GASTROENTEROLOGY 2004;127:1372–1380

# Hepatitis C Infection and the Increasing Incidence of Hepatocellular Carcinoma: A Population-Based Study

JESSICA A. DAVILA,* ROBERT O. MORGAN,* YASSER SHAIB,† KATHERINE A. McGLYNN,§ and HASHEM B. EL–SERAG†

*Section of Health Services Research and †Section of Gastroenterology, Houston Veterans Affairs Medical Center and Baylor College of Medicine, Houston, Texas; and the §Division of Cancer Epidemiology and Genetics, National Cancer Institute/Department of Health and Human Services

**Background & Aims: A significant increase in the incidence of hepatocellular carcinoma (HCC) has been reported in the United States. The risk factors underlying this increase remain unclear. Methods: By using Surveillance, Epidemiology, and End-Results program (SEER)-Medicare–linked data, we conducted a population-based study to examine temporal changes in risk factors for patients 65 years and older diagnosed with HCC between 1993 and 1999. Only patients with continuous Medicare enrollment for 2 years before and up to 2 years after HCC diagnosis were examined. Univariate and multiple logistic regression analyses were used to evaluate changes in risk factors over time (January 1993–June 1996 and July 1996–December 1999). Results: The age-adjusted incidence of HCC among persons 65 years of age and older significantly increased from 14.2 per 100,000 in 1993 to 18.1 per 100,000 in 1999. We identified 2584 patients with continuous Medicare enrollment 2 years before and up to 2 years after HCC diagnosis. The proportion of hepatitis C virus (HCV)-related HCC increased from 11% during January of 1993 to June of 1996 to 21% during July of 1996 to December of 1999, whereas hepatitis B virus (HBV)-related HCC increased from 6% to 11% ($P < .0001$). In multiple logistic regression analyses that adjusted for age, sex, race, and geographic region, the risk for HCV-related HCC and HBV-related HCC increased by 226% and 67%, respectively. Idiopathic HCC decreased from 43% to 39%. This decrease did not fully account for the significant increases observed for HCV and HBV. No significant changes over time were observed for alcohol-induced liver disease, nonspecific cirrhosis, or nonspecific hepatitis. Conclusions: There has been a significant recent increase in HCV- and HBV-related HCC. Increasing rates of HCV-related HCC can explain a substantial proportion of the reported increase in HCC incidence during recent years.**

A substantial increase in the incidence of hepatocellular carcinoma (HCC) has been reported during the past 2 decades in the United States.[1,2] The average annual age-adjusted incidence of HCC increased from 1.3 per 100,000 for the period from 1981 to 1983 to 3.0 per 100,000 for the period from 1996 to 1998.[2] The majority of this increase occurred during the 1990s; a 25% increase was observed between 1993 and 1998.

The cause of this increase remains uncertain. The major risk factors for HCC are hepatitis C virus (HCV), hepatitis B virus (HBV), and alcohol-induced liver disease. Two published studies have examined temporal trends in the prevalence of underlying risk factors among patients with HCC.[3,4] However, neither were population-based studies. A study from the Department of Veterans Affairs found a 3-fold increase in HCV-related HCC, whereas HCC associated with HBV or alcohol-induced liver disease, and idiopathic cirrhosis remained stable.[3] Findings from a single-center, hospital-based study detected an almost 2-fold increase in HCV-related HCC, although no significant changes in other risk factors were observed.[4] Thus, generalizability of these results to explain the national trends in HCC is limited.

In 1991, the investigators for the National Cancer Institute linked records of patients with cancer identified from the Surveillance, Epidemiology, and End-Results (SEER) population-based registries to Medicare claims from the Centers for Medicare and Medicaid Services.[5] In this study, we used SEER-Medicare–linked data to examine the temporal trends of risk factors in patients age 65 years of age and older with HCC.

## Methods

### Data Source

Data used for this study were obtained from the SEER-Medicare database, which is the linkage of SEER registry

*Abbreviations used in this paper:* HMO, health maintenance organization; ICD, International Classification of Diseases; SEER, Surveillance, Epidemiology, and End-Results program.

© 2004 by the American Gastroenterological Association
0016-5085/04/$30.00
doi:10.1053/j.gastro.2004.07.020

information with Medicare claims data. The SEER program is an ongoing contract-supported program of the National Cancer Institute to collect population-based cancer incidence and survival data. Since 1992, the SEER program has collected data on incident cancer cases from 11 population-based cancer registries in 5 states (Connecticut, Hawaii, Iowa, New Mexico, Utah) and 6 metropolitan areas (Los Angeles, San Francisco/Oakland, San Jose, Detroit, Seattle, Atlanta) that account for approximately 14% of the population in the United States.[5] For each case identified, the SEER program collects demographic features, date of cancer diagnosis, cancer site, and method of diagnosis (histology, cytology, microscopic confirmation [method not specified], laboratory test/marker study, direct visualization, or positive radiology test). The International Classification of Diseases for Oncology (ICD-O-2) is used by SEER to classify primary site and histologic type for all cancers ascertained by the program.[6]

Medicare claims data are collected for both Medicare part A and part B benefits. Medicare is the primary health insurer for approximately 97% of individuals age 65 years and older in the United States. Persons less than 65 years of age are eligible for Medicare benefits owing to disability or end-stage renal disease. Approximately 95% of Medicare beneficiaries are covered by both part A and part B benefits.[5] Claims information from in-patient hospitalizations covered by Medicare part A benefits are included in the Medicare Provider Analysis and Review files. This file contains up to 10 diagnoses and 10 procedure codes using ICD 9th revision (9-CM) codes. Medicare claims data for all part B–covered benefits includes outpatient hospital services and physician office visits. These files contain dates of services, as well as both ICD-9-CM diagnosis codes and Current Procedural Terminology-4 codes for all billed claims.[5]

