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Hepatitis C Virus Infection in 2,744 Hemodialysis Patients Followed Regularly at Nine Centers in Hiroshima During November 1999 Through February 2003

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Patients on maintenance hemodialysis (HD) are at increased risk of infection with hepatitis C virus (HCV). A prospective follow-up study on HCV infection from November 1999 to February 2003 was conducted in nine hemodialysis (HD) units in Hiroshima. A total of 2,744 HD patients were surveyed regularly for HCV RNA in serum. The prevalence of HCV RNA decreased from 15.7% (262/1,664) on the first survey to 12.9% (242/1,882) in the last one ($P < 0.05$). This decrease may be attributed to the inclusion of patients with a lower prevalence of HCV RNA compared to patients leaving dialysis centers (111/1,080 [10.3%] vs. 132/862 [15.3%], $P < 0.01$). During the 40 months of this study, 16 de novo HCV infections were documented in the nine HD units corresponding to an incidence of 0.33% per year. These cases included eight new HCV infections, three re-infections, and five infections that presumably occured in the window period when tested during the first survey. Our study shows that the annual incidence of de novo HCV infection during HD was 0.33%, and emphasizes the need for frequent serum HCV RNA testing and for stringent dis-infection procedures in order to prevent the transmission of HCV in these settings. ***J. Med. Virol. 76:498–502, 2005.*** © 2005 Wiley-Liss, Inc.

KEY WORDS: antibody to hepatitis C virus; chronic hepatitis C; hemodialysis; hepatitis C virus

INTRODUCTION

Hepatitis C virus (HCV) is highly prevalent in hemodialysis (HD) units. The increase in HCV infection among HD patients is directly proportional to the duration of HD and also to the number of transfusions these patients have received in the past. Exclusion of blood units that are positive for antibody to HCV (anti-HCV) has decreased posttransfusion HCV infection in clinical settings [Watanabe et al., 1993]. Nevertheless, HCV infection remains a major global problem in most dialysis centers.

The prevalence of HCV in HD units varies widely from country to country. In a recent study [Fissell et al., 2004], HCV infection in HD units ranged from 2.6% to 22.9%, with an annual incidence varying from 1.2% to 3.9%. It is indeed very difficult to prevent transmission of HCV infection in dialysis units due to lack of concrete evidence for its mode of transmission. Nosocomial transmission has been implicated recently as the major route of HCV infection in HD units [Stuyver et al., 1996; Fabrizi et al., 2000]. Other studies, however, are needed to verify these findings.

In order to prevent de novo HCV infection in HD units, we surveyed 2,744 HD patients prospectively over a period of 40 months for HCV serum markers at frequent intervals. Patients that have developed HCV infection were followed closely. This investigation was

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undertaken to study the prevalence of HCV infection in selected Japanese HD units and to suggest methods to minimize the spread of HCV infection in these units.

MATERIALS AND METHODS

Patients on Maintenance Hemodialysis

In June 1999, seven patients at one of 75 dialysis centers in Hiroshima came down with an HCV infection. A committee was immediately organized to investigate this HCV outbreak. An immediate and thorough HCV virological survey of HD patients at this center was recommended as well as on nine other core dialysis centers in Hiroshima. A prospective study was planned and conducted from November 1999 to February 2003 of all the 2,744 HD patients attending these centers. Sera were collected every 3 months during 14 surveys, and were tested for anti-HCV, HCV RNA, and HCV core antigen utilizing the same procedures and the same source of diagnostic kits by a single laboratory. Routine biochemical tests such as alanine aminotransferase (ALT) were also performed every 3 months and when required.

Serological Markers of HCV Infection

Anti-HCV was determined in serial twofold dilutions of the test serum by passive hemmagglutination (PHA) with currently available commercial kits (Second-generation HCV PHA; Abbott Japan KK, Tokyo, Japan). Results were recorded as the highest twofold dilution that induced hemagglutination; values $\geq 2^3$ were considered as positive. HCV RNA was determined by polymerase chain reaction (PCR) with nested primers deduced from well-conserved areas within the 5′-noncoding region of the HCV genome [Okamoto et al., 1990]. HCV core antigen was determined by enzyme-linked immunosorbent assay of the second generation (Ortho Clinical Diagnostics KK, Tokyo, Japan).

During the collection of sera, the tenets of the Declaration of Helsinki were observed and the study had the approval of our Internal Review Boad.

Statistical Analysis

Differences in the frequency of categorical variables between groups were evaluated by the χ^2 test or the Fisher's exact test, and those of continuous variables by the Student's t test.

