranted when interpreting death rates and cancer-specific survival for racial groups other than NH whites and blacks, because both racial/ethnic misclassification on death certificates and nonrandom censoring because of biases in patient follow-up are more likely to occur. One recent analysis indicated that APIs and Hispanics were substantially more likely to be censored (lost to follow-up) within the first 5 years after a cancer diagnosis than NH whites, particularly for cancers with an unfavorable prognosis.[111] Finally, liver cancer incidence and mortality rates in AIs/ANs were based on a relatively modest number of outcomes and should be interpreted with caution.

Conclusions

The burden of liver cancer in the United States is significant and is expected to increase in the decades to come. Moreover, despite some improvements in localized and regional disease survival rates in the 2 most recent decades of available data, the overall prognosis for liver cancer remains poor. Wide disparities in liver cancer death rates by sex, race/ethnicity, and state persist, reflecting differences in the prevalence of major risk factors and, to some extent, inequalities in access to high-quality care. However, most liver cancers are potentially preventable, and interventions to curb the rising burden of liver cancer and reduce racial/ethnic disparities should include the targeted application of existing knowledge in prevention, early detection, and treatment, including improvements in HBV vaccination, screening and treatment of HCV, maintaining a healthy body weight, access to high-quality diabetes care, prevention of excessive alcohol drinking, and tobacco control. ■

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin.* 2017;67:7-30.
2. Ryerson AB, Eheman CR, Altekruse SF, 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. Jemal A, Ward EM, Johnson CJ, et al. Annual Report to the Nation on the Status of Cancer, 1975-2014, featuring survival. *J Natl Cancer Inst.* 2017;109. doi: 10.1093/jnci/dx030.
4. Howlader N, Noone AM, Krapcho M, et al, eds. SEER Cancer Statistics Review, 1975-2013; based on the November 2015 SEER data submission, posted to the SEER web site, April 2016. Bethesda: MD: National Cancer Institute; 2016. Available at: seer.cancer.gov/csr/1975_2013/. Accessed April 12, 2017.
5. Petrick JL, Kelly SP, Altekruse SF, McGlynn KA, Rosenberg PS. Future of hepatocellular carcinoma incidence in the United States forecast through 2030. *J Clin Oncol.* 2016;34:1787-1794.
6. Denniston MM, Jiles RB, Drobeniuc J, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. *Ann Intern Med.* 2014;160:293-300.
7. Campbell PT, Newton CC, Freedman ND, et al. Body mass index, waist circumference, diabetes, and risk of liver cancer for US adults. *Cancer Res.* 2016;76:6076-6083.
8. Li J, Hansen BE, Peppelenbosch MP, De Man RA, Pan Q, Sprengers D. Factors associated with ethnical disparity in overall survival for patients with hepatocellular carcinoma. *Oncotarget.* 2017;8:15193-15204.
9. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol.* 2009;27:1485-1491.
10. Njei B, Rotman Y, Ditah I, Lim JK. Emerging trends in hepatocellular carcinoma incidence and mortality. *Hepatology.* 2015;61:191-199.
11. Altekruse SF, Henley SJ, Cucinelli JE, McGlynn KA. Changing hepatocellular carcinoma incidence and liver cancer mortality rates in the United States. *Am J Gastroenterol.* 2014;109:542-553.
12. Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Mortality-All COD, Aggregated With State, Total US (1969-2014) <Katrina/Rita Population Adjustment>. Bethesda, MD: National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Surveillance Systems Branch; 2016; underlying mortality data provided by National Center for Health Statistics 2016 (cdc.gov/nchs).
13. Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence-SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2015 Submission (1973-2013 varying)-Linked To County Attributes-Total US, 1969-2014 Counties, released April 2016. Bethesda, MD: National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Surveillance Systems Branch; 2016.
14. Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: North American Association of Central Registries (NAACCR) Incidence Data-CiNA Analytic File, 1995-2013. Public Use (which includes data from the Centers for Disease Control and Prevention [CDC's] National Program of Cancer Registries [NPCR], the Canadian Council of Cancer Registries' [CCCR's] Provincial and Territorial Registries, and the National Cancer Institute's [NCI's] SEER Registries), certified by the NAACCR as meeting high-quality incidence data standards for the specified time periods, submitted December 2015. Bethesda, MD: National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Surveillance Systems Branch; 2016.
15. Fritz A, Percy C, Jack A, et al, eds. International Classification of Diseases for Oncology. 3rd ed. Geneva, Switzerland: World Health Organization; 2000.
16. World Health Organization. International Statistical Classification of Diseases and Related Health Problems. 10th Revision. Vol I-III. Geneva, Switzerland: World Health Organization; 2011.

