

The Continuing Increase in the Incidence of Hepatocellular Carcinoma in the United States: An Update

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Background: The incidence of hepatocellular carcinoma was reported to be increasing in the United States. However, alternate explanations were diagnostic or reclassification bias and changes in the demographic features of the general population.

Objective: To examine the temporal trends in the incidence of hepatocellular carcinoma.

Design: Retrospective cohort study.

Setting: Information collected by population-based registries of the Surveillance, Epidemiology, and End Results (SEER) program.

Patients: Persons given a diagnosis of hepatocellular carcinoma between 1975 and 1998.

Measurements: Linear Poisson multivariate regression model, controlling for differences in age, sex, race or ethnicity, and geographic region among patients with hepatocellular carcinoma and in the underlying population.

Results: The overall age-adjusted incidence rates of hepatocellular

carcinoma increased from 1.4 per 100 000 in 1975 to 1977 to 3.0 per 100 000 in 1996 to 1998. There was a 25% increase during the last 3 years of the study compared with the preceding 3 years (1993 to 1995). The increase affected most age groups above 40 years, with the greatest increase in the 45- to 49-year-old age group. White men had the greatest increase (31%) in the last time period (1996 to 1998) compared with 1993 to 1995. The Poisson regression model confirmed an almost 2-fold increase in the incidence rate ratio for hepatocellular carcinoma between 1975 to 1978 and 1996 to 1998.

Conclusions: The incidence of hepatocellular carcinoma continues to increase rapidly in the United States, with rates increasing the fastest in white men 45 to 54 years of age. These findings are consistent with a true increase and could be explained by consequences of hepatitis C virus acquired during the 1960s and 1970s.

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We previously reported an increase in the incidence and mortality rates of hepatocellular carcinoma in the United States (1). Studies among U.S. hospitalized veterans, as well as those conducted in large single centers, indicated that approximately half of the observed increase was attributable to hepatitis C virus (HCV) infection, whereas the incidence of hepatocellular carcinoma related to hepatitis B virus (HBV), alcoholic liver disease, or idiopathic cirrhosis remained relatively stable (2, 3). If HCV were indeed responsible for the increasing rates of hepatocellular carcinoma, this increase would be expected to continue for at least several more years since 2 to 4 decades of chronic HCV infection is required to develop cirrhosis and subsequent hepatocellular carcinoma (4). On the other hand, if the increased rates of hepatocellular carcinoma were related to better detection due to technologically improved diagnostic testing, such an effect would be expected to plateau at some point in the future.

The observed increase in hepatocellular carcinoma could have other explanations. Changes in the demographic structure (age, sex, ethnicity, and geography) of the underlying population may have resulted in an increasing number of persons at high risk for hepatocellular carcinoma (older age and increased number of ethnic and racial minorities). Hepatocellular carcinoma is an age-dependent cancer that peaks in incidence between 75 and 79 years of age, and direct standardization methods may not have been sufficient to control for the effect of aging in the underlying population (5). The observed increase could also have resulted from an increase in high-risk sex or racial or ethnic

groups or the population residing in 1 or a few high-risk geographic regions (6). For example, rates of hepatocellular carcinoma were severalfold higher in Asian Americans than in white people, and African Americans had rates between those of the other 2 groups (1).

The current study was designed to update the recent trends in hepatocellular carcinoma incidence by using data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) registries and to examine the temporal trends in hepatocellular carcinoma through adjustments for potential changes in several influential factors.

METHODS

Data Sources: SEER

Beginning in 1973, the SEER registry program was established to identify all new cancer cases diagnosed in 7 geographic areas. By 1975, SEER included 9 geographic regions, 5 states (Connecticut, Hawaii, Iowa, New Mexico, and Utah) and 4 metropolitan areas (San Francisco–Oakland in California; Seattle–Puget Sound in Washington; Detroit, Michigan; and Atlanta, Georgia). In 1992, the Los Angeles County and San Jose–Monterey areas in California joined the SEER program, expanding the representation to approximately 14% of the U.S. population. Overall, the SEER population is similar to the general U.S. population, particularly in measures of poverty and education. However, SEER regions are more urban and have a higher proportion of foreign-born persons than the general U.S. population. Data for this study were obtained from

Context

Incidence rates of hepatocellular carcinoma have been increasing in the United States.

