

Hepatocellular Carcinoma and Hepatitis C in the United States

Hashem B. El-Serag

Chronic infection with hepatitis C virus (HCV) is a major risk factor for development of hepatocellular carcinoma (HCC). In general, HCC develops only after 2 or more decades of HCV infection and the increased risk is restricted largely to patients with cirrhosis or advanced fibrosis. Factors that predispose to HCC among HCV-infected persons include male sex, older age, hepatitis B virus (HBV) coinfection, heavy alcohol intake, and possibly diabetes and a transfusion-related source of HCV infection. Viral factors play a minor role. The likelihood of development of HCC among HCV-infected persons is difficult to determine because of the paucity of adequate long-term cohort studies; the best estimate is 1% to 3% after 30 years. Once cirrhosis is established, however, HCC develops at an annual rate of 1% to 4%. Successful antiviral therapy of patients with HCV-related cirrhosis may reduce the future risk for HCC. The incidence of and mortality caused by all HCC has doubled in the United States over the past 25 years, an increase that has affected all ethnic groups, both sexes, and younger age groups. Given the current prevalence of HCV infection among persons 30 to 50 years of age, the incidence and mortality rates of HCC are likely to double in the United States over the next 10 to 20 years. Future research should focus on improving understanding of the incidence and risk factors for HCC, causes of HCV-related carcinogenesis, means of early detection, and better treatment for HCC. (HEPATOLOGY 2002;36: S74-S83.)

Hepatocellular carcinoma (HCC) affects approximately half a million persons each year worldwide making it the fifth most common malignancy in men and the ninth most common in women. HCC is a rapidly fatal cancer that mostly affects persons in developing countries where hepatitis B virus (HBV) is endemic. Recently, however, a trend of increasing rates of HCC has been reported from several developed countries in North America, Europe, and Asia. Hepatitis C virus (HCV) infection appears to play an important role in these new trends.

Hepatitis C and HCC

Several lines of evidence indicate a strong causal association between HCV and HCC. HCV RNA can be

found in the serum, liver, and tumor tissues of patients with HCC, but unlike HBV it does not integrate into the host genome.¹ Markers of HCV infection are found in a variable proportion of HCC cases in Europe with an increasing gradient from North to South²; for example, 44% to 66% in Italy,³⁻⁵ 27% to 58% in France,⁶ 60% to 75% in Spain,⁷ and in 80% to 90% of HCC cases in Japan.^{8,9} Moreover, the age-standardized death rates owing to HCC in several European countries are significantly correlated with the seroprevalence of HCV in the general population.¹⁰ The frequency of HCV seropositivity among persons with HCC compiled from a summary of published studies of HCC in the United States is shown in Fig. 1. Of 1,429 patients assumed to have been tested, 384 (27%) were positive for HCV.¹¹⁻¹⁵ However, a higher but undefined proportion of patients with HCC might have had HCV detected by polymerase chain reaction testing of liver tissue and/or serum, even if antibody to HCV (anti-HCV) was not detectable,¹⁶ particularly if first-generation tests were used. On the other hand, 240 of 1,670 (14%) patients with HCC in the United States tested positive for hepatitis B surface antigen, and an additional 149 (9% of the 1,670) were found to be positive for antibody to hepatitis B core antigen (anti-HBc).

HCV increases the risk for HCC probably by promoting fibrosis and cirrhosis; virtually all HCV-related HCC

Abbreviations: HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; CI, confidence interval.

From the Sections of Gastroenterology and Health Services Research at the Houston Department of Veterans Affairs Medical Center and Baylor College of Medicine, Houston, TX.

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Address reprint requests to: Hashem B. El-Serag, M.D., M.P.H., The Houston Veterans Administration Medical Center (152), 2002 Holcombe Blvd., Houston, TX 77030. E-mail: hasheme@bcm.tmc.edu; fax: 713-748-7359.