17. Surveillance Research Program, National Cancer Institute. SEER*Stat software (seer.cancer.gov/seerstat), version 8.3.2 [software program]. Bethesda, MD: National Cancer Institute; 2016.

18. Clegg LX, Feuer EJ, Midthune DN, Fay MP, Hankey BF. Impact of reporting delay and reporting error on cancer incidence rates and trends. *J Natl Cancer Inst*. 2002; 94:1537-1545.

19. National Cancer Institute. Joinpoint Regression Program, Version 4.3.1.0 [software program]. Bethesda, MD: National Cancer Institute, Statistical Research and Applications Branch; 2016.

20. StataCorp. Stata Statistical Software: Release 13 [software program]. College Station, TX: StataCorp LP; 2013.

21. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in obesity among adults in the United States, 2005 to 2014. *JAMA*. 2016;315:2284-2291.

22. Roberts H, Kruszon-Moran D, Ly KN, et al. Prevalence of chronic hepatitis B virus (HBV) infection in US households: National Health and Nutrition Examination Survey (NHANES), 1988-2012. *Hepatology*. 2016;63:388-397.

23. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and trends in diabetes among adults in the United States, 1988-2012. *JAMA*. 2015;314:1021-1029.

24. Ruhl CE, Everhart JE. Fatty liver indices in the multiethnic United States National Health and Nutrition Examination Survey. *Aliment Pharmacol Ther*. 2015;41: 65-76.

25. Jamal A, King BA, Neff LJ, Whitmill J, Babb SD, Graffunder CM. Current cigarette smoking among adults—United States, 2005-2015. *MMWR Morb Mortal Wkly Rep*. 2016;65:1205-1211.

26. Han BH, Moore AA, Sherman S, Keyes KM, Palamar JJ. Demographic trends of binge alcohol use and alcohol use disorders among older adults in the United States, 2005-2014. *Drug Alcohol Depend*. 2017;170:198-207.

27. Ha J, Yan M, Aguilar M, et al. Race/ethnicity-specific disparities in cancer incidence, burden of disease, and overall survival among patients with hepatocellular carcinoma in the United States. *Cancer*. 2016;122:2512-2523.

28. Makarova-Rusher OV, Altekruse SF, McNeel TS, et al. Population attributable fractions of risk factors for hepatocellular carcinoma in the United States. *Cancer*. 2016;122:1757-1765.

29. Welzel TM, Graubard BI, Quraishi S, et al. Population-attributable fractions of risk factors for hepatocellular carcinoma in the United States. *Am J Gastroenterol*. 2013; 108:1314-1321.

30. Siegel RL, Jacobs EJ, Newton CC, et al. Deaths due to cigarette smoking for 12 smoking-related cancers in the United States. *JAMA Intern Med*. 2015;175:1574-1576.

31. US Department of Health and Human Services. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General, 2014. Washington, DC: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014. surgeongeneral.gov/library/reports/50-years-of-progress/. Accessed April 10, 2017.

32. Watt GP, Vatcheva KP, Beretta L, et al. Hepatitis C virus in Mexican Americans: a population-based study reveals relatively high prevalence and negative association with diabetes. *Epidemiol Infect*. 2016;144: 297-305.

33. Kallwitz ER, Daviglus ML, Allison MA, et al. Prevalence of suspected nonalcoholic fatty liver disease in Hispanic/Latino individuals differs by heritage. *Clin Gastroenterol Hepatol*. 2015;13:569-576.

