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RISING INCIDENCE OF HEPATOCELLULAR CARCINOMA IN THE UNITED STATES

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ABSTRACT

Background and Methods Clinical observations have suggested that the number of cases of hepatocellular carcinoma has increased in the United States. We analyzed data from the Surveillance, Epidemiology, and End Results (SEER) data base to determine the age-adjusted incidence of hepatocellular carcinoma from 1976 to 1995, data from the U.S. vital-statistics data base to determine age-adjusted mortality rates from 1981 to 1995, and data from the Department of Veterans Affairs to determine age-adjusted rates of hospitalization for the disease from 1983 to 1997.

Results The incidence of histologically proved hepatocellular carcinoma increased from 1.4 per 100,000 population (95 percent confidence interval, 1.3 to 1.4) for the period from 1976 to 1980 to 2.4 per 100,000 (95 percent confidence interval, 2.3 to 2.4) for the period from 1991 to 1995. Among black men, the incidence was 6.1 per 100,000 for the period from 1991 to 1995, and among white men, it was 2.8 per 100,000. There was a 41 percent increase in the mortality rate from primary liver cancer and a 46 percent increase in the proportion of hospitalizations attributable to this disease during the periods studied. The incidence increased significantly among younger persons (40 to 60 years old) during the period from 1991 to 1995 as compared with earlier periods.

Conclusions An increase in the number of cases of hepatocellular carcinoma has occurred in the United States over the past two decades. The age-specific incidence of this cancer has progressively shifted toward younger people. (N Engl J Med 1999;340:745-50.)

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incidence of hepatocellular carcinoma was relatively stable and low from 1970 to 1986 (2.1 to 2.5 cases per 100,000 population).² A recent report suggested that the rate of death from primary liver cancer has increased,⁶ but no published studies have analyzed epidemiologic trends of hepatocellular carcinoma in the United States. We analyzed these trends over time using information from three large independent data bases that deal with different aspects of the epidemiology of hepatocellular carcinoma in the United States.

METHODS

Data Sources

We used three data bases to analyze trends in the incidence of, mortality from, and rate of hospitalization for hepatocellular carcinoma. Data on incidence were obtained from the nine population-based cancer registries that constitute the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. These registries account for approximately 14 percent of the U.S. population and include the states of Connecticut, Hawaii, New Mexico, and Utah and the metropolitan areas of San Francisco–Oakland, Detroit, Seattle, and Atlanta.⁷ In this data base, the cancers are coded according to the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM)⁸ and the *International Classification of Diseases for Oncology* (ICD-O).⁹

Data on mortality are accumulated yearly by the National Center for Health Statistics as part of the U.S. vital-statistics data base. Each annual data set is compiled from all death certificates (range, 1.9 million to 2 million) issued in the United States. Data on mortality were obtained for the years 1979 through 1995¹⁰ and included the age, sex, race or ethnic group, and cause of death of each decedent. Since 1979 the causes of death have been coded according to the ICD-9-CM.

The Patient Treatment File, which is the computerized data base of the Department of Veterans Affairs (VA), was used to provide data on hospitalization for primary liver cancer. The Patient Treatment File contains the records of all inpatients at all 172 VA hospitals. Each annual file, from 1970 to 1997, contains the records of approximately 1 million hospitalizations of 600,000 patients. Since 1981, discharge diagnoses have been coded according to the ICD-9-CM. We analyzed data collected from 1983 to

HEPATOCELLULAR carcinoma is the most common primary cancer of the liver. The disease has a dismal five-year survival rate of less than 5 percent.^{1,2} Hepatocellular carcinoma is an infrequent cancer in developed countries.² However, its incidence has substantially increased in Japan³ during the past three decades, and slight increases have been reported in the United Kingdom and France.^{4,5} In the United States, the in-

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1997. Data were analyzed according to age and race or ethnic group but not sex, because 98 percent of hospitalized veterans are men.

Diagnostic Codes

We included data on patients with a diagnosis of primary liver cancer (ICD-9-CM code 155.0) from the U.S. vital-statistics data base as well as from the VA data base. We included data on patients in the SEER data base only if the patients had a confirmed histologic diagnosis of hepatocellular carcinoma (ICD-O code 8170).