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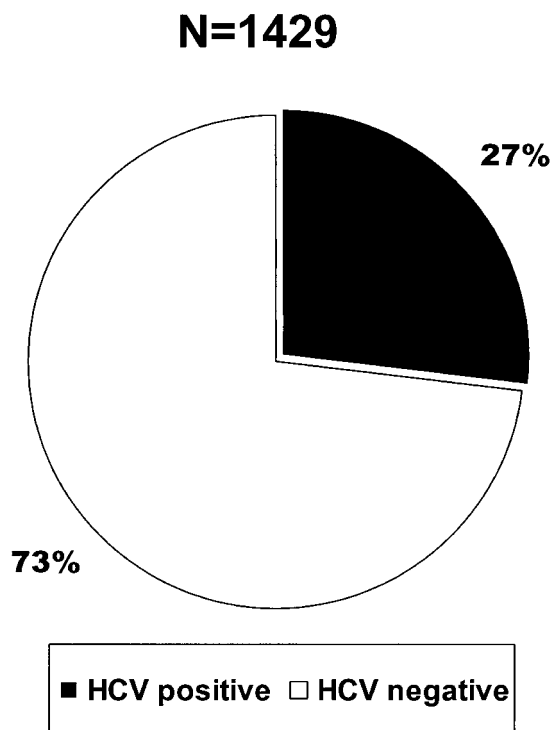


Fig. 1. The proportion of patients with HCC in the United States who have serologic evidence of HCV infection. Combined results from 7 studies including 1,429 cases of HCC.

cases occur among patients with cirrhosis. With the exception of areas in the world where hepatitis B is endemic, it is uncommon to find HCC in the absence of cirrhosis.¹⁷⁻¹⁹ The duration of HCV infection is especially relevant to HCC development, with most cases of HCC occurring after 25 to 30 years of chronic infection (Fig. 2).²⁰⁻²² This long period probably reflects the time needed for the development of cirrhosis.

Relative Risk For HCC in HCV

HCV infection increases the risk for HCC several-fold (up to 25 times) when noninfected people are used as an index population.²³ In a meta-analysis of 21 case-control studies in which second-generation enzyme immunoassay tests for anti-HCV were used, the risk for HCC was increased 17-fold in HCV-infected patients compared with HCV-negative controls (95% confidence interval (CI): 14- to 22-fold).²⁴ Similarly, prospective studies have shown a significant increase in the incidence of HCC among HCV-infected cohorts^{25,26}; these rates represent a several-fold increase over what is expected for cohorts of the same age.

Absolute Risk (Incidence) of HCC in HCV

Estimates of the incidence of cirrhosis and HCC in HCV-infected persons have varied widely. Many studies

have examined subjects seeking care for HCV-related liver disease rather than entire cohorts of HCV-infected persons, thus creating the potential for selection bias. In HCV-infected persons, the true incidence of cirrhosis and HCC can be determined only by examining entire cohorts over time, with knowledge of the onset of HCV infection. Recently, a systematic review of all articles published between 1980 and 2001 was undertaken to identify and analyze studies that examine such cohorts.²⁷ Studies excluded in this review consisted of those in which cohorts were selected from patients with liver disease, studies in which the onset of infection could not be estimated, and studies in which patients were treated for hepatitis C. In the 21 articles that fulfilled the selection criteria for this review, the time to cirrhosis ranged between 13 and 23 years, and to HCC between 17 and 31 years. Even within this select group of studies, there were large variations in the estimates of cirrhosis and HCC. Short duration of follow-up evaluation, small sample size, as well as possible publication bias explains some of these variations. These variations preclude simple pooling of the results as a one-size-fits-all estimate of the frequency of cirrhosis or HCC. The mode of HCV acquisition seems to be an independent predictor of the incidence of cirrhosis and HCC in HCV-infected cohorts.^{27,28} The highest pooled incidence rates for cirrhosis and HCC were found in studies involving recipients of blood or blood products who developed transfusion-associated hepatitis C (14 and 1 per 1,000 person-years, respectively) and studies of persons with hemophilia (5 and 0.7 per 1,000 person-years, respectively). The lowest rates were reported in studies of women who received a one-time contaminated anti-D immune globulin (1 and 0 per 1,000 person-years, respectively),

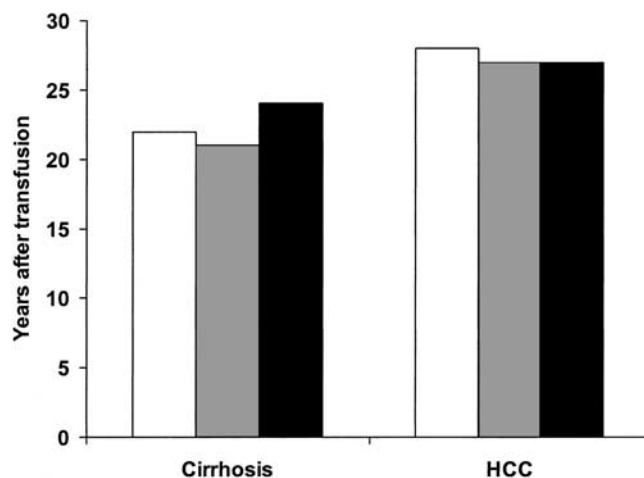


Fig. 2. The duration of HCV infection after known blood transfusion before clinical diagnosis of cirrhosis (left panel) or HCC (right panel). Results of 3 studies from 3 countries: Data from Tong et al. (□),²⁰ Kiyosawa et al. (shaded bars),²¹ Castells et al. (■).²²