Contribution

This large, retrospective, population-based cohort study confirmed an almost 2-fold increase in the incidence of hepatocellular carcinoma from 1975 to 1998. Increases were seen in all ethnic groups and in most age groups after 40 years of age. Although black people and older people remained most at risk, the largest recent increase in rates (from 1995 to 1998) occurred in white men 45 to 54 years of age.

Implications

The incidence of hepatocellular carcinoma continues to increase rapidly in the United States, especially in white, middle-aged men.

—The Editors

SEER*STAT public-use data files (National Cancer Institute, Bethesda, Maryland), available on CD-ROM from the National Cancer Institute (7). Data from the SEER public-use CD-ROM were converted into SAS datasets for further analyses (SAS software, version 8.2, SAS Institute, Inc., Cary, North Carolina).

Demographic and cancer-related information included in this database are obtained by medical record review. Studies are conducted annually at each SEER registry site to verify that data are being collected accurately and that case ascertainment is at least 98%. Types of cancer are coded according to the International Classification of Disease for Oncology (ICD-O) (8). There are several categories of race or ethnicity, including Hispanic white, non-Hispanic white, Chinese, Japanese, Filipino, Pacific Islander, and American Indian. However, accurate information on the underlying population in the areas covered by the SEER program is available only on race classified as white (which includes Hispanic), black, or other (which includes all other ethnic groups listed). As a result, valid incidence rates can be calculated for only these 3 broad racial or ethnic groups (white, black, and other).

Study Sample

Patients eligible for inclusion in this study were all individuals with hepatocellular carcinoma (ICD-O code 8170) identified from 9 SEER registries between 1975 and 1998. Patients younger than 20 years of age were excluded to avoid including those with hepatoblastoma (<1% of total cases). Cases in which the patient's race or ethnicity was unknown (<1% of total cases) also were excluded. To examine the potential role of diagnostic bias, we calculated the proportion of cases with microscopic confirmation, which is defined by SEER as the presence of a confirmatory

histologic or cytologic evidence of hepatocellular carcinoma.

Statistical Analysis

The age-adjusted incidence rates for hepatocellular carcinoma were calculated for 3-year periods between 1975 and 1998. Sex- and ethnicity-specific, age-adjusted incidence rates and their 95% CIs were calculated. Adjustment was made to the 1990 U.S. population. Age-specific incidence rates were calculated for all patients and for each of the 3 broad categories of race or ethnicity (white, black, and other). Among patients with hepatocellular carcinoma, we calculated the proportions of cases belonging to the following racial or ethnic groups: Hispanic white, non-Hispanic white, Asian (Chinese, Japanese, Filipino, or Pacific Islander), and others. We also calculated the proportion of patients with liver cancer who had microscopic confirmation for each time period. These calculations were made by using the SEER*STAT statistical software (7).

The temporal trends of the incidence of hepatocellular carcinoma were examined in linear Poisson multivariate regression models. We used SAS PROC GENMOD for this task. The model was used to analyze the effect of the period of diagnosis (independent variable) on the incidence of hepatocellular carcinoma (dependent variable), while controlling for several other independent variables including age (20 to 49, 50 to 64, 65 to 74, or ≥ 75 years), sex, race or ethnicity (white, black, or other), and differences in the geographic regions (9 SEER registries). Similar categories were assembled for the underlying population and were included as an offset variable in the model. Risk estimates (incidence rates and incidence rate ratios) and 95% CIs were calculated for all the independent variables in the final model. The model was tested for interactions between time of diagnosis and each variable of age, sex, and race or ethnicity.