Statistical Analysis

For each year, the number of hospital discharges of patients with primary liver cancer was broken down according to race or ethnic group and 10-year age groups. The total number of discharges for all diagnoses was also broken down according to race or ethnic group and age. To calculate proportional hospitalization rates for each five-year period analyzed, we divided the number of age-specific hospitalizations for primary liver cancer by the total number of all hospitalizations during a particular five-year period. The numbers of age-specific discharges for each of the five consecutive years were added up, and these race-specific and age-specific rates were then adjusted according to the method of direct standardization to reflect the age distribution of all hospitalized veterans in 1990.¹¹ The age-adjusted rates of consecutive five-year periods were expressed as proportional rates per 10,000 hospitalizations. We used a similar method to calculate age-adjusted mortality rates and age-adjusted incidence, except that the denominator was 100,000 persons.

We calculated the standard error of the age-adjusted rates according to a method suggested by Breslow and Day.¹² To calculate the 95 percent confidence interval for each rate, we multiplied the standard error by 1.96 and then added or subtracted this value from the rate. Any two rates whose confidence intervals did not overlap were considered significantly different.

To examine the age distribution of the patients with cancer, we plotted the age-specific incidence of hepatocellular carcinoma according to data obtained from the SEER data base for each five-year period from 1981 to 1995. We subsequently performed a birth-cohort analysis in which the age-specific incidence of hepatocellular carcinoma according to the year of birth was calculated for the entire population included in the SEER data base.

RESULTS

Incidence

In the SEER data base, 73.5 percent of all primary liver cancers were histologically confirmed to be hepatocellular carcinoma (ICD-O code 8170). The rates of histologic confirmation were 75 percent for the period from 1986 to 1990 and 78 percent for the period from 1991 to 1995. The incidence of hepatocellular carcinoma increased from 1.4 per 100,000 (95 percent confidence interval, 1.3 to 1.4) for the period from 1976 to 1980 to 2.4 per 100,000 (95 percent confidence interval, 2.3 to 2.4) for the period from 1991 to 1995 (Table 1). Figure 1 shows the trends in the incidence of hepatocellular carcinoma over time among black men and women and white men and women. Among black men, the incidence increased from 4.0 per 100,000 (95 percent confidence interval, 3.4 to 4.8) for the period from 1976 to 1980 to 6.1 per 100,000 (95 percent confidence interval, 5.4 to 6.9) for the period from 1991 to 1995. Similarly, among white men, the incidence of hepa-

TABLE 1. OVERALL INCIDENCE OF HEPATOCELLULAR CARCINOMA IN THE UNITED STATES AND MORTALITY AND HOSPITALIZATION RATES.*

VARIABLE	AGE-ADJUSTED RATE (95% CI)†	TOTAL NUMBER
Hospitalization rate		
1983–1987	2.9 (2.6–3.2)	1,368
1988–1992	2.8 (2.4–3.1)	1,451
1993–1997	4.1 (3.7–4.5)	1,474
Incidence‡		
1976–1980	1.4 (1.3–1.4)	1,438
1981–1985	1.6 (1.5–1.7)	1,837
1986–1990	1.9 (1.9–2.0)	2,364
1991–1995	2.4 (2.3–2.4)	3,107
Mortality rate§		
1981–1985	1.7 (1.7–1.8)	13,833
1986–1990	2.0 (2.0–2.1)	17,278
1991–1995	2.4 (2.4–2.5)	22,307

*The analysis includes data on both sexes and all races and ethnic groups. CI denotes confidence interval.

†The hospitalization rate is the rate per 10,000 hospitalizations for all causes, and the incidence and mortality rates are the rates per 100,000 population.

‡Only histopathologically confirmed cases (73.5 percent of all primary liver cancers) were included in the analysis.

§Data are for the entire U.S. population.

tocellular carcinoma increased from 1.7 per 100,000 (95 percent confidence interval, 1.6 to 1.8) for the period from 1976 to 1980 to 2.8 per 100,000 (95 percent confidence interval, 2.7 to 3.0) for the period from 1991 to 1995. During the same periods, there was a less pronounced increase among white women and black women. Overall, the incidence of hepatocellular carcinoma among men was three times that among women.

