Background: A recent increase in the incidence of hepatocellular carcinoma was reported in the United States. The cause of this witnessed rise remains unknown.

Methods: We examined the temporal changes in both age-specific and age-standardized hospitalization rates of primary liver cancer associated with hepatitis C, hepatitis B, and alcoholic cirrhosis in the Department of Veterans Affairs Medical Center's Patient Treatment File.

Results: A total of 1605 patients were diagnosed with primary liver cancer between 1993 and 1998. The overall age-adjusted proportional hospitalization rate for primary liver cancer increased from 36.4 per 100000 (95% confidence interval [CI], 34.0-38.9) between 1993 and 1995 to 47.5 per 100000 (95% CI, 44.6-50.1) between 1996 and 1998. There was a 3-fold increase in the age-adjusted rates for primary liver cancer associated with hepatitis C virus, from 2.3 per 100000 (95% CI, 1.8-3.0) between 1993 and 1995 to 7.0 per 100000 (95% CI, 5.9-8.1) between 1996 and 1998. Concomitant with this rise, the age-specific rates for primary liver cancer associated with hepatitis C also shifted toward younger patients. During the same periods, the age-adjusted rates for primary liver cancer associated with either hepatitis B virus (2.2 vs 3.1 per 100000) or alcoholic cirrhosis (8.4 vs 9.1 per 100000) remained stable. The rates for primary liver cancer without risk factors also remained without a statistically significant change, from 17.5 (95% CI, 15.8-19.1) between 1993 and 1995 to 19.0 per 100000 (95% CI, 17.3-20.7) between 1996 and 1998.

Conclusions: Hepatitis C virus infection accounts for most of the increase in the number of cases of primary liver cancer among US veterans. The rates of primary liver cancer associated with alcoholic cirrhosis and hepatitis B virus infection have remained stable.

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hospitalization rates, which amounted to 11.1 per 100000, specific risk factors for hepatocellular carcinoma were present in 77% of patients, while the rest were without identified risks. Patients from the 2 periods were similar in age and ethnic distribution.

**Figure 1** illustrates the age-adjusted rates for patients with primary liver cancer, broken down by risk factors for hepatocellular carcinoma. The age-adjusted hospitalization rate for primary liver cancer associated with hepatitis C virus has increased significantly from 2.3 per 100000 (95% CI, 1.8-3.0) during 1993 to 1995 to 7.2 per 100000 (95% CI, 6.1-8.3) during 1996 to 1998. Patients with liver cancer and hepatitis C infection represent almost half (49%) of the observed increase in the overall rate of cases of primary liver cancer. On the other hand, age-adjusted hospitalization rates for patients with primary liver cancer associated with alcoholic cirrhosis remained unchanged from 11.0 per 100000 (95% CI, 9.7-12.2) during 1993 to 1995 to 12.9 per 100000 (95% CI, 11.5-14.4) during 1996 to 1998. Similarly, hospitalization rates for patients with primary liver cancer and hepatitis B virus did not change significantly from 2.2 per 100000 (1.6-2.8) between 1993 and 1995 and 3.1 (95% CI, 2.4-3.8) between 1996 and 1998 (Figure 1). Age-adjusted hospitalization rates for primary liver cancer associated with autoimmune hepatitis were 1.3 (95% CI, 0.8-1.8) for 1993 to 1995 and 2.0 (95% CI, 1.5-2.6) for 1996 to 1998, while those associated with hereditary hemochromatosis were 0.15 per 100000 between 1993 and 1995 and 0.27 per 100000 between 1996 and 1998 (data not shown).

Finally, primary liver cancer with none of the specific risk factors increased from 17.5 per 100000 (95% CI, 15.8-19.1) between 1993 and 1995 to 19.0 per 100000 (95% CI, 17.4-20.7) between 1996 and 1998. In the entire study population, 38% of these “idiopathic” cases were diagnosed as nonspecific cirrhosis, while the rest involved no documented liver disease.

**Figure 2** shows the age-specific hospitalization rates for patients with primary liver cancer associated with hepatitis C. The increase in hospitalization rates between 1993 and 1995 and 1996 and 1998 affected all age groups, particularly those between the ages of 46 and 60 years. For example, hospitalization rates for patients between 41 and 45 years of age increased from 4.3 per 100000 (95% CI, 0.2-8.7) to 19.3 per 100000 (95% CI, 9.6-29.0) during 1996 to 1998. The shift toward younger ages was not consistently present for primary liver cancer associated with the other risk factors (data not shown). Because of the relatively small number of patients in each specific age group, the CIs associated with the hospitalization rates tended to be wide.

**COMMENT**

Consistent with the findings of our previous study, the current results have shown a significant increase in the number of patients hospitalized with primary liver can-
cancer in VA hospitals between 1993 and 1998. Patients infected with hepatitis C virus represented half of the witnessed increase in primary liver cancer. The combination of all other major risk factors for hepatocellular carcinoma, such as alcoholic cirrhosis, crypogenic cirrhosis, autoimmune hepatitis, and hepatitis B infection, was responsible for the rest of the increase. The age-adjusted rates for primary liver cancer associated with hepatitis C virus increased 3-fold between 1993 and 1998. This increase was particularly prominent among relatively younger patients. During the same period, there was no statistically significant increase in the age-adjusted rates or the age distribution in cases of liver cancer associated with the rest of the individual risk factors.

