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Liver Cancer Survival in the United States by Race and Stage (2001–2009): Findings From the CONCORD-2 Study

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Abstract

BACKGROUND—Worldwide, liver cancer is a leading cause of death for both men and women. The number of Americans who are diagnosed with and die of liver cancer has been rising slowly each year. Using data from the CONCORD-2 study, this study examined population-based survival by state, race, and stage at diagnosis.

METHODS—Data from 37 statewide registries, which covered 81% of the US population, for patients diagnosed during 2001–2009 were analyzed. Survival up to 5 years was adjusted for background mortality (net survival) with state- and race-specific life tables, and it was age-standardized with the International Cancer Survival Standard weights.

RESULTS—Liver cancer was diagnosed overall more often at the localized stage, with blacks being more often diagnosed at distant and regional stages than whites. 5-year net survival was 12.2% in 2001–2003 and 14.8% in 2004–2009. Whites had higher survival than blacks in both calendar periods (11.7% vs 9.1% and 14.3% vs 11.4%, respectively). During 2004–2009, 5-year survival was 25.7% for localized-stage disease, 9.5% for regional-stage disease, and 3.5% for distant-stage disease.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Behnoosh R. Momin: Writing–original draft and supervision. **Paulo S. Pinheiro:** Writing–review and editing. **Helena Carreira:** Data validation, formal analysis, and visualization. **Chunyu Li:** Writing–review and editing. **Hannah K. Weir:** Conceptualization and writing–review and editing.

CONCLUSIONS—Some progress has occurred in survival for patients with liver cancer, but 5-year survival remains low, even for those diagnosed at the localized stage. Efforts directed at controlling well-established risk factors such as hepatitis B may have the greatest impact on reducing the burden of liver cancer in the United States.

Keywords

cancer registries; hepatitis; liver; population-based survival

INTRODUCTION

Worldwide, liver cancer is the fifth most common cancer among men, the ninth most common cancer among women, and the second most common cause of cancer death for men and women combined.[1] Recent reports from North America, Europe, and Japan have shown that the incidence of hepatocellular carcinoma (HCC), the most common histological type, is increasing.[2–5] The number of Americans who are diagnosed with and die of liver cancer each year has been rising slowly for several decades.[6] In 2013, 21,143 men and 8330 women were diagnosed with liver cancer, and 16,300 men and 7732 women died of liver cancer.[7] According to the 2015 annual report to the nation, US death rates for most cancers declined or were stable from 2003 to 2012 among men and women of each racial and ethnic group; an exception was liver cancer, for which the incidence rates increased for most racial and ethnic groups.[8] For men and women, US liver cancer incidence rates were highest among American Indians/Alaskan Natives, followed by Asian Pacific Islanders and Hispanics. Liver cancer incidence rates among US men were more than twice those among US women.[8]

Chronic hepatitis B virus (HBV) and chronic hepatitis C virus (HCV) infection, and cirrhosis all contribute to the risk of HCC. HBV and HCV infections account for an estimated 78% of global HCC cases.[9] In addition, excessive alcohol consumption, obesity, rare metabolic disorders, type 2 diabetes mellitus, and nonalcoholic fatty liver disease are other known risk factors for liver cancer.[10] Most cases of HCC are preventable. Methods to reduce the risk of liver cancer include evidence-based strategies and interventions related to the risks associated with hepatitis. Vaccination against HBV infection for all infants at birth and for adults who may be at increased risk as well as testing for HCV and linking patients to follow-up care after testing leads to declines in the incidence of HCC.[8]

In contrast to many other cancers, the prognosis of patients with HCC is not highly correlated with the tumor stage. Cirrhosis underlies the neoplasm in most cases and has a major impact on the prognosis of patients with HCC.[11] The CONCORD-2 study reported survival for patients with cancer diagnosed from 1995 through 2009 in 67 countries, and it enabled comparison of the survival of patients in the United States with the survival of patients in other countries.[12] Liver cancer survival was low in all countries. The 5-year age-standardized net survival for patients diagnosed with liver cancer in 2005–2009 was less than 20% everywhere in Europe, in the range 15% to 19% in North America, and as low as 7% to 9% in Mongolia and Thailand. Between 1995–1999 and 2005–2009, 5-year age-standardized net survival for patients with liver cancer increased in the United States from 9% to 15%. This may be due to improved viral hepatitis services and medical management.