The age-adjusted incidence in a heterogeneous group that included Hispanics, Asians, Pacific Islanders, and Native Americans, both men and women, was 5.6 per 100,000 for the period 1976 to 1980, 6.1 per 100,000 for the period 1981 to 1985, 7.0 per 100,000 for the period 1986 to 1990, and 7.4 per 100,000 for the period 1991 to 1995. Among all cases of hepatocellular carcinoma in the SEER data base, the proportion represented by this heterogeneous group was 23 percent for the period from 1981 to 1985, 25 percent for the period from 1986 to 1990, and 23 percent for the period from 1991 to 1995. The lack of a reliable population denominator precluded detailed analysis of this heterogeneous group.

Mortality Rates

The trends in the age-adjusted mortality rates for hepatocellular carcinoma (Table 1 and Fig. 2) were virtually identical to the trends in the incidence of the disease. There was a 41 percent increase in the overall mortality rate. The age-adjusted mortality rate among black men increased from 5.3 per 100,000 (95 per-

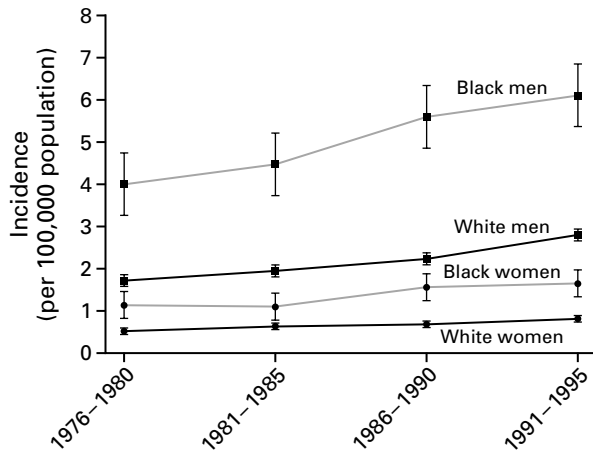


Figure 1. Age-Adjusted Incidence of Hepatocellular Carcinoma among Black Men and Women and White Men and Women in the United States, 1976-1995.

Each point represents the average incidence. The I bars are the 95 percent confidence intervals.

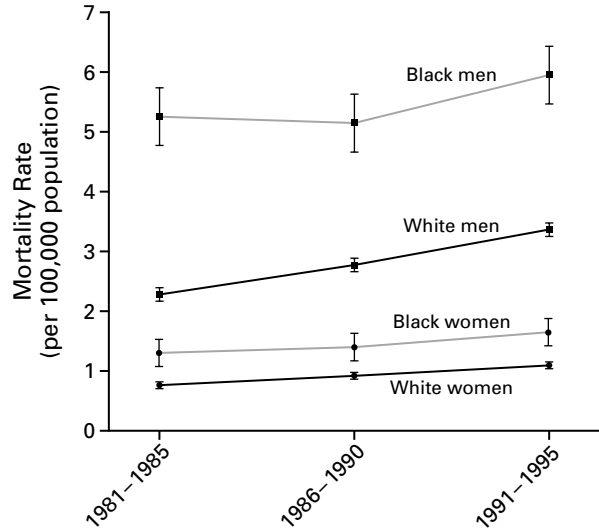


Figure 2. Age-Adjusted Rates of Death from Primary Liver Cancer among Black Men and Women and White Men and Women in the United States, 1981-1995.

Each point represents the average rate. The I bars are the 95 percent confidence intervals.

cent confidence interval, 4.8 to 5.8) for the period from 1981 to 1985 to 6.0 per 100,000 (95 percent confidence interval, 5.5 to 6.4) for the period from 1991 to 1995 (Fig. 2). The respective rates among white men also increased significantly, from 2.3 per 100,000 (95 percent confidence interval, 2.2 to 2.4) to 3.4 per 100,000 (95 percent confidence interval, 3.2 to 3.5). There were smaller but still significant increases in mortality rates from liver cancer among both black women and white women.

