Aging of patients with hepatitis C virus-associated hepatocellular carcinoma: Long-term trends in Japan

NAOTA TAURA[1], KEISUKE HAMASAKI[1], KAZUHIKO NAKAO[1], TATSUKI ICHIKAWA[1], DAISUKE NISHIMURA[1], TAKASHI GOTO[1], MARIKO FUKUTA[1], HIROSHI KAWASHIMO[1], HISAMITSU MIYAAKI[1], MASUMI FUJIMOTO[1], KOUICHIRO KUSUMOTO[1], YASUHIDE MOTOYOSHI[1], HIDETAKA SHIBATA[1], KAORU INOKUCHI[2] and KATSUMI EGUCHI[1]

[1]The First Department of Internal Medicine, Nagasaki University School of Medicine, Sakamoto 1-7-1, Nagasaki 852-8501; [2]Nagasaki Tarami Hospital, Kayana 986-2, Tarami, Isahaya, Nagasaki 859-0497, Japan

Received March 21, 2006; Accepted June 13, 2006

Abstract. The incidence of hepatocellular carcinoma (HCC) in Japan has been increasing. The aim of the present study was to analyze epidemiological changes in Japanese HCC patients. A total of 463 patients with HCC diagnosed at our hospital between 1982 and 2001 were recruited for this study. Cohorts of patients with HCC were categorized into intervals of five years. The number of HBV- and HCV-associated HCC cases had decreased and increased in 1987-1991, respectively, and thereafter reached a plateau. The mean age of patients at diagnosis of HCV-associated HCC showed a steady significant increase from 60 to 68 years of age during the period, suggesting that these findings were associated with a shift toward an older-age group that had the highest rate of HCV infection. The mean age of patients with other types of HCC did not significantly change during the period. Since it is known that the prevalence of HCV infection in young Japanese persons is low and that the incidence of HCV infection is very low at present, our findings may indicate that the prevalence of HCC will decline in Japan, an advanced country with regard to HCV-associated HCC, in the near future.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver. HCC accounts for approximately 6% of all human cancers. It is estimated that half a million cases occur worldwide annually, making HCC the fifth most common malignancy in men and the ninth in women (1-6). The age-adjusted HCC mortality rate has increased in recent decades in Japan (7). Similarly, a trend of increasing rates of HCC has been reported from several developed countries in North America, Europe and Asia (8,9). HCC often develops in patients with liver cirrhosis caused by hepatitis B virus (HBV), hepatitis C virus (HCV), excessive alcohol consumption or non-alcoholic fatty liver disease. Of the hepatitis viruses that cause HCC, HCV is more common than HBV in Japan (10-13).

Although the age-adjusted incidence rates of HCC have increased during the period of rising HCC mortality in Japan, sequential changes in background features of HCC patients are not fully understood (14). Yoshizawa *et al* report that deaths due to HCC in Japan have continued to increase in males, particularly in those older than 60 years of age in the past 3 decades, although the reasons for this are unclear (15). To clarify factors affecting epidemiological changes in Japanese HCC patients, especially the change in age distribution, we analyzed the underlying features of HCC patients in a single-center, hospital-based study, including demographic data, etiology and stage of liver disease, and tumor characteristics.

Patients and methods

Patients. A total of 463 patients with HCC diagnosed between January 1982 and December 2001 in the First Department of Internal Medicine, Nagasaki University School of Medicine, were recruited for this study. The diagnosis of HCC was based on AFP levels and imaging techniques including ultrasonography (USG), computerized tomography (CT), magnetic resonance imaging (MRI), hepatic angiography (HAG), and/or liver biopsy. The diagnostic criteria for HCC were either a confirmative liver biopsy or elevated AFP (≥20 ng/ml) and neovascularization in HAG and/or CT. Cohorts of patients with HCC were categorized into five-year intervals (1982-1986, 1987-1991, 1992-1996 and 1997-2001).

