Epidemiology of Hepatocellular Carcinoma in Japan

Short title: Epidemiology of HCC in Japan

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Abstract
Primary liver cancer, 95% of which is hepatocellular carcinoma (HCC), is ranked third in men and fifth in women as a cause of death from malignant neoplasms in Japan. The number of deaths and death rate of HCC began to increase sharply in 1975. These numbers peaked at 34,510 and 27.4/100,000, respectively, in 2004, but decreased to 33,662 annual deaths and 26.7/100,000 death rate in 2006. Although hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are both major causes of HCC, HCV-related HCC represents 70% of all cases. The incidence of HCC without hepatitis B surface antigen (HBsAg) or antibodies to HCV (anti-HCV) accounts for 8–15% of HCC patients nationwide. Geographically, HCC is more frequent in western than eastern Japan, and death rates of HCC in each prefecture correlate with anti-HCV, but not HBsAg, prevalence. Interferon therapy for chronic hepatitis C reduces the risk of development of HCC, especially among patients with sustained virological response. Further research should focus on the mechanisms of carcinogenesis by HCV and HBV, development of more effective treatments, and establishment of early detection and preventative approaches. Better understanding of HCC unrelated to HCV and HBV, possibly due to steatohepatitis and diabetes, should also be a major concern in future studies.
Key words: HCC, HCV, HBV, NASH, Interferon

Introduction

The three leading causes of death in Japan since 1981 are malignant neoplasms, cardiovascular diseases, and cerebrovascular diseases. For the last 30 years, liver cancer has been the third leading cause of death from malignant neoplasms in men, following lung and stomach cancer. In women, liver cancer has ranked fifth as a cause of death during the past decade, following colon, stomach, lung, and breast cancer. Primary liver cancer can be classified into three types according to the cell from which the cancer originated, namely, hepatocellular carcinoma (HCC), cholangiocellular carcinoma, and other. As HCC accounts for up 95% of all primary cancer cases, the term 'liver cancer' usually means HCC.(1)

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the two major causes of HCC in Japan.(2, 3) The increase in incidence of HCC in Japan, however, is largely attributable to the increase of HCV infection in the general population over the last 50 to 60 years.(2)

Changes in deaths and death rates of primary liver cancer

Changes in annual deaths from primary liver cancer among different age groups between 1958 and 2006 are shown in Figure 1. The total number of deaths from HCC was stable at less than 10,000 people/year until 1975 before showing a sharp increase. The spike in 1995 was due to a change in the International Classification of Disease (ICD) code from ICD 9 to ICD 10, which included intrahepatic bile duct cancer accounting for approximately 5% of HCC deaths.

The majority of HCC mortalities were in patients below the age of 69 until 1999, when this age reached 70 years. In 2006, 66% of patients with HCC were over 70. The number of deaths from HCC reached 34,510 in 2004, but decreased to 33,662 in 2006.

The death rates of liver cancer by gender are shown in Figure 2 and are consistently higher in men than in women. A sharp rise in the death rate of primary liver cancer in men began in 1975, and a more gradual rise in women commenced in 1980. The total age-adjusted death rate peaked in 2002 (27.5/100,000 people in 2002), and decreased to 27.0 in 2003. In 2006, the total age-adjusted death rate stood at 26.7/100,000. This is due to a decrease in death rate (36.7) in men, but offset by an increase in women to 17.2.

Age and gender in HCC

Changes in the mean age of HCC patients and male/female ratio every two years between 1984 and 2003 are shown in Figure 3. In that period, the mean age of female HCC patients was higher than that of males, and the mean ages of both genders progressively increased. As reported previously, however, HBV-related HCC was stable from1982 to 2003, implying that this change originated from HCV-related HCC patients. The male/female ratio was 4.5 in 1984/1985 and 2.5 in 2002/2003 (Figure 3), showing that the proportion female patients with HCC had increased. This increase in female patients is also considered as a consequence of increased HCV-related HCC.

Changes in etiology of HCC in Japan

A nationwide survey on primary liver cancer has been conducted every 2 years since 1968 by the Liver Cancer Study Group of Japan.(1, 4-9) Five serologic surveys performed between 1990 and 2001 have documented that most patients with HCC are

positive for either HBsAg or antibodies to HCV (anti-HCV). Tests for HBsAg became available in 1975 and those for anti-HCV in 1990. HBsAg-positive cases of HCC constituted 42% of patients in 1977-1978, but only 15.5% in 2002-2003 (Figure 4). In contrast, anti-HCV-positive cases of HCC accounted for more than 70% of cases diagnosed until 2000-2001. However, this number dipped to 69.6% in 2002-2003, and has since remained at less than 70%. In contrast, HCV of unknown origin and other cases of HCC have been increasing gradually, and constituted 14.9% of all cases in 2002-2003.