The linkage of SEER-Medicare data is a collaborative effort by the National Cancer Institute, the SEER registries, and Centers for Medicare and Medicaid Services.[5] This database contains Medicare part A and part B claims data for all patients identified by SEER registries between 1973 and 1999, although Medicare claims only are available beginning in 1991. To link patients identified by the SEER registries to information contained in the Medicare claims files, the SEER and Medicare Enrollment Databases are merged using an algorithm that matches social security number, name, sex, and date of birth. The use of this methodology to perform the linkage captures approximately 93% of patients in the SEER database age 65 years and older.[5]

## Study Population

All patients age 65 years and older diagnosed with HCC in SEER registries who also were enrolled in Medicare between 1993 and 1999 were eligible for inclusion. Only patients with diagnostic confirmation of HCC (ICD-O code = 8170) were included in our analysis. Diagnostic confirmation was defined as having positive histology, cytology, laboratory test/marker study, direct visualization, or positive radiology tests. Patients with clinical diagnosis only or unknown method of confirmation were excluded. In addition, we excluded patients diagnosed with stomach, colon, lung, pancreatic, breast, or rectal cancers within the 5 years before the date of HCC diagnosis to ensure the inclusion of only HCC, rather than metastatic liver cancers.

To include patients with equal exposure to risk factor information, we selected only patients with continuous enrollment in Medicare parts A and B for at least the 2 years before and up to 2 years after the HCC diagnosis or until death. We excluded patients enrolled in a health maintenance organization (HMO) during this time frame because Medicare HMO plans have not been required to submit individual claims to CMS for specific services received by patients' enrolled in Medicare.[5] Patients whose HCC diagnoses were reported exclusively by death certificates or at autopsy also were excluded. These patients did not have a diagnosis of HCC while they were alive and no other sources of information were available.

## Definitions of Risk Factors for HCC

By using ICD-9 codes, we identified several potential risk factors for HCC.[7] These included HCV (ICD-9 codes: 070.41, 070.44, 070.51, 070.54, V02.62), HBV (ICD-9 codes: 070.22, 070.23, 070.32, 070.33, V02.61), and alcohol-induced liver disease. Alcohol-induced liver disease was defined by the presence of ICD-9 codes for alcohol-induced fatty liver disease (ICD-9 code: 571.0), alcohol-induced hepatitis (ICD-9 code: 571.1), alcohol-induced cirrhosis (ICD-9 code: 571.2), alcohol-induced liver damage (ICD-9 code: 571.3), and cirrhosis (ICD-9 codes: 571.5, 571.6) in the presence of alcoholism (ICD-9 code: 291, 303, 305.0). Nonspecific cirrhosis was defined by the presence of cirrhosis (ICD-9 codes: 571.5, 571.6) without the presence of HCV, HBV, or alcohol-induced liver disease. Nonspecific hepatitis was defined by the presence of nonspecific hepatitis (ICD-9 codes: 571.4, 573.3) without the presence of HCV, HBV, alcohol-induced liver disease, or nonspecific cirrhosis. Patients without any reported major risk factors (HCV, HBV, alcohol-induced liver disease, nonspecific cirrhosis, or nonspecific hepatitis) were denoted as idiopathic. Risk factors were identified based on Medicare part A or B claims for the 2 years preceding and 2 years succeeding the date of HCC diagnosis. We assumed that HCC risk factors recorded after HCC diagnosis most likely were acquired before HCC diagnosis. All of these HCC risk factors were unlikely to be acquired late in life, or to be caused by HCC.

## Other Collected Information

Demographic information included age, race, geographic region, and Medicare/Medicaid dual enrollment. Age was categorized into 5-year age groups. Race was classified as white, black, Hispanic, Asian, and other. Geographic region was categorized based on the 11 SEER registries. The state buy-in variable in Medicare indicates whether a third-party payer was paying for a beneficiary's Medicare premiums, and

served as a proxy for socioeconomic status. These individuals were considered Medicare/Medicaid dually enrolled.

### Statistical Analysis

Age-adjusted incidence rates for HCC were calculated for the entire time period (1993–1999), as well as 2 equal time periods (January 1993–June 1996 and July 1996–December 1999). To calculate these rates, the age-specific proportions of patients with HCC were calculated for 5-year age groups and then summed and adjusted according to the method of direction standardization to reflect the age-distribution of the 2000 US standard population.[8] Similar methods were used to calculate age-adjusted incidence rates for HCV-related HCC, HBV-related HCC, and alcohol-induced liver disease–related HCC. All rates were expressed as proportional rates per 100,000 of the underlying population. We calculated the standard error and 95% confidence interval for each age-adjusted rate.[9] Any 2 rates whose confidence intervals did not overlap were considered significantly different.

We compared the demographic features and prevalence of risk factors associated with HCC between patients diagnosed with HCC during 2 time periods (January 1993–June 1996 and July 1996–December 1999). $\chi^2$ tests were conducted for categoric variables and *t* tests were performed for continuous variables. Unadjusted relative risks and 95% confidence intervals, as well as *P* values, were calculated for each risk factor.

The proportions of patients diagnosed by testing modality obtained from SEER were compared between 2 time periods (January 1993–June 1996 and July 1996–December 1999). These comparisons were conducted for all patients as well as for categories with the major risk factors for HCC. We also compared the proportions of patients who had any computed tomography scan and/or ultrasound of the abdomen obtained from Medicare claims within 1 year before HCC diagnosis.