Of the persons who visited Nagasaki Tarami hospital for health screening during the period from January 1996 to December 2002, 13869 were first-time visitors. There are same region of Nagasaki University School of Medicine and Nagasaki Tarami hospital. All of them received blood screening for the anti-HCV antibody (HCVAb) and the data were

Correspondence to: Dr Naota Taura, The First Department of Internal Medicine, Nagasaki University School of Medicine, Sakamoto 1-7-1, Nagasaki 852-8501, Japan
E-mail: ntaura-gi@umin.ac.jp

Key words: hepatitis C virus, hepatocellular carcinoma, aging, Japan

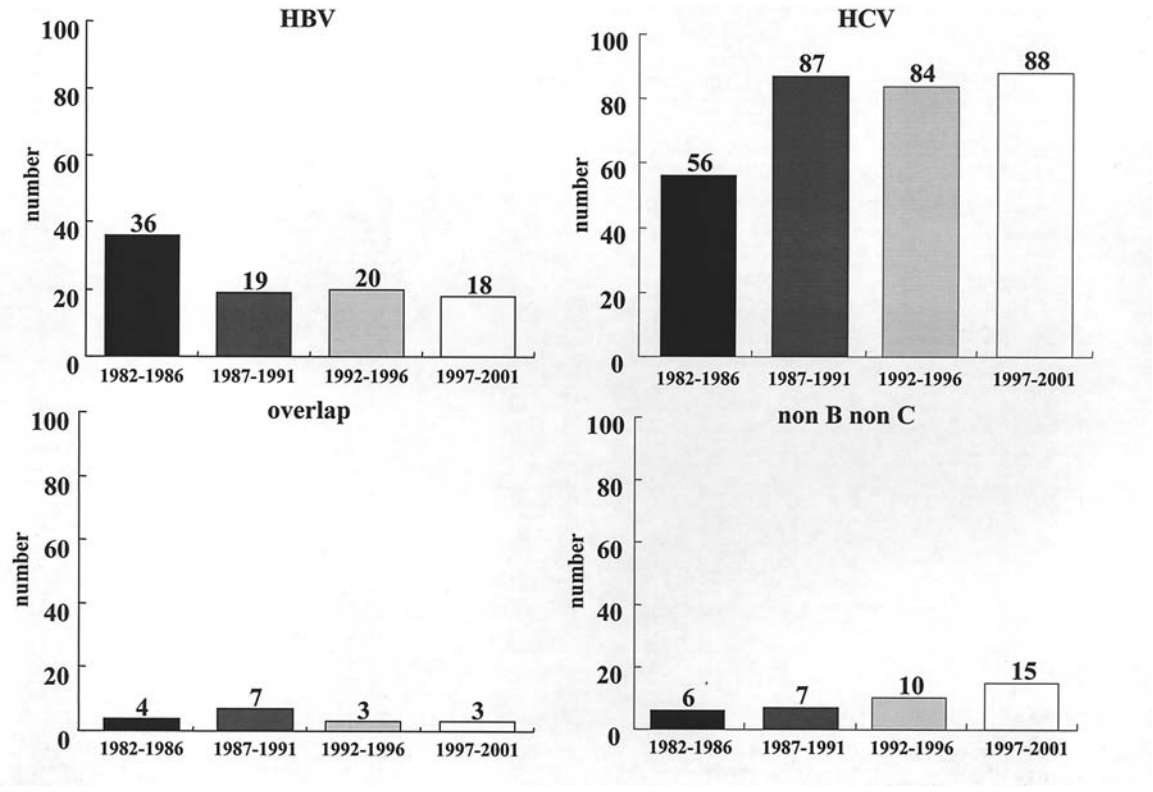

Figure 1. Sequential changes in the number of HCC patients categorized by etiology during the observation period. *P<0.05.

representative of the prevalence of HCV infection in the general population of Nagasaki prefecture, Japan.