In cross-sectional studies conducted at Shinshu University Hospital, HCV-related HCC was found in the vast majority of cases (72%) (Figure 5). Non-B non-C HCC (NBNC-HCC) accounted for 10% of cases in 2002 - 2007. In these 28 patients, nonalcoholic steatohepatitis (NASH) accounted for 14%.

Geographic Variation of Liver Cancer and HBV/HCV Infection

Although Japan is a relatively small country with a homogenous population, the incidence of HCC varies greatly among different regions. The Vital Statistics of Japan for 2005 published in 2007 by the Japanese Ministry of Health, Labour, and Welfare on the incidence of deaths as a result of HCC in its 48 prefectures shows a steady increase in death rates of HCC from east to west of Japan. The average age-adjusted death rate of HCC among 48 prefectures was 27.2 per 100,000 people in 2005 (Figure 6). Furthermore, nationwide health screening for HBsAg and anti-HCV in citizens over 40 years of age has been performed since 2002, and the prevalence rates of these markers have been analyzed for each prefecture in Japan. In 2006, the average HBsAg and anti-HCV prevalences were 1.0% and 0.7%, respectively, in this group (Figure 6). There was a highly significant association between the death rate of HCC and prevalence of anti-HCV in each prefecture (Figure 7; correlation coefficient = 0.66; $P < 0.001$, $Y = 16.3X + 16.1$), but no correlation with the prevalence of HBsAg was seen (Figure 6). For instance, although Okinawa Prefecture had the highest prevalence of HBsAg (2.6%), its HCC death rate was the lowest (12.5/100,000 people). A possible explanation for this discrepancy is that the HBV genotype Bj, which shows good clinical prognosis (10, 11), is the dominant HBV genotype in Okinawa. In contrast, areas with high rates of anti-HCV, especially in western Japan, had high death rates from HCC. HCV appears to be the major contributor to primary liver cancer in these regions; Saga prefecture shows both the highest HCC death rate (46.9/100,000) and highest prevalence rate of anti-HCV (2.1%) in Japan.

Antiviral therapy suppresses the incidence of HCC

As described in prior sections, HCV infection is the major cause of HCC in Japan, suggesting that eradication of HCV may decrease the incidence of HCC. A summary of different studies on the incidence of HCC among patients with chronic hepatitis C who were treated with interferon in Japan can be found in Table 1.(12-17) These studies show a moderate decrease in the risk of HCC in patients with chronic hepatitis C treated with interferon, especially in patients with sustained virologic response as compared with non-responders and non-treated patients.

Recently, Ikeda *et al.* prospectively studied patients with chronic HCV infection and evidence of occult HBV infection (negative results for HBsAg and HBV DNA but positive results for antibodies to hepatitis B core antigen [anti-HBc] in serologic

testing).(17) Patients with HCV-related cirrhosis and positive results for anti-HBc were at high risk for HCC, even in patients with a sustained virologic response to interferon therapy. Thus, anti-HBc–positivity is a marker of high risk for HCC among patients with HCV-related cirrhosis.

Between 1992 and 2001, approximately 300,000 patients with chronic hepatitis C received IFN mono-therapy in Japan. As shown in Figure 1, it is remarkable that the number of deaths and the death rate of HCC began to decrease in 2005. These phenomena suggest that antiviral treatment indeed reduces the risk of HCC in patients with HCV infection.

Conclusion

The number of deaths and death rate of HCC showed a sharp increase from 1975 onwards, but had begun to decrease in 2006. Although both HBV and HCV infection play a major role in HCC in Japan, HCV-related HCC represents 70% of all cases. The incidence of HCC without HBsAg or anti-HCV accounts for 7-15% in Japan, and half of NBNC-HCC cases are of unknown origin. Geographically, HCC is more frequent in western Japan than eastern, and the death rates of HCC in each prefecture correlate with anti-HCV, but not HBsAg, prevalence. IFN therapy for chronic hepatitis C reduces the risk of development of HCC, especially in patients with sustained viral response.

Acknowledgements

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Figure legends

Figure 1.
Changes in annual deaths of patients with primary liver cancer between 1958 and 2006. (Taken from the Vital Statistics of Japan released every year by the Ministry of Health, Labor, and Welfare)

Figure 2.
Changes in the death rate of primary liver cancer in males (▲), females (▬), and in total (◆).