The prevalence of risk factors among patients with HCC, as well as changes in the prevalence over time, could have been affected by a selection bias arising from the inclusion and exclusion criteria used for this study. A sensitivity analysis was conducted to quantify potential systematic error in the risk factor estimates because of differences between patients included in the study cohort and the population of Medicare-enrolled HCC patients' age 65 years and older in the SEER-Medicare database. We calculated the proportion of HCV, HBV, and alcohol-induced liver disease in the population of Medicare-enrolled HCC patients age 65 years and older in the SEER-Medicare database during the 2 time periods (January 1993–June 1996 and July 1996–December 1999) and applied these proportions to the study cohort to determine the expected number of HCC patients with each risk factor. Based on these expected numbers, we calculated the prevalence of HCV, HBV, and alcohol-induced liver disease during each time period, and determined the percent change in the prevalence of these risk factors. The percent change in the prevalence of HCV, HBV, and alcohol-induced liver disease observed in the study cohort was compared with the expected percent change in these risk factors and differences between these values were evaluated.[10]

Six separate multiple logistic regression models were constructed to examine the association between diagnosis of each HCC risk factor (HCV, HBV, alcohol-induced liver disease, nonspecific cirrhosis, nonspecific hepatitis, or idiopathic) and time of diagnosis (January 1993–June 1996 and July 1996–December 1999), adjusting for age, sex, race, geographic region, and Medicare/Medicaid dual enrollment. Wald $\chi^2$ tests were used to determine the significance of each variable. Adjusted odds ratios and 95% confidence intervals were calculated for each parameter estimate.

## Results

We initially identified 4015 patients age 65 years and older in the SEER-Medicare database with diagnostically confirmed HCC between 1993 and 1999. Of these cases, 2584 patients with HCC satisfied our criteria for inclusion in the study cohort. The 1431 patients were excluded for the following reasons: enrollment in a Medicare HMO plan during the 2 years before or after the date of HCC diagnosis (n = 960); enrollment in Medicare part A and part B for less than 2 years before the index date (n = 330); diagnosis of stomach, colon, lung, pancreatic, breast, or rectal cancer within the 5-year period before the date of HCC diagnosis (n = 107); and reporting source of autopsy of death certificate (n = 34).

### Demographic Features of the Study Cohort

The study cohort included 2584 patients, with a mean age of 74 years (SD = 8.4 y). Approximately 19% were between ages 65 and 69, 30% between ages 70 and 74, 27% between ages 75 and 79, and 24% age 80 years and older (Table 1). The majority (67%) were men. Approximately 66% were white, 9% were black, 4% were Hispanic, 12% were Asian, and 9% were of other race. Almost 28% were dually enrolled in Medicare/Medicaid programs. Among the 11 geographic regions, Utah had the lowest number of patients (n = 63, 2%), and Los Angeles had the greatest number of patients (n = 603, 23%). Of the remaining geographic regions, 410 patients (16%) were reported in Detroit, 287 (11%) in San Francisco, 283 (11%) in Connecticut, 221 (9%) in Seattle, 222 (9%) in Iowa, 130 (5%) in New Mexico, 123 (5%) in Atlanta, 124 (5%) in Hawaii, and 118 (5%) in San Jose.

### Age-Adjusted Incidence Rates of HCC

Between 1993 and 1999, the age-adjusted incidence was 16.2 per 100,000 among all Medicare-enrolled patients age 65 years and older. The age-adjusted inci-

**Table 1.** Comparison of Demographic Characteristics and Risk Factors Among Patients Diagnosed With HCC During 1993 and 1999

| | Frequency of patients diagnosed with HCC during 1/1993–6/1996 (%) (n = 1259) | Frequency of patients diagnosed with HCC during 7/1996–12/1999 (%) (n = 1325) | Relative risk (95% confidence interval)[a] | *P* value |
|---|---|---|---|---|
| Age at HCC diagnosis, y | | | | |
| 65–69 | 235 (18.7) | 243 (18.3) | 1.00 (reference) | .7737 |
| 70–74 | 383 (30.4) | 394 (29.8) | 1.00 (.92–1.09) | |
| 75–79 | 346 (27.5) | 354 (26.7) | .99 (.91–1.09) | |
| ≥80 | 295 (23.4) | 334 (25.2) | .99 (.91–1.09) | |
| Sex | | | | |
| Men | 829 (65.8) | 892 (67.3) | 1.00 (reference) | .4614 |
| Women | 430 (34.2) | 433 (32.7) | .95 (.86–1.07) | |
| Race | | | | |
| White | 876 (69.6) | 841 (63.6) | 1.00 (reference) | <.0001 |
| Black | 110 (8.7) | 114 (8.7) | 1.07 (.84–1.37) | |
| Hispanic | 42 (3.3) | 64 (4.8) | 1.54 (1.06–2.26) | |
| Asian | 100 (7.8) | 203 (15.5) | 1.89 (1.51–2.37) | |
| Other | 133 (10.6) | 101 (7.6) | .81 (.64–1.04) | |
| Geographic region | | | | |
| Atlanta | 59 (4.7) | 64 (4.8) | 1.00 (reference) | .2793 |
| Utah | 32 (2.5) | 31 (2.3) | .93 (.62–1.69) | |
| Connecticut | 153 (12.2) | 130 (9.8) | .93 (.82–1.06) | |
| Detroit | 191 (15.2) | 219 (16.5) | 1.01 (.92–1.11) | |
| Hawaii | 53 (4.2) | 71 (5.4) | 1.11 (.86–1.43) | |
| Iowa | 113 (9.0) | 109 (8.2) | .96 (.82–1.12) | |
| Los Angeles | 310 (24.6) | 293 (22.1) | .98 (.91–1.04) | |
| New Mexico | 60 (4.8) | 70 (5.3) | 1.03 (.81–1.32) | |
| San Francisco | 138 (10.9) | 149 (11.3) | 1.00 (.88–1.13) | |
| San Jose | 48 (3.8) | 70 (5.3) | 1.16 (.89–1.52) | |
| Seattle | 102 (8.1) | 119 (9.0) | 1.08 (.69–1.67) | |
| Medicare/Medicaid dual enrollment | 366 (28.2) | 349 (27.1) | .91 (.80–1.03) | .1209 |
| Risk Factors | | | | |
| HCV | 139 (11.0) | 281 (21.2) | 1.92 (1.59–2.32) | <.0001 |
| HBV | 80 (6.4) | 146 (11.0) | 1.73 (1.34–2.25) | <.0001 |
| Alcohol-induced liver disease | 259 (20.6) | 291 (22.0) | 1.07 (.92–1.24) | .3882 |
| Nonspecific cirrhosis | 233 (18.5) | 208 (15.7) | .85 (.72–1.01) | .0578 |
| Nonspecific hepatitis | 61 (4.2) | 42 (3.7) | .95 (.81–1.12) | .5428 |
| Idiopathic | 632 (43.4) | 435 (38.5) | .86 (.79–0.94) | .0008 |