In the current study, using the largest data set available (population-based registry data from 37 states with 80.6% coverage of the US population), we expand the CONCORD-2 study by reporting liver cancer survival in the United States by race and stage at diagnosis. This information is critical for prioritizing, planning, and implementing cancer control interventions.

MATERIALS AND METHODS

Data Source and Variables

Thirty-seven state cancer registries that were affiliated with the National Program of Cancer Registries or the Surveillance, Epidemiology, and End Results Program and that participated in the CONCORD-2 study,[12] covering 81% of the US population, agreed to the inclusion of their data in these analyses. We analyzed individual tumor records for 126,261 adults (aged 15–99 years) who were diagnosed with cancer of the liver or intrahepatic bile ducts (*International Classification of Diseases for Oncology*, 3rd edition, codes C22.0-C22.1)[13] during 2001–2009 and were followed up through December 31, 2009. We included the first primary, invasive cancer of the liver, regardless of whether an individual had a previous cancer. If an individual was diagnosed with 2 or more cancers of the liver between 2001 and 2009, only the first was considered in the survival analysis.

We grouped patients by the year of diagnosis into 2 calendar periods (2001–2003 and 2004–2009) to reflect changes in the methods used by US registries to collect Surveillance, Epidemiology, and End Results Summary Stage 2000 (SS2000) data at diagnosis.[14] During 2001–2003, most registries coded SS2000 directly from the medical records. During 2004–2009, all registries derived SS2000 with the Collaborative Staging System.[15]

Survival Analyses

We analyzed survival by state, race (all races, black, and white), SS2000 (local, regional, distant, and unknown), and calendar period of diagnosis. Using the Pohar Perme estimator[16] we estimated net survival up to 5 years after diagnosis, with 95% confidence intervals. Net survival can be interpreted as the probability of survival up to a given time since diagnosis, after one has controlled for other causes of death (background mortality). To control for the wide differences in background mortality between participating states, we constructed life tables[17] of all-cause mortality in the general population of each state from the number of deaths and the population by single year of age, sex, calendar year, and, whenever possible, race (black or white), with a flexible Poisson model.[18]

We estimated net survival with the cohort approach for patients diagnosed in 2001–2003 because all patients had been followed up for at least 5 years by December 31, 2009. We used the complete approach to estimate net survival for patients diagnosed from 2004–2009 because 5 years of follow-up data were not available for all patients. Net survival was estimated for 5 age groups (15–44, 45–54, 55–64, 65–74, and 75–99 years). We obtained age-standardized survival estimates with the International Cancer Survival Standard weights.[19] If 2 or more of the 5 age-specific estimates could not be obtained, we present only the pooled, unstandardized survival estimates for all ages combined. Unstandardized

estimates are italicized in the tables. Trends, geographic variations, and differences in age-standardized net survival by race are presented graphically in bar charts and funnel plots.[20] Funnel plots of net survival for 2001–2003 and 2004–2009 provide insight into the variability of cancer survival in the United States by race and state, and show how much a particular survival estimate deviates from the pooled estimate of US registries (horizontal line) given the precision of each estimate. More details on data and methods are provided in the accompanying article.[21]

RESULTS

Liver cancer case distribution by race and stage at diagnosis by calendar period of diagnosis is reported in Table 1. In 2004–2009, liver cancer was mostly diagnosed at the localized stage (overall 41%), which was followed by the regional (24%) and distant stages (18%). The stage at diagnosis varied slightly by race, with blacks being more often diagnosed at distant and regional stages (20% and 26%, respectively, vs 17% and 24% for whites). However, state-specific analyses showed that the proportion of patients with an unknown stage at diagnosis ranged from 8% to 30%, and this makes accurate comparisons by race at the national level difficult (Supporting Table 1). Between the 2 calendar periods, there is an indication of a shift toward an earlier diagnosis of liver cancer, with an increase of 8% with localized-stage disease, an increase of 2% with regional-stage disease, and an increase of less than 1% with for distant-stage disease. In addition, there was a substantial decline in the proportion of cases recorded with an unknown stage at diagnosis (from 26% to 17%).