RESULTS

Prevalence of HCV Infection in Hemodialysis Patients

During November 1999 through February 2003, 2,744 HD patients at the nine centers in Hiroshima were tested for HCV infection on 14 surveys at a 3-month interval. Among them, men predominated and accounted for 58.8% (1,613/2,744). The mean age was significantly lower in men than women (63.3 ± 13.1 vs. 65.7 ± 13.2 years, $P < 0.01$), while the mean duration on HD was not different between them (6.7 ± 6.4 vs. 6.7 ± 6.5 years). The prevalence of HCV RNA decreased gradually from 15.7% to 12.9% ($P < 0.05$). This is attributed, in part, to entry of patients with a lower prevalence of HCV RNA compared to patients leaving the dialysis centers (111/1,080 [10.3%] vs. 132/862 [15.3%], $P < 0.01$). HCV RNA was found to be more frequent in men than in women (14.5%–16.9% vs. 10.5%–14.4%, $P < 0.01$).

During the survey, 862 (31.4%) patients left the dialysis centers. Some due to sudden death (49.3%) and others due to transfer to other dialysis centers (47.7%). This loss accounted to 97.0% of patients.

Incidence of HCV Infection in Hemodialysis Patients

In this study, HCV RNA positive patients with high level anti-HCV titers were excluded at first and during later surveys. These patients must have acquired their infection before the initiation of HD. This left 2,114 patients who were at risk of HCV infection. These patients were followed for longer than 3 months. Among these patients, 16 (0.8%) were infected persistently with HCV, an incidence of 0.33%. Low-titered anti-HCV ($<2^{12}$) was detected in 125 (5.9%) of these patients. Of the remaining 1,989 patients who were anti-HCV negative, 5 were HCV RNA positive on the first survey. It was concluded that these five patients were in the "window period" of HCV infection. The remaining 1,984 (93.9%) patients were negative for both anti-HCV and HCV RNA.

As shown in Figure 1, three patterns of HCV infection were identified in HD patients. Among these patients, eight became positive for HCV RNA then seroconverted to anti-HCV (Fig. 1a). These patients must have acquired their HCV infection de novo. Among the 125 patients who were HCV RNA negative but with low-titered serum anti-HCV, 3 (2.4%) developed HCV infection and became HCV RNA positive with marked increases in anti-HCV titers (Fig. 1b). It was concluded that these three patients were infected recently with HCV. Another five patients were found to be HCV RNA positive without anti-HCV on the first survey (Fig. 1c). These patients were in the "window period" of HCV infection, since they seroconverted to slow-rising anti-HCV levels on other surveys. HCV core antigen with increasing titers was detected in all 16 patients, an indirect confirmation of a newly acquired HCV infection in these patients (Fig. 1a–c).

Figure 1d illustrates the course of persistent HCV infection in a patient with low anti-HCV titers. This patient was a 71-year-old woman with persistent low anti-HCV titers (2^3–2^5) through 11 surveys. Anti-HCV became undetectable in her serum ($<2^3$) on two occasions. Despite persistent HCV infection, her ALT serum levels remained within the upper limit of normal (<45 IU/L) throughout the observation period.

Figure 2 illustrates both the incidence and the increase in HCV infection during 14 surveys over

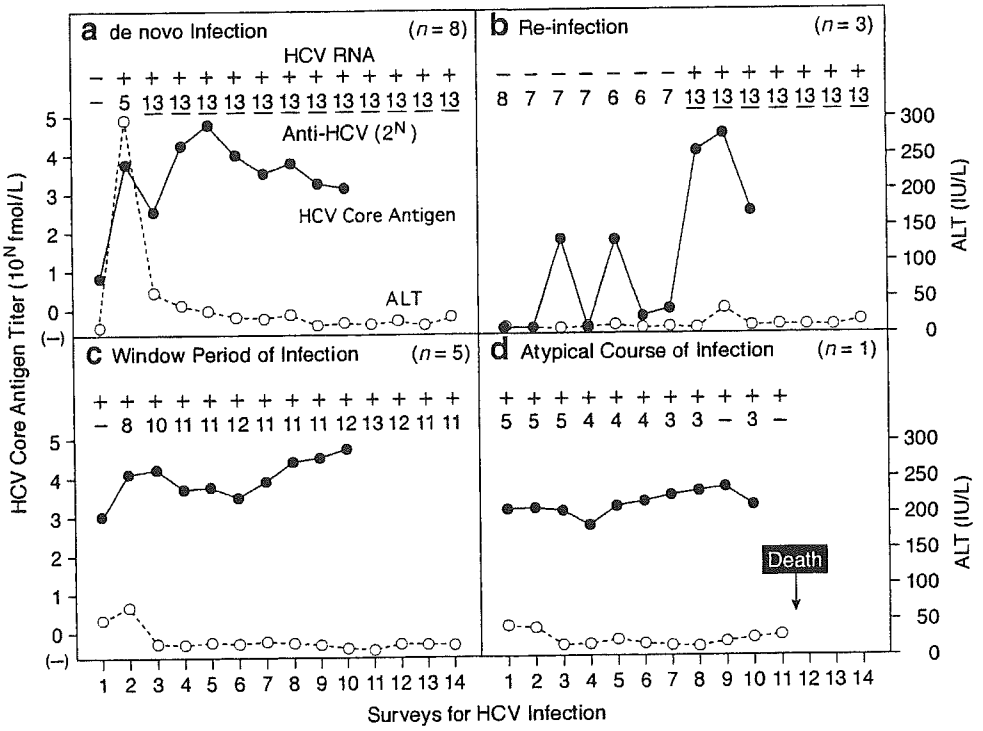

Fig. 1. Clinical courses of the 16 hemodialysis patients who developed HCV infection during the 14 surveys and the single patient with low anti-HCV titers. The course of a patient representative of each course is shown with the number of patients in that category in parentheses for those with de novo HCV infection (**a**), those with re-infection (**b**) and those in the window period of HCV infection (**c**). The course is shown also for the single patient in whom ant-HCV in low titers continued despite persistent infection (**d**). Underlined anti-HCV PHA titers indicate titers ≥13.