NOTE. N = 2584.
[a]Comparison for the relative risk is between the 2 time periods (1/1993–6/1996, 7/1996–12/1999).

dence rates increased from 14.2 per 100,000 in 1993 to 18.1 per 100,000 in 1999, representing a 27% increase.

### Prevalence of HCC Risk Factors

Among risk factors for HCC, the proportion of HCC patients with alcohol-induced liver disease was the largest (21.2%), followed by HCV (16.3%), nonspecific cirrhosis (17.1%), HBV (8.8%), and nonspecific hepatitis (4.0%) (Table 1). Approximately 41.3% of HCC patients were identified as having idiopathic disease. Among 1196 patients with at least 1 of the 3 major risk factors (HCV, HBV, and alcohol-induced liver disease), 7.5% had HCV and alcohol-induced liver disease, 4.3% had HCV and HBV, 2.5% had HBV and alcohol-induced liver disease, and 2.0% had all 3 of these risk factors (Figure 1).

### Temporal Changes in Risk Factors and Demographic Features in HCC Patients

The risk factor–specific age-adjusted incidence rates were calculated for HCV-related HCC, HBV-related HCC, and alcohol-induced liver disease–related HCC. During the period from 1993 to 1999, the age-adjusted incidence rates were 1.68 per 100,000 for HCV, 0.92 per 100,000 for HBV, and 2.19 per 100,000 for alcohol-induced liver disease. HCV significantly increased from 1.13 per 100,000 during January of 1993–June of 1996 to 2.30 per 100,000 during July of 1996–

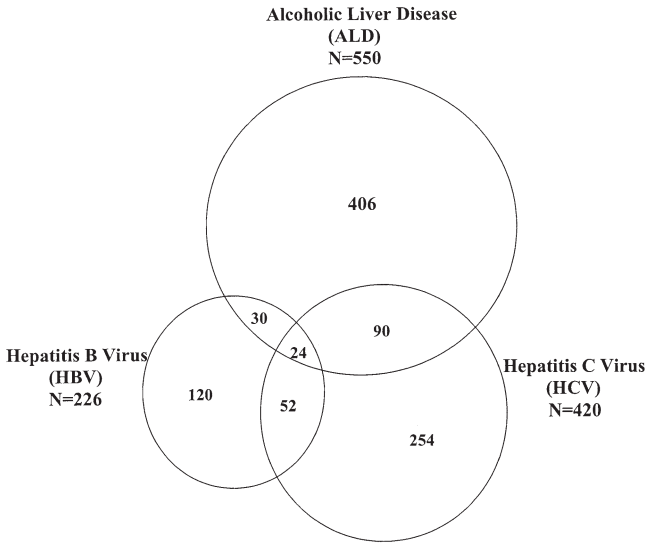


**Figure 1.** The frequency of HCV, HBV, and/or alcohol-induced liver disease (ALD) among 2584 patients diagnosed with HCC during 1993–1999.

December of 1999, representing a 102% increase. During these same time periods, HBV also increased from 0.65 per 100,000 to 1.19 per 100,000, representing an 83% increase. No significant changes were observed for alcohol-induced liver disease.

In univariate analyses, more recent time period of diagnosis (July 1996–December 1999 vs. January 1993–June 1996) was associated with a significant increase in the proportion of HCC patients with HCV (11.0% to 21.2%) and HBV (6.4% to 11.0%) (Figure 2). The corresponding unadjusted relative risks were 1.92 for HCV-related HCC and 1.73 for HBV-related HCC (Table 1). The proportion of patients with idiopathic HCC also significantly decreased from 43.4% to 38.5% (unadjusted relative risk = .92; $P = .01$). No significant changes over time were observed for HCC patients with alcohol-induced liver disease, nonspecific cirrhosis, or nonspecific hepatitis (Figure 2).

Among demographic features, only the racial distribution of patients with HCC significantly changed between January of 1993–June of 1996 and July of 1996–December of 1999. The proportion of Asians among HCC patients increased from 7.8% to 15.5%, whereas the proportion of whites decreased from 69.6% to 63.5% during the more recent time period. No significant changes were observed by age, sex, geographic region, or Medicare/Medicaid dual enrollment (Table 1).