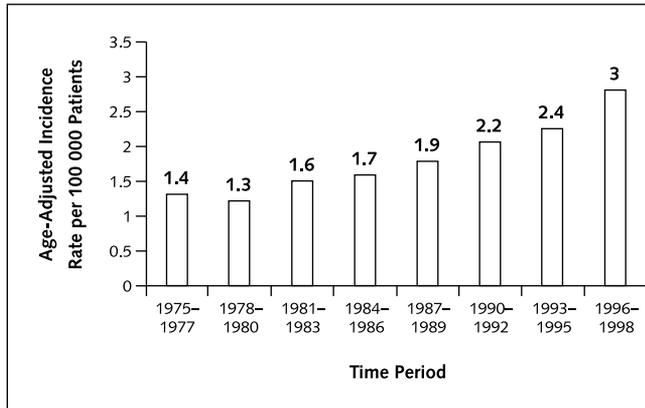
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RESULTS

Between 1975 and 1998, there were 11 547 cases of hepatocellular carcinoma. The overall age-adjusted incidence rates of hepatocellular carcinoma started to increase in the early 1980s, from 1.3 per 100 000 persons in 1981 to 1983 to 3.0 per 100 000 persons in 1996 to 1998 (Figure 1). This is equivalent to a 114% overall increase throughout the study period. There was a 25% increase during the last 3 years of the study (1996 to 1998) compared with the previous 3 years (1993 to 1995). The proportions of patients with liver cancer who underwent microscopic confirmation were relatively stable during the study period: 86%, 86%, 84%, 82%, 78%, and 80% in consecutive 3-year periods between 1981 and 1998, respec-

Figure 1. The overall age-adjusted incidence rates for hepatocellular carcinoma for consecutive 3-year periods between 1975 and 1998.



tively. All hepatocellular carcinoma cases were included in subsequent analyses regardless of microscopic confirmation.

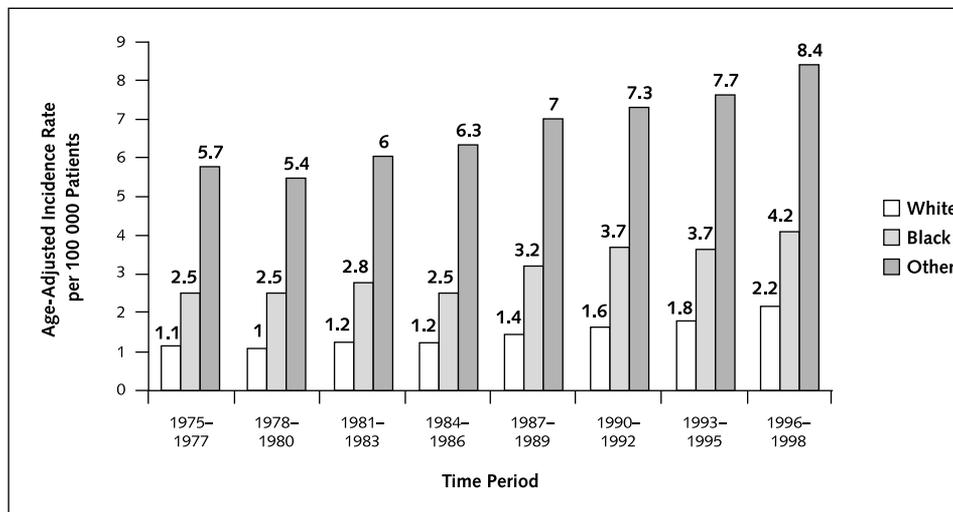
In addition to the variable of more recent time period, age, sex, race or ethnicity, and geographic region were statistically significant determinants of the incidence of hepatocellular carcinoma. Hepatocellular carcinoma was rare among individuals younger than 40 years of age, and the incidence peaked at 75 to 79 years of age. Concomitant with the increase in incidence, the age distribution of patients with hepatocellular carcinoma progressively shifted toward relatively younger persons. **Figure 2** shows the temporal changes in the age distribution of new cases of hepatocellular carcinoma in men, with age-specific incidence rates for consecutive 3-year periods from 1975 to 1998. The incidence has increased in most age groups older than 40 years; the greatest increase occurred in patients 45 to 55

years of age. For example, in the 1990s, the incidence rates increased 110% among white men 45 to 49 years of age and 60% among white men 50 to 54 years of age (**Figure 3**). Similar trends were seen for women (data not shown); the greatest increase in incidence occurred in women 60 to 69 years of age.