Although 5-year age-standardized net survival was low in the US (12% in 2001–2003 and 15% in 2004–2009), an improvement between the 2 calendar periods was observed (Fig. 1). Age-standardized estimates were available for 35 states; net survival increased between 2001–2003 and 2004–2009 in 30 states, whereas only 5 states showed a decrease. There was considerable variation by state in 2004–2009 in 5-year survival, which ranged from 8.1% in Wyoming to 20.9% in Florida (Supporting Table 2).

The 1-, 3-, and 5-year age-standardized net survival estimates for 2004–2009 were 38%, 21%, and 15%, respectively (Table 2). At each of these 3 time points, blacks showed lower age-standardized net survival than whites for all states combined. The difference was most pronounced in the first year after diagnosis, and this suggests that blacks have lower survival in the short term in addition to lower survival 5 years after the diagnosis. Only 4 states (Alabama, Michigan, North Carolina and Texas) in 5-year age-standardized net survival had a survival disadvantage for blacks versus whites. There was, however, a 5-year survival improvement for both races from 2001–2003 to 2004–2009: an absolute increase of 2.6% for whites and a 2.3% increase for blacks. The 5-year age-standardized net survival was 14.3% for whites and 11.4% for blacks. Overall 5-year survival for all races combined was 14.8%, which was higher than survival for both blacks and whites.

The 5-year age-standardized net survival estimates by stage (Table 3) for 2004–2009 were uniformly low at 26%, 10%, and 4% for localized, regional, and distant stages, respectively. For the localized stage, increases in survival were observed between 2001–2003 and 2004–2009 with a 2.8% increase for all races, a 2.4% increase for whites, and a 5.0% increase for

blacks. For regional and distant stages, smaller increases were observed, except for blacks diagnosed with regional-stage disease, for whom there was a decline in survival of 1%. Although 5-year net survival was low in all states, there was considerable variation by stage and state (Supporting Table 3).

Figure 2 shows funnel plots of net survival for 2001–2003 and 2004–2009 to provide further insight into the variability of liver survival in the United States by race and state. Although survival for patients with liver cancer was generally low in all states in both calendar periods, survival for black patients was lower than survival for white patients, and in most states, it was lower than the pooled US value.

DISCUSSION

Using recent population-based data, this study reports the most comprehensive comparison of trends in the United States for 5-year survival for patients with liver cancer. The 5-year age-standardized net survival for patients with liver cancer reported in this analysis was low (15%) for the most recent period, but it was slightly higher than in 2001–2003 (12%). This slight increase may be partially explained by the increased proportion of patients diagnosed at the localized stage, who have shown improved survival in the most recent years. Five-year survival in the United States is slightly lower but is still closely aligned with the 5-year survival estimates of Canada (17.7% [16.8%–18.7%], 2005–2009) and is slightly higher than survival in the United Kingdom (9.3% [8.7–9.9%], 2005–2009).[12] This study noted some variations in survival by state and race. Whites had higher survival than blacks in both calendar periods. In addition, five-year net survival was higher in white women than white men, and higher in black women than black men (data not shown). The survival advantage for women contrasts with the findings reported for Europe in the late 1990s: Micheli et al[22] reported an advantage for women for 11 of 26 cancer sites; this advantage was not reported for liver cancer. This difference may reflect a difference in US and European populations. An early diagnosis of liver cancer is challenging because many of the symptoms associated with this disease do not present until later stages. In addition, because of the location of the liver beneath the rib cage, liver tumors are difficult to detect.

This study suggests that there has been some improvement in liver cancer survival. Advances in treatment strategies have likely contributed to this improvement. Surgical resection, liver transplantation, and ablation are associated with best long-term survival. Surgical resection is usually performed in patients with localized HCC and sufficient preserved liver function. Liver transplantation is the best option for patients with decompensated cirrhosis and a solitary lesion (<5 cm) or early multifocal disease (≤3 lesions, ≤3 cm in diameter).[23] When liver resection or transplantation is feasible, ablation may be used, particularly for patients with early-stage HCC that is centrally located in the liver. Disparities in access to and receipt of appropriate surgical care may play an essential role in the racial differences that we observed in liver cancer survival. Studies have shown that African Americans and Asians with localized HCC are significantly less likely to receive a transplant than their white counterparts.[24] In addition, African American patients have been found to be younger and to have a more advanced stage of disease than white patients, and they are also more likely to die while waiting for a transplant.[25] However,

survival disparities by race may not be explained by differences in care only. Artinyan et al[26] reported that racial differences in survival remained significant among patients who underwent liver transplantation.