The proportion of patients diagnosed by testing modality (histology, cytology, microscopic confirmation specified, laboratory test/marker study, direct visualization, or positive radiology test) during the 2 time periods between January of 1993–June of 1996 and July of 1996–December of 1999 are shown in Table 2. These categories are constructed by SEER in a hierarchic mutually exclusive fashion in the order shown earlier. For example, the presence of positive histologic examination supercedes all other modalities, whereas positive radiology diagnosis is considered only in the absence of all diagnostic modalities. Most patients had microscopic confirmation of HCC. Among all patients diagnosed with HCC, the proportion of patients diagnosed solely on the basis of laboratory tests/marker studies increased from 1.9% to 3.3%. However, no significant changes over time were observed among patients with HCV, HBV, or alcohol-induced liver disease. There were also no changes in the proportion of patients who had an ultrasound (62% vs. 63%) or computed tomography scan of the abdomen (79% vs. 79%) for the 2 time periods, respectively.

## Sensitivity Analysis

In the study cohort, we observed a 102% increase in HCV, an 83% increase in HBV, and a 12% increase in alcohol-induced liver disease between January of 1993–June of 1996 and July of 1996–December of 1999. To assess the potential for selection bias as a result of our exclusion criteria affecting the estimated changes in the prevalence of HCV, HBV, and alcohol-induced liver disease over time, we compared the expected percent change in the prevalence of these risk factors between the 2 time periods if no exclusions were made to the prevalence observed in this study. During January of 1993–June of 1996 and July of 1996–December of 1999, the expected prevalence of HCV (11% to 18%) and HBV (6% to 10%) increased, whereas the expected

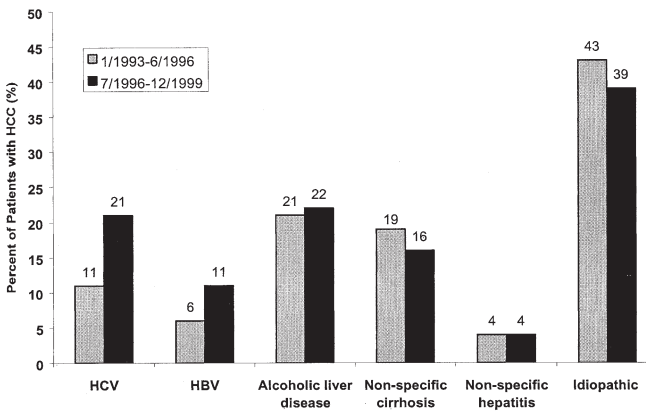


**Figure 2.** Changes in the proportion of HCV, HBV, alcohol-induced liver disease, nonspecific cirrhosis, nonspecific hepatitis, and idiopathic among 2584 patients with HCC over 2 time periods (▩, January 1993–June 1996; ■, July 1996–December 1999).

**Table 2.** Comparison of the Frequency and Proportion of Patients With HCC Diagnosed by Testing Modality Between 1/1993–6/1996 and 7/1996–12/1999

| | Total cohort (N = 2584) | | | | HCV (n = 420) | | | HBV (n = 226) | | | Alcoholic liver disease (n = 550) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Overall | 1/1993–6/1996 | 7/1996–12/1999 | *P* value | 1/1993–6/1996 | 7/1996–12/1999 | *P* value | 1/1993–6/1996 | 7/1996–12/1999 | *P* value | 1/1993–6/1996 | 7/1996–12/1999 | *P* value |
| Histology | 1587 (61.4) | 757 (60.1) | 830 (62.6) | .19 | 79 (56.8) | 166 (59.1) | .66 | 52 (65.0) | 79 (54.1) | .11 | 152 (58.7) | 159 (54.6) | .34 |
| Cytology | 522 (20.2) | 294 (23.4) | 228 (17.2) | .33 | 25 (18.0) | 41 (14.5) | .37 | 16 (20.0) | 30 (20.5) | .92 | 48 (18.5) | 43 (14.8) | .24 |
| Microscopic confirmation, method not specified | 10 (.4) | 1 (.1) | 9 (.7) | .01[a] | 0 (.0) | 3 (1.1) | .22 | 0 (.0) | 1 (.7) | .46 | 0 (.0) | 4 (1.4) | .058 |
| Laboratory test/marker study | 68 (2.6) | 24 (1.9) | 44 (3.3) | .03[a] | 4 (2.9) | 15 (5.3) | .25 | 1 (1.3) | 9 (6.2) | .09 | 10 (3.9) | 14 (4.8) | .58 |
| Direct visualization | 3 (.1) | 1 (.1) | 2 (.2) | .59 | 1 (.7) | 1 (.4) | .61 | 0 (.0) | 0 (.0) | [b] | 1 (.4) | 0 (.0) | .28 |
| Radiology | 394 (15.3) | 182 (14.4) | 212 (16.0) | .28 | 30 (21.6) | 55 (19.6) | .63 | 11 (13.7) | 27 (18.5) | .36 | 48 (18.5) | 71 (24.4) | .09 |

NOTE. N = 2584.

[a]Indicates significance at $P \leq .05$.

[b]*P* value could be not calculated.

prevalence of alcohol-induced liver disease remained unchanged (18% to 19%). Based on the prevalence of these risk factors if no exclusions were made, we estimated an 87% increase in HCV, a 71% increase HBV, and an 8% increase in alcohol-induced liver disease over time.

### Multiple Logistic Regression Analysis

In 6 separate multiple logistic regression models examining the association between time of HCC diagnosis (January 1993–June 1996 and July 1996–December 1999) and each of the risk factors (HCV, HBV, alcohol-induced liver disease, nonspecific cirrhosis, nonspecific hepatitis, and idiopathic) while adjusting for age, sex, race, geographic region, and Medicare/Medicaid dual enrollment, the more recent time period of diagnosis continued to be associated with an increased risk for HCV and HBV (Table 3). Similar to the unadjusted analyses, no significant association was found between time of diagnosis and alcohol-induced liver disease, nonspecific cirrhosis, or nonspecific hepatitis (Table 3). Compared with the earlier time period, the risk for being diagnosed with HCV-related HCC increased by 2-fold during the more recent time period, whereas HBV-related HCC increased by 67%. Compared with the earlier time period, the risk for having idiopathic disease decreased by 17% during the more recent time period.