40 months. Although five patients were HCV RNA positive on the first survey, they were considered to be in the window period of an HCV infection that they already had acquired before the survey (Fig. 1c). Thereafter, the incidence was lower with only 1 or 2 HCV infections until the 8th survey. No new HCV infections were detected at the 9th, 10th, 13th, and 14th surveys. One patient developed an HCV infection on the 11th survey and two others developed an infection on the 12th survey.

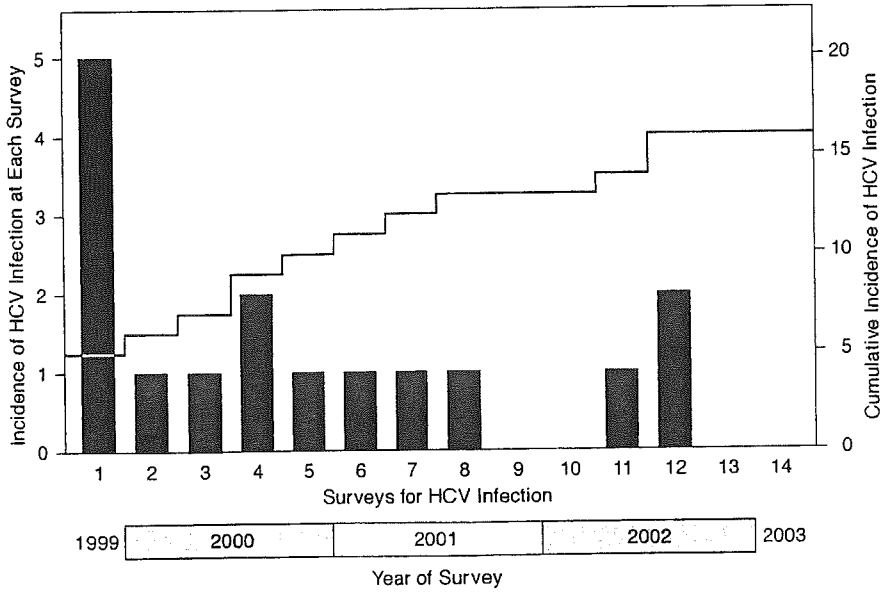

Fig. 2. Incidence of HCV infection during 14 surveys in hemodialysis patients attending the nine centers in Hiroshima, Japan.

TABLE I. HCV Infection in Hemodialysis Patients Stratified by Age and Sex

	Total		Men		Women	
Age (years)	n	HCV RNA	n	HCV RNA	n	HCV RNA
≤29	10	0	5	0	5	0
30–39	72	1 (1.4%)	47	1 (2.1%)	25	0
40–49	208	19 (9.1%)	134	13 (9.7%)	74	6 (8.1%)
50–59	468	65 (13.9%)	287	41 (14.3%)	181	24 (13.3%)
60–69	551	75 (13.6%)	321	51 (15.9%)	230	24 (10.4%)
≥70	573	82 (14.3%)	309	54 (17.5%)	264	28 (10.6%)
Total	1,882	242 (12.9%)	1,103	160 (14.5%)	779	82 (10.5%)

Influence of Age and the Year of Hemodialysis on HCV Infection

The frequency of HCV RNA increased with age in men, but it remained almost constant in women (Table I). Table II compares the prevalence of HCV infection in patients who had been on HD for ≥30 to ≤4 years. HCV infection was found to be very frequent (>44%) in patients who were treated by HD during ≥20 years, but infrequent (about 10%) in those during 15 years or less. There was approximately sixfold difference in the frequency between these patients. During 30 years on HD, the incidence of posttransfusion hepatitis fell dramatically (Table II). The decrease was attributed to anti-HCV screening by the first and second-generation assays that were mandated in 1989 and 1992, respectively. Of note, the prevalence of HCV infection in HD patients paralleled the incidence of posttransfusion hepatitis in the year when these patients started treatment by HD. In addition, the use of recombinant human erythropoietin which was introduced in 1990 decreased the need for transfusion in these patients. HCV infection prevailed, however, in ≥10% of the patients who started HD since 1993 when the incidence of posttransfusion hepatitis was decreased due to mandated screening.