Clinical Implications

To improve the survival of patients with liver cancer, adherence to evidence-based treatment protocols among all population groups, and other factors, including biologic factors, responses to therapy, patient comorbidities, posttreatment follow-up and care, and tumor recurrence, all need to be considered. Increased recruitment of non-white populations to liver cancer clinical trials may help to alleviate racial differences in survival and improve the understanding of race-based differences in cancer biology.[27] HBV or HCV can cause persistent active hepatitis and hepatic fibrosis, which lead to the development of HCC and also have a major impact on the prognosis of patients with HCC by affecting the rate of recurrence after surgery.[28–30] Interferon therapy has shown to be beneficial for patients with hepatitis virus–associated HCC and can improve their outcome after curative resection.[31]

Cancer Control Implications

Because most liver cancers are preventable,[8] cancer control efforts and resources that support preventing infection and promoting viral hepatitis services should be prioritized.[8,32,33] Approximately 22% of HCC cases among those 65 years old or older in the United States can be attributed to HCV,[10] and an estimated 1.6 million persons will be eligible for HCV treatment by 2020.[34] Antiviral therapies for HBV and HCV can help to prevent liver cancer, and they also result in decreased neuroinflammation in the liver and over time cause a reversal of fibrosis, which also leads to a decreased HCC risk.[35] In 2012, the CDC recommended 1-time HCV testing for persons born from 1945 to 1965 (47–67 years old in 2012).[36] In the following year, the US Preventive Services Task Force issued similar recommendations.[37] According to the National Academies of Science, Engineering, and Medicine,[38] limited public and provider awareness and limited public resource allocation are the primary underlying causes of high rates of chronic HBV and HCV infections in the United States.[38] In the United States, Asians have the highest incidence of HBV infection.[39] However, for other populations (non-Asians), the incidence of HBV infection is not as much a concern as the incidence of HCV infection, which assumes a bigger role in the etiology of liver cancer.[40] For the latter group, the patterns among immigrants are consistent and sex-specific: males, when coming to the United States, have higher incidence and mortality rates, but females have stabilized or slightly decreased rates. This has been shown for different populations (Hispanics and non-Hispanic blacks).[41–43] The CDC's National Comprehensive Cancer Control Program is currently working on the development and implementation of an action plan that would facilitate greater implementation and uptake of strategies within selected pilot programs among population groups that have a high liver cancer burden.[44] The action plan will contain interventions specific to increasing support for vaccine-based strategies to eliminate HBV transmission and for the development of prevention and health services that include screening for HBV and HCV infections, linked to appropriate medical management and care (in alignment with recommendations), community education about HBV and HCV, and the improvement of viral hepatitis surveillance. Improved surveillance for HBV and for patients with HCV-

related cirrhosis has the potential to result in the detection of more cancers at a localized stage, when surgery may be possible and more beneficial.[45]

Strengths and Limitations

This analysis has several strengths, including the inclusion of a very large number of US states, which makes it the most geographically comprehensive survival study to our knowledge. Also, the sophisticated and complex methodology takes into account competing risks of death, which are higher for elderly cancer patients than younger cancer patients. Finally, more than 70% of all the cases included in this analysis were morphologically verified, and this contributed to the high quality of the data used.

A limitation of our analysis is that some stage and race categories had missing data or small numbers. The small black population in some states precluded the construction of life tables for the black populations in these states; therefore, the state-specific life tables for all races combined were used instead. In addition, data on populations with a higher burden of liver cancer, including Asians/Pacific Islanders and Hispanics, were not collected or analyzed in this study.