In these models, an increased risk for having HCV, HBV, or alcohol-induced liver disease was associated with younger age, male gender, and non-white race (Table 4). Among these variables, race was the strongest confounder of the association between the time period of diagnosis and the presence of HCV, HBV, or alcohol-induced liver disease, as indicated by the change in the parameter estimate value for the time period of diagnosis. Inclusion of race most significantly decreased the effect of more recent time on the presence of HCV, HBV, and alcohol-induced liver disease.

**Table 3.** Results From 6 Separate Multiple Logistic Regression Analyses Examining the Association Between the Time Period of HCC Diagnosis (7/1996–12/1999 vs 1/1993–6/1996) and Each of the HCC Risk Factors (HCV, HBV, Alcohol-Induced Liver Disease, Nonspecific Cirrhosis, Nonspecific Hepatitis, and Idiopathic)

| | Unadjusted odds ratio for time period of HCC diagnosis and risk factor | Adjusted odds ratio for time period of HCC diagnosis and risk factor | *P* value for adjusted odds ratio |
|---|---|---|---|
| HCV (n = 420) | 2.17 (1.74–2.70) | 2.26 (1.79–2.86) | <.0001 |
| HBV (n = 226) | 1.82 (1.37–2.43) | 1.67 (1.22–2.28) | .0013 |
| Alcohol-induced liver disease (n = 550) | 1.09 (.90–1.31) | 1.16 (.95–1.42) | .1361 |
| Nonspecific cirrhosis (n = 441) | .82 (.66–1.01) | .84 (.68–1.03) | .0959 |
| Nonspecific cirrhosis (n = 103) | .88 (.59–1.32) | .89 (.60–1.34) | .5864 |
| Idiopathic (n = 1067) | .82 (.70–.96) | .83 (.70–.98) | .0238 |

NOTE. N = 2584. All models adjusted for age at HCC diagnosis, sex, race, geographic region (SEER registry), and Medicare/Medicaid dual enrollment.

**Table 4.** Multiple Logistic Regression Analysis Examining Association Between HCV and Time Period of HCC Diagnosis, Adjusting for Age, Sex, Race, Geographic Region (SEER Registry), and Medicare/Medicaid Dual Enrollment

| | Odds ratio | 95% confidence interval | Wald $\chi^2$ test | *P* value |
|---|---|---|---|---|
| Year of diagnosis | | | | |
| 1/1993–6/1996 | 1.00 | — | — | Reference |
| 7/1996–12/1999 | 2.26 | 1.79–2.86 | 46.65 | <.0001 |
| Age at HCC diagnosis | | | | |
| 65–69 | 1.00 | — | — | Reference |
| 70–74 | .69 | .51–.93 | 6.01 | .0142 |
| 75–79 | .64 | .47–.87 | 8.12 | .0044 |
| ≥80 | .25 | .17–.37 | 52.35 | <.0001 |
| Sex | | | | |
| Male | 1.00 | — | — | Reference |
| Female | 1.93 | 1.53–2.43 | 31.09 | <.0001 |
| Race | | | | |
| White | 1.00 | — | — | Reference |
| Black | 2.49 | 1.73–3.60 | 23.89 | <.0001 |
| Hispanic | 1.40 | .82–2.39 | 1.53 | .2157 |
| Asian | 2.18 | 1.49–3.18 | 16.17 | <.0001 |
| Other | 1.22 | .79–1.88 | .82 | .3653 |
| Registry | | | | |
| Atlanta | 1.00 | — | — | Reference |
| Utah | .20 | .04–.89 | 4.48 | .0343 |
| Connecticut | .51 | .26–.98 | 4.10 | .0429 |
| Detroit | .77 | .44–1.36 | .83 | .3619 |
| Hawaii | .46 | .21–1.02 | 3.69 | .0548 |
| Iowa | .41 | .19–.86 | 5.54 | .0186 |
| Los Angeles | 2.08 | 1.22–3.57 | 7.14 | .0075 |
| New Mexico | .98 | .49–1.97 | .0041 | .9491 |
| San Francisco | .84 | .46–1.55 | .31 | .5796 |
| San Jose | 1.92 | .98–3.76 | 3.64 | .0561 |
| Seattle | .94 | .50–1.76 | .036 | .8493 |
| Medicare/Medicaid dual enrollment | .63 | .47–.85 | 9.38 | .0022 |

NOTE. N = 2584.

## Discussion

Our study was a population-based study to examine the underlying risk factors among patients with HCC in the United States between 1993 and 1999. Among Medicare-enrolled patients with HCC, significant increases in HCV- and HBV-related HCC occurred over the past decade, whereas HCC associated with alcohol-induced liver disease, nonspecific cirrhosis, and nonspecific hepatitis has remained unchanged. HCV-related HCC doubled from 11% to 21% of all HCCs, whereas HBV-related HCC increased from 6% to 11% during the same time. These increases persisted after adjusting for other significant predictors of these risk factors including age, race, and sex.