Throughout the study period, the age-adjusted incidence rates of hepatocellular carcinoma were 3 to 4 times higher in men than women. Similarly, the incidence rates were 2 times higher in black people than white people and 2 times higher in patients of “other” race or ethnicity (predominantly Asian) than black people (**Figure 4**). However, the age-adjusted incidence rates increased statistically significantly in both men and women in all racial or ethnic groups during more recent time periods. Over the entire study span (1975 to 1998), white men had the greatest rate of increase. In the subgroups, white men had the greatest percentage increase (31%) during the last time period (1996 to 1998) as compared with 1993 to 1995, whereas men of “other” race or ethnicity had the lowest percentage increase (11%). The age-adjusted incidence rates of hepatocellular carcinoma also varied statistically significantly by geographic region (as represented by the 9 SEER registries). The highest overall rates were in Hawaii (4.5 per 100 000 persons) and the lowest were in Utah (1.0 per 100 000 persons).

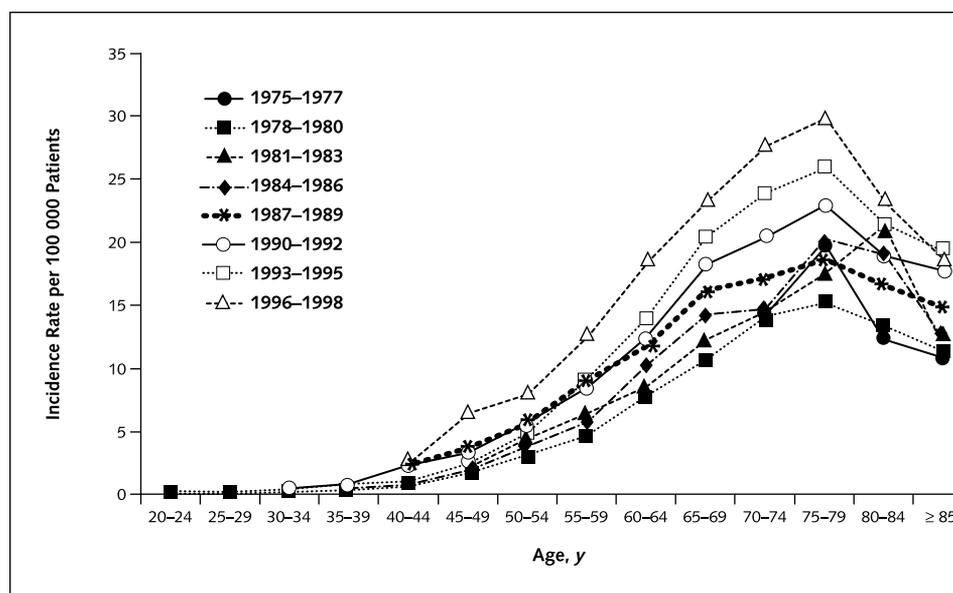
Of all patients with hepatocellular carcinoma, white people made up 63.4%, black people made up 12.5%, and people of “other” race or ethnicity made up 24.1%. Hispanics constituted 5% of patients with hepatocellular carcinoma labeled as white, and this proportion did not change appreciably throughout the study period. Similarly, persons of “other” race or ethnicity were predominantly Asian American (88%), with little change in this proportion throughout the study period. Age-adjusted rates could

Figure 2. Temporal trends in the age distribution of hepatocellular carcinoma.



Age-specific incidence rates are shown for consecutive 3-year periods between 1975 and 1998.