whereas studies involving community-acquired HCV that included injection drug users had an intermediate, weighted pooled incidence (5 and 0 per 1,000 person-years, respectively) for cirrhosis and HCC. Thus, the frequency of evolution to cirrhosis 25 years after infection ranged between 3% and 35% and evolution to HCC after 30 years ranged between 0% and 3%.

Risk Factors for HCC in HCV

In HCV-infected patients, factors related to the host or environment or both appear to be more important than viral factors in determining the progression of HCV infection to cirrhosis. These factors include older age, older age at the time of acquisition of infection,²⁸ male sex, heavy alcohol intake (more than 50 g/d),²⁹ coinfection with HBV,^{24,30} or HIV,³¹ and a transfusion-related mode of HCV acquisition.^{27,28}

Alcohol Consumption. HCV infection and alcohol-induced liver disease are both risk factors for HCC, although the former seems to be the more predominant risk factor.³² Presumably, they operate together to increase the risk for HCC by more actively promoting cirrhosis. Studies that compared development of HCC among HCV-infected patients with the development of HCC in persons with noncirrhotic liver disease or controls without liver disease have found only a modest effect of alcohol (mostly heavy alcohol use of more than 50 g/d).³²⁻³⁶ For example, a recent study by Donato et al.³² reported that among alcohol drinkers, the risk for HCC increased in a linear fashion with a daily intake greater than 60 g, and that the presence of HCV had a positive synergistic action with an additional 2-fold increase in the risk over that caused by alcohol alone. In addition, the proportion of patients testing positive for anti-HCV increased significantly among heavy drinkers with severe liver disease (cirrhosis or HCC) as compared with those with mild or no disease.

Hepatitis B Virus. In the meta-analysis of 32 case-control studies by Donato et al.,³³ concomitant infection with HBV and HCV was associated with an odds ratio of 165 (95% CI, 81 to 374) as compared with an odds ratio of 17 with HCV positivity alone and an odds ratio of 23 with HBV positivity alone, thus, suggesting a synergism between the 2 infections.

HIV. Although several studies have indicated that HCV/HIV coinfection is associated with an increased risk for cirrhosis as compared with patients with HIV who are not coinfecting,³¹ there is less information regarding the reverse situation of the risk for cirrhosis in patients with dual infection as compared with those who are only HCV

infected, and almost no information on the risk for HCC. Two studies in HCV-infected patients with hemophilia have reported a nonsignificant trend toward lower rates of HCC in patients with coinfection as compared with those infected only with HCV.^{37,38}

Diabetes and Obesity. Several reports have suggested that persons with diabetes mellitus are at an increased risk for developing HCC,³⁹⁻⁴² whereas others have found either a weak association⁴³ or no association⁴⁴ between HCC and diabetes. Diabetes predisposes to non-alcohol-induced steatohepatitis, which may progress to cirrhosis in up to 5% of cases.⁴⁵ Diabetes also is associated with increased levels of insulin-like factors that are potential carcinogenic factors.⁴⁶ Obesity, which frequently accompanies diabetes, has been reported to increase the risk for hepatic steatosis and fibrosis in HCV-infected patients.^{47,48} In a large, case-controlled study among veterans (823 patients with HCC and 3,459 controls), type 2 diabetes was associated with a 1.5-fold increase in the risk for HCC.¹⁴ However, this risk was significant only in the presence of other major HCC risk factors such as HCV, HBV, and alcohol-induced cirrhosis. The link between diabetes and HCC should be examined in future studies.

Viral Factors. In cross-sectional studies, HCV genotype 1 (1b in particular) is the most prevalent genotype worldwide and also is the most common genotype found among patients with HCC. However, all HCV genotypes have been described in HCV-related HCC. There are conflicting data as to whether genotype 1 is a risk factor for cirrhosis or HCC independent of older age.⁴⁹⁻⁵¹ It has been suggested that the higher prevalence of these genotypes reported in some studies represents a cohort effect in which older persons (those at greatest risk for cirrhosis and HCC) were infected at a time when genotype 1 was most prevalent.⁵¹ Lastly, there is no evidence that either viral load or viral quasispecies are important in determining the risk for HCV progression to cirrhosis or HCC.