These findings indicate that HCV has contributed to a significant proportion of the increase in HCC, and that in this population of patients 65 years and older, HCV-related HCC disproportionately affected relatively younger patients. Prior studies have estimated that the HCV infection epidemic in the United States began in the 1960s and reached a peak in the 1980s, with persons in their 20s to 30s being at the highest risk for acquiring the infection.[11] Transmission of HCV likely was associated with injection drug use, and the transfusion of unscreened blood and blood products. These individuals are at significantly increased risk for developing HCC after 3 decades or more of chronic HCV infection. Therefore, during the time frame of the current study (the 1990s), one would expect only a small fraction of HCV-related HCC to affect elderly persons (65 years and older). Indeed, national trends indicate that HCC rates have increased more dramatically among men between ages 45 and 65 than among any other group. Several mostly retrospective nonrandomized studies have suggested that interferon-alfa therapy in patients with HCV-related cirrhosis can decrease the risk for HCC.[12–14] However, because many patients with HCV are ineligible for antiviral therapy because of comorbid illnesses,[15,16] current therapy is unlikely to result in a large-scale change in the clinical course of HCV. Therefore, within the next several years, one would also expect HCC-related HCV eventually to account for a greater proportion of HCC cases among the elderly.

Findings from this study also indicate that HBV has contributed to the increase in HCC. HBV is the primary risk factor for HCC among Asian populations. Serologic studies have shown that recent immigrants from HBV endemic areas are at high risk for developing chronic HBV infection and HBV-related HCC.[17] In the current study, the proportion of Asians with HCC significantly increased from 8% to 15%, which partly could explain the increasing rates of HBV observed during the more recent time period. However, the increase in HBV persisted after adjusting for racial differences, indicating that the increasing proportion of Asians in the more recent time period could not fully account for the increase in HBV, and that other factors not examined in this study were responsible for this increase.

The significant increase in HCV- and HBV-related HCC could partly reflect an effect of improved detection or reclassification. Although we did not observe an increase in the proportions of overall or type of diagnostic tests among patients with HCV-related HCC, an increased awareness of HCC risk and improvements in the sensitivity of the enzyme-linked immunosorbent assay for HCV antibody could have resulted in higher rates of HCV detection during the more recent time period.[18] The use of HCC screening tests, particularly among patients with HCV- and HBV-related cirrhosis, also potentially could explain the increase in HCV- and HBV-related HCC.[19] However, the use of ultrasound or computed tomography scan of the abdomen within 1 year preceding the HCC diagnosis did not change over time during the study period. Further, given that the proportion of HCC patients without a recorded known specific risk factor decreased only slightly from 43% to 39%, a detection bias is unlikely to account completely for the increase in HCV- and HBV-related HCC.

Alternatively, patients with HCV could have been misclassified as having nonspecific cirrhosis or nonspecific hepatitis during the earlier time period because no ICD-9 code was available to specify HCV before 1992. Instead, patients with HCV may have been classified as having nonspecific hepatitis or nonspecific cirrhosis. However, we observed no significant changes in nonspecific cirrhosis or nonspecific hepatitis over time. These findings suggest that misclassification owing to changes in diagnostic coding cannot fully explain the increase in HCV-related HCC observed in this study.

These results corroborate and extend our previous 3 non–population-based studies. The first was conducted using the Department of Veterans Affairs national administrative datasets from more than 170 facilities, and indicated a 3-fold increase in age-adjusted proportional hospitalization for HCV-associated HCC during 1993–1998.[3] However, contrary to our current findings, no significant change over time was observed for HBV-related HCC. This may have resulted from the low proportion of Asians who receive care from the Department of Veterans Affairs. The second study, using data from a single-site referral center (MD Anderson, Houston, TX) between 1993 and 1998, also found an increase in HCV but not HBV infections among patients with HCC.[4] Finally, a study released in abstract form indicated similar findings only among patients born in the United States who were seen at a large county hospital in Houston.[20]

It is important to highlight that although HCV and HBV were the 2 specific risk factors that increased among patients with HCC, they only accounted for one third of all cases during the late 1990s. Approximately 40% of HCC patients did not have a recorded risk factor. These findings might indicate a limitation of the data source but they are consistent with previous studies reporting that 20% to 50% of HCC patients in the United States have idiopathic disease.[3,4,20,21] Recent studies have implicated diabetes and non–alcohol-induced fatty liver disease as risk factors for at least a proportion of these idiopathic cases.[22–24]

There are limitations to this study that are related to the uncertain accuracy and completeness of the information on risk factors in the SEER-Medicare–linked database. We have taken several steps to maximize the possibility of capturing risk factor information from claims data. For patients 65 years of age or older with continuous Medicare part A and part B enrollment and no enrollment in a HMO plan, Medicare files capture 100% of their Medicare claims for tests, procedures, out-patient visits, and hospitalization.[5] We restricted the study cohort to these patients and we searched for risk factor information for up to a 4-year period (2 years before and up to 2 years after the HCC diagnosis). This time span was selected based on an earlier analysis that showed a small difference in the ability to identify more recorded risk factors among HCC patients beyond this 4-year period. However, restricting the study sample to include only those patients with an adequate exposure time to the Medicare system, as well as excluding those patients enrolled in a Medicare HMO plan, could have biased our results. Results from the sensitivity analysis indicated that the exclusion criteria used for this study resulted in a generally greater proportion of patients with HCV, HBV, and alcohol-induced liver disease in the study cohort as compared with the entire population of Medicare-enrolled HCC patients' age 65 years and older.

The magnitude of the bias affecting the estimates of changes in these risk factors over time was greatest for HCV, and, to a lesser extent, HBV. Finally, although some risk factors may have been missed, this loss of information is likely to have occurred randomly.

Important strengths of this study are related to its data source as well as case definition. The SEER-Medicare database is population based, and the registries are selected to represent the entire US population, and therefore our overall findings probably are generalizable to the entire US population age 65 years and older.[5] The SEER program maintains at least a 98% completeness rate for case ascertainment.[5] All cases of HCC included in this analysis were confirmed by pathology, radiology, and/or laboratory testing.