34. Nguyen LH, Nguyen MH. Systematic review: Asian patients with chronic hepatitis C infection. *Aliment Pharmacol Ther*. 2013;37:921-936.

35. Kuniholm MH, Jung M, Everhart JE, et al. Prevalence of hepatitis C virus infection in US Hispanic/Latino adults: results from the NHANES 2007-2010 and HCHS/SOL studies. *J Infect Dis*. 2014; 209:1585-1590.

36. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. *Lancet Glob Health*. 2016;4:e609-e616.

37. Thrift AP, El-Serag HB, Kanwal F. Global epidemiology and burden of HCV infection and HCV-related disease. *Nat Rev Gastroenterol Hepatol*. 2017;14:122-132.

38. Edlin BR, Eckhardt BJ, Shu MA, Holmberg SD, Swan T. Toward a more accurate estimate of the prevalence of hepatitis C in the United States. *Hepatology*. 2015;62:1353-1363.

39. Allison RD, Hale SA, Harvey BJ, et al. The American College of Preventive Medicine position statement on hepatitis C virus infection. *Am J Prev Med*. 2016;50:419-426.

40. Yalamanchili K, Saadeh S, Lepe R, Davis GL. The prevalence of hepatitis C virus infection in Texas: implications for future health care. *Proc (Bayl Univ Med Cent)*. 2005;18:3-6.

41. Neumeister AS, Pilcher LE, Erickson JM, et al. Hepatitis-C prevalence in an urban Native-American clinic: a prospective screening study. *J Natl Med Assoc*. 2007; 99:389-392.

42. Wisconsin Department of Health Services. Epidemiologic Profile of Hepatitis C Virus (HCV) in Wisconsin 2014. Madison, WI: Wisconsin Department of Health Services, Division of Public Health; 2014. dhs.wisconsin.gov/publications/p0/p00860.pdf. Accessed April 10, 2017.

43. Takeuchi LC, Pham TK, Katz AR. Hepatitis C virus antibody prevalence, demographics and associated factors among persons screened at Hawai'i community-based health settings, 2010-2013. *Hawaii J Med Public Health*. 2015;74:9-15.

44. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. *Vaccine*. 2012;30:2212-2219.

45. Ott JJ, Horn J, Krause G, Mikolajczyk RT. Time trends of chronic HBV infection over prior decades—a global analysis. *J Hepatol*. 2017;66:48-54.

46. Kowdley KV, Wang CC, Welch S, Roberts H, Brosgart CL. Prevalence of chronic hepatitis B among foreign-born persons living in the United States by country of origin. *Hepatology*. 2012;56:422-433.

47. McMahon BJ, Bulkow LR, Singleton RJ, et al. Elimination of hepatocellular carcinoma and acute hepatitis B in children 25 years after a hepatitis B newborn and catch-up immunization program. *Hepatology*. 2011;54:801-807.

48. Abara WE, Collier MG, Teshale EH. Impact of universal infant hepatitis B vaccination in the US-affiliated Pacific Islands, 1985-2015. *Vaccine*. 2017;35:997-1000.

49. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA*. 2014;311:806-814.

50. Ogden CL, Carroll MD. Prevalence of Overweight, Obesity, and Extreme Obesity Among Adults: United States, Trends 1960-1962 Through 2007-2008. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Health Statistics, Health E-Stats; 2010. cdc.gov/nchs/data/hestat/obesity_adult_07_08/obesity_adult_07_08.htm. Accessed April 10, 2017.

51. Beckles GL, Chou CF. Disparities in the prevalence of diagnosed diabetes—United States, 1999-2002 and 2011-2014. *MMWR Morb Mortal Wkly Rep*. 2016;65:1265-1269.

52. Kanwal F, Kramer JR, Duan Z, Yu X, White D, El-Serag HB. Trends in the burden of nonalcoholic fatty liver disease in a United States cohort of veterans. *Clin Gastroenterol Hepatol*. 2016;14:301-308.e1-e2.

53. Sayiner M, Koenig A, Henry L, Younossi ZM. Epidemiology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis in the United States and the rest of the world. *Clin Liver Dis*. 2016;20:205-214.

