View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Shinshu University Institutional Repository

Original Article

Epidemiology of hepatocellular carcinoma in Japan

Takeji Umemura and Kendo Kiyosawa

Department of Internal Medicine, Gastroenterology, and Hepatology, Shinshu University School of Medicine, Matsumoto, Japan

Primary liver cancer, 95% of which is hepatocellular carcinoma (HCC), has ranked third in men and fifth in women as a cause of death from malignant neoplasm in Japan. Although the numbers of deaths and death rates from HCC increased until 2002 in Japan, annual deaths (34 089) and the death rate (27.0/100 000) from liver cancer decreased in 2003. Hepatitis C virus (HCV)-related HCC represents 75% of all HCC in Japan. The incidence of HCC without hepatitis B surface antigen (HBsAg) or anti-HCV accounted for 7–12% of HCC in Japan and half of non-B non-C-HCC was of unknown origin. Geographically, HCC is more frequent in western than eastern Japan, and the death rates from HCC in each prefecture correlate with the prevalence of anti-HCV, but not with HBsAg prevalence. Interferon therapy for chronic hepatitis C has reduced the risk factors for development of HCC, especially among patients with sustained response.

Key words: HCC, HBV, HCV, NASH, IFN

INTRODUCTION

The three leading causes of death in Japan are malignant neoplasms, cardiovascular diseases, and cerebrovascular diseases. Since 1981, malignant neoplasms have been the leading cause of death in Japan. For the last 30 years, liver cancer has been the third leading cause of death from malignant neoplasms in men. In women, liver cancer has ranked fifth during the past decade.[1] Primary liver cancer can be classified into three types according to the cell from which the cancer arises, including hepatocellular carcinoma (HCC) and cholangiocellular carcinoma. HCC accounts for up 95% of all cases; therefore, “liver cancer” usually means HCC.[2]

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the two major causes of HCC in Japan.[3] The increase in incidence of HCC in Japan, however, has largely been attributable to HCV infection and the increase of HCV in the general population during the last 50–60 years.[4]

CHANGES IN NUMBERS OF DEATHS AND DEATH RATES FOR PRIMARY LIVER CANCER

Changes in annual numbers of deaths from primary liver cancer in different age groups between 1958 and 2003 are shown in Figure 1. The total number of deaths from HCC was stable, and fewer than 10 000 people/year until 1975 when numbers showed a sharp increase with years. The increase in 1995 was caused by the change in International Classification of Disease (ICD) codes from ICD-9 to ICD-10, which includes intrahepatic bile duct cancer (less than 5%). Peak numbers of deaths from HCC were in patients below the age of 69 years until 1999, when the peak age increased to over 70 years. Although numbers of deaths from HCC increased until 2002, the total numbers of deaths from HCC decreased to 34 089 in 2003.

Deaths rate from liver cancer by gender are shown in Figure 2. Rates were consistently higher in men than women. A sharp rise in death rates from primary liver cancer in men began in 1975, and a more gradual rise in women in 1980. Total age-adjusted death rates also increased until 2002 (27.5/100 000 people in 2002); however, it decreased to 27.0 in 2003. Therefore, number of deaths and the death rate from primary liver cancer decreased in 2003.

AGE AND GENDER IN HCC

Changes in mean age of HCC patients and the male/female ratio every 2 years between 1984 and 2001 are shown in Figure 3. For 18 years, the mean age for females was higher than for males. The mean ages of males and females progressively increased from 1984–1985 to 2000–2001. As reported previously, however, it was unchanged in HBV-related HCC 1982 and 2003. Thus, this sharp increase originated in HCV-related HCC patients. The male/female ratio was 4.5 in 1983–1985 and 2.57 in 2000–2001 (Fig. 3). The ratio became clearly smaller, which indicates an

increase in female patients with HCC. This tendency is found in HCV-related HCC predominantly. The mean ages of male and female patients with HCC have increased each year (Fig. 3). The mean age of females was higher than for males throughout. The increase for female patients and the elevation of mean age are considered to increase because of HCV-related HCC.

CHANGES IN ETIOLOGY OF HCC IN JAPAN

A nationwide survey of primary liver cancer has been conducted every 2 years since 1968 by the Liver Cancer Study Group of Japan.[5–10] Five serologic surveys performed between 1990 and 2001 documented that most patients with HCC are positive for either hepatitis B surface antigen (HBsAg) or antibody 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 cases in 1977–1978, but only 15.5% in 2000–2001 (Fig. 4). In contrast, anti-HCV-positive cases of HCC have accounted for more than 70% of cases diagnosed in the last 10 years. Unknown origin and other cases of HCC have increased gradually and constituted 12.7% of cases in 2000–2001.