DISCUSSSION

The present survey was carried out in nine core HD centers in Hiroshima. These centers, however, are not representative of other HD centers in Japan. Despite this, key issues have emerged as to current status of HCV infection among HD patients and means to prevent its future spread. During this survey of 3 years duration, the prevalence of HCV RNA in HD patients decreased from 15.7% to 12.9%. As shown in Table II, although the rate of HCV infection increased with the duration of HD, it was higher in those patients who started HD earlier. This is partly attributed to a decrease in the incidence of posttransfusion hepatitis C across the years between 8% and 19% before 1990 to practically negligent levels after 1992 [Yoshizawa, 2002]. Recombinant human erythropoietin that was introduced to patients in 1990 might have decreased further the exposure to HCV through transfusion.

The incidence of HCV infection has decreased since the survey was initiated. The five new infections that were detected on the first survey were attributed to acquisition of HCV before the survey was initiated (Figs. 1a and 2). The overall annual incidence was 0.33%, compared to 3.1% in a previous survey that was carried out in Japanese patients on maintenance HD [Fissell et al., 2004]. These investigatiors, unlike our current study, detected HCV infection by testing for anti-HCV rather than HCV RNA.

A strict adherence to HCV infection control by emphasizing regular and more frequent screening for HCV RNA during this survey would have brought attention of the risks in these nine HD centers concerning nosocomial transmission of HCV.

TABLE II. Prevalence of HCV Infection in Hemodialysis Patients With Reference to the Duration on Hemodialysis and the Year of Start

		HCV RNA				
Duration on hemodialysis (years)	n	n	Odds ratio (95% CI[a])	Differences (P value)	Started on HD[a]	Posttransfusion hepatitis[b]
≥30	5	3 (60.0%)	12.9 (3.2–52.3)	$P < 0.01$	1968–1972	16.2%
25–29	45	20 (44.4%)	6.9 (4.0–11.9)	$P < 0.01$	1973–1977	9.6%
20–24	92	41 (44.6%)	6.9 (4.6–10.5)	$P < 0.01$	1978–1982	19.3%
15–19	123	16 (13.0%)	1.3 (0.7–2.3)		1983–1987	12.3%
10–14	224	17 (7.6%)	0.7 (0.4–1.2)		1988–1992	3.1%
5–9	492	51 (10.4%)	1.0 (0.7–1.4)		1993–1997	Close to 0%
≤4	901	94 (10.4%)	1.0		1998–2002	Close to 0%

[a]Confidence interval. 1989: screening for anti-HCV by the first-generation EIA with c100-3; 1990: recombinant human erythropoietin approved for health insurance; 1992: Screening for anti-HCV by the second-generation immunoassays.
[b]Extracted from data reported by Yoshizawa [2002].

HD patients are at high risk of developing an HCV infection, and most often than not are in the "window period" before the emergence of serum anti-HCV. It has been reported by other investigators [Schroter et al., 1997; Furusyo et al., 2001] that anti-HCV in these patients does not emerge in serum for a period of 6.5–13 months compared to only 2.7 months in patients who acquire posttransfusion HCV infection [Schreiber et al., 1996]. In our study, 5 of 16 (31%) patients with de novo HCV infection were in the "window period" and subsequently developed serum anti-HCV in high titers during the next survey of 3 months later. This is in disagreement with the findings of Dalekos et al. [1998] who reported the absence of HCV RNA in 81 HD patients who were also anti-HCV negative.

Although it is difficult to investigate thoroughly the means of transmission of HCV infection among HD patients in our nine HD units, possibility of a nosocomial route of infection cannot be excluded. This possibility has been reported by others [Stuyver et al., 1996; Fabrizi et al., 2000]. Of interest is the finding that high titers of HCV RNA have been found in the wash of gloves worn by HD nurses [Alfurayh et al., 2000]. Thus it is imperative to take every necessary precaution to prevent HCV infection in such settings [Kellerman and Alter, 1999].

In conclusion, our data supports more frequent testing of HCV RNA in HD units. Based on our experience, testing for HCV RNA on a monthly bases may be necessary to reduce the transmission of HCV in HD units. This is in agreement with the recommendation of Moreira et al. [2003].

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National Prevention of Hepatocellular Carcinoma in Japan Based on Epidemiology of Hepatitis C Virus Infection in the General Population

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Key Words
Chronic hepatitis · Cirrhosis · Epidemiology · Hepatitis C virus · Hepatocellular carcinoma · Prevention · Transfusion