Etiology of HCC. Sera were stored at -80˚C. A diagnosis of chronic HCV infection was based on the presence of HCVAb (microparticle enzyme immunoassay; Abbott Laboratories) and HCV-RNA detected by polymerase chain reaction (PCR), whereas diagnosis of chronic HBV infection was based on the presence of hepatitis B surface antigen (HBsAg) (enzyme-linked immunosorbent assay; Abbott Laboratories). Serum AFP was measured by a radioimmunoassay (Abbott Laboratories). The history of alcohol intake was noted from medical records. Habitual drinking was defined as an average daily consumption of an amount equivalent to 80 g of pure ethanol over a period of more than 10 years.

Statistical analysis. The data were analyzed by the Mann-Whitney test for the continuous ordinal data between two qualitative variables. For multiple group comparisons, homogeneity of variance was assessed by the Levene test. Parametric comparisons used analysis of variance (ANOVA). The significance of individual differences was evaluated by using the Scheffé test. The standard deviation was calculated based on the binomial model for the response proportion. $P<0.05$ was considered statistically significant.

Results

Clinical features of the studied patients. A total of 463 patients with HCC were diagnosed at our hospital from 1982 to 2001. There were 362 male (78.2%) and 101 female (21.8%) patients, with a mean age of 63 years. The proportion of patients diagnosed with HBV-associated HCC was 20.1% (93 of 463), whereas 68.0% (315 of 463) had HCV-associated HCC, and an additional 3.7% (17 of 463) had HCC associated with both viruses. Seven of the other 38 patients had a history of significant alcohol intake and the remaining 31 had no known etiology.

As shown in Figs. 1 and 2, the number of HBV-associated HCC cases decreased in 1987 -1991 and thereafter stabilized, whereas HCV-associated HCC increased and reached a plateau in 1987-1991. On the other hand, the mean age at diagnosis of HCV-associated HCC steadily increased, although patients with other types of HCC had no significant change during the observation period. Fig. 3 shows the age distribution of patients with HBV- and HCV-associated HCC during the four 5-year periods. There was no difference in the age distribution of patients with HBV-associated HCC during these periods. In contrast, HCV-associated HCC obviously had an increase in the number of patients aged more than 60 years.

Background features for patients with HBV- and HCV-associated HCC. To examine the factors affecting the change in age distribution, the mean age of patients with HBV- and HCV-associated HCC was analyzed according to each background in Tables I and II, respectively. The mean age of patients with HBV-associated HCC was not significantly different except for gender. On the other hand, in HCV-associated HCC, patients with excessive alcohol consumption, diabetes mellitus or Child-Pugh stage C in addition to male gender were younger age than those without as described above.