NON-B, NON-C HCC IN JAPAN

In cross-sectional studies conducted at the Shinshu University Hospital, HCV-related HCC has increased to become the majority of cases (72%). Non-B non-C HCC accounted for 7% of cases in 2003.[3] The survey of non-B non-C HCC was conducted by the Inuyama Hepatitis Research Group from 1995 to 2003 (Hayashi N., 2005, personal communication). In total, 10 143 patients have been enrolled and HCV-related HCC constituted 72.6% of cases. Among them, non-B non-C HCC accounted for 9.3%. In 946 patients with non-B non-C HCC, half of the cases were of unknown origin, and nonalcoholic steatohepatitis/diabetes mellitus caused only 5.4% in non-B non-C HCC.

GEOGRAPHIC VARIATION IN 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 2003 published in 2005 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 gradient increase of death rates for HCC along the axis of Japan from east to west. The average age-adjusted death rate of HCC among 48 prefectures was 27.0 per 100 000 people (Fig. 5). Nationwide health screening for HBsAg and anti-HCV in the over 40 years of age population has been performed since 2002, and prevalence rates for these markers have been analyzed by each prefecture in Japan. In 2003, the average HBsAg prevalence and anti-HCV were 1.1 and 1.0%, respectively, in the total Japanese population (Fig. 5). There were highly significant associations between death rate from HCC in each prefecture and prevalence of anti-HCV (Fig. 6), but there was no correlation with the prevalence of HBsAg (Fig. 6). For instance, although Okinawa Prefecture has the highest prevalence rate of HBsAg (3.1%), death rate from HCC was the lowest (10.6/100 000 people). For an explanation on this discrepancy, HBV genotype Bj, which shows good clinical prognosis,[11,12] is the dominant source in Okinawa. In contrast, areas with high rates of anti-HCV, especially western Japan, had high death rates from HCC. HCV appears to be the major contributor to rates of primary liver cancer. Saga Prefecture shows the highest death rates in Japan (43.1/100 000), and the highest prevalence rate of anti-HCV (3.9%).

ANTIVIRAL THERAPY SUPPRESSES INCIDENCE OF HCC

As described above, HCV infection is a major cause of HCC in Japan, suggesting eradication of HCV contributes to the decrease in incidence of HCC and death rates from HCC. A summary of different studies on the incidence of HCC among patients with chronic hepatitis C who were treated with interferon in Japan is noted[13–18] (Table 1). These studies suggested a moderate decrease in the risk for HCC in patients with chronic hepatitis C treated with interferon. Especially, the reduction of incidence of HCC was more convincingly shown in patients with sustained virological response, compared with no responders and non-treated patients.

Between 1992 and 2001, approximately 300 000 patients with chronic hepatitis C had received interferon (IFN) monotherapy in Japan. As shown in Figure 1, it was remarkable that the numbers of deaths and the death rate from HCC decreased in 2003. These phenomena suggest that antiviral treatment reduces the risk of HCC in patients with HCV infection.

In cases of hepatitis B, Matsumoto *et al*.[19] reported that antiviral treatment with lamivudine might suppress the risk of HCC in patients with chronic hepatitis B by multicenter, retrospective study.

CONCLUSION

The numbers of deaths and death rates from HCC showed sharp increases beginning in 1975. However, the annual deaths (34 089) and death rate (27.0/100 000) from liver cancer decreased in 2003. Although both HBV and HCV

infections have a major role in HCC in Japan, HCV-related HCC represents 75% of all HCC in Japan. The incidence of HCC without HBsAg or anti-HCV accounted for 7–12% in Japan and half of non-B non-C-HCC was of unknown origin. Geographically, HCC is more frequent in western than eastern Japan, and the death rates of HCC in each prefecture correlate with prevalence of anti-HCV, but not with HBsAg prevalence. IFN therapy for chronic hepatitis C has reduced the risk factors for development of HCC, especially among patients with sustained response.