Abstract
During the past 30 years, hepatocellular carcinoma (HCC) in Japan has kept linearly increasing from 10 to 30 per 100,000 population per year and is expected to grow further. The increment is attributed to infection with hepatitis C virus (HCV). Hence, there is a pressing need to find subjects with persistent HCV infection in the general population of Japan and take necessary measures to prevent HCC developing in them. As a first approach toward this goal, the sex- and age-specific prevalence of ongoing HCV infection was surveyed in 3,485,648 first-time blood donors during 1995–2000. Taking into account the size of subpopulations with different sex and age in Japan registered at the Census 2000, there are an estimated 884,954 HCV carriers aged from 16 to 69 years, and 759,316 (86%) of them are older than 40 years, with an increased risk for HCC; they are hidden in the society, without overt liver disease. The national 5-year project searching for HCV carriers in the general population was started in April 2002. Subjects are examinees of health check-ups, which they receive every 5 years when reaching the age of 40, as well as those at increased risk for HCV infection. The project detected HCV RNA in 14,672 of the 1,298,746 (1.1%) health check examinees and in 16,721 of the 624,734 (2.7%) high-risk individuals during the first fiscal year. Subjects found with HCV RNA have been referred to clinics and hospitals with expert hepatologists. Hopefully, this project will decrease HCC development in HCV carriers in Japan and be considered in other countries where increases in HCC are predicted from the current age-specific prevalence of anti-HCV.

Introduction

Hepatocellular carcinoma (HCC) ranks as the fourth most frequent cause of death due to malignancy in the world. HCC in men is the third most frequent malignancy in Japan, only next to lung and stomach cancers, while it is the fourth in women, following stomach, colon and lung cancers. The vast majority of patients with HCC are persistently infected with hepatitis B virus (HBV) or hepatitis C virus (HCV). The roles of HBV and HCV in the development of HCC vary widely in different countries and have changed with time. On the global scale, HBV

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induces HCC much more frequently than HCV. There are an estimated 350 million HBV carriers (corresponding to 6% of the world population) [1], which is twice as many as 190 million who are presumed with persistent HCV infection [2].

However, several lines of epidemiological and clinical evidence predict that the role of HCV will increase and exceed that of HBV in the future. First and foremost, there is no means of preventing HCV infection with vaccines, unlike the infection with HBV that has been prevented since 1980 by hepatitis B vaccine [3]; it is proven to have a long-term effect in suppressing HCC associated with HBV infection [4]. Secondly, HCV infection can persist in 80% of adults parenterally exposed to it [5], in contrast to only a few percent of HBV infection in the adulthood that becomes chronic [6]. Thirdly, HCV infection prevails globally and keeps spreading, in remarkable contrast to HBV infection that is restricted to Asia and Africa. Finally, new HBV infections have been prevented by the global mass vaccination campaign advocated by the World Health Organization.

Hence, there is every reason to believe that HCV will have an ever increasing role in the development of HCC anywhere in the world where HCV prevails. However, it is not easy to foresee with a reasonable precision when and how often HCC develops in persistently infected individuals. The natural history of HCV infection is poorly defined [7, 8]. It varies widely according to the influence of diverse host and virus factors, of which the time factor is most important. It is presumed that 30 years elapse before HCC develops in the recipients of transfusion contaminated with HCV [9, 10]. However, the incubation time for HCC may not be constant in view of the velocity of fibrosis that differs widely by many factors, including the age at infection and gender [11–13].

Despite these differences in the development of HCC after HCV infection, a tendency would emerge if many HCV carriers are observed macroscopically en masse, in a national scale for instance. Furthermore, observing trends in HCV infection and associated HCC would help predict what will happen in the future and allow taking measures to prevent HCC arising in HCV carriers. Considering the Japanese as a whole, there has been a unique tendency for HCC during the past 50 years. Remarkably, the yearly incidence of HCC started to increase abruptly in 1975, and the role of HCV has kept increasing; now, it surpasses that of HBV by a margin of fourfold [14].

Driven by the need to comprehend how many people are at risk of developing HCC, we surveyed persistent infections with HBV and HCC in 3,485,648 first-time blood donors during 1995–2000 in the 8 jurisdictions of the Japanese Red Cross Blood Centers [15]. Based on the sex- and age-specific prevalence of infection, there are an estimated 759,316 HCV carriers in Japan who are older than 40 years and at increased risk of developing HCC. These trains of evidence have strongly indicated that HCC deaths in Japan will keep increasing at least until 2010, then flatten out and decline. This instigated doctors, as well as the personnel in the Ministry of Health, Labour and Welfare of Japan, to launch a 5-year project (which started in April 2002) to spot HCV carriers older than 40 years in Japan, urging them to take medical examination and receive treatment as required.

Geographical Distribution of Deaths due to HCC in Japan Shifting from 1975–1980 through 1991–1995 toward 1996–2000

Figure 1 pictures the distribution of deaths due to HCC examined over three 5-year ranges. Japan consists of four major islands, with Hokkaido situated up in the north, the mainland lying from northeast to southwest, accompanied by Shikoku down in the south and Kyushu in the west. There are 48 jurisdictions which are further broken down into many cities and villages. The standardized mortality rate (SMR) due to HCC in each of the 3,212 municipalities was determined by the Bay's method. The mortality rate of each municipality was classified as follows: highest (SMR >140, red), higher (SMR 140–120, orange), medium (SMR 120–80, yellow), lower (SMR 80–60, green) and lowest (SMR <60, blue). During 1971–1975, the annual incidence of HCC was pretty much the same all over Japan with most municipalities colored in yellow with the average frequency, although some areas in the southern Kyushu were in red with the highest incidence. During 1991–1995, the coloring became uneven, with areas in red or orange increasing all over Japan. The trend for this uneven distribution is further intensified on the last survey during 1996–2000. Although municipalities in green or blue increased in number, this by no means represents the incidence of decreased HCC. On the contrary, yearly incidence of HCC as well as the average total deaths due to HCC more than tripled during the three surveys covering 30 years from 1971 to 2000. Overall, the coloring highlights the incidence of HCC in Japan that decreases from Kyushu in the southwest, along the axis of Honshu toward Hokkaido in the northeast.