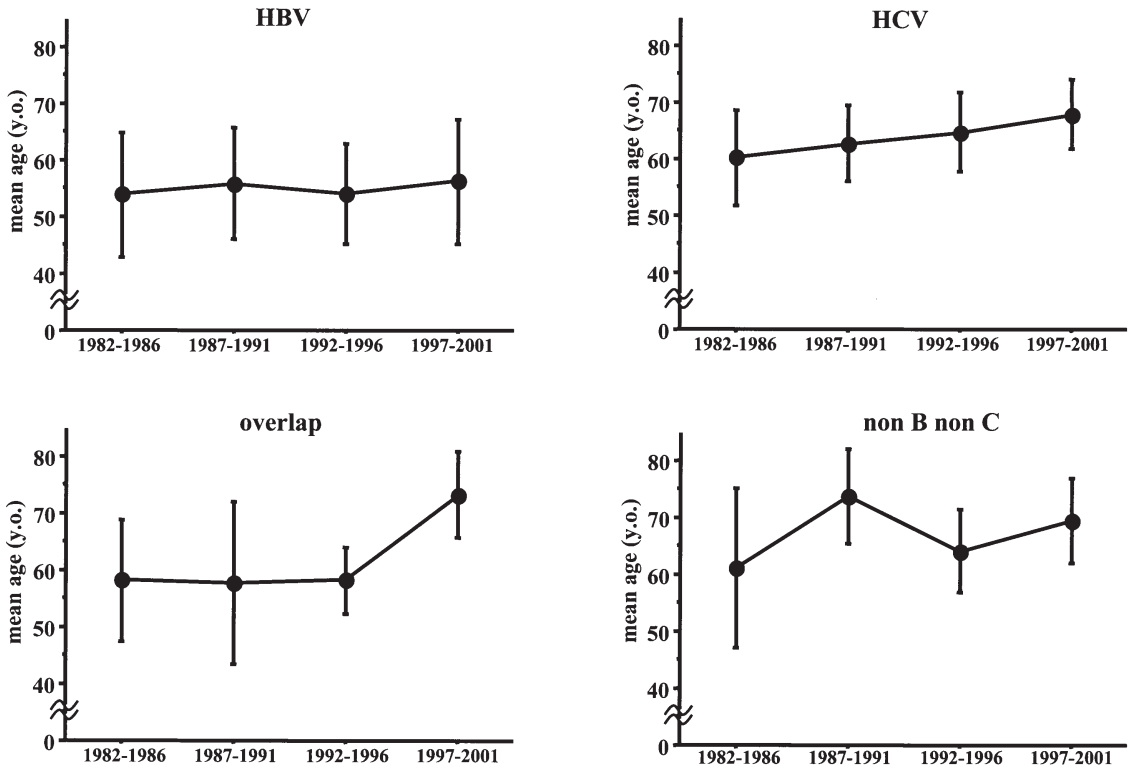

Figure 2. Sequential changes in the mean age of HCC patients categorized by etiology during the observation period. *P<0.05. The bars is standard deviation (SD).