REFERENCES

1 Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare, Health and Welfare Statistics Association. *Vital Statistics of Japan 2003.* Tokyo: Ohwa Sogo Insatsu Co., 2005.
2 Ikai I, Okita K, Omata M *et al.* Report of the 15th follow-up survey of primary liver cancer. *Hepatol Res* 2004; **28:** 21–9.
3 Kiyosawa K, Umemura T, Ichijo T *et al.* Hepatocellular carcinoma: recent trends in Japan. *Gastroenterology* 2004; **127:** S17–26.
4 Tanaka Y, Hanada K, Mizokami M *et al.* 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* 2002; **99:** 15 584–9.
5 Liver Cancer Study Group in Japan. Survey and follow-up study of primary liver cancer in Japan-Report 11. *Kanzo* 1995; **36:** 208–18.
6 Liver Cancer Study Group in Japan. Survey and follow-up study of primary liver cancer in Japan-Report 12. *Kanzo* 1997; **38:** 317–30.
7 Liver Cancer Study Group in Japan. Survey and follow-up study of primary liver cancer in Japan-Report 13. *Kanzo* 1999; **40:** 288–300.
8 Liver Cancer Study Group in Japan. Survey and follow-up study of primary liver cancer in Japan-Report 14. *Kanzo* 2000; **41:** 799–811.
9 Liver Cancer Study Group in Japan. Survey and follow-up study of primary liver cancer in Japan-Report 15. *Kanzo* 2003; **44:** 157–75.
10 Liver Cancer Study Group in Japan. Survey and follow-up study of primary liver cancer in Japan-Report 16. *Kanzo* 2005; **46:** 234–54.
11 Sumi H, Yokosuka O, Seki N *et al.* Influence of hepatitis B virus genotypes on the progression of chronic type B liver disease. *Hepatology* 2003; **37:** 19–26.
12 Orito E, Sugauchi F, Tanaka Y *et al.* Differences of hepatocellular carcinoma patients with hepatitis B virus genotypes of Ba, Bj or C in Japan. *Intervirology* 2005; **48:** 239–45.
13 Nishiguchi S, Kuroki T, Nakatani S *et al.* Randomized trial of effects of interferon-alpha on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. *Lancet* 1995; **346:** 1051–5.
14 Kasahara A, Hayashi N, Mochizuki K *et al.* Risk factors for hepatocellular carcinoma and its incidence after interferon treatment in patients with chronic hepatitis C. *Hepatology* 1998; **27:** 1394–402.
15 Imai Y, Kawata S, Tamura S *et al.* Relation of interferon therapy and hepatocellular carcinoma in patients with chronic hepatitis C. *Ann Intern Med* 1998; **129:** 94–9.
16 Ikeda K, Saitoh S, Arase K *et al.* Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis C. A long-term observation study of 1643 patients using statistical bias correction with proportional hazard analysis. *Hepatology* 1999; **29:** 1124–30.
17 Yoshida H, Tateishi R, Arakawa Y *et al.* Benefit of interferon therapy in hepatocellular carcinoma prevention for individual patients with chronic hepatitis C. *Gut* 2004; **53:** 425–30.
18 Okanoue T, Minami M, Makiyama A, Sumida Y, Yasui K, Itoh Y. Natural course of asymptomatic hepatitis C virus-infected patients and hepatocellular carcinoma after interferon therapy. *Clin Gastroenterol Hepatol* 2005; **3:** S89–91.
19 Matsumoto A, Tanaka E, Rokuhara A *et al.* Efficacy of lamivudine for preventing hepatocellular carcinoma in chronic hepatitis B. A multicenter retrospective study of 2795 patients. *Hepatol Res* **32:** 173–84.

Figure 1 Changes in annual numbers of deaths of patients with primary liver cancer between 1958 and 2003, after data from the Vital Statistics of Japan, to which statistics are reported 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 mean ages of male (■) and female (□) patients with HCC between 1984 and 2001.

Figure 4 Changes in etiology of HCC between 1990 and 2001. HBsAg+ (■), anti-HCV+ (shaded gray), unknown and others (□).

Figure 5 (a) Death rates from primary liver cancer (per 100 000), total 27.0, (b) HBsAg prevalence, total 1.1%, and (c) anti-HCV prevalence, total 1.0% among people over 40 years of age in 48 prefectures in 2003.

Figure 6 Relationships between death rate of primary liver cancer and prevalence of (a) HBsAg ($r = 0.85$, $P = 0.57$), and (b) anti-HCV ($r = 0.67$, $P < 0.0001$, $y = 14.2x + 14.98$ among the general population over 40 years of age in 2003.

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

Author	Untreated		Treated					
	No. HCC/ No. cases	%	Non-SVR		SVR		Total	
			No. HCC/ No. cases	%	No. HCC/ No. cases	%	No. HCC/ No. cases	%
Nishiguchi *et al.*[13]	17/45	38					2/45	4.4
Kasahara et al.[14]			41/709	5.8	5/313	1.6	46/1022	4.5
Imai *et al.*[15]	19/140	13					18/419	4.3
Ikeda *et al.*[16]	67/452	15	23/730	3.2	5/461	1.1	28/1191	2.4
Yoshida *et al.*[17]	67/395	17	214/1556	13.8	27/836	3.2	241/2392	10.1
Okanoue *et al.*[18]			119/849	14.0	8/397	2.0	127/1246	10.2
Total	170/1032	17	397/3844	10.3	45/2007	2.2	462/6315	7.3