Figure 3. Temporal trends in age-specific incidence rates for white men 45 to 49 years of age and 50 to 54 years of age.

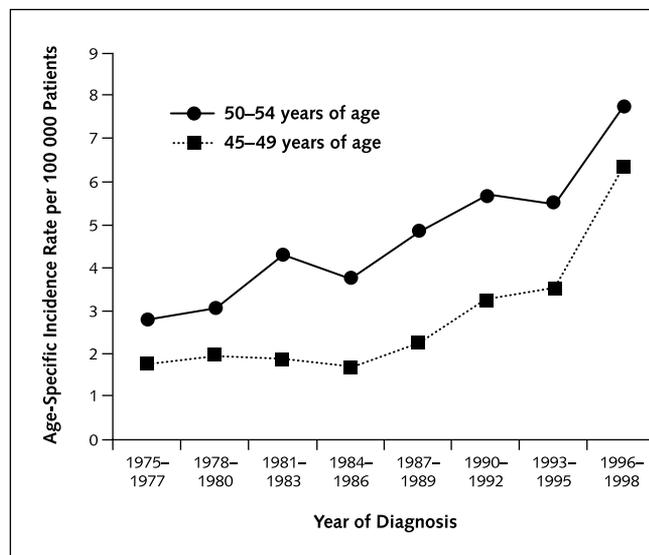


not be calculated for Hispanics, who were included with white people, or for subgroups constituting the “other” race or ethnicity category because of the absence of an appropriate denominator in the SEER database (see Methods section).

The Poisson regression analyses allowed adjustment for changes over time in the demographic features of patients with hepatocellular carcinoma, as well as in those of the underlying population at risk. Table 1 shows the results of the model. The model confirmed an almost 2-fold increase (82%) in the incidence rate ratio of hepatocellular

carcinoma between 1975 to 1978 and 1996 to 1998 while controlling for concomitant changes in age, race or ethnicity, sex, and geographic region. The model also calculates an approximately 3-fold and 5-fold higher incidence rate ratio in black people and people of “other” race or ethnicity (predominantly Asian), respectively, as compared with white people. However, significant interaction between time of diagnosis and race or ethnicity was detected ($P < 0.0001$). This interaction indicated that white people had a greater incidence rate ratio of hepatocellular carcinoma than black people and persons of “other” race or ethnicity during more recent time periods (data not shown).

Figure 4. Age-adjusted incidence rates for hepatocellular carcinoma broken down by sex and race or ethnicity for consecutive 3-year periods between 1975 and 1998.



DISCUSSION

The incidence of hepatocellular carcinoma continues to increase in the United States, with a 2-fold increase between 1975 and 1998 and a 25% increase since our last report in 1995. Our analysis of this increase in hepatocellular carcinoma incidence has accounted for potential changes over time in the age, sex, and race or ethnicity of patients with hepatocellular carcinoma as well as those of the underlying population. In addition, we controlled for differences in incidence among the geographic regions in which cases were diagnosed and for the potential clustering of persons with similar characteristics in the same geographic region. Among the races or ethnicities examined, white people had the lowest overall incidence rates of hepatocellular carcinoma but were affected the most by the recent increase. Persons of “other” race or ethnicity (predominantly Asian), on the other hand, had the highest overall rates but were affected the least by the increase. Although older people remain most at risk for hepatocel-

lular carcinoma, a shift toward increasing incidence in young age groups continues.