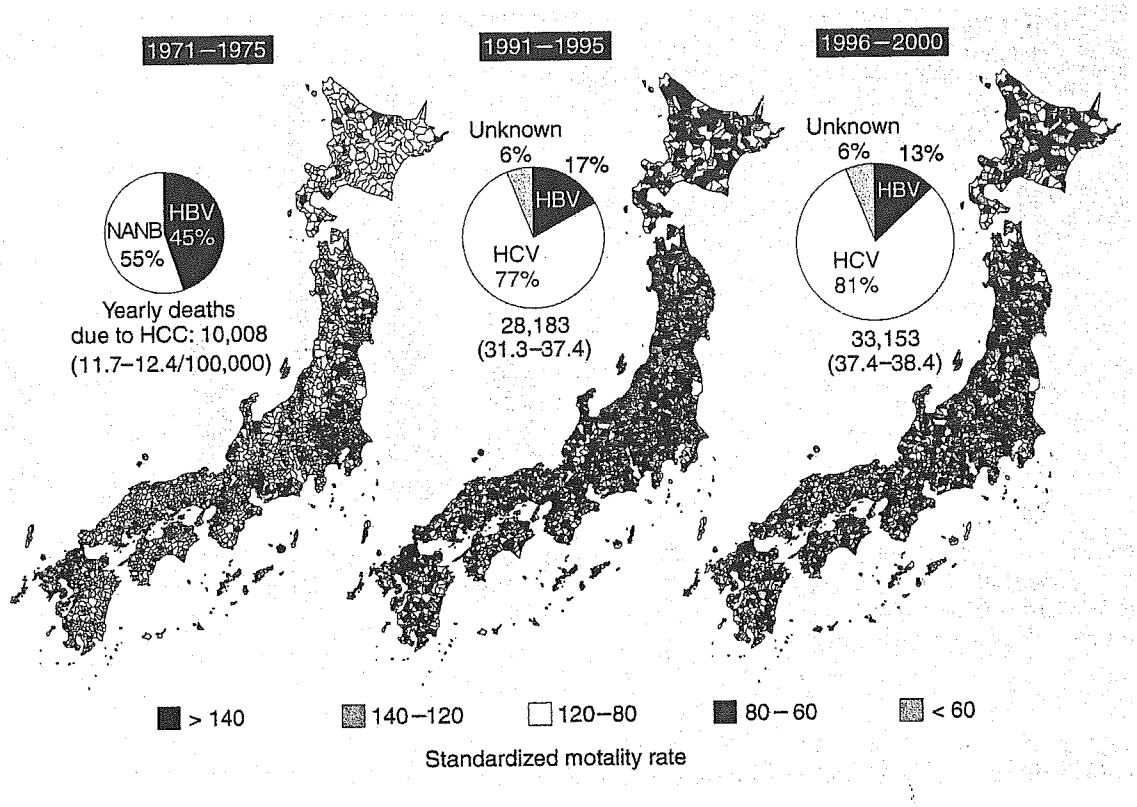

Fig. 1. Changes in the geographical distribution of deaths due to HCC in men during the past 30 years in 3,212 municipalities in Japan. Etiology of HCC is shown in a pie graph in size reflecting the yearly HCC during the survey period, with the average yearly deaths during the 5 years below and deaths due to HCC in 100,000 population per year in parentheses. Maps were produced by Dr. Yoshihiko Mirua of Saitama Prefectural University.

The center of Honshu over the skirt of Mount Fuji is an exception to this gradient. The incidence of HCC in Yamanashi prefecture stands out in red. This is due to the endemic *Schistosoma japonicum* along the Fuji River running through Yamanashi. Intravenous injection with antimony sodium tartar, performed during 1923–1980, spread HCV among patients infected with this parasite through repeated intravenous injections with insufficiently sterilized needles and syringes [16]. Similar endemic *S. japonicum* and iatrogenic diffusion of HCV happened in Saga and Fukuoka (both in northern Kyushu) and Hiroshima (in the western tail of Honshu) [17]. This was also the case along the riverside of the Nile in Egypt where *Schistosoma mansoni* once prevailed [18]. In Japan, parenteral antischistosomal treatment started to locally create small cores of HCV infection since the 1920s, and a more robust outbreak of HCV infection occurred since the end of World War II in 1945, through the 1960s to the 1970s [14].