SVR, sustained virological response

Figure 1

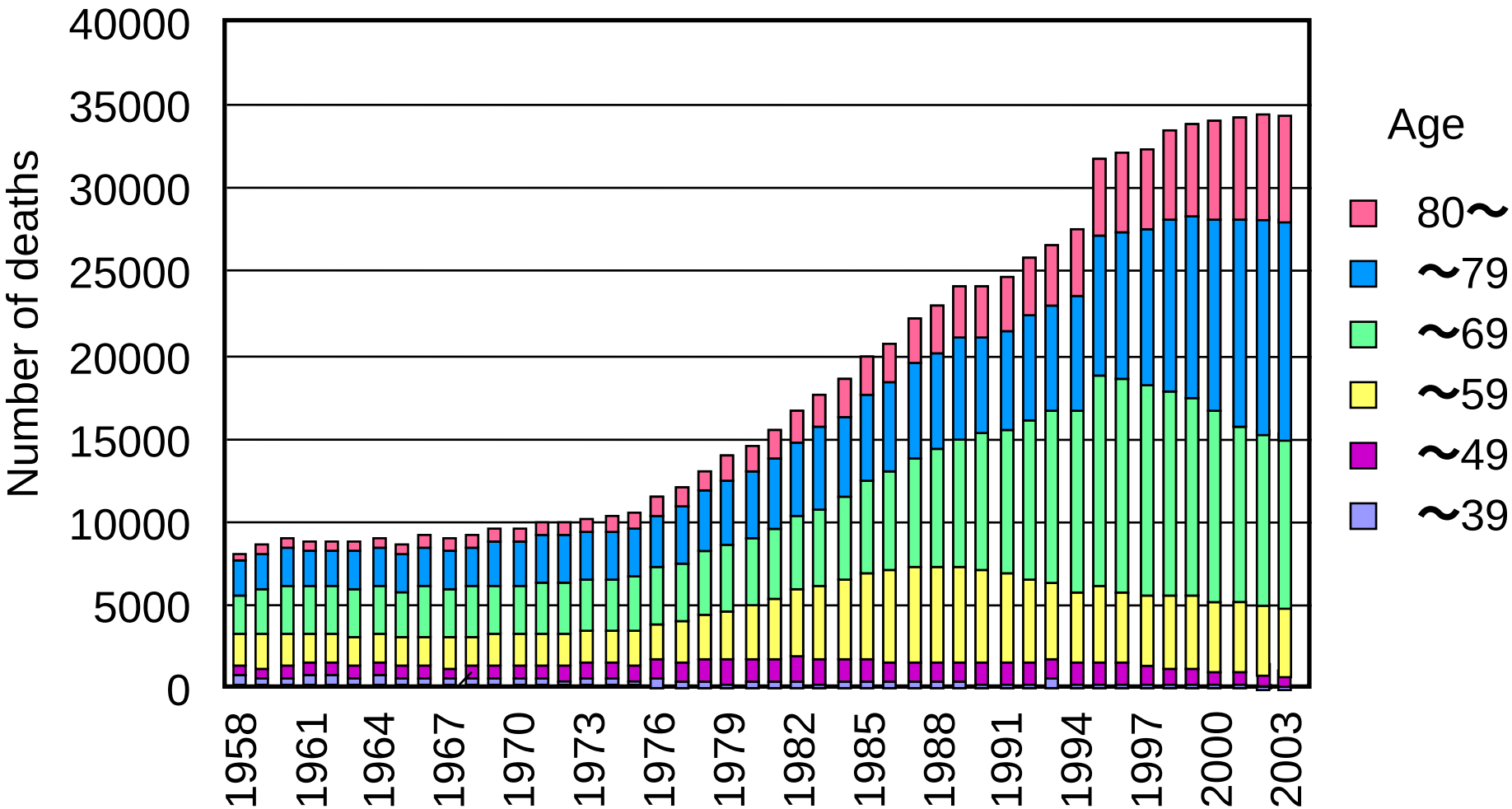

Number of deaths
40000
35000
30000
25000
20000
15000
10000
5000
0
1958
1961
1964
1967
1970
1973
1976
1979
1982
1985
1988
1991
1994
1997
2000
2003
Age
80～
～79
～69
～59
～49
～39