54. Chuang SC, Lee YC, Wu GJ, Straif K, Hashibe M. Alcohol consumption and liver cancer risk: a meta-analysis. *Cancer Causes Control*. 2015;26:1205-1231.

55. National Center for Chronic Disease Prevention and Health Promotion. Excessive Alcohol Use. Preventing a Leading Risk for Death, Disease, and Injury at a Glance 2016. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion; 2016. cdc.gov/chronicdisease/resources/publications/aag/alcohol.htm. Accessed April 10, 2017.

56. Islami F, Ward EM, Jacobs EJ, et al. Potentially preventable premature lung cancer deaths in the USA if overall population rates were reduced to those of educated whites in lower-risk states. *Cancer Causes Control*. 2015;26:409-418.

57. Mitchell AE, Colvin HM, Palmer Beasley R. Institute of Medicine recommendations for the prevention and control of hepatitis B and C. *Hepatology*. 2010;51:729-733.

58. Jemal A, Fedewa SA. Recent hepatitis C virus testing patterns among Baby Boomers [published online ahead of print March

1, 2017]. *Am J Prev Med.* doi: 10.1016/j.amepre.2017.01.033.

59. Reilley B, Leston J, Hariri S, et al. Birth cohort testing for hepatitis C virus—Indian Health Service 2012-2015. *MMWR Morb Mortal Wkly Rep.* 2016;65:467-469.
60. He T, Li K, Roberts MS, et al. Prevention of hepatitis C by screening and treatment in US prisons. *Ann Intern Med.* 2016;164:84-92.
61. Chhatwal J, Wang X, Ayer T, et al. Hepatitis C disease burden in the United States in the era of oral direct-acting antivirals. *Hepatology.* 2016;64:1442-1450.
62. National Academies of Sciences, Engineering, and Medicine. Eliminating the Public Health Problem of Hepatitis B and C in the United States: Phase One Report. Washington, DC: The National Academies Press; 2016.
63. Revill P, Testoni B, Locarnini S, Zoulim F. Global strategies are required to cure and eliminate HBV infection. *Nat Rev Gastroenterol Hepatol.* 2016;13:239-248.
64. Wei L, Kao JH. Benefits of long-term therapy with nucleos(t)ide analogues in treatment-naive patients with chronic hepatitis B. *Curr Med Res Opin.* 2017;33:495-504.
65. Centers for Disease Control and Prevention. Hepatitis B vaccination—United States, 1982-2002. *MMWR Morb Mortal Wkly Rep.* 2002;51:549-552, 563.
66. Qu C, Chen T, Fan C, et al. Efficacy of neonatal HBV vaccination on liver cancer and other liver diseases over 30-year follow-up of the Qidong hepatitis B intervention study: a cluster randomized controlled trial [serial online]. *PLoS Med.* 2014;11:e1001774.
67. La Torre G, Mannocci A, Saulle R, et al. Economic evaluation of HBV vaccination: a systematic review of recent publications (2000-2013). *Hum Vaccin Immunother.* 2016;12:2299-2311.
68. National Center for Health Statistics. Health, United States, 2015: With Special Feature on Racial and Ethnic Health Disparities. Hyattsville, MD: US Department of Health and Human Services, National Center for Health Statistics; 2016.
69. Reagan-Steiner S, Yankey D, Jeyarajah J, et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13-17 years—United States, 2015. *MMWR Morb Mortal Wkly Rep.* 2016;65:850-858.
70. Kumar S, Kelly AS. Review of childhood obesity: from epidemiology, etiology, and comorbidities to clinical assessment and treatment. *Mayo Clin Proc.* 2017;92:251-265.
71. Juonala M, Magnussen CG, Berenson GS, et al. Childhood adiposity, adult adiposity, and cardiovascular risk factors. *N Engl J Med.* 2011;365:1876-1885.
72. Ogden CL, Carroll MD, Lawman HG, et al. Trends in obesity prevalence among children and adolescents in the United States, 1988-1994 through 2013-2014. *JAMA.* 2016;315:2292-2299.
73. Long MW, Ward ZJ, Resch SC, et al. State-level estimates of childhood obesity prevalence in the United States corrected for report bias. *Int J Obes (Lond).* 2016;40:1523-1528.
74. Cauchi D, Glonti K, Petticrew M, Knai C. Environmental components of childhood obesity prevention interventions: an overview of systematic reviews. *Obes Rev.* 2016;17:1116-1130.
75. Pulgaron ER, Delamater AM. Obesity and type 2 diabetes in children: epidemiology and treatment [serial online]. *Curr Diab Rep.* 2014;14:508.
76. Ochoa A, Berge JM. Home Environmental influences on childhood obesity in the Latino population: a decade review of literature. *J Immigr Minor Health.* 2017;19:430-447.
77. Ward DS, Welker E, Choate A, et al. Strength of obesity prevention interventions in early care and education settings: a systematic review. *Prev Med.* 2017;95(suppl):S37-S52.
78. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002;346:393-403.
79. Houston DK, Leng X, Bray GA, et al. A long-term intensive lifestyle intervention and physical function: the Look AHEAD Movement and Memory Study. *Obesity (Silver Spring).* 2015;23:77-84.
80. Wing RR, Tate DF, Espeland MA, et al. Innovative self-regulation strategies to reduce weight gain in young adults: the Study of Novel Approaches to Weight Gain Prevention (SNAP) randomized clinical trial. *JAMA Intern Med.* 2016;176:755-762.
81. Wadden TA, Butryn ML, Hong PS, Tsai AG. Behavioral treatment of obesity in patients encountered in primary care settings: a systematic review. *JAMA.* 2014;312:1779-1791.
82. Sim LA, Lebow J, Wang Z, Koball A, Murad MH. Brief primary care obesity interventions: a meta-analysis. *Pediatrics.* 2016;138. pii: e20160149.
83. Wolfenden L, Jones J, Williams CM, et al. Strategies to improve the implementation of healthy eating, physical activity and obesity prevention policies, practices or programmes within childcare services [serial online]. *Cochrane Database Syst Rev.* 2016;10:CD011779.
84. Batsis JA, Gill LE, Masutani RK, et al. Weight loss interventions in older adults with obesity: a systematic review of randomized controlled trials since 2005. *J Am Geriatr Soc.* 2017;65:257-268.
85. Alamuddin N, Bakizada Z, Wadden TA. Management of obesity. *J Clin Oncol.* 2016;34:4295-4305.
86. Sherrington A, Newham JJ, Bell R, Adamson A, McColl E, Araujo-Soares V. Systematic review and meta-analysis of internet-delivered interventions providing personalized feedback for weight loss in overweight and obese adults. *Obes Rev.* 2016;17:541-551.
87. Harvey-Berino J, West D, Krukowski R, et al. Internet delivered behavioral obesity treatment. *Prev Med.* 2010;51:123-128.
88. Godino JG, Merchant G, Norman GJ, et al. Using social and mobile tools for weight loss in overweight and obese young adults (Project SMART): a 2 year, parallel-group, randomised, controlled trial. *Lancet Diabetes Endocrinol.* 2016;4:747-755.
89. Cecchini M, Sassi F, Lauer JA, Lee YY, Guajardo-Barron V, Chisholm D. Tackling of unhealthy diets, physical inactivity, and obesity: health effects and cost-effectiveness. *Lancet.* 2010;376:1775-1784.
90. Batis C, Rivera JA, Popkin BM, Taillie LS. First-year evaluation of Mexico's tax on nonessential energy-dense foods: an observational study [serial online]. *PLoS Med.* 2016;13:e1002057.
91. Colchero MA, Popkin BM, Rivera JA, Ng SW. Beverage purchases from stores in Mexico under the excise tax on sugar sweetened beverages: observational study [serial online]. *BMJ.* 2016;352:h6704.
92. Sallis JF, Cerin E, Conway TL, et al. Physical activity in relation to urban environments in 14 cities worldwide: a cross-sectional study. *Lancet.* 2016;387:2207-2217.
93. Golden SH, Brown A, Cauley JA, et al. Health disparities in endocrine disorders: biological, clinical, and nonclinical factors—an Endocrine Society scientific statement. *J Clin Endocrinol Metab.* 2012;97:E1579-E1639.
94. Lopez L, Golden SH. A new era in understanding diabetes disparities among US Latinos—all are not equal. *Diabetes Care.* 2014;37:2081-2083.
95. Sohn MW, Kang H, Park JS, et al. Disparities in recommended preventive care usage among persons living with diabetes in the Appalachian region [serial online]. *BMJ Open Diabetes Res Care.* 2016;4:e000284.
96. Islami F, Stoklosa M, Drope J, Jemal A. Global and regional patterns of tobacco smoking and tobacco control policies. *Eur Urol Focus.* 2015;1:3-16.
97. Lortet-Tieulent J, Goding Sauer A, Siegel RL, et al. State-level cancer mortality attributable to cigarette smoking in the United States. *JAMA Intern Med.* 2016;176:1792-1798.
98. Khalaf N, Ying J, Mittal S, et al. Natural history of untreated hepatocellular carcinoma in a US cohort and the role of cancer surveillance. *Clin Gastroenterol Hepatol.* 2017;15:273-281.e1.
99. Grandhi MS, Kim AK, Ronnekleiv-Kelly SM, Kamel IR, Ghasebeh MA, Pawlik TM. Hepatocellular carcinoma: from diagnosis to treatment. *Surg Oncol.* 2016;25:74-85.
100. Llovet JM, Zucman-Rossi J, Pikarsky E, et al. Hepatocellular carcinoma [serial online]. *Nat Rev Dis Primers.* 2016;2:16018.
101. Bruix J, Reig M, Sherman M. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. *Gastroenterology.* 2016;150:835-853.
102. PDQ Adult Treatment Editorial Board. Adult Primary Liver Cancer Treatment (PDQ): Health Professional Version. PDQ Cancer Information Summaries. Bethesda, MD: National Cancer Institute; 2017.

