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ORIGINAL REPORT

Future of Hepatocellular Carcinoma Incidence in the United States Forecast Through 2030

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose

Hepatocellular carcinoma (HCC) incidence rates have been increasing in the United States for the past 35 years. Because HCC has a poor prognosis, quantitative forecasts could help to inform prevention and treatment strategies to reduce the incidence and burden of HCC.

Methods

Single-year HCC incident case and population data for the years 2000 to 2012 and ages 35 to 84 years were obtained from the SEER 18 Registry Database. We forecast incident HCC cases through 2030, using novel age-period-cohort models and stratifying by sex, race/ethnicity, and age. Rates are presented because absolute numbers may be influenced by population increases.

Results

Rates of HCC increased with each successive birth cohort through 1959. However, rates began to decrease with the 1960 to 1969 birth cohorts. Asians/Pacific Islanders (APIs) have had the highest HCC rates in the United States for many years, but the rates have stabilized and begun to decline in recent years. Between 2013 and 2030, rates among APIs are forecast to decline further, with estimated annual percentage changes of −1.59% among men and −2.20% among women. Thus, by 2030, Asians are forecast to have the lowest incidence rates among men, and Hispanics are forecast to have the highest rates among men (age-standardized rate, 44.2). Blacks are forecast to have the highest rate among women (age-standardized rate, 12.82).

Conclusion

Although liver cancer has long had some of the most rapidly increasing incidence rates, the decreasing rates seen among APIs, individuals younger than 65 years, and cohorts born after 1960 suggest that there will be declines in incidence of HCC in future years. Prevention efforts should be focused on individuals in the 1950 to 1959 birth cohorts, Hispanics, and blacks.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the dominant histologic type of liver cancer in the United States and accounts for approximately 75% of liver cancer cases.[1] In the United States, hepatitis C virus (HCV) is an important risk factor for HCC, particularly among persons born between 1945 and 1965, known as baby boomers.[2] The prevalence of chronic HCV infection among the 1945 to 1965 birth cohort is approximately 2.5% (2.06 million individuals), five times the rates seen among adults born in other years.[3] Compared with previous birth cohorts, the 1945 to 1965 birth cohorts also experience higher rates of other HCC risk factors, such as obesity and excess alcohol consumption.[4] Additional risk factors for HCC include chronic hepatitis B virus (HBV), diabetes, nonalcoholic fatty liver disease, and smoking.[5]

Because of the aging of the large 1945 to 1965 birth cohort, the age structure of the US population is changing. In a span of less than 20 years, the population of individuals older than 65 years is expected to increase from 43 million in 2012 to nearly 73 million in 2030. Consequently, the percentage of adults older than 65 years will also increase from 13.7% in 2012 to 20.3% in 2030,[6] when the youngest members of the 1945 to 1965 birth cohort will celebrate their 65th birthday. Thus, the 1945 to 1965 birth cohorts could experience a substantial burden of HCC in the coming years.

Because HCC has a poor prognosis, with a median survival time of approximately 11 months,[7] quantitative forecasts could help to inform

prevention and treatment strategies to reduce the incidence and burden of HCC. Therefore, we forecast incident HCC cases in the United States through 2030, using novel age-period-cohort (APC) models and stratifying by sex, race/ethnicity, and age.

METHODS

Incident HCC Data

Single-year HCC incident case and population data for calendar years 2000 to 2012 and ages 35 to 84 years were obtained from the Surveillance, Epidemiology, and End Results (SEER) 18 Registry Database.[8] Incident primary liver cancer was defined by International Classification of Diseases for Oncology, 3rd Edition, using topography code C22.0.[9] Because primary liver cancers identified by the C22.0 code may include rare primary liver cancers that are not HCC, HCC cases were identified by restricting cases to those with histology codes of 8170 to 8175. We also excluded intrahepatic bile duct tumors (ie, cholangiocarcinoma) by eliminating cases coded as C22.1. Individuals with unknown ethnicity were excluded (n = 191; 0.3%), for a total of 59,675 HCC cases. For examination of HCC incidence by birth cohort, we used the SEER 9 Registry Database for years 1975 to 2012.[10]

Population Data

The US Census Bureau 2012 National Population Projections provide projected population estimates for July 1, 2012 through July 1, 2060. These estimates of the US population are stratified by age (single years), sex, race, and Hispanic ethnicity. The population projections are constructed on the basis of July 1, 2011, estimates and assumptions about future births, deaths, and net migration. Population projections are provided as point estimates for planning purposes.[11]