Figure 2

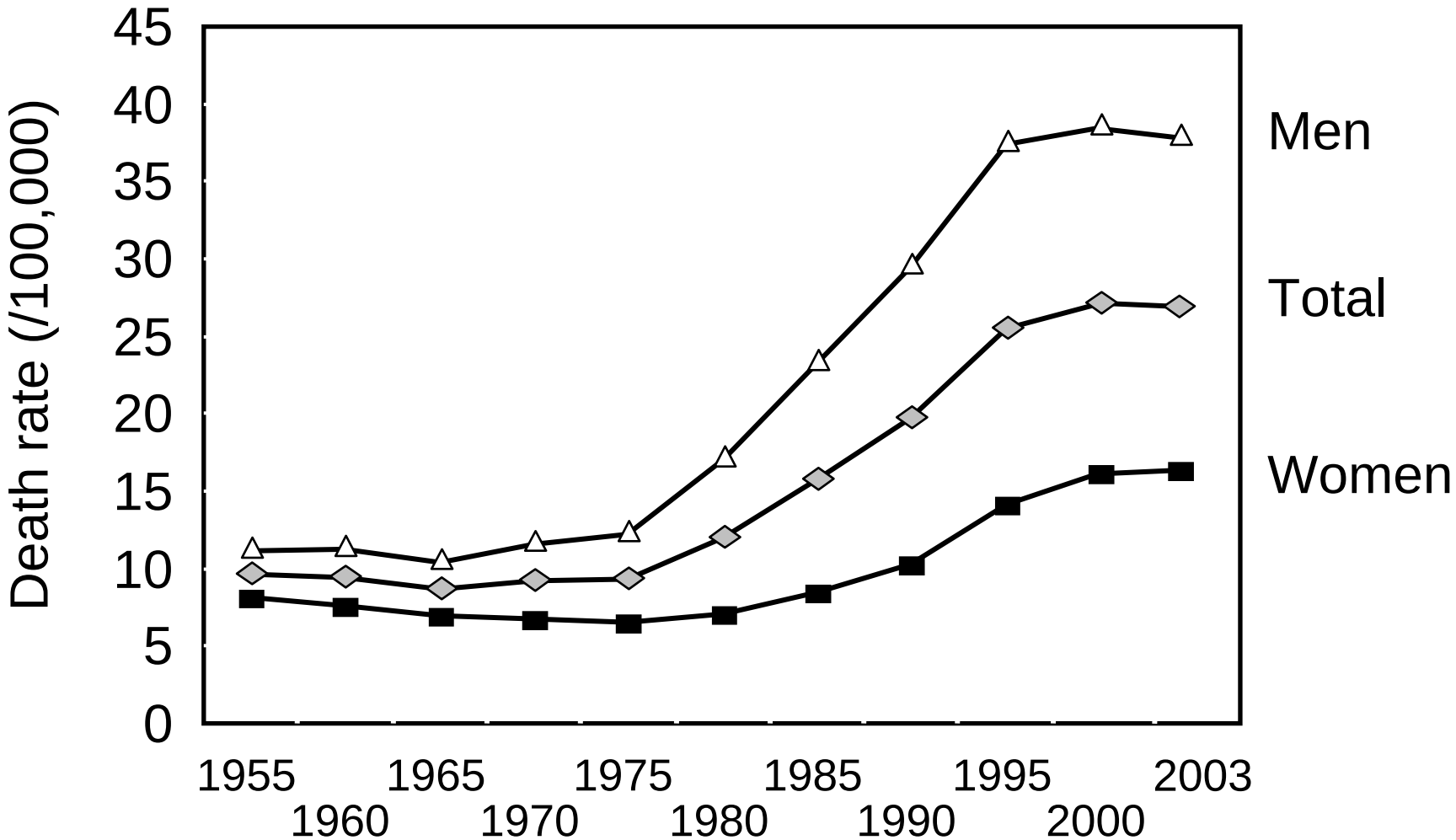

Death rate (/100,000)
45
40
35
30
25
20
15
10
5
0
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2003
Men
Total
Women