Hospitalization Rates

The age-adjusted proportional rates of hospitalization for primary liver cancer among U.S. veterans remained stationary from 1983 to 1992 (Table 1). However, in the period from 1993 to 1997, the hospitalization rate was 4.1 per 10,000 hospitalizations for all causes (95 percent confidence interval, 3.7 to 4.5), a 46 percent increase over the rate for the period from 1988 to 1992. The actual total number of hospitalizations for primary liver cancer in the VA hospitals ranged from 1368 for the period from 1983 to 1987 to 1474 for the period from 1993 to 1997. The mean annual number of hospitalized veterans, the denominator, declined by 13 percent, from 1,017,976 for the period from 1983 to 1987 to 886,697 for the period from 1993 to 1997.

Age-Specific Incidence

Figure 3 shows the age-specific incidence of hepatocellular carcinoma among white men for the period from 1981 to 1995. The age-specific incidence increased progressively, reaching a peak at about 80 to 84 years of age for the period from 1981 to 1985.

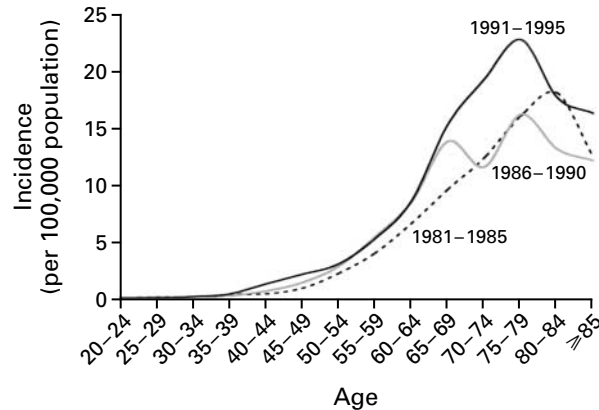


Figure 3. Age-Specific Incidence of Hepatocellular Carcinoma (ICD-O Code 8170) among White Men in the SEER Data Base, 1981-1995, According to Age.

The differences between the rates for the period from 1981 to 1985 and those for the period from 1991 to 1995 were significant for ages 40 to 49 and for ages 60 to 79.

The same trend was observed for the more recent periods, but the peak shifted toward those 75 to 79 years of age. More important, the slopes preceding the peaks significantly shifted toward younger age groups; the age-specific incidence for the period from 1991 to 1995 is significantly to the left of the incidence for the period from 1981 to 1985. Sixty percent of the 95 percent confidence intervals for the

rates for the two curves for men from 40 to 85 years of age or older did not overlap and thus were significantly different. For example, the incidence among men who were 65 to 69 years of age was 9.6 per 100,000 (95 percent confidence interval, 8.1 to 11.2) for the period from 1981 to 1985, as compared with 15.2 per 100,000 (95 percent confidence interval, 13.5 to 17.2) during the period from 1991 to 1995. Similar trends were observed when the age-adjusted incidence rates among black men and among all women were plotted (data not shown). For example, among women, beginning at the age of 60, there were significant increases in the incidence of hepatocellular carcinoma for the period from 1991 to 1995 as compared with the period from 1981 to 1985.

A birth-cohort analysis of the entire population included in the SEER data base was performed by analyzing age-specific incidence according to the year of birth (data not shown). A birth cohort is a group of people who were all born during the same period. Since data on incidence were available for the period from 1973 to 1995 for persons ranging in age from 20 to more than 85 years, the birth dates for the cohort ranged from 1888 to 1975. For cohorts born in the period from 1888 to 1958, there was a progressive increase in all age-specific rates that reached a peak in cohorts born in the period from 1953 to 1958 and then declined slightly in younger cohorts. However, the rates among these younger cohorts were low (less than 0.2 per 100,000) and hence were relatively unstable.

DISCUSSION

We found a statistically significant increase in the incidence of hepatocellular carcinoma in the United States over the past two decades. The incidence rose from 1.4 per 100,000 during the period from 1976 to 1980 to 2.4 per 100,000 during the period from 1991 to 1995. Men were affected three times as often as women, and blacks were affected twice as often as whites. Older age was associated with a higher risk, but the incidence among younger persons also rose progressively.