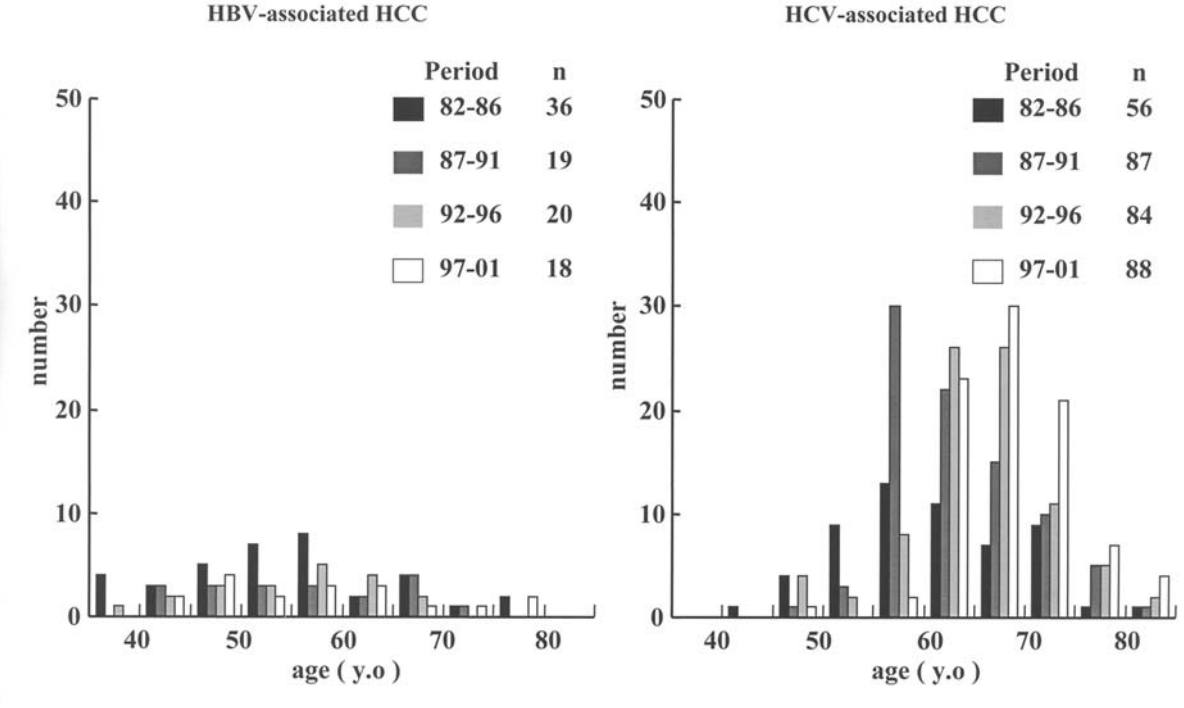

Figure 3. The age distribution of patients with HBV- and HCV-associated HCC during the four 5-year periods.

Table III shows the mean age and other characteristics at diagnosis of HCV-associated HCC in five-year intervals (1982-1986, 1987-1991, 1992-1996, and 1997-2001). In addition to mean age, the number of patients with Child-Pugh stage A showed a significant increase during the studied periods. Alcohol consumers significantly decreased during the periods.

In analysis of patients without alcohol consumption and Child-Pugh stage C in HCV-associated HCC, the mean ages in 1982-1986, 1987-1991, 1992-1996 and 1997-2001 were

Table I. The background of the 93 patients with HBV-associated HCC.

	No.	(%)	Mean age	(SD)	P-value
All	93	100	55	(10)	
Gender					
Male	71	76	53	(10)	
Female	22	24	60	(9)	0.0065[a]
Alcohol consumption					
Not excessive	84	90	55	(10)	
Excessive	9	10	52	(8)	NS[a]
IFN therapy					
(-)	91	98	55	(10)	
(+)	2	2	51	(3)	NS[a]
BMI					
<25	76	82	56	(10)	
≥25	17	18	54	(9)	NS[a]
Diabetes mellitus					
(-)	83	89	55	(11)	
(+)	10	11	58	(10)	NS[a]
Child-Pugh staging					
A	57	61	55	(1)	
B	28	30	56	(2)	
C	8	9	50	(3)	NS[b]
Tumor size					
<3 cm	38	41	56	(9)	
≥3 cm	55	59	54	(11)	NS[a]
Tumor no.					
Single	50	54	56	(10)	
Multiple	43	46	53	(10)	NS[a]

[a]Mann-Whitney U test. [b]ANOVA. SD, standard deviation; NS, not significant.

Table II. The background of the 315 patients with HBV-associated HCC.

	No.	(%)	Mean age	(SD)	P-value
All	315	100	64	(7)	
Gender					
Male	251	80	64	(7)	
Female	64	20	67	(7)	0.0032[a]
Alcohol consumption					
Not excessive	266	84	65	(7)	
Excessive	49	16	62	(7)	0.0107[a]
IFN therapy					
(-)	298	95	64	(8)	
(+)	17	5	66	(4)	NS[a]
BMI					
<25	255	81	63	(7)	
≥25	60	19	65	(8)	NS[a]
Diabetes mellitus					
(-)	229	73	65	(8)	
(+)	86	27	63	(7)	0.0173[a]
Child-Pugh staging					
A	207	66	65	(7)	
B	93	30	64	(8)	
C	15	4	60	(10)	0.0181[b]
Tumor size					
<3 cm	136	43	65	(7)	
≥3 cm	179	57	64	(8)	NS[a]
Tumor no.					
Single	165	52	65	(8)	
Multiple	150	48	64	(7)	NS[a]

[a]Mann-Whitney U test. [b]ANOVA. SD, standard deviation; NS, not significant.

62, 63, 64 and 68 years of age, respectively (1982-1986 vs. 1997-2001, p=0.0001) (Table IV).