In conclusion, the incidence of cancer in the United States is expected to increase greatly because of demographic changes such as an aging population and a larger proportion of individuals from non-White racial/ethnic groups; it is estimated that liver cancer will have the second highest increase (59%) between 2010 and 2030 among all cancer sites.[46] This analysis suggests some progress in 5-year survival for liver cancer in the United States; however, there is still much more work that needs to be done to reduce the burden of this cancer. Improvements in the surveillance, prevention, and detection of HBV and HCV infections may have the greatest potential for earlier detection and thus increased survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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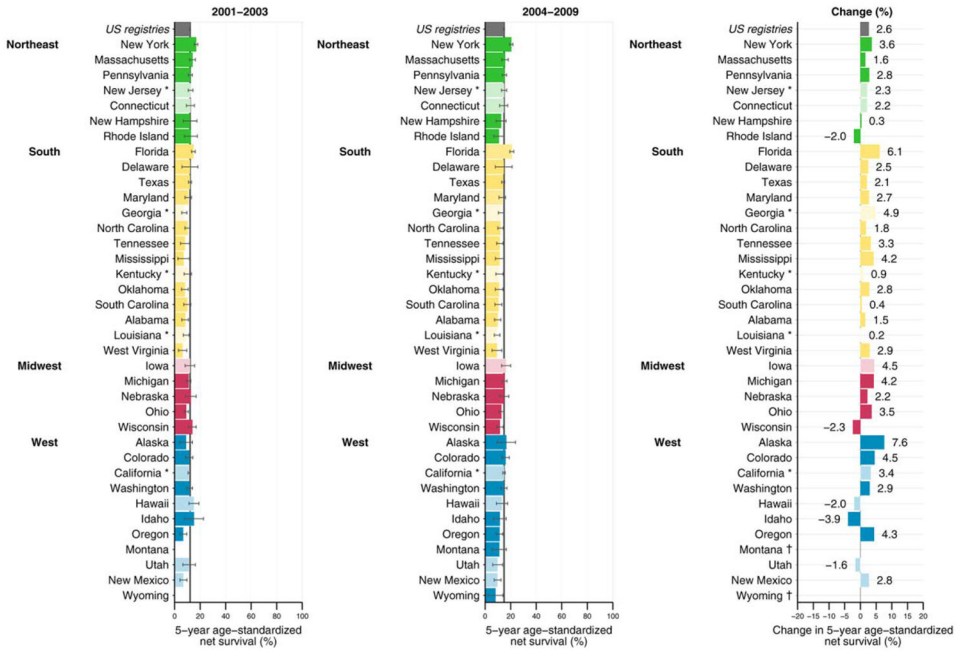

Figure 1.

Liver cancer: 5-year age-standardized net survival for males and females (15–99 years old) diagnosed 2001–2003 and 2004–2009 and absolute changes (%). The states are grouped by US Census region. Data from 37 statewide cancer registries (covering 80.6% of the population) are ranked within US Census regions by decreasing survival estimate for 2004–2009. Dark colors denote states affiliated with the National Program of Cancer Registries; pale colors denote states affiliated with the Surveillance, Epidemiology, and End Results Program; and an asterisk denotes states affiliated with both federal surveillance programs. † Indicate changes were not plotted if a survival estimate was not available for 1 calendar period or if 1 or more estimates were not age-standardized.

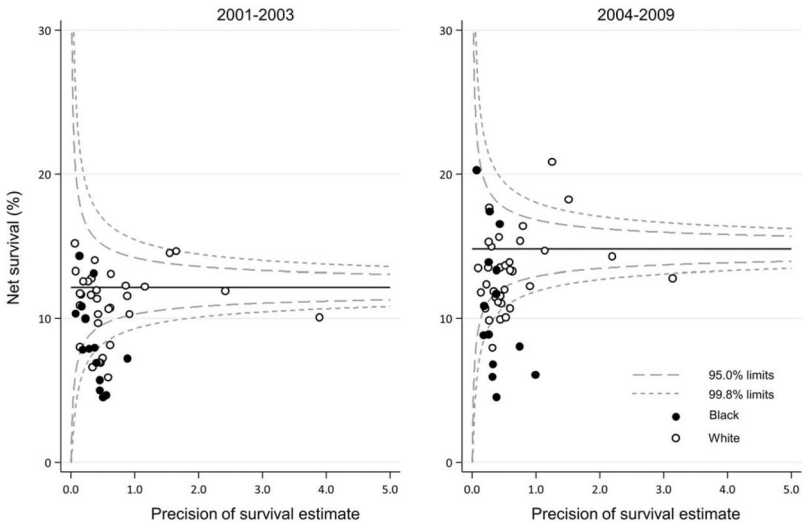

Figure 2.

