

Risk Factors for the Rising Rates of Primary Liver Cancer in the United States

Hashem B. El-Serag, MD, MPH; Andrew C. Mason, MD

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 100 000 (95% confidence interval [CI], 34.0-38.9) between 1993 and 1995 to 47.5 per 100 000 (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 100 000 (95% CI, 1.8-3.0) between 1993 and 1995 to 7.0 per 100 000 (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 100 000) or alcoholic cirrhosis (8.4 vs 9.1 per 100 000) 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 100 000 (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.

Arch Intern Med. 2000;160:3227-3230

RECENTLY, WE reported a statistically significant increase in the number of cases of hepatocellular carcinoma diagnosed in the United States over the past 2 decades.¹ Information about the incidence, hospitalization, and mortality in cases of hepatocellular carcinoma were obtained from 3 data sources: the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, the Department of Veteran Affairs (VA) Patient Treatment File (PTF), and the US vital statistics, respectively.¹ However, the cause(s) of this rise in the number of cases of hepatocellular carcinoma remains unknown. Of the 3 databases used, only the VA PTF contains information about the main risk factors and medical conditions associated with hepatocellular carcinoma, such as alcoholic cirrhosis or viral hepatitis. In the present study, information from the main files of the VA PTF were

used to examine the temporal trends of risk factors among patients diagnosed as having primary liver cancer between 1993 and 1998.

RESULTS

A total of 1605 patients were diagnosed as having primary liver cancer between 1993 and 1998. The majority of these patients were men (99.5%). The mean age of patients with primary liver cancer was 64 years (SD, 9 years). The ethnic distribution was as follows: whites (65%), blacks (21%), Hispanics (10%), American Indians, (1%), Asians (1%), and unspecified, 2%. The age-adjusted proportional hospitalization rate for all patients with primary liver cancer increased significantly from 34.4 per 100 000 hospitalizations for the period 1993 to 1995 (95% CI, 32.0-36.8) to 44.5 per 100 000 hospitalizations for the period 1996 to 1998 (95% CI, 41.9-47.0). Out of this increase in overall

From the Gastroenterology and Health Services Sections, Houston Department of Veterans Affairs Medical Center and Baylor College of Medicine, Houston, Tex (Dr El-Serag); and the Department of Gastroenterology, University of New Mexico, Albuquerque (Dr Mason).

PATIENTS AND METHODS

DATABASE

The main files of the PTF contain records of all hospitalizations at 172 VA facilities throughout the United States. Since 1981, discharge diagnoses have been coded according to the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*.² Beginning in 1992, hepatitis C infection first appeared as a separate ICD code in the main files.

STUDY POPULATION

All patients diagnosed as having primary liver cancer (ICD-9-CM code 155.0) between 1993 and 1998 were identified. Using social security numbers as a unique identifier, each patient's medical history preceding the liver cancer diagnosis from 1986 through 1998 was retrospectively searched for the diagnoses of hepatitis C infection (ICD-9-CM codes 0705.1, 0705.4, 0704.1, and 0704.4), chronic hepatitis B infection (ICD-9-CM codes V0261, 0703.2, and 0702.2), and alcoholic cirrhosis (ICD-9-CM code 751.2). Other risk factors, such as hemochromatosis, autoimmune hepatitis, and non-specific cirrhosis, were also identified.

STATISTICAL ANALYSIS

For each year, the number of hospital discharges of patients with primary liver cancer was broken into 10-year

age groups. The total number of discharges for all diagnoses was also broken down into 10-year age groups. Proportional age-specific hospitalization rates were calculated by dividing the number of age-specific hospitalizations for primary liver cancer by the total number of age-specific hospitalization for all diagnoses during the same period. Proportional hospitalization rates were calculated for each individual year as well as for the 3-year periods 1993 to 1996 and 1996 to 1998. Next, all age-specific hospitalization rates were adjusted according to the method of direct standardization to reflect the age distribution of all hospitalized veterans in 1990.³ Sex-specific analysis was not done because the overwhelming majority of hospitalized veterans (98%) are men. In a similar method, the age-adjusted proportional hospitalization rates for primary liver cancer cases that are associated with each of the individual risk factors for primary liver cancer were determined. The SE of the age-adjusted rates was calculated according to the method suggested by Breslow and Day.⁴ To calculate the 95% confidence interval (CI) of each rate, the value of 1.96 times the SE was added or subtracted from it. Any 2 rates were considered significantly different if their CIs did not overlap.