The observed increase in the incidence of hepatocellular carcinoma is unlikely to have resulted from changes in the demographic features (age, sex, and race or ethnicity) of the underlying population toward traditionally high-risk groups for this malignant condition. First, an aging population is an unlikely explanation for the increase in hepatocellular carcinoma, evidenced by increasing age-adjusted rates, the shift of cases with hepatocellular carcinoma toward younger age groups, and the persistence of the time-related increase while adjusting for age in a multilevel, multivariate model. Second, although men consistently had higher age-adjusted incidence rates than women, no disproportionate increase was detected in the frequency of men in either cases of hepatocellular carcinoma or in the underlying population at risk. In general, men constituted a constant proportion of patients with hepatocellular carcinoma and persons at risk during a consecutive 3-year time period. Third, changes in the race or ethnic composition of the underlying population were unlikely to account for the observed temporal changes in the incidence of hepatocellular carcinoma. Although black men or those of "other" race or ethnicity have the highest rates of hepatocellular carcinoma compared with women and white people, respectively, the incidence has increased in all racial or ethnic groups and has affected white men disproportionately in the most recent time period. In this study, the inclusion of sex or race or ethnicity as independent variables in the regression model had little effect on the observed increase over time. Although Hispanics were included with white people, they constituted approximately 5% of cases; thus, hepatocellular carcinoma in Hispanics is unlikely to have statistically significantly affected the overall rates for whites. Similarly, although the underlying population (denominator) was not available for persons of "other" race or ethnicity, Asian Americans were a constant majority (88%) throughout the study period.

The role of HBV in this increase is likely to be less important than that of HCV, with the exception of HBV among Asian Americans. Serologic studies have shown that recent immigrants from HBV-endemic areas (for example, Southeast Asia) and their descendants are at high risk for chronic HBV infection and HBV-related hepatocellular carcinoma (9). However, in our study, Asian Americans and Pacific Islanders made up a relatively constant proportion that ranged between 18% and 25% of the total cases with hepatocellular carcinoma. Increased detection and diagnosis might also have contributed to the observed trends, although continuing increase and the relatively unchanged rates of microscopically confirmed cases argues in favor of a true increase.

Another strength of this study relates to the validity and generalizability of its data source. Annual studies of SEER registries evaluate quality and completeness of data being reported. The SEER data are considered highly valid;

Table 1. Results of Multivariate Analysis Using Hierarchical Poisson Regression To Examine the Association between the Incidence of Hepatocellular Carcinoma and Time of Diagnosis, Age, Race or Ethnicity, Sex, and Geographic Region

Variable	Incidence Rate Ratio (95% CI)	P Value
Time of diagnosis		
1975–1977 (reference)	1.0	
1978–1980	0.92 (0.84–1.01)	0.092
1981–1983	1.12 (1.02–1.23)	0.014
1984–1986	1.15 (1.05–1.25)	0.003
1987–1989	1.25 (1.14–1.36)	<0.001
1990–1992	1.42 (1.31–1.54)	<0.001
1993–1995	1.56 (1.43–1.69)	<0.001
1996–1998	1.82 (1.69–1.97)	<0.001
Age group		
20–49 y (reference)	1.0	
50–64 y	8.54 (8.03–9.09)	<0.001
65–74 y	19.43 (18.27–20.67)	<0.001
≥75 y	23.80 (22.32–25.39)	<0.001
Race or ethnicity		
White (reference)	1.0	
Black	2.66 (2.51–2.83)	<0.001
Other	5.47 (5.15–5.81)	<0.001
Sex		
Men (reference)	1.0	
Women	0.32 (0.31–0.33)	<0.001
Geographic region (registry)		
Seattle–Puget Sound (reference)	1.0	
Hawaii	0.66 (0.66–0.72)	<0.001
Iowa	0.74 (0.68–0.81)	<0.001
Utah	0.76 (0.67–0.86)	0.06
Detroit–metropolitan	0.94 (0.88–1.01)	0.11
Atlanta–metropolitan	1.00 (0.91–1.09)	>0.2
Connecticut	1.07 (1.00–1.16)	<0.001
San Francisco–Oakland	1.18 (1.10–1.26)	<0.001
New Mexico	1.27 (1.16–1.39)	<0.001