Age-specific prevalence of HCV infection in the general population of studied area. The age-specific prevalence of HCVAb among the 13869 persons who visited Nagasaki prefecture Tarami Hospital for health screening from 1996 to 2002 is shown in Table V. Although the positive rate for HCVAb was 1.64% (277 of 13869) as a whole, it was higher in the group aged more than 60 years irrespective of gender.

Discussion

Our study was a single-center, hospital-based study designed to examine the sequential change in backgrounds among patients with HCC during the past 2 decades. More than 90% of our patients had chronic HBV or HCV infections. During the observation period, the number of HBV- and HCV-associated HCC cases decreased and increased in 1987-1991, respectively, and thereafter reached a plateau. These findings were consistent with previous reports from Japan (7,14). Additionally, the age-

Table III. The mean age and the other characteristics of HCV-associated HCC at diagnosis in 5-year intervals.

Period	1982-1986	1987-1991	1992-1996	1997-2001	Total	P-value
No.	56	87	84	88	315	
Age (years) (SD)	60 (8)	63 (7)	65 (8)	68 (6)	64 (7)	<0.0001
Gender						
Male	47	68	67	69	251	
Female	9	19	17	19	64	
Ratio	5.2	3.6	3.9	3.6	3.9	NS
Alcohol consumption						
Not excessive	42	68	75	81	266	
Excessive	14	19	9	7	49	
Ratio	3.0	3.6	8.3	11.6	5.4	0.0078
Diabetes mellitus						
(-)	39	64	64	62	229	
(+)	17	23	20	26	86	
Ratio	2.3	2.8	3.2	2.4	2.7	NS
Child-Pugh staging						
A	28	52	57	70	207	
B	25	32	22	14	93	
C	3	3	5	4	15	0.0160

SD, standard deviation; NS, not significant.

Table IV. Mean age of HCV-associated HCC without excessive alcohol consumers and Child-Pugh stage C.

Year	1982-1986	1987-1991	1992-1996	1997-2001	Total
No.	40	66	71	77	254
Mean age (years)	62	63	64	68	65
SD	8	7	7	6	7
	NS	NS	0.0338		
	NS				
	0.0012				
	0.0001				

SD, standard deviation; NS, not significant.

specific prevalence of HCV infection in the general population of the studied area was also in agreement with Japanese epidemiological studies which showed a high prevalence of HCVAb in the population, 60 years of age and older (15-17).

In analysis of background features among HCC patients, HBV-associated HCC cases revealed no significant change, whereas the mean age of patients with HCV-associated HCC steadily increased from 60 to 68 years of age during the studied period. In patients with HCV-associated HCC, factors such as male gender, excessive alcohol consumption and diabetes mellitus, which are known to be risk factors for HCC, contributed to lowering the age of HCC occurrence. Furthermore, patients with Child-Pugh stage C were younger than those with stages A and B. When the mean age of HCV patients without alcohol consumption and Child-Pugh stage C, which may contribute to aging of HCV-associated HCC, was

Table V. Age-specific prevalence of HCV infection in Nagasaki prefecture, Japan.

	Male			Female			Total		
Age	No.	HCVAb(+)	(%)	No.	HCVAb(+)	(%)	No.	HCVAb(+)	(%)
0-19	0	0	0.00	0	0	0.00	0	0	0.00
20-29	7	0	0.00	7	0	0.00	7	0	0.00
30-39	594	3	0.51	303	4	1.32	897	7	0.78
40-49	2553	29	1.14	1051	9	0.86	3604	38	1.05
50-59	3188	38	1.16	1445	19	1.31	4633	56	1.21
60-69	2517	58	2.30	1309	37	2.83	3826	95	2.48
≥70	515	21	4.08	380	10	2.63	895	31	3.46
Total	9374	148	1.58	4495	79	1.76	13869	277	1.64

analyzed, a significant increase was also found during the studied period. Since the size and number of HCC cases was not associated with the mean age of HCV-associated HCC patients, it is unlikely that the delay in diagnosis of HCC accounted for aging of HCV-associated HCC cases. Indeed, it is possible that other factors contributed to the steady increase in the mean age of patients with HCV-associated HCC.