HCC in HCV-Related Cirrhosis

Once cirrhosis is established, the annual rate of HCC is relatively consistent in the published literature (Table 1), with most studies reporting rates between 1% and 4%.^{34,49,52-56} Higher estimates (up to 7%) have been reported from Japan.^{34,56} In general, the incidence rates for HCC in patients with HCV-related cirrhosis are higher than those reported for HBV or alcohol-related cirrhosis.⁵⁷ Once cirrhosis is established, it becomes more difficult to discern the effects of additional risk factors for HCC because cirrhosis seems to be the common pathway by which several risk factors exert their carcinogenic effects. Nevertheless, male sex (2 to 3 times), older age,⁵³ as

Table 1. Summary of Several Studies That Reported the Annual Incidence Rates of HCC Among Patients With HCV-Related Cirrhosis

Study	Country	Child Class	No.	HCC (%/y)
Gordon ⁵²	United States	A,B	189	1.2
Fattovich ⁵⁵	Italy	A	357	1.6
Bruno ⁴⁹	Italy	A,B	163	2.5
Degos ⁵³	France	A	416	4.3
Serfaty ⁵⁴	France	A	103	3.3
Nishiguchi ⁵⁶	Japan	A	45	6.9
Chiba ³⁴	Japan	A,B	180	5.9

well as the severity of the underlying cirrhosis⁵⁸ have been shown consistently to increase the risk for HCC even further. It is less certain whether alcohol consumption may further increase the risk for HCC in HCV-related cirrhosis.²⁹ Of the studies that have examined the joint effect of alcohol consumption and HCV for risk for HCC among persons with cirrhosis, 2 found a statistically significant positive association,^{34,59} 2 found a statistically nonsignificant positive association,^{36,60} and one study reported a nonsignificant protective effect.³⁵

Antiviral Therapy and HCC

Table 2 shows a summary of the results of several studies that addressed the effect of antiviral therapy on the risk for HCC in HCV-infected patients. There was only one prospective, randomized, controlled trial that examined the effects of therapy on HCC, a trial from Japan in which 100 patients were randomized to receive either 6 MU of interferon alfa 3 times weekly for 3 to 6 months or were followed-up without treatment.⁵⁶ After a 2- to 7-year period of follow-up evaluation, HCC was significantly reduced in the treated group (4%) as compared with the nontreated controls (38%), a 93% reduction in the adjusted risk ratio. However, a large degree of this risk reduction was a result of the unusually high rate of HCC in the control group.⁵⁶ In another prospective but nonrandomized trial, treatment was not associated with a significant reduction in the HCC risk.⁶¹ The rest of the studies, mostly retrospective and nonrandomized, suggested a moderate decrease in the risk for HCC among HCV-infected patients treated with interferon.^{54,8,62-69} In general, the reported preventive effect of interferon alfa therapy was less marked in European studies than in studies from Japan. The benefit was better appreciated in patients with sustained response than nonresponders.⁷⁰ However, the lack of randomization may have exaggerated treatment benefits because it is likely that healthier patients (less likely to develop HCC) tend to get treated more frequently than those with advanced liver disease (who are likely to develop HCC), requiring that the stud-

ies be interpreted with caution.⁷¹ In the United States, there is an ongoing prospective multicenter trial to address this issue.

Epidemiology of HCC in the United States

Temporal Trends in Incidence, Mortality, Hospitalizations and Survival. The registries of the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute collect population-based cancer incidence data from approximately 14% of the U.S. population. According to the program data, the age-adjusted incidence rate of HCC increased from 1.4 per 100,000 during 1976 to 1980 to 3.0 per 100,000 during 1996 to 1998, a 2-fold increase (El-Serag, unpublished data). These rates probably underestimate the true incidence by 20% to 30% because they represent only HCC confirmed by histopathologic examination.