Figure 3.
Changes in the mean age of male (■) and female (■) patients with HCC between 1984 and 2003.

Figure 4.
Changes in the etiology of HCC between 1990 and 2003. HBsAg+ (■), anti-HCV+ (■), unknown and others (■).

Figure 5.
Clinical features of HBV-and HCV-related HCC in 1982, 1990, and 2002-5 at Shinshu University Hospital

Figure 6.
(a) Death rate of primary liver cancer was 27.2 per 100,000 in 2005 among people over 40 years of age in 48 prefectures. (b) HBsAg prevalence was 1.0% and (c) anti-HCV prevalence was 0.7% in the same group in 2006.

Figure 7.
Relationship between the death rate of primary liver cancer and prevalence of (a) HBsAg (r = 0.02, P = NS) and (b) anti-HCV (r = 0.66, P < 0.001, y = 16.3x + 16.1) among the general population over 40 years of age in 2006.

Figure 1

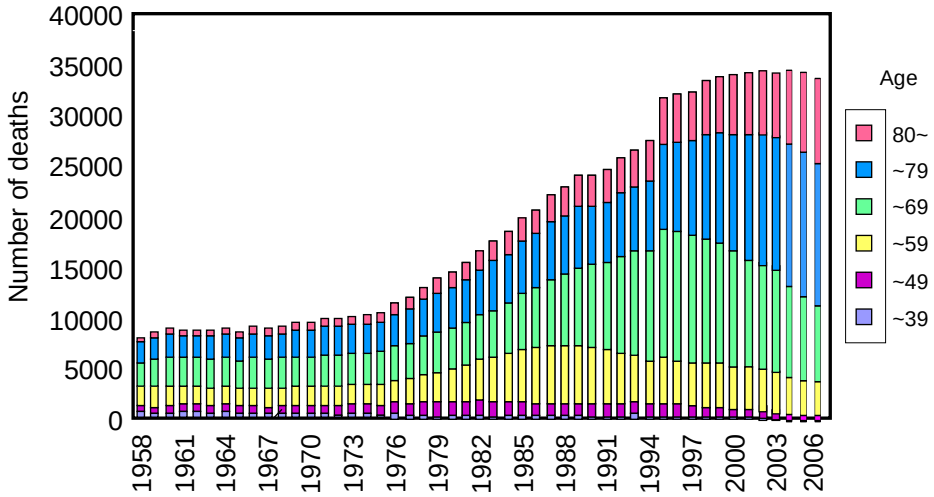


Figure 2

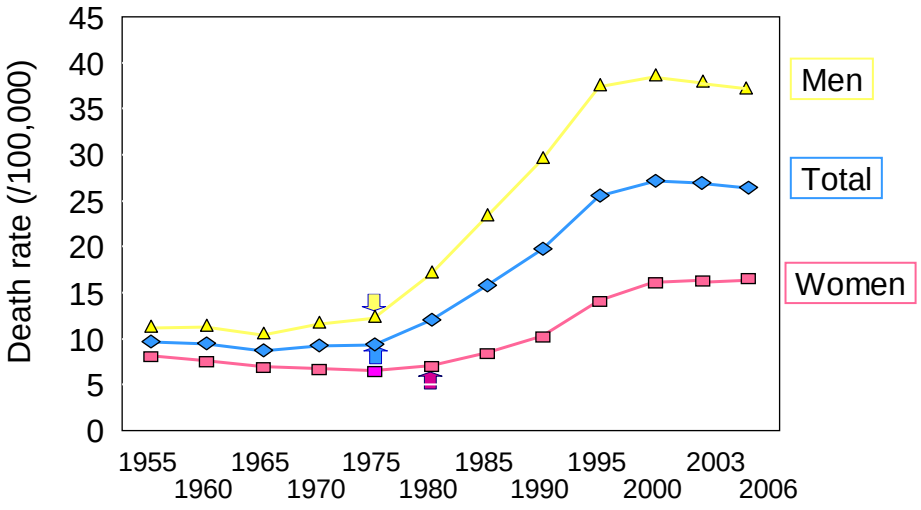


Figure 3

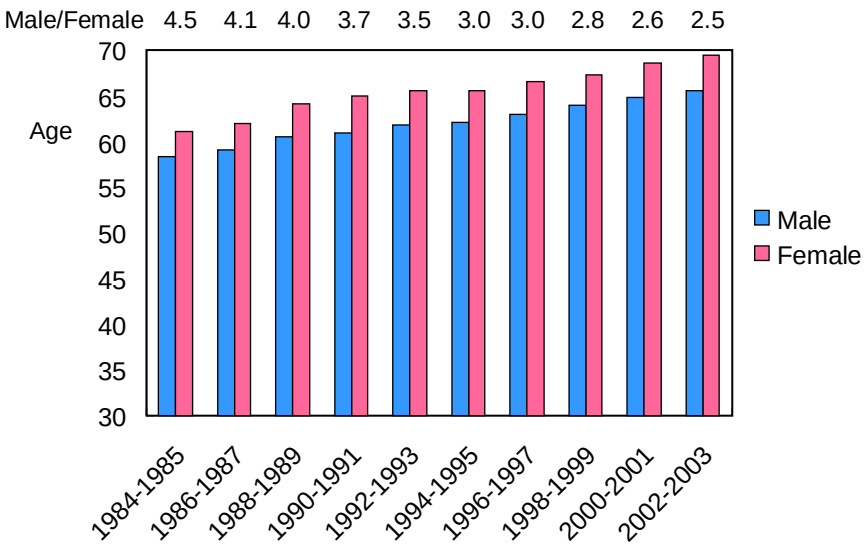


Figure 4

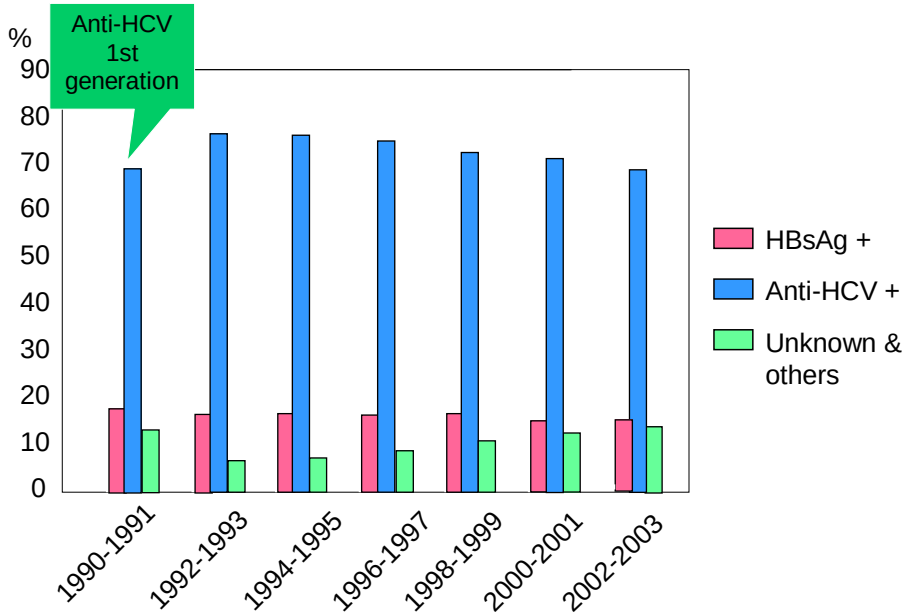
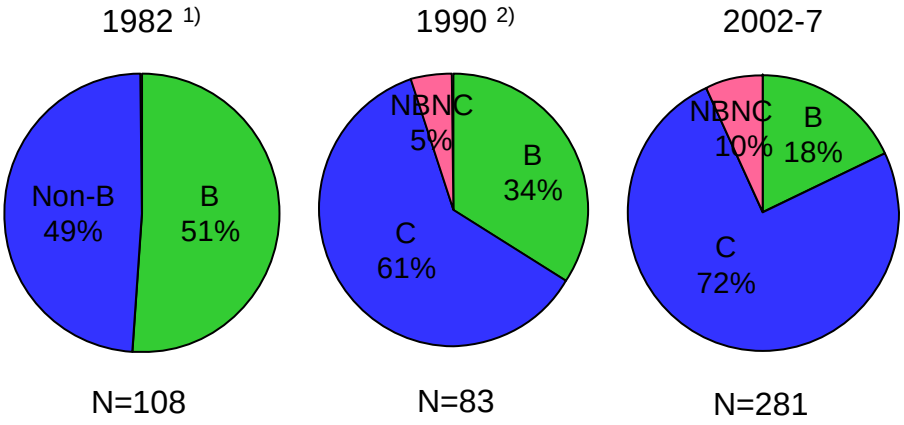


Figure 5



1) Vox Sang 1982
2) Hepatology 1990

(Shinshu University Hospital)