APC Forecasting Models and Statistical Analysis

Our forecasting method used APC models to estimate future birth cohort–specific incidence rates and 95% CIs by age.[12,13] Detailed methodology for the APC models can be found in the Supplementary Methods of Rosenberg et al. In brief, these estimates are obtained by multiplying the estimated longitudinal age incidence rate curve in a referent birth cohort by the rate ratio between birth-specific cohorts and the referent cohort. However, in each future year, a new birth cohort enters and must be accounted for in the projections. Hence, a rate ratio for these new cohorts is obtained by extrapolating from a joinpoint piecewise log-linear regression model, which can account for changes in the slope of the curve,[14] using the cohort rate ratios of the observed cohorts. Thus, if the trend in younger cohorts is significantly different than older cohorts, the model extrapolates from the trend among the younger cohorts.[12,14]

For each APC model, goodness of fit was evaluated on the basis of the magnitude of the over-dispersion statistic, normality of residuals, and similarity between observed and fitted rates (Data Supplement). For this study, the APC models had negligible over-dispersion and there was no evidence of lack of fit.

We age-standardized the incidence rates per 100,000 person-years (ASRs), using the 2000 US Standard Population. To compute the burden, or projected absolute number of new HCC cases, we multiplied the projected incidence rates by age from the APC model by the projected population size from the US Census Bureau.[12] We also calculated estimated annual percentage changes (EAPCs) for the observed 2000 to 2012 rates and forecast 2013 to 2030 rates and percent change in burden between 2013 and 2030. Analyses were conducted using MATLAB version 14.[15]

Sensitivity Analysis

To facilitate comparison with prior research, we performed a sensitivity analysis of all liver cancers: C22.0 (HCC and other rare primary liver cancers) and C22.1 (intrahepatic bile duct cancer; Data Supplement).

In addition, we examined the effect of HCV treatment on HCC projections. Under two scenarios, we examined a linear uptake of second-generation direct-acting antivirals, with a 50% or 80% uptake of these drugs by 2030 (Data Supplement).

RESULTS

In this study, data were observed for 2000 to 2012 and forecast for 2013 to 2030, because SEER data are currently only available through 2012. In the observed period, Asians/Pacific Islanders (APIs) had the highest HCC rates, but these have begun to stabilize and decline. Incidence rates of HCC among other racial/ethnic groups have been observed to be increasing between 2000 and 2012.

Figure 1 shows the observed and projected incidence rates (per 100,000 person-years) among men (Fig 1A) and women (Fig 1B), by race/ethnicity. Rates are approximately 3.5 times higher among men than women. Rates among APIs are forecast to continue declining, with an EAPC for 2013 to 2030 of −1.59% in men and −2.20% in women (Table 1). Thus, by 2030, APIs are forecast to have the lowest incidence rates among men (ASR, 26.3) and similar rates to whites among women (ASR, 7.6). The rates among Hispanics are forecast to continue increasing in the coming years and will start to stabilize between 2025 and 2030. In 2030, Hispanics are forecast to have the highest incidence rates among men (ASR, 44.2) and second highest among women (ASR, 12.0). Incidence rates among blacks are forecast to increase for both men ($EAPC_{2013\text{-}2030}$, 1.52%) and women ($EAPC_{2013\text{-}2030}$, 2.52%). However, among men, the HCC rates are forecast to begin decreasing slightly between 2025 and 2030. Among women, blacks are forecast to have the highest HCC rates by 2030 (ASR, 12.82).

When age-specific incidence was examined by birth cohort (Fig 2A), we observed increased rates in each successive birth cohort born between 1895 and 1964. When people born during 1945 to 1964 were examined by 5-year birth cohorts a new pattern emerged (Fig 2B). Although age-specific rates increased in the 1950 to 1954 birth cohort compared with the 1945 to 1949 birth cohort, age-specific rates were similar in the 1950 to 1954 and 1955 to 1959 birth cohorts. Compared with the peak rates in these two birth cohorts, age-specific rates were lower among persons born during 1960 to 1964 at both 45 to 49 and 50 to 54 years of age. A notable spike in rates for the 1950 to 1959 birth cohorts is seen in all racial/ethnic groups, with the exception of Asians (Data Supplement).