Figure 3

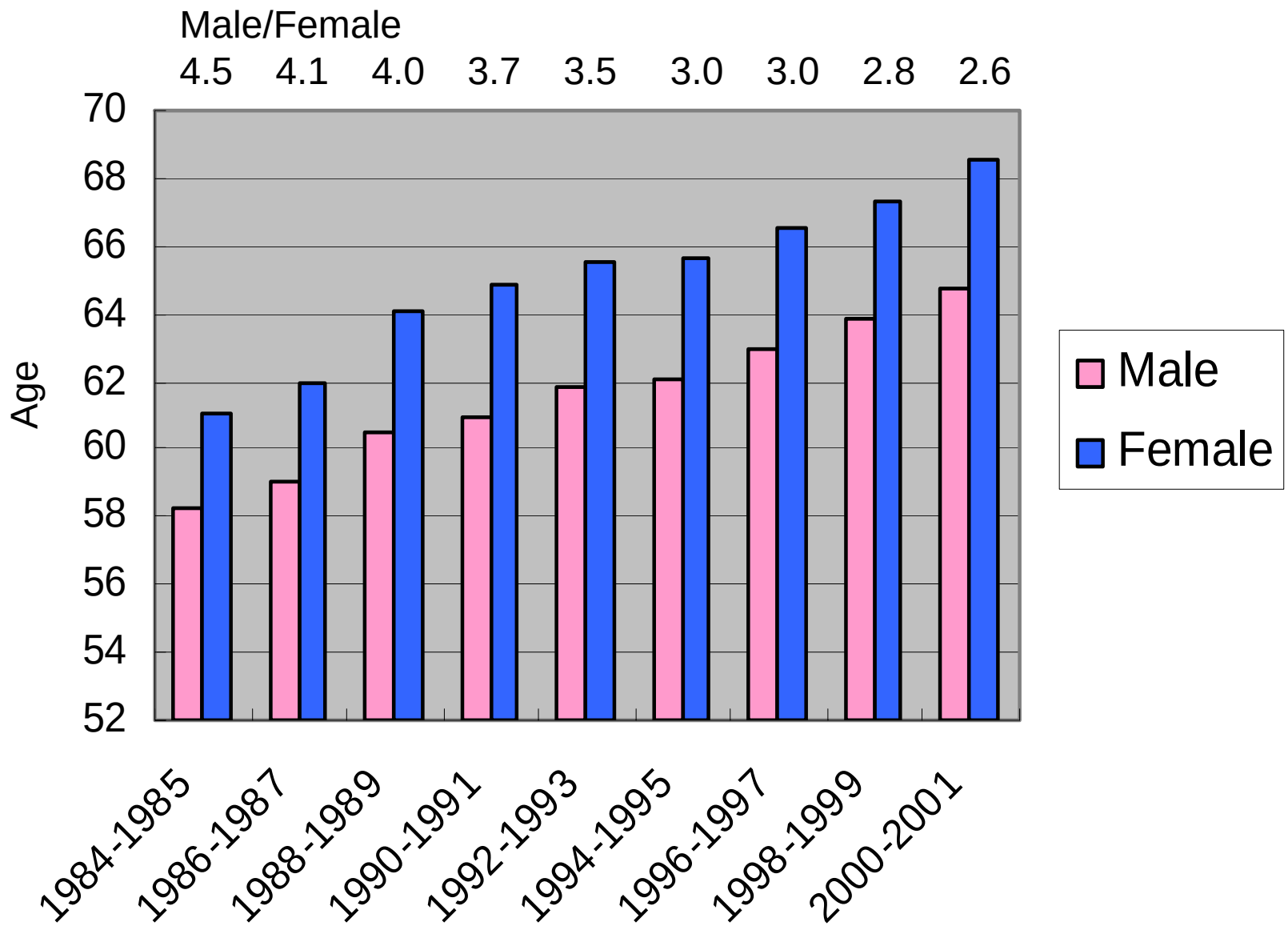

Male/Female
4.5 4.1 4.0 3.7 3.5 3.0 3.0 2.8 2.6
Age
70
68
66
64
62
60
58
56
54
52
1984-1985
1986-1987
1988-1989
1990-1991
1992-1993
1994-1995
1996-1997
1998-1999
2000-2001
Male
Female