Concomitant with the increasing incidence, there has been a progressive increase in HCC-related mortality. According to U.S. vital statistics, the overall age-adjusted mortality rate for HCC has increased significantly from 1.8 per 100,000 (95% CI, 1.8-1.9 per 100,000) during the time period of 1979 to 1983 to 3.1 per 100,000 (95% CI, 2.9-3.2 per 100,000) during the time period of 1994 to 1998 (Fig. 3). At the same time, the temporal trends for hospitalizations with primary liver cancer have mirrored those of the incidence and mortality. For example, data from 172 Veterans Administration Medical Centers show that the overall number of hospitalizations as well as the

Table 2. Summary of Studies on the Incidence of HCC Among Patients With HCV-Related Cirrhosis Treated With Interferon

Study	Untreated		Interferon-Treated	
	No. HCC/ No. Cases	(%)	No. HCC/ No. Cases	(%)
Nishiguchi, 1995 ⁵⁶	17/45	37.8	2/45	4.4
Mazzella, 1996 ⁶¹	9/91	9.8	5/193	2.6
Fattovich, 1997 ⁵⁵	16/136	11.8	7/193	3.6
Bruno, 1997 ⁶⁵	16/81	19.7	6/82	7.3
Serfaty, 1998 ⁵⁴	7/44	16.0	4/59	6.8
IIHCSG, 1998 ⁶⁶	48/259	18.5	21/232	9.0
Imai, 1998 ⁶⁷	7/20	35.0	8/32	25.0
Benvegno, 1998 ⁶⁹	20/77	26.0	4/75	5.3
Niederau, 1998 ⁶²	13/77	16.9	3/64	4.7
Valla, 1999 ⁶⁸	9/49	18.4	5/45	11.1
Ikeda, 1999 ⁶⁴	67/452	14.8	29/1,191	2.4
Yoshida, 1999 ⁵⁸	32/107	29.9	33/230	14.3
Okanoue, 1999 ⁶⁹	22/55	40.0	7/40	17.5
Gramenzi, 2001 ⁶³	19/72	26.4	6/72	8.3
Total	302/1,565	19.3	140/2,553	5.5

Abbreviation: IIHCSG, International Interferon Hepatitis C Study Group.

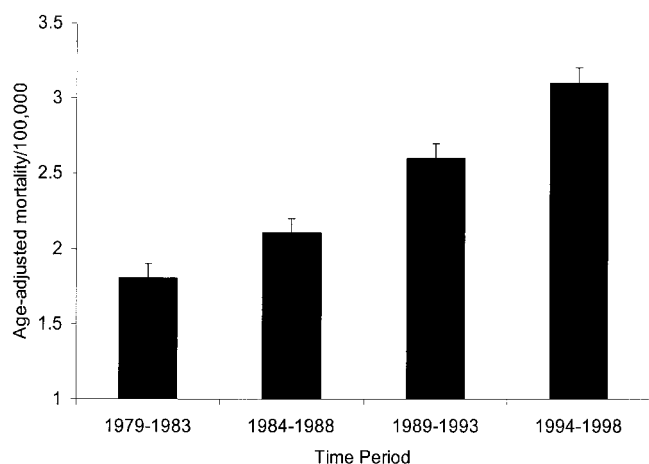


Fig. 3. The age-adjusted mortality rates in cases per 100,000 population for HCC in the United States for 4 time periods from 1979 to 1998. There has been a steady increase in the mortality rate of this cancer. Data from Vital Statistics (link for Vital Statistics: <http://www.cdc.gov/nchs>).

age-adjusted proportional hospitalization rates for HCC have increased by 42% between 1981 and 1997, reaching a hospitalization rate of 4.1 per 10,000 (95% CI, 3.7-4.5 per 10,000) during 1993 to 1997.⁷²

The similarity between incidence and mortality rates is indicative of the rapid death after diagnosis in most cases of HCC. The median survival rate remains dismal at 7 to 8 months with minor improvement over the past 25 years.⁷³ HCC usually is diagnosed at a late stage in patients with advanced cirrhosis, which makes complete surgical treatment and, therefore, cure highly unlikely. Fewer than 1% of patients diagnosed with HCC in the United States between 1974 and 1996 underwent surgical resection or transplantation and fewer than 8% underwent any surgical or local therapeutic intervention.

Sex-, Ethnicity-, Age-, and Geography-Related Variations in HCC

Examination of the incidence and mortality of HCC in the United States reveals remarkable sex-, ethnicity-, and age-related variations.⁷² In general, Caucasians are 2 to 3 times less affected than African Americans, who, in turn, are 2 to 3 times less affected than Asians, Pacific Islanders, or Native Americans. In all ethnic groups, men are 2 to 3 times more affected than women. The magnitude of these marked ethnic and gender differences in HCC have remained largely constant even when the overall rates of HCC have increased significantly. This indicates that increases in HCC did not result from the disproportionate increase in a single ethnic or gender group.