Uneven geographical distribution of HCC in Japan, increasing with time (fig. 1), reflects the prevalence of HCV infection that differs regionally. Age-specific prevalence of HCV infection in the 3,485,648 first-time blood donors during 1995–2000 is shown in figure 2, individually for the 8 jurisdictions of the Japanese Red Cross Blood Center [15]. The frequency of HCV infection is higher in the four jurisdictions in the southwest than the other four in the northeast; there is a trend in the frequency of HCV infection, showing a decreasing gradient through the axis of Honshu from Hiroshima to Tohoku. The pattern matches the distribution of HCC in Japan at the last survey during 1995–2000, depicted in figure 1.

There are marked differences in the age-specific prevalence of HCV infection in every district (fig. 2). HCV is least prevalent in the age group of 16–19 years, gradually increases in the age group of 50–59 years and is highest in the 60–69-year-olds. Looked at more closely, in blood donors divided by a 1-year notch, the increase of HCV infection with age is even more conspicuous and reaches

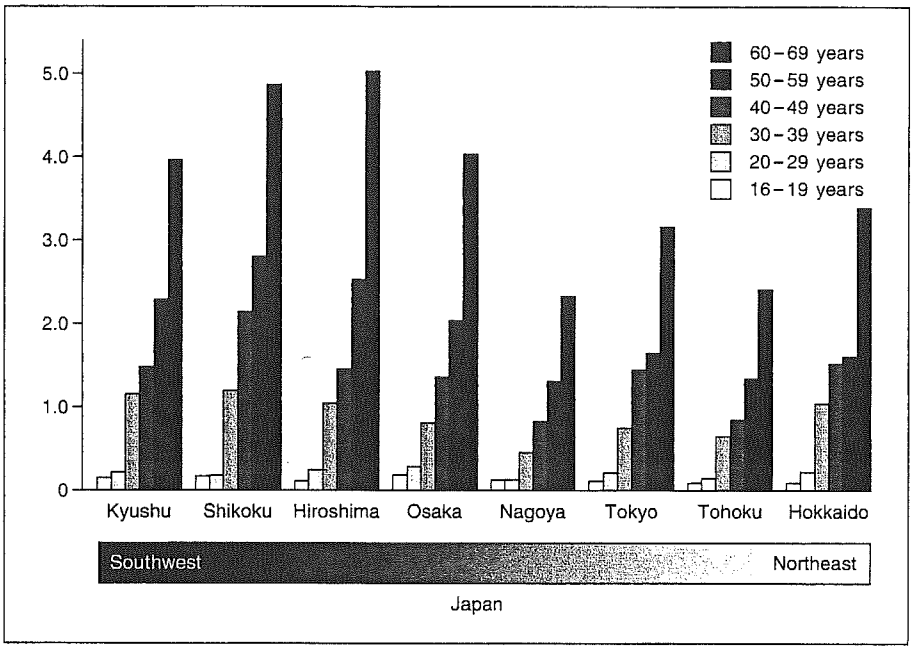

Fig. 2. Age-specific prevalence of anti-HCV in a large-scale survey on the first-time blood donors in eight districts of Japan in the order from southwest to northeast.

11% in those aged 70 years, extrapolated to the year 2000 (fig. 3). In Japan, in the year 2000, the number of total HCV carriers aged from 16 to 64 years who were eligible for blood donation was estimated at 884,954, 95% confidence interval (95% CI) 725,082–1,044,826, among 93,325,570 (0.95%) individuals aged 15–69 years [15]. They comprised 464,363 (95% CI 377,927–550,799) of the 46,638,636 (1.00%) men and 420,591 (95% CI 347,156–494,027) of the 46,686,934 (0.95%) women of the same ages. They were calculated as the sum of sex- and age-specific prevalence of HCV infection multiplied by the subpopulation with the corresponding sex and age. Thus, there are at least 759,316 HCV carriers older than 40 years who would be at increased risk of developing HCC.

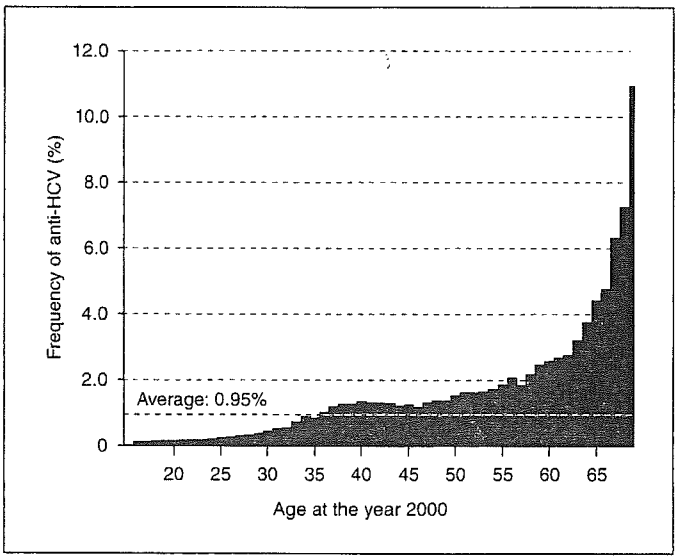

Fig. 3. Age-specific distributions in the 884,954 first-time blood donors with anti-HCV in Japan [modified from ref. 15].