Figure 4

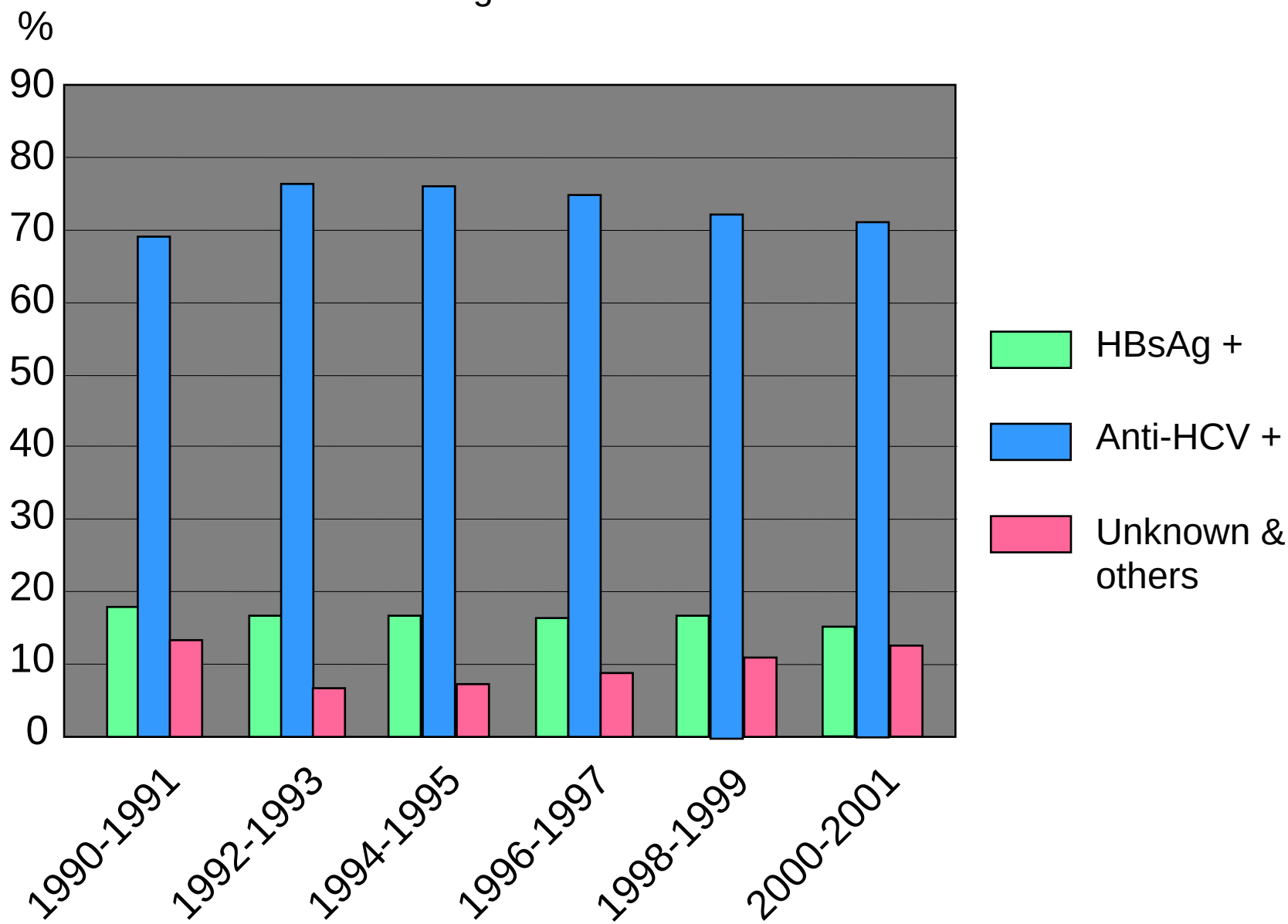

%
90
80
70
60
50
40
30
20
10
0
1990-1991
1992-1993
1994-1995
1996-1997
1998-1999
2000-2001
HBsAg +
Anti-HCV +
Unknown & others