For each year, the proportions of patients with primary liver cancer having any of the individual risk factors for hepatocellular carcinoma were calculated. The average proportions and their 95% CIs were also calculated for the 2 periods between 1993 and 1995 and 1996 and 1998. χ^2 Tests were used to compare the proportions of patients with cancer with each risk factor in these 2 periods.

hospitalization rates, which amounted to 11.1 per 100 000, 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 100 000 (95% CI, 1.8-3.0) during 1993 to 1995 to 7.2 per 100 000 (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 100 000 (95% CI, 9.7-12.2) during 1993 to 1995 to 12.9 per 100 000 (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 100 000 (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 100 000 between 1993 and

1995 and 0.27 per 100 000 between 1996 and 1998 (data not shown).

Finally, primary liver cancer with none of the specific risk factors increased from 17.5 per 100 000 (95% CI, 15.8-19.1) between 1993 and 1995 to 19.0 per 100 000 (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 100 000 (95% CI, 0.2-8.7) to 19.3 per 100 000 (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,¹ the current results have shown a significant increase in the number of patients hospitalized with primary liver can-

cer 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, cryptogenic 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*³ 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-

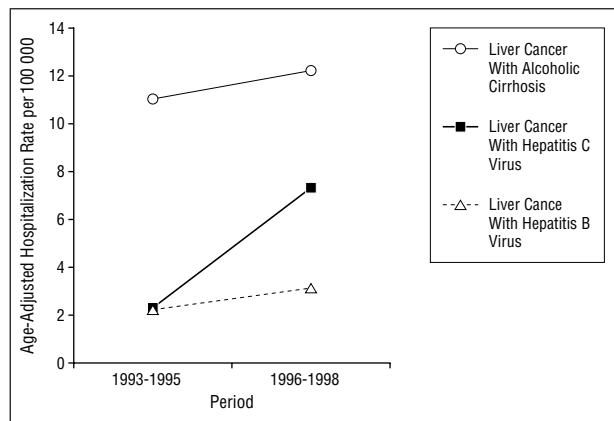


Figure 1. Temporal trends in age-adjusted proportional hospitalization rates for primary liver cancer broken down by the presence of risk factors for hepatocellular carcinoma. The rates are displayed for 2 periods: 1993 to 1995 and 1996 to 1998.

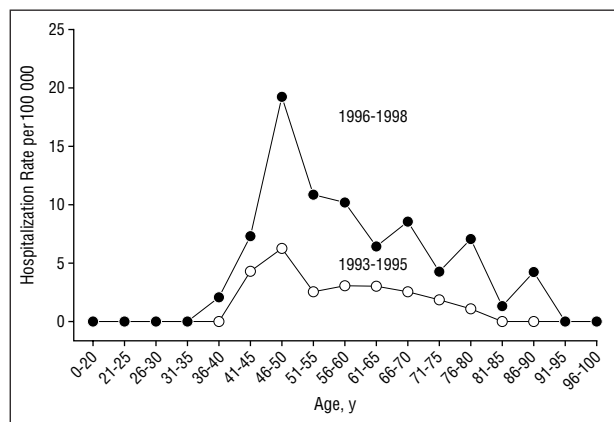


Figure 2. Age-specific proportional hospitalization rates (per 100,000) for primary liver cancer associated with hepatitis C virus infection from 1993 to 1995 and from 1996 to 1998.