Japan with overall HCV prevalence rates similar to that of the United States (approximately 1-2%) but with higher incidence rates of hepatocellular carcinoma (8-10 times lower in the United States) is thought to have had earlier onset and peaks of the HCV epidemic than the United States (5,8,9). A recent study examined the constant evolutionary rate of HCV over time ('the molecular clock') in retrospectively collected serum samples of HCV carriers in Japan and the United States (18). The study concluded that HCV first appeared in Japan around 1882 and in the United States around 1910, whereas widespread dissemination occurred from 1940s to 1960s in Japan and from 1960s to 1980s in the United States. Risk factors for transmitting HCV were rampant during this period (e.g, injection drug use, needle sharing, and transfusion of unscreened blood and blood products) (19). It is speculated that these modes of transmission are responsible for differences in the age-specific prevalence of HCV infection in the general population. In the United States, the incidence of HCC continues to increase with the fastest rate among 40- to 50-year-old persons who have the highest rate of HCV infection (20,21). Thus, it is likely that the increasing mean age of patients with HCV-associated HCC in our study was associated with a shift toward an older-age group who had the highest rate of HCV infection.

It is known that 2-4 decades of chronic HCV infection is required to develop cirrhosis and subsequent HCC (22-25). The number of HCC cases has increased in Japan, because individuals infected with HCV during the past have grown old and have reached the cancer-bearing age. The prevalence of HCV infection in young Japanese persons is low and the incidence of HCVAb is very low because of preventative actions against HCV infection such as the screening of blood products for HCV and the use of sterile medical equipment (26). Additionally, we showed that the number of patients with HCV-associated HCC cases reached a plateau together with an increase in the mean age, although the present study was a single-center, hospital-based study. These findings indicate that a decrease in the prevalence of HCC in Japan, a country that is far advanced with regard to HCV-associated HCC, is expected in the near future. We believe that long-term experience in Japan helps to plan strategies against HCV-associated HCC and to cope with its long-term sequelae in many other countries worldwide.

References

1. El-Serag HB and Mason AC: Risk factors for the rising rates of primary liver cancer in the United States. Arch Intern Med 160: 3227-3230, 2000.
2. El-Serag HB: Epidemiology of hepatocellular carcinoma. Clin Liver Dis 5: 87-107, 2001.
3. El-Serag HB, Hampel H, Yeh C and Rabeneck L: Extrahepatic manifestations of hepatitis C among United States male veterans. Hepatology 36: 1439-1445, 2002.
4. El-Serag HB: Hepatocellular carcinoma and hepatitis C in the United States. Hepatology 36: S74-S83, 2002.
5. El-Serag HB: Hepatocellular carcinoma: an epidemiologic view. J Clin Gastroenterol 35: S72-S78, 2002.
6. Hassan MM, Frome A, Patt YZ and El-Serag HB: Rising prevalence of hepatitis C virus infection among patients recently diagnosed with hepatocellular carcinoma in the United States. J Clin Gastroenterol 35: 266-269, 2002.
7. Kiyosawa K and Tanaka E: Characteristics of hepatocellular carcinoma in Japan. Oncology 62: 5-7, 2002.
8. McGlynn KA, Tsao L, Hsing AW, Devesa SS and Fraumeni JF Jr: International trends and patterns of primary liver cancer. Int J Cancer 94: 290-296, 2001.
9. Bosch FX, Ribes J, Diaz M and Cleries R: Primary liver cancer: worldwide incidence and trends. Gastroenterology 127: S5-S16, 2004.
10. Hamasaki K, Nakata K, Tsutsumi T, Tsuruta S, Nakao K, Kato Y, Shima M, Koji T and Nagataki S: Changes in the prevalence of hepatitis B and C infection in patients with hepatocellular carcinoma in the Nagasaki Prefecture, Japan. J Med Virol 40: 146-149, 1993.
11. Kato Y, Nakata K, Omagari K, Furukawa R, Kusumoto Y, Mori I, Tajima H, Tanioka H, Yano M and Nagataki S: Risk of hepatocellular carcinoma in patients with cirrhosis in Japan. Analysis of infectious hepatitis viruses. Cancer 74: 2234-2238, 1994.
12. Shiratori Y, Shiina S, Imamura M, Kato N, Kanai F, Okudaira T, Teratani T, Tohgo G, Toda N, Ohashi M, *et al*: Characteristic difference of hepatocellular carcinoma between hepatitis B- and C-viral infection in Japan. Hepatology 22: 1027-1033, 1995.