The incidence rates for calendar years 2000 to 2012 and 2013 to 2030 are shown in Figure 3. This graph shows how the rates are going to change as the 1945 to 1965 birth cohorts age. In 2000 to 2012, individuals in the 1945 to 1965 birth cohorts are age 35 to 67 years, and in 2013 to 2030, they will be age 48 to 85 years. Thus, the spike in HCC rates seen among 65- to 84-year-olds in 2013 to 2030 is due to the aging of these birth cohorts. It is apparent from this graph that the forecast rates will continue to increase as the 1945 to 1965 birth cohorts age, but rates in the younger birth cohorts will decrease. For instance, HCC rates will be lower in 2013 to 2030

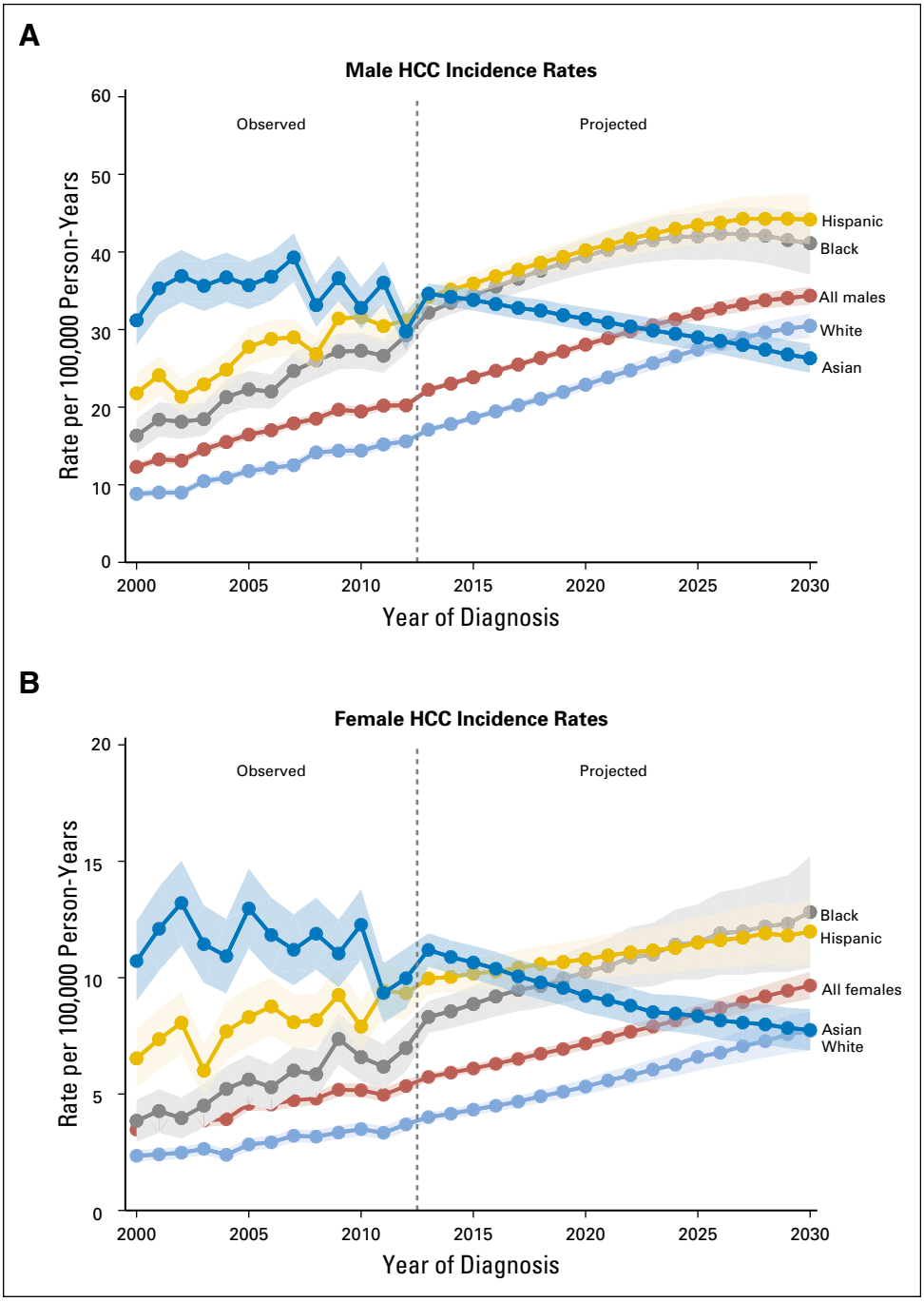

Fig 1. Observed and projected incidence of hepatocellular carcinoma (HCC; per 100,000 person-years) in SEER 18, overall and by race in (A) males and (B) females. Shaded bands show point-wise 95% confidence limits.

than 2000 to 2012 for persons age 55 years and younger, the majority of whom were born after 1965.

In Figure 4 and the Data Supplement, we note a similar trend in the younger age categories. As individuals in the 1945 to 1965 birth cohorts age beyond 64 years, the rates are forecast to continue to decline. However, the rates will continue to increase in the age category of 65 to 84 years, as individuals in 1945 to 1965 birth cohorts age.