all of the SEER registries hold the highest certification of data quality by the North American Association of Central Cancer Registries. Furthermore, the SEER standard for completeness of case ascertainment is 98%. The SEER registries provide population-based data with almost complete ascertainment of newly diagnosed cases of hepatocellular carcinoma between 1975 and 1998. This allows us to make comparisons over time while adjusting for changes in the demographic features of the underlying population in the 9 regions covered by SEER. Although the SEER registries were not randomly selected (rather they were chosen for the quality of the registries and to increase sampling of minorities), the SEER population is similar to the general U.S. population, particularly in measures of poverty and education (10, 11). However, SEER regions are more urban and have a higher proportion of foreign-born persons than the general U.S. population. We therefore believe that the overall findings from this study should also be generalizable to the entire U.S. population. Although it is impossible to control for all environmental factors in a region, linear modeling allowed for adjustment for racial differences in inhabitants of the geographic regions covered by SEER registries. However, given the absence of data on individual-level specific risk factors in the geographic re-

Table 2. Take-home points

The incidence of hepatocellular carcinoma has doubled in the United States between 1975 and 1998.

The biggest increase in the incidence of hepatocellular carcinoma occurred in the 1990s.

The increasing incidence of hepatocellular carcinoma cannot be explained by changes in demographic features of the general population.

White men 45 to 65 years of age are the most affected by the recent increase in hepatocellular carcinoma.

It seems likely that hepatitis C virus infection is partly responsible for the observed increase in hepatocellular carcinoma.

gion in which hepatocellular carcinoma was diagnosed, residual confounding is always possible.

We speculate that HCV infection is the likely explanation for at least a substantial portion of the increase in the incidence of hepatocellular carcinoma in the United States. Countries with overall HCV prevalence rates similar to that of the United States (approximately 2%) but with higher incidence rates of hepatocellular carcinoma (2 to 3 times higher in Italy and 8 to 10 times higher in Japan) (12, 13) are thought to have had earlier onset and peaks of the HCV epidemic than the United States. A study from the Centers for Disease Control and Prevention that used mathematical modeling estimated that the HCV epidemic started in the 1960s and peaked in the 1980s (14). Risk factors for transmitting HCV were rampant during this period (for example, injection drug use, needle sharing, and transfusion of unscreened blood and blood products). A recent study examined the constant evolutionary rate of HCV over time (“the molecular clock”) in retrospectively collected serum samples of HCV carriers in Japan and the United States (15). The study concluded that HCV first appeared in Japan around 1882 and in the United States around 1910, whereas widespread dissemination occurred in the 1930s in Japan and in the 1960s in the United States (15). These findings suggest that hepatocellular carcinoma in the United States will continue to increase for the near future. Currently, the highest prevalence HCV infection rate is among 40- to 50-year-old persons (16) who have been infected for 1 to 2 decades and are expected to live for another 2 to 3 decades with the increased potential for developing HCV-related complications.

We previously reported that hepatocellular carcinoma related to HCV accounted for approximately 50% of the recent increase in hepatocellular carcinoma among hospitalized veterans. In the meantime, non-statistically significant increases were observed in the incidence of hepatocellular carcinoma related to HBV, alcohol, or idiopathic cirrhosis (2). Similarly, in a single center study from the MD Anderson Cancer Center (3), hepatocellular carcinoma related to HCV increased from 18% during 1993 to 1995 to 31% during 1996 to 1998 ($P = 0.01$). Although not specifically examined with respect to the temporal trends of hepatocellular carcinoma, an increased risk for hepatocellular carcinoma in patients with nonalcoholic ste-

atohepatitis and those with diabetes is supported by growing evidence (17–19). No population-based studies have examined the presence of specific risk factors in patients with hepatocellular carcinoma; we strongly recommend that future studies use existing population-based SEER cancer registries to identify and collect these risk factors.

In conclusion (Table 2), hepatocellular carcinoma continues to increase rapidly in the United States, in all racial or ethnic groups, especially in white men, and in most age groups after 40 years of age, especially patients 45 to 55 years of age. The incidence of hepatocellular carcinoma in the United States is likely to continue to increase for the near future, as those infected with HCV ultimately develop cirrhosis, unless secondary prevention of hepatocellular carcinoma improves.

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