103. Yang JD, Larson JJ, Watt KD, et al. Hepatocellular carcinoma is the most common indication for liver transplantation and placement on the waitlist in the United States. *Clin Gastroenterol Hepatol.* 2017; 15:767-775.e3.

104. Lanza E, Donadon M, Poretti D, et al. Transarterial therapies for hepatocellular carcinoma. *Liver Cancer.* 2016;6:27-33.

105. Hoehn RS, Hanseman DJ, Jernigan PL, et al. Disparities in care for patients with curable hepatocellular carcinoma. *HPB (Oxford).* 2015;17:747-752.

106. Wong RJ, Devaki P, Nguyen L, Cheung R, Nguyen MH. Ethnic disparities and liver transplantation rates in hepatocellular carcinoma patients in the recent era: results from the Surveillance, Epidemiology, and End Results registry. *Liver Transpl.* 2014;20:528-535.

107. Stewart SL, Kwong SL, Bowlus CL, et al. Racial/ethnic disparities in hepatocellular carcinoma treatment and survival in California, 1988-2012. *World J Gastroenterol.* 2016;22:8584-8595.

108. Johnson P, Berhane S, Kagebayashi C, et al. Impact of disease stage and aetiology on survival in hepatocellular carcinoma: implications for surveillance. *Br J Cancer.* 2017;116:441-447.

109. Cadier B, Bulsei J, Nahon P, et al. Early detection and curative treatment of hepatocellular carcinoma: a cost-effectiveness analysis in France and in the United States. *Hepatology*. 2017;65: 1237-1248.

110. PDQ Screening and Prevention Editorial Board. Liver (Hepatocellular) Cancer Screening (PDQ): Health Professional Version. PDQ Cancer Information Summaries. Bethesda, MD: National Cancer Institute; 2016.

111. Pinheiro PS, Morris CR, Liu L, Bungum TJ, Altekruse SF. The impact of follow-up type and missed deaths on population-based cancer survival studies for Hispanics and Asians. *J Natl Cancer Inst Monogr.* 2014;2014:210-217.