Although whites are forecast to continue to have low HCC rates, compared with other race/ethnicities, they will have the greatest number of HCC cases, simply because of the proportion of the population that they represent. However, the largest increase in number of cases from 2013 to 2030 is faced by Hispanics (140.58%), as the population of Hispanics in the United States continues to grow (Table 1; Data Supplement).

In the sensitivity analysis (Data Supplement), we show potential scenarios of the impact of HCV treatment with second-generation direct-acting antivirals. If 50% of HCV infections are treated by 2030 (ie, 3.5% of remaining infections treated each year), we forecast a plateauing of HCC rates by 2025. If 80% of infections are treated by 2030, we forecast HCC rates will begin to decrease.

Table 1. Hepatocellular Carcinoma Incidence Rates (Per 100,000 Person-Years) and Burden Through 2030 by Sex and Race

Race/Ethnicity	2010*	2013		2020		2030		Burden (% change)	Rate EAPC	
	Rate	No.	Rate	No.	Rate	No.	Rate	2013-2030	2000-2012	2013-2030
All persons										
All	11.9	25,606	13.5	38,353	17.0	56,229	21.2	119.59	3.64	2.78
Asian	21.5	1,854	21.2	2,180	18.7	2,486	15.5	34.08	−1.14	−1.81
Hispanic	18.8	3,358	21.0	5,293	24.7	8,312	27.5	147.50	2.28	1.67
Black	15.7	4,072	18.6	6,090	23.2	7,868	25.5	93.23	3.37	1.92
White	8.7	14,644	10.2	22,862	13.6	35,191	18.3	140.32	4.22	3.65
Men										
All	19.4	20,072	22.2	29,882	28.1	42,411	34.4	111.29	3.65	2.69
Asian	32.8	1,398	34.6	1,650	31.4	1,861	26.3	33.14	−0.83	−1.59
Hispanic	31.6	2,604	34.2	4,097	40.2	6,273	44.2	140.93	2.24	1.59
Black	27.3	3,147	32.2	4,538	39.5	5,448	41.1	73.15	2.96	1.52
White	14.4	11,797	17.1	18,317	22.9	27,579	30.5	133.78	4.13	3.60
Women										
All	5.2	5,597	5.7	8,414	7.2	13,662	9.7	144.10	3.32	3.19
Asian	12.3	507	11.2	574	9.2	689	7.8	35.85	−2.14	−2.20
Hispanic	7.9	785	10.0	1,157	10.8	1,891	12.0	140.75	0.97	1.14
Black	6.6	964	8.3	1,467	10.2	2,220	12.8	130.30	2.81	2.52
White	3.5	2,923	4.0	4,527	5.3	7,627	7.7	160.90	3.90	4.07

Abbreviation: EAPC, estimated annual percentage change.
*Number of hepatocellular carcinoma cases for 2010 are not provided, because these numbers are based on SEER data and not extrapolated to the entire US population.

DISCUSSION

In the next 15 years, we project that HCC incidence rates among minority populations will begin to stabilize or decline and rates among whites will continue to increase. However, rates will remain highest in the black and Hispanic populations. The most striking finding is among men, where APIs are forecast to have significantly lower HCC rates than whites by 2030. In addition, we note that the rates among the 1945 to 1965 birth cohorts will continue to increase over time, and rates among younger birth cohorts will begin to decrease.

Previous publications have focused primarily on burden.[16-18] This can be misleading, because we expect the number of cases to increase simply because of the increasing size of the US population. Thus, we determined burden but focused on presenting HCC rates. One previous study[17] reported a higher number of expected cases than in the current report (Data Supplement), whereas the other two studies reported a lower number of liver cancer cases.[16,18] Rahib et al[17] reported a similar EAPC for 2010 to 2030 for women (2.9%) but a higher EAPC for men (3.7% *v* 2.4%). In addition, Weir et al[16] reported lower liver cancer rates in 2020. However, all of these studies are based on more limited SEER data, which were before the recent stabilization of HCC rates (2007 to 2011)[5,19] and unable to examine the trends among the minority populations of Hispanics and APIs.

The estimates of future incidence and burden in this study are the best assessment in light of current data. In particular, future prevalence rates of HBV, HCV, and obesity could alter these projections. Asian countries have some of the highest prevalence rates of HBV in the world.[20] Compared with other racial/ethnic groups, APIs in the United States historically have had the highest HCC rates, which has been attributed to the high rates of HBV infection among older individuals born outside the United States.[2] However, HCC rates among APIs have begun to decline in recent years.[19] Although vaccination penetration still varies by country,[21] in 1984 Taiwan became the first country to vaccinate newborns against HBV, and newborn HBV vaccination is now routine in many countries.[2] Thus, the high HCC rates forecast among APIs in the 35- to 49-year-old age group (Data Supplement) do not fully account for the effect of HBV vaccination, although this can vary depending on country and geographic area (ie, rural *v* urban) of immigrant origin. We predict that HCC rates among APIs in this youngest age group may likely be much lower than what the model forecasts, which is based on the current cohorts of 35- to 49-year-olds, who would have been born before newborn HBV vaccination. In addition, HBV rates are high in sub-Saharan Africa, with estimates as high as 22.4% in South Sudan,[20] and penetration of HBV vaccination remains low.[21] However, African immigration remains low, with 4% of the foreign-born population reporting Africa as region of birth compared with 28.2% reporting Asia in 2010.[22]