We searched three large data bases to obtain independent measures of the frequency of disease: the hospitalization rate, the incidence, and the mortality rate. As would be expected in the analysis of a rapidly fatal cancer, the results of our analyses of these three measures were similar in every important aspect, strengthening the internal validity of the observed trends. Mortality rates on the whole, however, were higher than the incidence of the disease. Differences in the way the diseases are coded by the SEER data base and by the U.S. vital-statistics data base help to explain this paradox. The SEER data on incidence included only tumors histopathologically confirmed to be hepatocellular carcinoma (ICD-O code 8170). Conversely, the diagnostic code for primary liver can-

cer (ICD-9-CM code 155.0) used by the U.S. vital-statistics data base encompasses other rare malignant liver tumors and, possibly, a few misclassified metastatic tumors.

The advent of precise diagnostic tests may introduce a detection bias whereby increased recognition of the disease, rather than a true increase in its occurrence, accounts for a rising incidence. However, in the case of hepatocellular carcinoma, detection bias is unlikely to account for the observed trends. The SEER data on incidence included only the 73.5 percent of primary liver cancers that were histopathologically confirmed, and this proportion remained largely the same throughout the study period. Moreover, the use of ultrasonography and measurements of serum alpha-fetoprotein, which has been routine since the early 1980s, could not explain the increase in cases of cancer detected between 1985 and 1995.

According to the VA data on hospitalization, the actual number of cases of liver cancer increased only slightly, but the rates of hospitalization for this illness were disproportionately high. With the recent shift from inpatient to ambulatory care, the total number of hospitalizations for all diagnoses has declined. However, for the same reason, the actual number of cases of liver cancer identified in patients during hospitalization may be underestimated, since some patients receive the diagnosis outside the hospital. One should keep these caveats in mind when interpreting data on hospitalization, especially in this era of managed care.

In developed countries, hepatocellular carcinoma predominantly affects the elderly. However, an effect due to an aging population alone cannot explain the rising rates of this cancer. We used age-adjusted rates to control for this variable among different populations. In addition, the rise in the incidence of hepatocellular carcinoma was coupled with a shift in the incidence of the cancer toward younger age groups. This trend is probably the result of environmental risk factors that affect all birth cohorts but that are stronger in cohorts of younger people. In our analysis, the overall incidence of hepatocellular cancer among cohorts born during the period from 1953 to 1958 was low, but the age-specific incidence was higher than the incidence among cohorts born immediately before or after them.

Our data show that approximately a quarter of the cases of hepatocellular cancer occurred among populations that were neither white nor black. This heterogeneous group includes Hispanics, Native Americans, Pacific Islanders, and Asians. Immigrants from areas where liver cancer is endemic, such as Southeast Asia and Africa, constitute an unknown proportion of this group. This group had the highest risk for hepatocellular carcinoma. Among all cases of hepatocellular carcinoma, the proportion represented by this group has remained virtually constant for the past

20 years, making it unlikely that the cases in this group alone caused the observed rise.

The three main risk factors associated with hepatocellular carcinoma in the United States are infection with hepatitis C virus (HCV), infection with hepatitis B virus (HBV), and alcoholic cirrhosis.^{1,2,13} The incidence of alcoholic liver disease is declining. Data from the National Hospital Discharge Survey show that alcohol-related diagnoses declined slightly from 1972 to 1987,¹⁴ and age-adjusted mortality related to alcoholic cirrhosis declined during the same period.¹⁵ This leaves HCV and HBV infections as the two biologically plausible culprits behind the rising incidence of hepatocellular carcinoma. The majority of the study population were 12 to 49 years of age during the 1960s and 1970s. This was a time when intravenous drug use, needle sharing, transfusion of unscreened blood and blood products, and unsafe sexual practices, all of which are risk factors for the transmission of HBV and HCV, were widespread. In persons infected with HBV or HCV in whom hepatocellular carcinoma develops, there is a latency period of one to three decades.¹⁶⁻¹⁸ Thus, among persons infected with HCV or HBV during the 1960s or 1970s, hepatocellular carcinoma would develop in the 1980s and 1990s, the period when the increase in cases of cancer began to occur. If HCV and HBV infections are to blame for the increase, this fact would explain the sexual and racial differences in the incidence of hepatocellular carcinoma. In the United States, blacks are at greater risk for HBV and HCV infection than whites, and both HBV infection and HCV infection are more common in men than in women.¹⁹⁻²¹