Figure 5

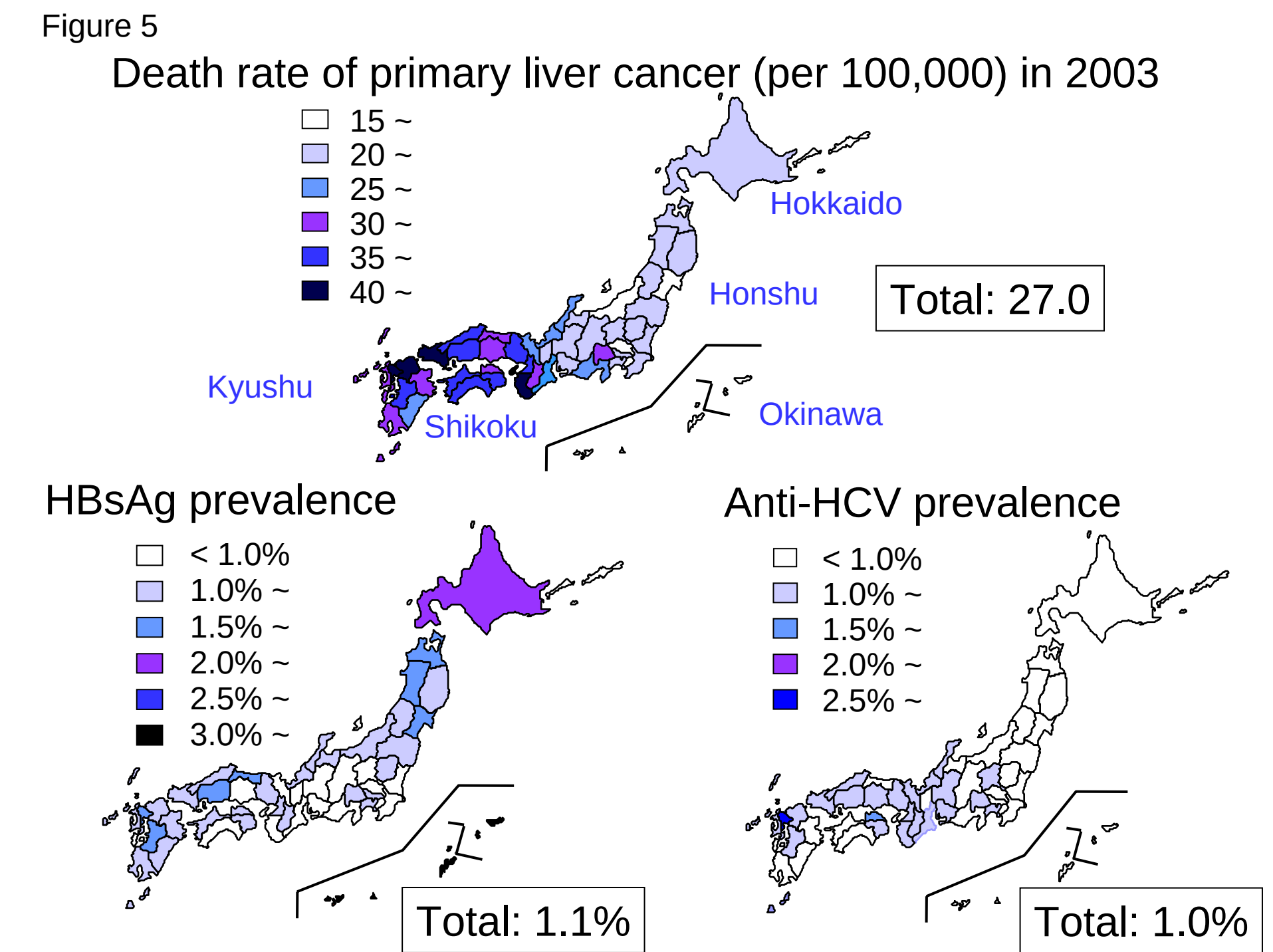
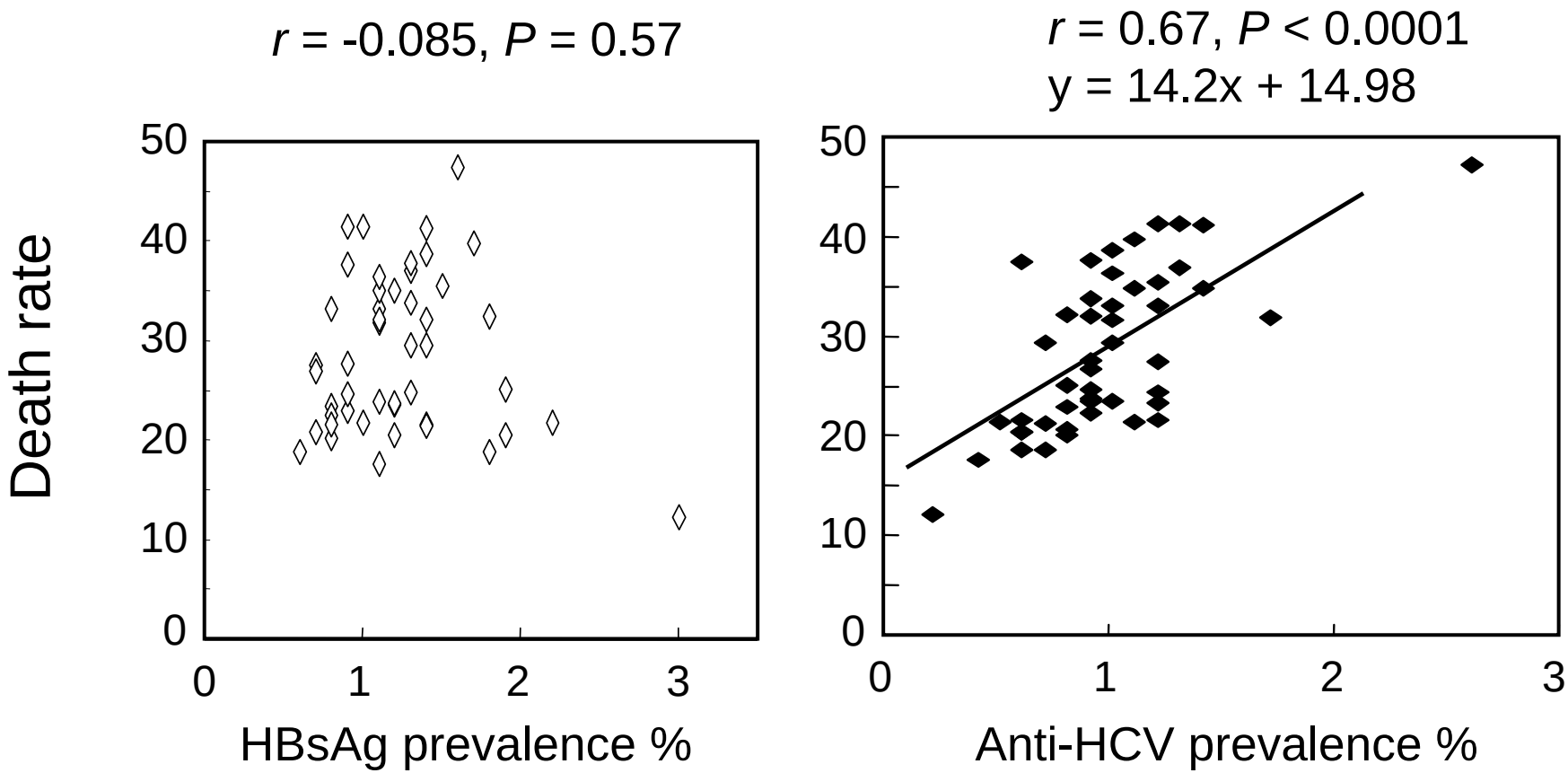

Death rate of primary liver cancer (per 100,000) in 2003
15 ~
20 ~
25 ~
30 ~
35 ~
40 ~
Hokkaido
Honshu
Kyushu
Shikoku
Okinawa
Total: 27.0
HBsAg prevalence
< 1.0%
1.0% ~
1.5% ~
2.0% ~
2.5% ~
3.0% ~
Total: 1.1%
Anti-HCV prevalence
< 1.0%
1.0% ~
1.5% ~
2.0% ~
2.5% ~
Total: 1.0%

Figure 6


r = -0.085, P = 0.57
r = 0.67, P < 0.0001
y = 14.2x + 14.98
Death rate
HBsAg prevalence %
Anti-HCV prevalence %
0
10
20
30
40
50
0
1
2
3