Approximately 22% of HCC in the United States is attributed to HCV,[23] and an estimated 1.60 million persons with HCV will be eligible for treatment between 2015 and 2020.[24] The prior standard of care (SOC) for HCV was interferon-based therapy, which is associated with considerable toxicity.[25] Second-generation direct-acting antivirals, including sofosbuvir, simeprevir, and sofosbuvir plus ledipasvir, were approved by the US Food and Drug Administration in 2013 and 2014.[26-28] These treatments have a sustained virologic response rate of $>$ 95% in most patients, are associated with fewer adverse effects than SOC therapy, and are given as a shorter course of treatment.[29,30] It is estimated that, compared with the SOC, sofosbuvir-ledipasvir could prevent an additional 310 HCC cases per 10,000 treated HCV cases.[24] However, these antivirals are expensive, with the per-patient cost of sofosbuvir-ledipasvir ranging from $66,000 to $154,000 depending on HCV genotype and treatment history.[24] At a willingness-to-pay threshold of $100,000 per quality-adjusted life-year, sofosbuvir-based therapies were estimated to be cost effective in 83% of patients.[24] However, this equates to $136 billion to treat

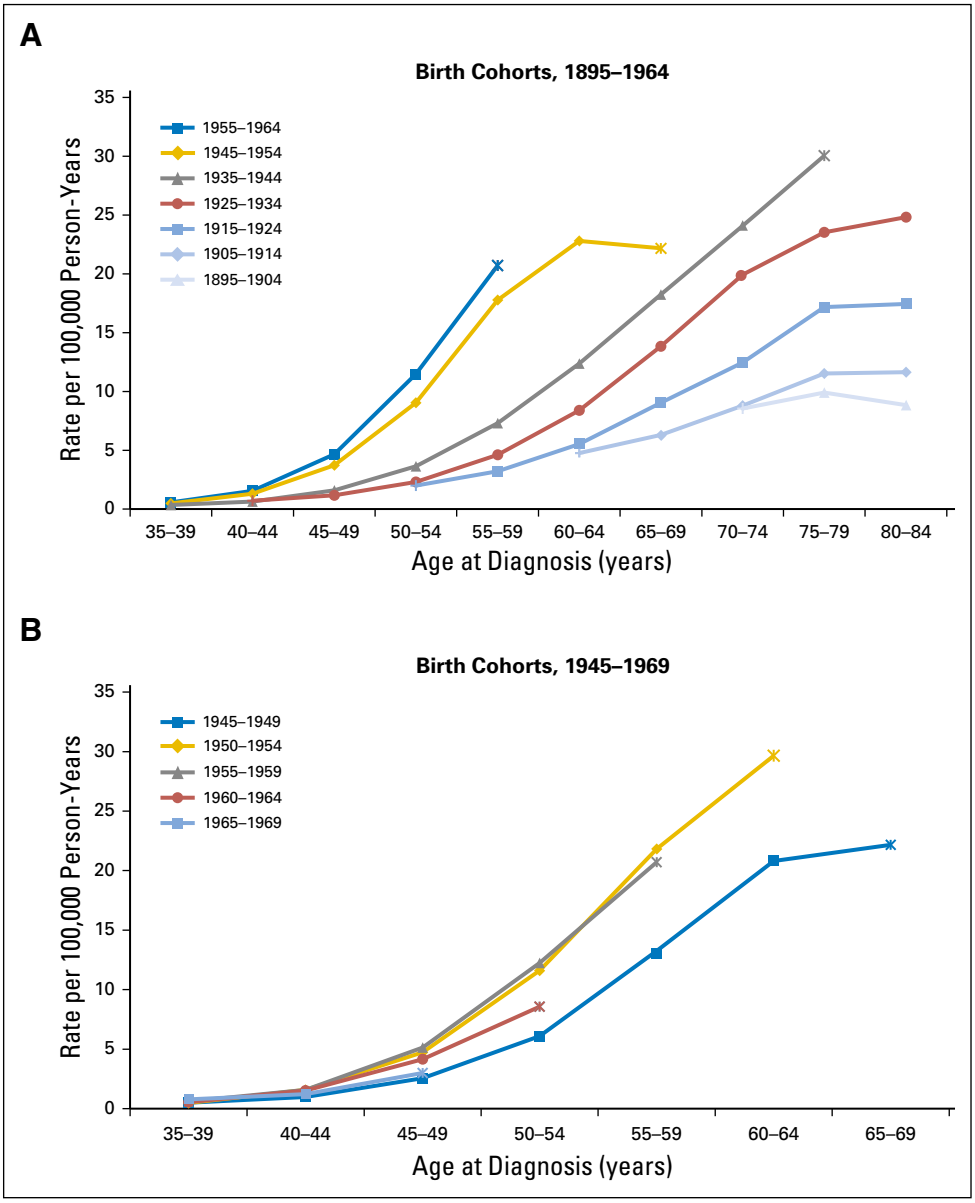

Fig 2. Age-specific hepatocellular carcinoma incidence rates per 100,000 person-years by decade of birth (cohort), (A) 1895 to 1964, and (B) 1945 to 1969, from SEER 9, 1975 to 2012. *Incidence rates for the most recent surveillance years are underestimated, as they do not include cases from the final birth years of each cohort and are not adjusted for delayed reporting. †Incidence rates for the most historic surveillance years are overestimated, as they do not include cases from the beginning birth years of each cohort.