The rise in hepatocellular carcinoma may continue for more than a few years. There is a large pool of persons infected with HCV, HBV, or both in whom the cancer is in the latency period. In addition, emigration from areas where hepatocellular carcinoma is endemic, such as Southeast Asia and parts of Africa, where perinatal HBV infection and exposure to environmental carcinogens such as aflatoxin are common, is likely to continue. The incidence of HCV infection remained steady throughout the 1980s (about 150,000 cases annually)²⁰ before declining by half during the early 1990s. The incidence of HBV infection reached a peak of 11.5 per 100,000 population in 1985 before declining to a rate of 6.3 per 100,000 in 1992. In approximately 85 percent of adults infected with HCV and 5 percent of those infected with HBV, the infection becomes chronic.^{20,22} Cirrhosis is estimated to develop during the first 10 years after transfusion in at least 20 percent of patients with post-transfusion chronic HCV infection. Once cirrhosis is established, carcinoma develops at a rate of 1 to 4 percent per year, which means that after 20 years hepatocellular carcinoma will develop in 1.9 to 6.7 percent of all patients with chronic HCV

infection.²³⁻²⁵ These projections are important, because approximately 3.9 million persons in the United States are infected with HCV.¹⁹ By contrast, the seroprevalence of HBV in the United States is low, with an estimated 1 million to 1.25 million persons, or 0.9 percent of blacks and 0.2 percent of whites, harboring a silent HBV infection.^{20,22} According to a consensus report of the National Institutes of Health, the annual probability of liver cancer among patients with HBV-related chronic hepatitis is 0.5 percent and that among patients with cirrhosis is 2.4 percent.²⁵

For patients who harbor chronic HCV or HBV infection, attention must be focused on the prevention of cirrhosis. Controlled trials in Japan²⁶ and France²⁷ indicate that interferon therapy in patients with HCV-related cirrhosis, even when complete biochemical and virologic clearing does not occur, is associated with a decreased risk of hepatocellular carcinoma.^{26,27} Interferon therapy is of moderate benefit in patients with HBV-related chronic hepatitis, with serum HBV DNA levels becoming undetectable in 37 percent of treated patients and hepatitis B surface antigen levels becoming undetectable in 7.8 percent.²⁸ A favorable response to interferon treatment in patients with HBV-related chronic hepatitis probably reduces the risk of hepatocellular carcinoma.²⁹

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REFERENCES

1. Kew MC. Hepatic tumors and cysts. In: Feldman M, Sleisenger MH, Scharschmidt BF, eds. Sleisenger & Fordtran's gastrointestinal and liver disease: pathology/diagnosis/management. 6th ed. Vol. 1. Philadelphia: W.B. Saunders, 1998:1364-87.
2. Godley PA, Sandler RS. Liver cancer. In: Everhart JE, ed. Digestive diseases in the United States: epidemiology and impact. Washington, D.C.: Government Printing Office, 1994:227-41. (NIH publication no. 94-1447)
3. Okuda K, Fujimoto I, Hanai A, Urano Y. Changing incidence of hepatocellular carcinoma in Japan. *Cancer Res* 1987;47:4967-72.
4. Taylor-Robinson SD, Foster GR, Arora S, Hargreaves S, Thomas HC. Increase in primary liver cancer in the UK, 1979-94. *Lancet* 1997;350:1142-3.
5. Deuffic S, Poynard T, Buffat L, Valleron AJ. Trends in primary liver cancer. *Lancet* 1998;351:214-5.
6. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1998. *CA Cancer J Clin* 1998;48:6-29. [Erratum, *CA Cancer J Clin* 1998;48:192.]
7. Surveillance, Epidemiology, and End Results (SEER) program public-use CD-ROM (1973-1995). Bethesda, Md.: National Cancer Institute, April 1998 (software).
8. Department of Health and Human Services. The international classification of diseases, 9th rev., clinical modification: ICD-9-CM. 3rd ed. Vol. 1. Diseases: tabular list. Washington, D.C.: Government Printing Office, March 1989. (DHHS publication no. (PHS) 89-1260.)
9. Percy C, Van Holten V, Muir C, eds. International classification of diseases for oncology. 2nd ed. Geneva: World Health Organization, 1990.
10. Grant BF, Zobeck T. Liver cirrhosis mortality in the United States, 1972-1986. Surveillance report no. 11. Rockville, Md.: National Institute on Alcohol Abuse and Alcoholism, 1989.
11. Kahn HA, Sempos CT. Statistical methods in epidemiology. Vol. 12 of Monographs in epidemiology and biostatistics. New York: Oxford University Press, 1989:87-95.
12. Breslow NE, Day NE. Statistical methods in cancer research. Vol. 2. The design and analysis of cohort studies. Lyon, France: International Agency for Research on Cancer, 1987:58-61. (IARC scientific publications no. 82.)
13. Takano S, Yokosuka O, Imazeki E, Tagawa M, Omata M. Incidence of