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,¹⁰ up to a third of whom may develop cirrhosis.¹¹ It takes, on average, 20 years for cirrhosis to develop after the onset of hepatitis C virus infection,^{12,13} and once cirrhosis is established, hepatocellular carcinoma occurs at an annual rate of 1% to 4%.¹² 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.¹⁴⁻¹⁶ 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.

Accepted for publication June 14, 2000.

Dr El-Serag is a recipient of an unrestricted educational grant from Schering-Plough Pharmaceuticals, Kenilworth, NJ.

The authors thank James E. Everhart, MD, MPH, for his valuable advice in preparing the manuscript and Denis M. McCarthy, MD, MSc, for his overall support.

Reprints: Hashem B. El-Serag, MD, MPH, Houston VA Medical Center (152), 2002 Holcombe Blvd, Houston, TX 77030 (e-mail: hasheme@bcm.tmc.edu).

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. *International Classification of Diseases, Ninth Revision, Clinical Modification*. Washington, DC: Public Health Service, US Dept of Health and Human Services; 1988.
3. Kahn HA, Sempos CT. *Statistical Methods in Epidemiology*. New York, NY: Oxford University Press; 1989:87-95.
4. Breslow NE, Day NE. Statistical methods in cancer research. In: *The Design and Analysis of Cohort Studies*. Vol 2. Lyon, France: International Agency for Research on Cancer; 1987:58-61.
5. Percy C, Van Holten V, Muir C, eds. *International Classification of Diseases for Oncology*. 2nd ed. Geneva, Switzerland: World Health Organization; 1990.
6. DiBisceglie AM, Carithers RL Jr, Gores GL. Hepatocellular carcinoma. *Hepatology*. 1998;28:1161-1165.
7. Kew MC. Hepatic tumors and cysts. In: Feldman M, Sleisenger MH, Scharschmidt BF, Klein S, eds. *Sleisenger's and Fordtran's Gastrointestinal and Liver Disease: Pathology/Diagnosis/Management*. Vol 1. 6th ed. Philadelphia, Pa: WB Saunders Co; 1998:1364-1387.
8. Paterlini P, Gerken G, Nakajima E, et al. Polymerase chain reaction to detect hepatitis B virus DNA and RNA sequences in primary liver cancers from patients negative for hepatitis B surface antigen. *N Engl J Med*. 1990;323:80-85.
9. Liang TK, Jeffers LJ, Reddy KJ, et al. Viral pathogenesis of hepatocellular carcinoma in the United States. *Hepatology*. 1993;18:1326-1333.
10. Alter MJ. Epidemiology of hepatitis C. *Hepatology*. 1997;26(suppl 1):62S-63S.
11. Poynard T, Bedossa P, Opolon P, for the OBSVIRC, MTAVIR, CLINIVIR, and DOSVIRC groups. Natural history of liver fibrosis progression in patients with chronic hepatitis C. *Lancet*. 1997;349:825-832.
12. DiBisceglie AM. Hepatitis C and hepatocellular carcinoma. *Hepatology*. 1997;26(suppl 1):34S-38S.
13. DiBisceglie AM, Goodman ZD, Ishak KG, Hoofnagle JH, Melpolder JJ, Alter HJ. Long-term clinical and histopathological follow-up of chronic posttransfusion hepatitis. *Hepatology*. 1991;14:969-974.
14. Nishiguchi S, Kuroki T, Nakatani S, et al. Randomized trial of effects of interferon-alpha on incidence of hepatocellular carcinoma in chronic active hepatitis with cirrhosis. *Lancet*. 1995;346:1051-1055.
15. Ikeda K, Saitoh S, Arase Y, et al. Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: a long-term observation study of 1,643 patients using statistical bias correction with proportional hazard analysis. *Hepatology*. 1999;29:1124-1130.
16. Yoshida H, Shiratori Y, Moriyama M, et al. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and non-cirrhotic patients with chronic hepatitis C in Japan. *Ann Intern Med*. 1999;131:174-181.