The use of ICD-CM code 155.0, denoting primary liver cancer as a surrogate for hepatocellular carcinoma, may erroneously include patients with metastatic liver cancer or other rare types of primary liver cancer. However, the use of this code in the VA PTF to study cases of hepatocellular carcinoma has been validated against the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) database, which uses more precise histologic coding (International Classification of Diseases for Oncology® code 8170). Temporal trends for hospitalization rates of patients with primary liver cancer in the VA PTF were virtually identical to the incidence rates of patients with hepatocellular carcinoma in the SEER database.1

Although hepatitis C virus was identified first in 1989, and its association with hepatocellular carcinoma was described in 1991, testing for hepatitis C virus infection in patients with primary liver cancer may not have been widespread in the early 1990s. Part of the increase in hepatitis C virus found among patients with primary liver cancer may represent testing bias. However, the combination of a rising total number of primary liver cancer cases, coupled with stable rates of cases associated with other risk factors, suggests a true increase in newly diagnosed cases of primary liver cancer associated with hepatitis C virus. Also, the shifting hospitalization rates of hepatitis C–related primary liver cancer toward younger patients are similar to the changes in age distribution that have been noted in the overall incidence data in the United States.1

Fewer than half (44%) of the total number of patients with primary liver cancer in the current study did not have any identifiable risk factor. However, in a large proportion of the latter group (38%), nonspecific cirrhosis was present. The search for risk factors in the inpatient medical history files ranged between 7 and 13 years prior to the primary liver cancer diagnosis. However, outpatient diagnoses, pharmacy data, and diagnoses made outside VA facilities were not captured by the study; therefore, additional risk factors may have been missed. These errors, however, are nondifferential and should have little effect on the temporal trends of hospitalizations in cases of primary liver cancer and its associated risk factors. Also, the current results are consistent with those of previous US studies, in which no specific risk factor was found in 20% to 50% of patients with primary liver cancer.6,7 Despite the absence of conventional viral serological mark-

ers, some patients with hepatocellular carcinoma have evidence of hepatitis B virus or hepatitis C virus detected by polymerase chain reaction testing of serum and liver specimens.8,9 Genetic mutations, exposure to environmental carcinogens, and medications are potential candidates that remain to be studied.

Large cancer registries, such as the SEER database, are not readily linked to other sources of information about risk factors and comorbid medical conditions. The use of administrative databases, such as the VA PTF, is an available alternative to study risk factors. The PTF in turn offers several advantages over other sources of administrative hospitalization data. Its large size allows the study of large numbers of patients with a relatively uncommon malignancy. The long time span covered by the PTF increases the chance of capturing diagnoses made well before the cancer diagnosis. The information was contributed from 172 VA facilities throughout the United States and therefore is less likely to be biased by the skewed referral base of a few large centers. On the other hand, there are also potential disadvantages to the use of hospitalization data. Criteria for hospital admissions can be subject to change over time, thus introducing a selection bias toward certain diagnoses. The use of ICD codes...
to study risk factors can also be associated with errors in diagnosis and coding. Uniform criteria may not have been used to diagnose alcoholic liver disease or autoimmune hepatitis. However, such errors are likely to occur at random throughout the study period and thus have little effect on the observed trends.

In the United States and other developed countries, cirrhosis of liver is present in most patients with hepatocellular carcinoma. Several factors have probably contributed to the high prevalence of cirrhosis, which consequently has led to the rise in hepatocellular carcinoma. Despite the recent sharp decline in the incidence of hepatitis C virus, a large pool of approximately 3.9 million persons is estimated to be chronically infected with hepatitis C virus in the United States, up to a third of whom may develop cirrhosis. It takes, on average, 20 years for cirrhosis to develop after the onset of hepatitis C virus infection, and once cirrhosis is established, hepatocellular carcinoma occurs at an annual rate of 1% to 4%. On the other hand, alcoholic cirrhosis and hepatitis B virus–related cirrhosis occur at a steady rate. Finally, the high prevalence of patients with cirrhosis is also maintained by improving survival as a result of better treatment of complications such as esophageal varices, peritonitis, and encephalopathy.

Studies from Japan and France suggest that interferon treatment of hepatitis C virus–infected patients with cirrhosis, even if it does not completely eradicate the infection, may reduce the future risk of hepatocellular carcinoma. Reduction of hepatocellular carcinoma risk may also be achieved with treatment at early stages of hepatitis C virus infection. Recent Japanese data suggest that treating hepatitis C virus–infected patients with interferon has reduced the incidence of hepatocellular carcinoma, irrespective of the degree of hepatic fibrosis. The reproducibility of these results in the United States, and their effect on the current trends of hepatocellular carcinoma, remains to be seen.

In conclusion, we found that primary liver cancer associated with hepatitis C virus infection was the most important underlying cause of increase in the overall rates of hospitalization for liver cancer among US veterans. These findings may not be readily extrapolated to patients with liver cancer seen in non-VA settings. Future studies of liver cancer risk factors from non-VA hospitals are needed for better definition of the underlying cause of the rising rates of liver cancer in the United States.

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