hepatocellular carcinoma in chronic hepatitis B and C: a prospective study of 251 patients. *Hepatology* 1995;21:650-5.

14. Dufour MC. Chronic liver disease and cirrhosis. In: Everhart JE, ed. *Digestive diseases in the United States: epidemiology and impact*. Washington, D.C.: Government Printing Office, 1994:615-46. (NIH publication no. 94-1447)
15. Grant BF, Zobeck TS, Pickering RP. Liver cirrhosis mortality in the United States, 1973-1978. Rockville, Md.: National Institute on Alcohol Abuse and Alcoholism, 1990.
16. Sherlock S. Viruses and hepatocellular carcinoma. *Gut* 1994;35:828-32.
17. Yarrish RL, Werner BG, Blumberg BS. Association of hepatitis B virus infection with hepatocellular carcinoma in American patients. *Int J Cancer* 1980;26:711-5.
18. Castells L, Vargas V, Gonzalez A, Esteban J, Esteban R, Guardia J. Long interval between HCV infection and the development of hepatocellular carcinoma. *Liver* 1995;15:159-63.
19. Alter MJ. Epidemiology of hepatitis C. *Hepatology* 1997;26:Suppl 1: 62S-65S.
20. McQuillan GM, Alter MJ, Everhart JE. Viral hepatitis. In: Everhart JE, ed. *Digestive diseases in the United States: epidemiology and impact*. Washington, D.C.: Government Printing Office, 1994:127-56. (NIH publication no. 94-1447)
21. Kelen GD, Green GB, Purcell RH, et al. Hepatitis B and hepatitis C in emergency department patients. *N Engl J Med* 1992;326:1399-404.
22. 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:Suppl 3A:5S-10S.
23. Di Bisceglie AM. Hepatitis C and hepatocellular carcinoma. *Hepatology* 1997;26:Suppl 1:34S-38S.
24. Di Bisceglie AM, Goodman ZD, Ishak KG, Hoofnagle JH, Melpolder JJ, Alter HJ. Long-term clinical and histopathological follow-up of chronic posttransfusion hepatitis. *Hepatology* 1991;14:969-74.
25. Di Bisceglie AM, Rustgi VK, Hoofnagle JH, Dusheiko GM, Lotze MT. NIH conference: hepatocellular carcinoma. *Ann Intern Med* 1988; 108:390-401.
26. Nishiguchi S, Kuroki T, Nakatani S, et al. Randomised trial of effects of interferon- α on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. *Lancet* 1995;346:1051-5.
27. Serfaty L, Aumaitre H, Chazouillères O, et al. Determinants of outcome of compensated hepatitis C virus-related cirrhosis. *Hepatology* 1998; 27:1435-40.
28. Wong DKH, Cheung AM, O'Rourke K, Naylor CD, Detsky AS, Heathcote J. Effect of alpha-interferon treatment in patients with hepatitis B e antigen-positive chronic hepatitis B: a meta-analysis. *Ann Intern Med* 1993;119:312-23.
29. Wong JB, Koff RS, Tinè F, Pauker SG. Cost-effectiveness of interferon-alpha 2b treatment for hepatitis B e antigen-positive chronic hepatitis B. *Ann Intern Med* 1995;122:664-75.