Asian men (Chinese, Korean, Filipino, and Japanese) have the highest age-adjusted incidence rates (up to 23 per

100,000). However, Caucasians, despite having the lowest age-adjusted incidence rates, constitute the majority of HCC cases because they are the largest ethnic group. The reason(s) for these ethnic differences probably relate to the prevalence and acquisition time of the major HCC risk factors (HCV, HBV, and alcohol-induced liver disease). For example, the prevalence of HCV, HBV, and alcohol-induced cirrhosis is 2- to 3-fold higher in African Americans than Caucasians.⁷⁴

HCC rarely is seen during the first 4 decades of life except in populations in whom HBV infection is hyperendemic. The incidence of HCC increases progressively with older age, reaching a peak between the ages of 70 and 75 years.⁷⁴ However, the increase in HCC cannot be explained solely by the effect of aging in the general population. The age distribution for patients with HCC has shifted toward relatively younger patients between the ages of 50 to 70. The shift toward a younger age is seen in men and women alike and in all ethnic groups. In addition, there is an increase in incidence rates in all age groups among cohorts born during recent years. This indicates that several generations' birth cohorts were exposed relatively early in life to carcinogenic factor(s) leading to a lifetime increase in HCC risk among these cohorts.^{72,74}

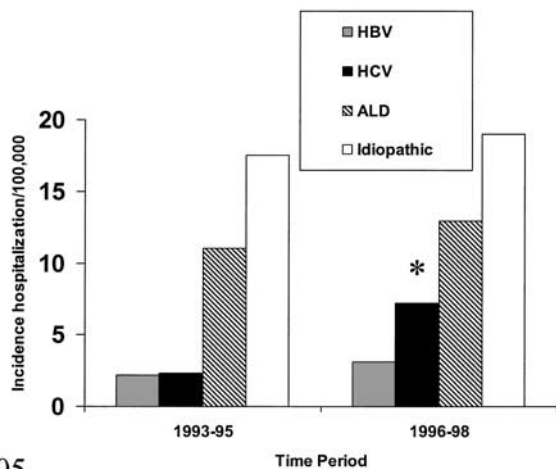
Among the Surveillance, Epidemiology, and End Results Program registries, Hawaii had the highest age-adjusted incidence rate (4.6 per 100,000), followed by San Francisco-Oakland, and New Mexico, whereas Iowa and Utah had the lowest rates, with approximately 1.0 per 100,000. Adjusting for variations in ethnicity, sex, age, and geographic region confirms the significant increase in incidence of HCC of almost 2-fold over the time period between 1975 and 1998.⁷⁵

The Underlying Cause of the Increase in HCC in the United States

Because of the essential role of cirrhosis in the development of HCC in most patients, an increase in the number of persons living with cirrhosis is the likely explanation for the increasing incidence of HCC (Table 3). This has resulted from an increase in the incidence as well as the survival of patients with cirrhosis. The improved survival of patients with cirrhosis with improvements in clinical

Table 3. Why HCC Rates Are Increasing

Increasing prevalence of patients with cirrhosis	
A. Increasing incidence of cirrhosis	
●	HCV
●	HBV infection acquired 2 to 3 decades earlier
●	Alcohol
B. Improved survival of patients with cirrhosis	
●	Improved outcomes of esophageal varices and peritonitis



*p<0.05

Fig. 4. Temporal trends in incidence of hospitalization for HCC by risk factor. The largest increase has been in HCV-related HCC. The incidence of cases that were idiopathic or related to HBV or alcohol-induced liver disease did not increase significantly. The data were obtained from 172 hospitals of the Department of Veteran Affairs between 1993 to 1995 and 1996 to 1998. (Reprinted with permission from *Archives of Internal Medicine*, 2000, vol 160, pp 3227-3230. Copyrighted 2000. American Medical Association.⁷⁷)

management (e.g., esophageal variceal hemorrhage⁷⁶) may allow enough time for some patients to develop symptomatic HCC.⁷⁴

To a limited extent, the increasing trends may be related to improvements in the screening or diagnosis of HCC. Screening with diagnostic modalities such as serum α -fetoprotein, ultrasonography, or computed tomography have been in place during most of the past 2 decades. There has been no known increase in screening/surveillance rates and there are no formal population-based HCC surveillance programs (except for Alaska).