In conclusion, our results indicate that there have been significant increases in HCV- and, to a lesser extent, in HBV-related HCC among persons 65 years of age and older. These increases have contributed to a large degree to the increasing rates of HCC observed during the past decade in the United States. Other risk factors, such as alcohol-induced liver disease and nonspecific cirrhosis, remained unchanged over time. Increases in HBV- and HCV-related HCC could not be explained by secular changes in age, sex, race, or geographic region. We strongly recommend that future studies use existing population-based SEER cancer registries to prospectively identify and collect these risk factors (Figure 2).

## References


1. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999;340:745–750.
2. El-Serag HB, Davila J, Petersen N, McGlynn K. The continuing rise in hepatocellular carcinoma in the United States: an update. Ann Intern Med 2003;139:817–823.
3. El-Serag HB, Mason AC. Risk factors for the rising rates of primary liver cancer in the United States. Arch Intern Med 2000;160: 3227–3230.
4. Hassan MM, Frome A, Patt YZ, El-Serag HB. Rising prevalence of hepatitis C virus infection among patients recently diagnosed with hepatocellular carcinoma in the United States. J Clin Gastroenterol 2002;35:266–269.
5. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. Med Care 2002;40(Suppl 8):IV3–18.
6. Fritz A, Ries L, eds. The SEER Program Code Manual. 3rd ed. Bethesda, MD: National Cancer Institute, 1998.
7. Karaffa MC, ed. Centr for Classification of Diseases in North America. International Classification of Diseases, Ninth Revision, Clinical Modification. 4th ed. Washington, DC: Public Health Service, US Dept of Health and Human Services, 1991.
8. Fleiss JL, Levin B, Paik MC. Statistical methods for rates and proportions. 3rd ed. Hoboken, NJ: John Wiley & Sons, Inc., 2003: 636–638.
9. Breslow DE, Day NE. Statistical methods in cancer research. In: Heseltine E, ed. The design and analysis of cohort studies. Vol 2. Lyon, France: International Agency for Research on Cancer, 1987:58–61.
10. Greenland S. Basic methods for sensitivity analysis and external adjustment. In: Rothman KJ, Greenland S, eds. Modern epidemiology. Philadelphia, PA: Lippincott-Raven Publishers, 1998:343–358.
11. Armstrong GL, Alter MJ, McQuillan GM, Margolis HS. The past incidence of hepatitis C virus infection: implications for the future burden of chronic liver disease in the United States. Hepatology 2000;31:777–782.
12. Ikeda K, Saitoh S, Arase Y, Chayama K, Suzuki Y, Kobayashi M, Tsubota A, Nakamura I, Murashima N, Kumada H, Kawaanishi M. Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: a long-term observation study of 1643 patients using statistical bias correction with proportional hazard analysis. Hepatology 1999;29:1124–1130.
13. Nishiguchi S, Kuroki T, Nakatani S, Morimoto H, Takeda T, Nakajima S, Shiomi S, Seki S, Kobayashi K, Otani S. Randomised trial of effects of interferon-alpha on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. Lancet 1995;346:1051–1055.
14. Yoshida H, Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata M, Inoue O, Yano M, Tanaka M, Fujiyama S, Nishiguchi S, Kuroki T, Imazeki F, Yokosuka O, Kinoyama S, Yamada G, Omata M. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of hepatocarcinogenesis by interferon therapy. Ann Intern Med 1999;131:174–181.
15. El-Serag HB, Kunik M, Richardson P, Rabeneck L. Psychiatric disorders in veterans infected with hepatitis C. Gastroenterology 2002;123:476–482.
16. Falck-Ytter Y, Kale H, Mullen KD, Sarbah SA, Sorescu L, McCullough AJ. Surprisingly small effect of antiviral treatment in patients with hepatitis C. Ann Intern Med 2002;136:288–292.
17. McQuillan GM, Townsend TR, Fields HA, Carroll M, Leahy M, Polk BF. Seroepidemiology of hepatitis B virus infection in the United States. 1976 to 1980. Am J Med 1989;87:5S–10S.
18. Carithers RL Jr, Marquardt A, Gretch DR. Diagnostic testing for hepatitis C. Semin Liver Dis 2000;20:159–171.
19. Chalasani N, Said A, Ness R, Hoen H, Lumeng L. Screening for hepatocellular carcinoma in patients with cirrhosis in the United States: results of a national survey. Am J Gastroenterol 1999; 94:2224–2229.
20. Kulkerni K, Barcak E, El-Serag HB, Goodgame R. Increasing incidence of hepatocellular carcinoma among US born residents of Houston, TX. Am J Gastroenterol 2003;98:S84.
21. Sallie R, Di Bisceglie AM. Viral hepatitis and hepatocellular carcinoma. Gastroenterol Clin North Am 1994;23:567–579.
22. Adami HO, Chow WH, Nyren O, Berne C, Linet MS, Ekbom A, Wolk A, McLaughlin JK, Fraumeni JF Jr. Excess risk of primary liver cancer in patients with diabetes mellitus. J Natl Cancer Inst 1996;88:1472–1477.
23. El-Serag HB, Tran T, Everhart J. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma: a cohort study among US veterans. Gastroenterology 2004;126:460–468.
24. Hassan MM, Hwang LY, Hatten CJ, Swaim M, Li D, Abbruzzese JL, Beasley P, Patt YZ. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. Hepatology 2002;36:1206–1213.


**Received April 15, 2004. Accepted July 15, 2004.**

**Address requests for reprints to: Hashem B. El-Serag, MD, MPH, The Houston Veterans Affairs Medical Center, 2002 Holcombe Boulevard (152), Houston, Texas 77030. e-mail: hasheme@bcm.tmc.edu; fax: (713) 748-7359.**