all eligible patients with HCV with sofosbuvir-ledipasvir in the next 5 years, which is $65 billion more than the SOC, and the cost offsets (ie, reduced downstream costs from conditions such as HCC) would only be $16 billion.[24] Although the American Association for the Study of Liver Disease and the Infectious Diseases Society of America recommend treatment of all HCV cases with antiviral therapy except those with a short life expectancy due to comorbidities, the cost of antiviral treatment precludes widespread delivery. Thus, the American Association for the Study of Liver Disease and the Infectious Diseases Society of America have recommended that antiviral therapy be prioritized for individuals with the most near-term need, that is, individuals at highest risk of substantial morbidity and mortality from untreated HCV infection, including individuals with advanced fibrosis or compensated fibrosis, transplant recipients, and those with severe extrahepatic manifestations.[31] Although antivirals are currently prioritized for the most severe HCV infections, if treatment costs are reduced and antivirals can be administered to all persons presenting with HCV, this could have a notable impact on future HCC rates, as shown in our sensitivity analysis. However, cost of treatment is likely to remain a barrier to eradication of HCV for the foreseeable future.[32,33]

Although HBV and HCV are the strongest risk factors for HCC, obesity and related metabolic disorders, including diabetes, remain the most important risk factors for HCC in the United States, because 36.6% of HCC is attributed to obesity and diabetes.[23] In 2012, more than one third (34.9%) of adults were categorized as obese (body mass index $\geq$ 30 kg/m^2).[34] However, the obesity epidemic is predicted to continue in the near future, with rates in 2030 forecast to be between 39.5% and 50.7%.[35] We observed the effects of metabolic disorders in our HCC forecasts, because the subgroups with the highest obesity prevalence (ie, blacks and Hispanics)[34] also have the highest forecast HCC rates.

Our forecasts are based on 18 cancer registries rather than the entire population. The SEER program, however, covers approximately