There are only 2 published studies that have examined the temporal trends of the underlying HCC risk factors. In the first, the electronic records of 1,605 patients diagnosed with HCC between 1993 and 1998 in 172 Veterans Administration hospitals were examined for the presence of HCC risk factors.⁷⁷ There was a 3-fold increase in the age-adjusted rates for HCC associated with HCV, from 2.3 per 100,000 (95% CI, 1.8-3.0 per 100,000) between 1993 and 1995 to 7.0 per 100,000 (95% CI, 5.9-8.1 per 100,000) between 1996 and 1998 (Fig. 4). Patients with HCV-related HCC in 1996 to 1998 were significantly younger than those diagnosed with HCC during earlier times (Fig. 5). At the same time, the age-adjusted rates for HCC with either HBV (2.2 vs. 3.1 per 100,000) or alcohol-induced cirrhosis (8.4 vs. 9.1 per 100,000) remained stable. The rates for HCC without risk factors also remained without a statistically significant change, ranging 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 per 100,000) between 1996 and 1998.⁷⁷ Thirty-eight percent of patients without specific risk factors had a diagnosis of nonspecific cirrhosis. In another study, all patients residing in the United States who were referred to MD Andersen Medical Center in Houston, TX, with HCC were tested for markers of HCV and HBV infection.⁷⁸ The number of patients referred with HCC steadily increased from 143 in 1993 to 1995 to 216 in 1996 to 1998. During these 2 time periods, 26 patients (18%) and 66 patients (31%), respectively, were HCV positive ($P = .01$). During the same period, there were no significant differences in the proportions of patients with hepatitis B surface antigen or anti-HBc or those with no viral markers.¹⁵

Countries With a Similar HCV Prevalence (Japan, Italy, United States): Will They Have Similar HCC Trends?

Other developed countries in Europe and Asia also have experienced an increase in the incidence of HCC related to HCV. In Japan, HCV-related HCC has more than tripled during the past 4 decades and it accounts for up to 90% of all HCC cases in that country.^{78,79} The HCV prevalence in that country is estimated to be 2%, mostly acquired after World War II through blood transfusion and contaminated needles used for medical purposes. The peak of the HCV epidemic is thought to have occurred 2 to 3 decades before that in the United States. This is supported by the fact that currently the peak prevalence of anti-HCV in Japan is among persons aged 70 years as compared with a peak prevalence in the United States in persons aged 40 to 49. Furthermore, a study that used molecular evolutionary analysis reported that genetic

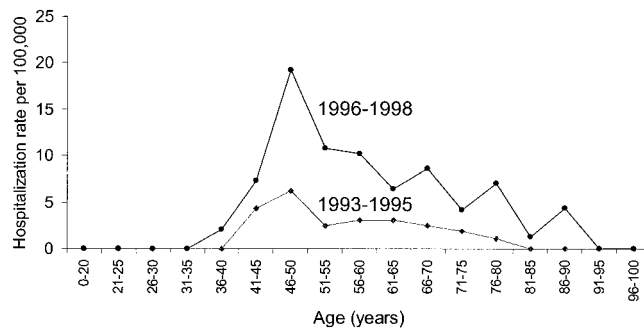


Fig. 5. Age-specific rates of hospitalization (per 100,000) for primary liver cancer associated with HCV infection during 1993 to 1995 and 1996 to 1998 in the Department of Veteran Affairs. Rates increased during the time periods studied, particularly among persons between the ages of 45 and 60 years. (Reprinted with permission from *Archives of Internal Medicine*, 2000, vol 160, pp 3227-3230. Copyrighted 2000. American Medical Association.⁷⁷)

divergence of genotype 1b (which indicates the time of HCV spread) occurred in Japan between 1943 and 1949⁸⁰ and, in the United States, for genotype 1a, 20 years later, thus implying that the United States might be 20 years behind Japan in the epidemic of HCV-related HCC.^{9,80} However, it is difficult to extrapolate the association between the HCV prevalence and HCC incidence observed in Japan to other places such as the United States. The reported incidence of HCC in HCV-infected cohorts, as well as in those with HCV-related cirrhosis, tends to be higher in Japan than it is elsewhere. Moreover, the development of HCC in patients without cirrhosis also is routinely reported, even with mild degrees of fibrosis. For example, in a large retrospective cohort study (n = 2,890) from Japan, the annual HCC incidence was 0.5% with low-grade fibrosis and 7.9% for severe fibrosis.⁵⁸ Lastly, most patients with cirrhosis in Japan seem to die from HCC-related complications rather than from other end-stage liver disease-related complications.⁸¹ Additional unknown genetic or environmental factors might explain this exceptionally high tendency to develop HCC in HCV-infected Japanese patients.