Figure 6

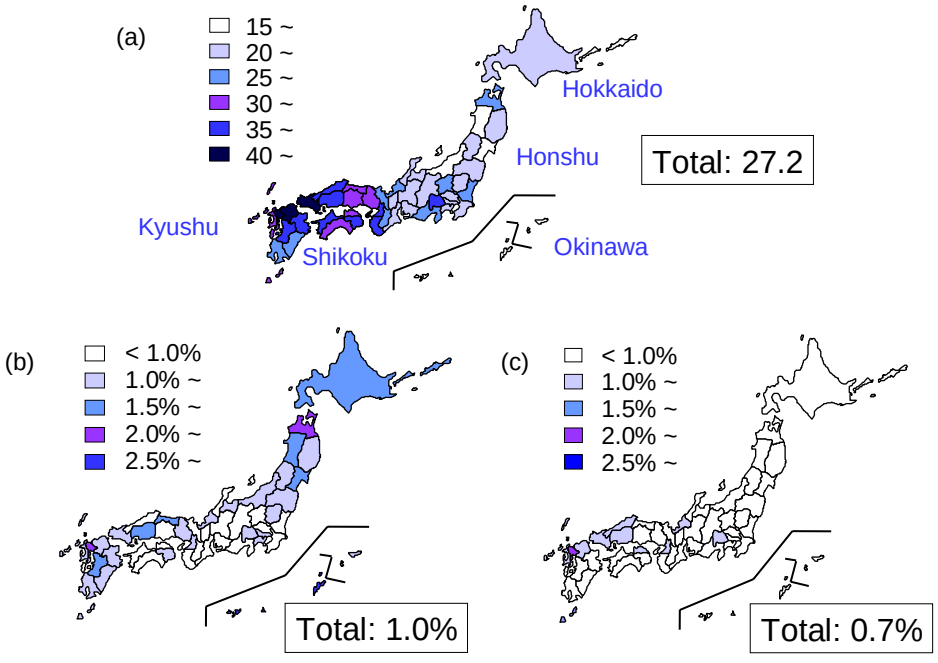


Figure 7

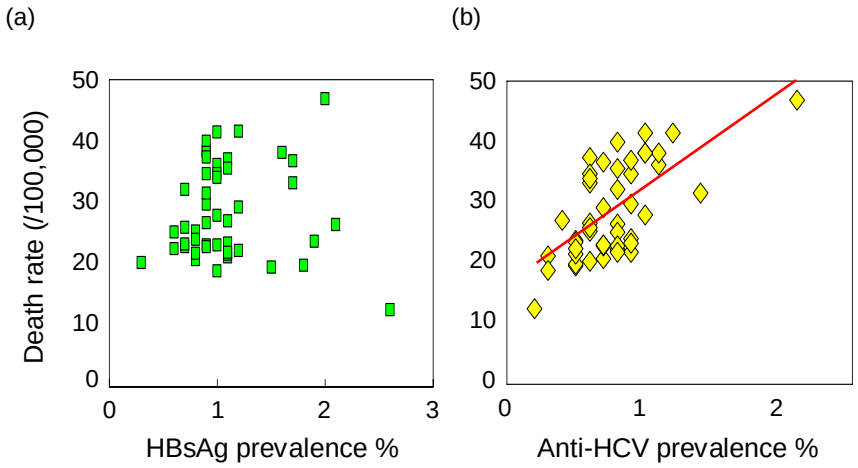

(a)
(b)
Death rate (/100,000)
50
40
30
20
10
0
0
1
2
3
HBsAg prevalence %
Anti-HCV prevalence %

Table 1. Summary of findings in representative studies on the incidence of HCC among patients with chronic HCV infection treated with interferon alone in Japan

			Treated					
	Untreated		Non-SVR		SVR		Total	
Author	No. HCC/ No. cases	%	No. HCC/ No. cases	%	No. HCC/ No. cases	%	No. HCC/ No. cases	%
Kasahara [12]			41/709	5.8	5/313	1.6	46/1,022	4.5
Imai [13]	19/140	13					18/419	4.3
Ikeda [14]	67/452	15	23/730	3.2	5/461	1.1	28/1,191	2.4
Yoshida [15]	67/395	17	214/1,556	13.8	27/836	3.2	241/2,392	10.1
Okanoue [16]			119/849	14.0	8/397	2.0	127/1,246	10.2
Ikeda [17]	59/352	17	34/171	19.9	1/53	1.9	94/576	16.3
Total	212/1,339	16	432/4,015	10.8	46/2,060	2.2	554/6,846	8.1