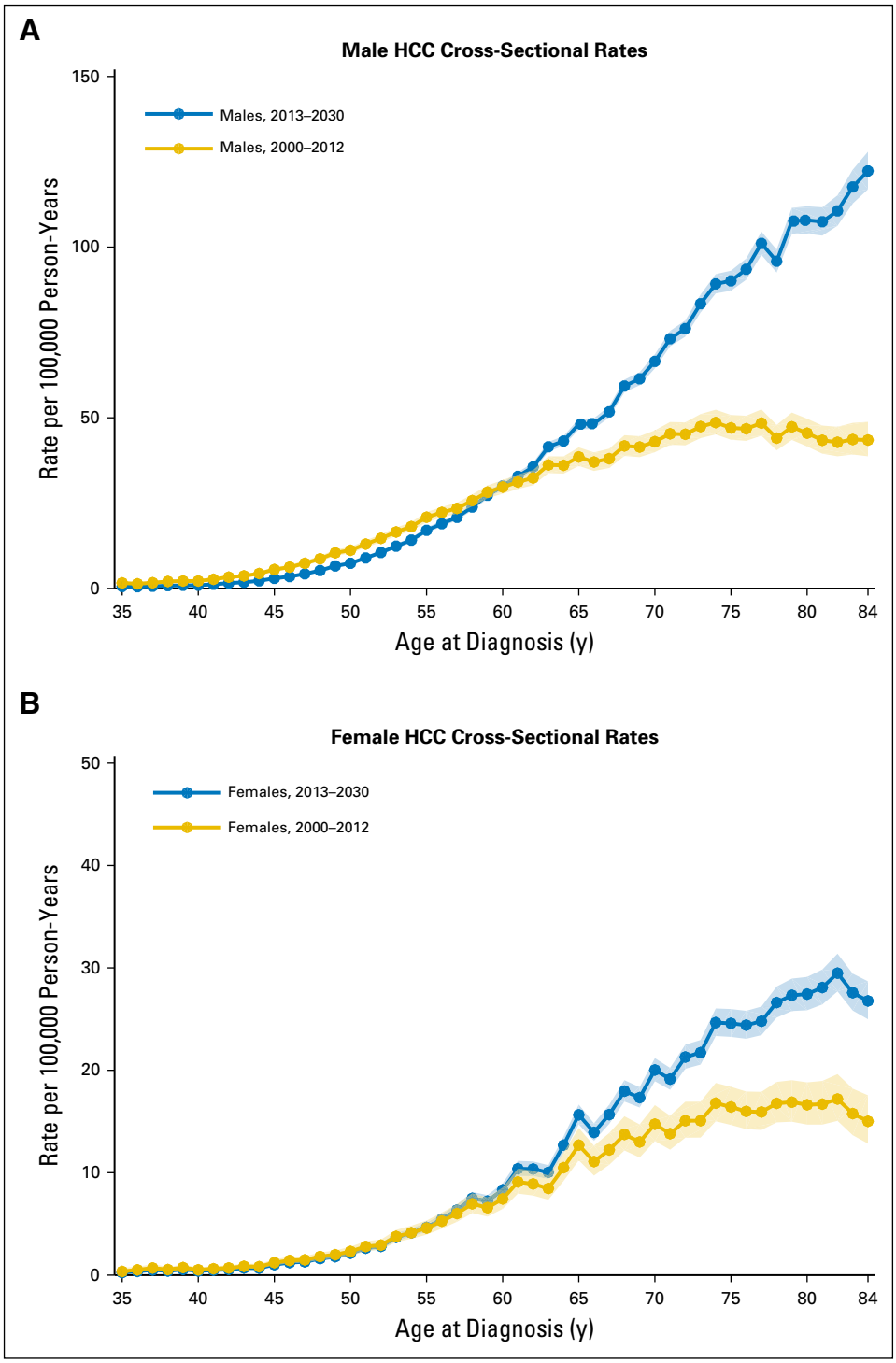

Fig 3. Incidence rates (per 100,000 person-years) of hepatocellular carcinoma (HCC) in SEER 18 by calendar period, 2000 to 2012 and 2013 to 2030 in (A) males, and (B) females. Shaded bands show point-wise 95% confidence limits.

28% of the United States and is believed to be fairly representative of the US population. In addition, SEER uses the North American Association of Central Cancer Registries Hispanic Identification Algorithm,[36] which may incorrectly classify individuals but has been shown to have high sensitivity (92.9), specificity (98.0), and positive predictive values (95.6).[37] Nevertheless, previous work has shown that the Hispanic population, as defined by the North American Association of Central Cancer Registries Hispanic Identification Algorithm, may be heterogeneous in terms of cancer risk[38] and screening practices.[39] Hispanic ethnicity may also be associated with race, and these associations could vary by region.[36] However, we were unable to examine further stratification of Hispanic ethnicity because of small sample size. We were also unable to examine first- versus second-generation immigrants, because HCC rates are known to vary by generation of immigration.[40] Another limitation is that we did not adjust for delayed data reporting.[41] However, delay in case reporting has been shown to be minimal for liver cancer.[42,43] In addition, there is underreporting due to lack of data from Veterans Affairs hospital