Conversely, there are similarities in the epidemiology of HCC in Italy and that in the United States. In Italy, the HCV prevalence in the general population ranges from 0.9% in central⁸² to 12.6% in southern areas.⁸³ Most HCV infection is believed to have been acquired between 1950 and 1980 owing to injection drug use, blood transfusion, and the use of nondisposable needles in medical practice.⁸⁴ The HCC incidence rates increased in Italian men from 3.3 per 100,000 in the 1970s to 9.2 per 100,000 in 1994 and then decreased to 6.0 in 1998; a similar trend also was seen in women.⁸⁵ HCV-related HCC has been estimated to comprise 44% to 66% of all HCC cases.³⁻⁵ In comparison with the United States, Italy has 1.5 to 3 times higher overall HCV prevalence, a higher HCC incidence (8 vs. 3 per 100,000), and an earlier peak time by a decade of HCV acquisition. This suggests that there could be an approximate doubling of the HCC incidence in the United States over the next 10 to 15 years followed thereafter by a reduction. As described later, these estimates are close to what can be derived by modeling the natural history estimates to the existing cohort of HCV-infected persons in the United States.

The Projection of Future HCC Trends in the United States

A large proportion of patients with HCC in the United States were between the ages of 20 and 40 during the 1960s and 1970s.⁷² This was a time when risk factors for the transmission of HCV and HBV were rampant (*e.g.*,

injection drug use, needle sharing, transfusion of un-screened blood and blood products, and unsafe sexual practices). With the passage of 2 to 3 decades since then, a proportion of those originally infected have or will advance to cirrhosis, some of whom will progress further to HCC (1980s and 1990s). It has been estimated through mathematic modeling studies that the HCV epidemic started in the 1960s and reached a peak in the 1980s. It also is estimated that approximately 2% of the population (4 million persons) were infected with HCV (3 million with active viremia).⁸⁶ The highest infection rate currently is among persons in their 40s and 50s who have been infected already for 1 to 2 decades and can be expected to live for an additional 2 to 3 decades with the potential of developing HCV-related complications.⁸⁷

Therefore, barring a major alteration in our current knowledge of the clinical course of HCV infection, the incidence of HCC in the United States is likely to continue to increase in the near future as those infected with HCV ultimately develop cirrhosis and HCC. In addition, the influx of immigrants from countries with high HBV prevalence is likely to continue and further contribute to the increasing incidence of HCC.

A recent publication reported efforts to project the burden of HCV in the U.S. population by using a computer simulation Markov model.⁸⁸ The authors project a total of 27,200 deaths in the 10-year period 2010 through 2019 as a consequence of HCV-induced HCC. Some of the estimates used in that study might have been conservative in comparison with more current knowledge. For example, the annual incidence of HCC in patients with cirrhosis was assumed to be 0.5%, and the baseline number of HCV-related HCC cases in 1991 was assumed to be approximately 1,700 cases. If these 2 estimates were both to be substituted by 3% and 2,500, respectively, then close to 5,000 cases of HCV-related HCC per year could be expected in the year 2010 (Wong J, personal communication). If HCC unrelated to HCV also maintains its current trends, the incidence of HCC could approximately double (5-7 per 100,000) within the next 1 to 2 decades.

Future Research Needs

There is a critical need for further basic research on HCV and carcinogenesis to identify viral, cellular, immune, and host-genetic factors that contribute to the development of HCC. Identification of the steps that lead from chronic HCV infection to cancer would help in developing means of prevention, early detection, and treatment.

There are major needs in epidemiologic and clinical research on HCC. To reduce the amount of speculation

regarding the contribution of HCV to the current (and hence future) toll of HCC in the United States, population-based studies are needed to examine known and suspected risk factors and to collect appropriate biologic samples for assessment of markers for early detection of HCC. These studies also could provide valuable information on the risk factors for progression of chronic hepatitis C. The relationship between HCV and the obesity, insulin-resistance syndromes, diabetes, and non-alcohol-induced fatty liver disease need further study, especially given the high prevalence of these conditions and the large proportion of HCC cases in which no specific risk factor can be identified.

Despite the apparent plethora of studies examining the clinical course of hepatitis C, there is still a need for long-term studies that examine entire cohorts of patients with a well-defined time of onset of HCV infection and a properly characterized risk factor profile. Given that current therapies are applicable to only a proportion of HCV-infected persons and response rates are still not excellent, there continues to be a need for prospective studies focusing on means of early detection of HCC to show whether screening or surveillance methods are effective in reducing morbidity and mortality. Furthermore, prospective controlled trials of new and innovative therapies of HCV-related HCC are needed, which are areas of little clinical and research experience in this country.

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