Liver cancer: 5-year age-standardized net survival for males and females (15–99 years old) by state, race, and calendar period of diagnosis. The pooled (US) survival estimate for each calendar period is shown by the horizontal (solid) line with corresponding 95.0% and 99.8% control limits (dotted lines).

TABLE 1

Liver Cancer: Number of Males and Females (15–99 Years) Diagnosed Between 2001 and 2009 and Distribution by SEER Summary Stage 2000 at Diagnosis, Race, and Calendar Period of Diagnosis

	2001–2003			2004–2009		
SEER Summary Stage 2000	**All Races (n = 33,690)**	**Whites (n = 25,500)**	**Blacks (n = 4225)**	**All Races (n = 92,571)**	**Whites (n = 69,374)**	**Blacks (n = 13,002)**
Localized, %	33.4	33.2	30.4	41.0	40.9	38.8
Regional, %	22.4	21.6	23.6	24.4	23.8	25.9
Distant, %	18.4	18.2	20.4	17.6	17.4	19.8
Unknown, %	25.8	27.0	25.6	17.0	17.8	15.5

Abbreviation: SEER: Surveillance, Epidemiology, and End Results.

TABLE 2

Liver Cancer: Age-Standardized Net Survival (%) at 1, 3, and 5 Years for Patients (15–99 Years Old) Diagnosed Between 2001 and 2009 by Race and Calendar Period of Diagnosis

	2001–2003						2004–2009					
	All Races		Whites		Blacks		All Races		Whites		Blacks	
Years	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI
1	**31.8**	31.3–32.3	**31.7**	31.1–32.3	**27.3**	25.8–28.9	**38.2**	37.8–38.5	**38.0**	37.6–38.4	**32.9**	31.9–33.9
3	**16.2**	15.8–16.7	**15.7**	15.3–16.2	**13.2**	11.9–14.4	**20.5**	20.1–20.8	**19.9**	19.5–20.3	**16.5**	15.5–17.5
5	**12.2**	11.8–12.5	**11.7**	11.3–12.1	**9.1**	8.0–10.2	**14.8**	14.4–15.2	**14.3**	13.8–14.8	**11.4**	10.3–12.5

Abbreviations: CI, confidence interval; NS, net survival.

TABLE 3

Liver Cancer: 5-Year Age-Standardized Net Survival (%) for Males and Females (15–99 Years Old) Diagnosed 2001–2009 by SEER Summary Stage 2000 at Diagnosis, Race, and Calendar Period of Diagnosis

	2001–2003						2004–2009					
	All Races		Whites		Blacks		All Races		Whites		Blacks	
SEER Summary Stage 2000	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI
All stages	**12.2**	11.8–12.5	**11.7**	11.3–12.1	**9.1**	8.0–10.2	**14.8**	14.4–15.2	**14.3**	13.8–14.8	**11.4**	10.3–12.5
Localized	**22.9**	22.1–23.8	**22.4**	21.4–23.4	**15.8**	13.3–18.2	**25.7**	24.9–26.5	**24.8**	23.9–25.7	**20.8**	18.4–23.3
Regional	**8.3**	7.6–9.0	**7.6**	6.8–8.4	**8.3**	6.3–10.4	**9.5**	8.8–10.2	**9.2**	8.4–9.9	**7.1**	5.4–8.9
Distant	**2.8**	2.4–3.3	**2.4**	2.0–2.9	**2.5**	1.2–3.8	**3.5**	3.0–4.0	**2.9**	2.3–3.4	**3.8**	2.6–5.1
Unknown	**8.2**	7.6–8.9	**7.9**	7.2–8.7	**7.0**	5.3–8.8	**8.9**	8.2–9.6	**9.0**	8.1–9.8	**6.2**	4.6–7.8

Abbreviations: CI, confidence interval; SEER, Surveillance, Epidemiology, and End Results.