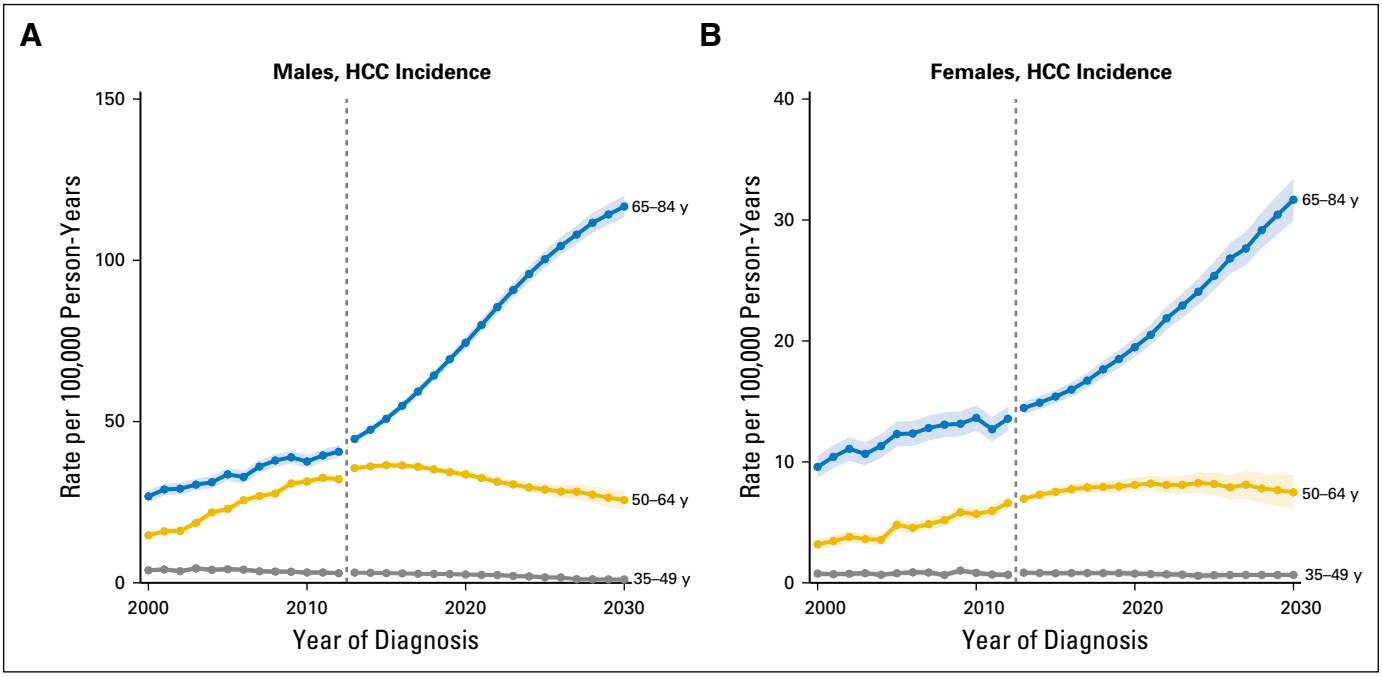

Fig 4. Observed and projected incidence of hepatocellular carcinoma (HCC; per 100,000 person-years) in SEER 18, by age group in (A) males, and (B) females. Shaded bands show point-wise 95% confidence limits.

patients during some years.[44] We also do not account for potential changes in HCC surveillance, which may result in lead-time bias (ie, early diagnosis of HCC) and affect the reported incidence patterns. However, previous reports have found that despite improvements in earlier HCC diagnosis, curative therapies did not follow the same trends.[45] Finally, as discussed above, it is unclear at this time how HBV vaccination of immigrant populations, HCV treatments, or obesity prevention measures may affect these projections.

Because previous forecasting efforts included all cancer types, they included all primary liver cancers (including intrahepatic cholangiocarcinoma as well as other rare liver cancers) and were not able to forecast HCC only, which may have different etiologic factors than other primary liver cancers.[46] In addition, because we focused solely on HCC, we were able to examine race/ethnic and age subgroups by sex. Thus, although our overall projections are similar to previous publications, no one has reported on the sharp decline in projected HCC rates seen in Asians. Finally, we were able to tease out increases in rates that are attributable to the 1945 to 1965 birth cohorts and project what the rates and burden will look like for younger birth cohorts.

Continued efforts should be focused on identifying and treating HCV among the baby boomer cohort, particularly for the birth cohorts of 1950 to 1959, where the highest HCC rates are noted. In addition, prevention efforts should focus on Hispanics and blacks, because both populations have high HCC rates, which will continue to increase in the coming years. Because there is no current end in sight to the obesity epidemic, continued efforts need to also focus on primary prevention of obesity. However, we predicted that rates among APIs will begin decreasing, until they have some of the lowest HCC rates in the future. Although liver cancer has long had some of the most rapidly increasing incidence rates,[47] the decreasing rates already seen among APIs, individuals younger than 65 years, and birth cohorts born after 1959 suggest that we may see continued declines in incidence of HCC in future years.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Jessica L. Petrick, Sean F. Altekruse, Katherine A. McGlynn, Philip S. Rosenberg
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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GLOSSARY TERMS

hepatocellular carcinoma (HCC): a type of adenocarcinoma. The most common form of liver cancer.

Surveillance, Epidemiology, and End Results (SEER): a national cancer registry that collects information from all incident malignancies in multiple geographic areas of the United States.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The Future of Hepatocellular Carcinoma Incidence in the United States Forecast Through 2030

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