13. Shiratori Y, Shiina S, Zhang PY, Ohno E, Okudaira T, Payawal DA, Ono-Nita SK, Imamura M, Kato N and Omata M: Does dual infection by hepatitis B and C viruses play an important role in the pathogenesis of hepatocellular carcinoma in Japan? Cancer 80: 2060-2067, 1997.
14. Kiyosawa K, Umemura T, Ichijo T, Matsumoto A, Yoshizawa K, Gad A and Tanaka E: Hepatocellular carcinoma: recent trends in Japan. Gastroenterology 127: S17-S26, 2004.
15. Yoshizawa H: Hepatocellular carcinoma associated with hepatitis C virus infection in Japan: projection to other countries in the foreseeable future. Oncology 62: 8-17, 2002.
16. Moriya T, Koyama T, Tanaka J, Mishiro S and Yoshizawa H: Epidemiology of hepatitis C virus in japan. Intervirology 42: 153-158, 1999.
17. Okayama A, Stuver SO, Tabor E, Tachibana N, Kohara M, Mueller NE and Tsubouchi H: Incident hepatitis C virus infection in a community-based population in Japan. J Viral Hepat 9: 43-51, 2002.
18. Tanaka Y, Hanada K, Mizokami M, Yeo AE, Shih JW, Gojobori T and Alter HJ: Inaugural Article: a comparison of the molecular clock of hepatitis C virus in the United States and Japan predicts that hepatocellular carcinoma incidence in the United States will increase over the next two decades. Proc Natl Acad Sci USA 99: 15584-15589, 2002.
19. Zanetti AR, Romano L and Bianchi S: Primary prevention of hepatitis C virus infection. Vaccine 21: 692-695, 2003.
20. Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA, Kaslow RA and Margolis HS: The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med 341: 556-562, 1999.
21. Armstrong GL, Alter MJ, McQuillan GM and Margolis HS: The past incidence of hepatitis C virus infection: implications for the future burden of chronic liver disease in the United States. Hepatology 31: 777-782, 2000.
22. Deuffic S, Poynard T and Valleron AJ: Correlation between hepatitis C virus prevalence and hepatocellular carcinoma mortality in Europe. J Viral Hepat 6: 411-413, 1999.
23. El-Serag HB and Mason AC: Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 340: 745-750, 1999.
24. Planas R, Balleste B, Antonio Alvarez M, Rivera M, Montoliu S, Anton Galeras J, Santos J, Coll S, Maria Morillas R and Sola R: Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 200 patients. J Hepatol 40: 823-830, 2004.
25. Davila JA, Morgan RO, Shaib Y, McGlynn KA and El-Serag HB: Hepatitis C infection and the increasing incidence of hepatocellular carcinoma: a population-based study. Gastroenterology 127: 1372-1380, 2004.
26. Sasaki F, Tanaka J, Moriya T, Katayama K, Hiraoka M, Ohishi K, Nagakami H, Mishiro S and Yoshizawa H: Very low incidence rates of community-acquired hepatitis C virus infection in company employees, long-term inpatients, and blood donors in Japan. J Epidemiol 6: 198-203, 1996.