Liver Disease in Blood Donors Found with Ongoing HCV Infection at the Screening

Liver disease induced by persistent HCV infection is insidious and progresses slowly at the speed differing according to various factors. Therefore, patients with HCV-associated liver disease are not aware of it before they develop signs and symptoms of cirrhosis or HCC, which even then can be missed for years due to ample reserve in the life-maintaining capacity of the liver. Hence, most HCV carriers are asymptomatic, as those typically identified among blood donors. During 10 years, from 1991 to 2000, 912 apparently healthy individuals were found to be persistently infected with HCV at a screening for blood donation at the Japanese Red Cross Blood Center in Hiroshima. They consulted doctors and were clinically examined [19]. It does strike us as a surprise that chronic

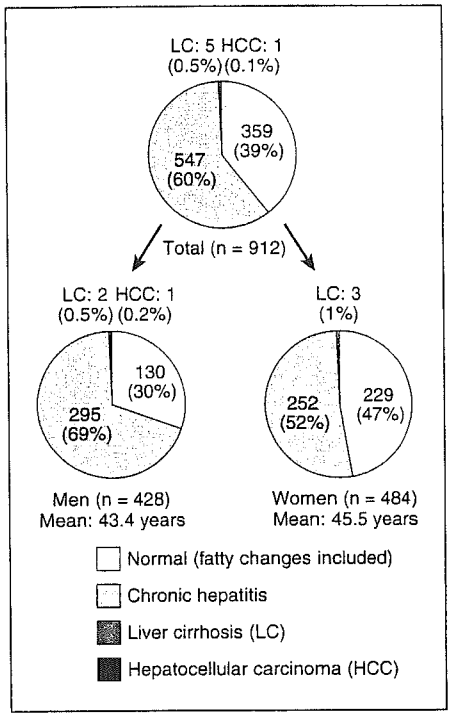

Fig. 4. Distribution of liver disease in 912 blood donors in Hiroshima who were found with HCV infection.

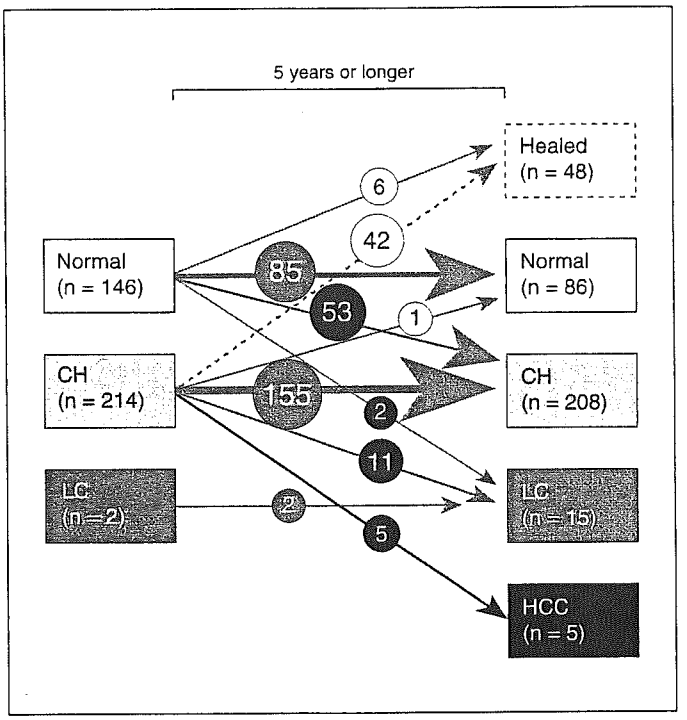

Fig. 5. Evolution of liver disease in 362 blood donors with anti-HCV in Hiroshima during follow-ups for 5 years or longer. CH = Chronic hepatitis; LC = liver cirrhosis.

hepatitis C with elevated serum levels of alanine aminotransferase was diagnosed in 60% of the subjects who had felt healthy enough to donate blood (fig. 4). Furthermore, cirrhosis had developed in 5 (0.5%) patients and HCC already in 1 (0.1%). Men had chronic hepatitis more frequently than women – 252/428 (69%) versus 252/486 (52%), $p < 0.01$ – despite the mean age which was comparable between them.

At least 5 years later (average 8.2 years, range 5.0–10.3 years), 362 (39.7%) subjects again received medical examination [19]. Clinical diagnoses remained unchanged in the majority of asymptomatic carriers and in those found with chronic hepatitis at the time of blood donation (fig. 5). However, 5 patients with chronic hepatitis had developed HCC, including 4 men at the ages of 53, 62, 64 and 68 years and 1 woman at the age of 67 years. In addition, liver cirrhosis had elicited in 11 of the 214 (5.1%) blood donors who were found with chronic hepatitis and in 2 of the 146 (1.4%) who were asymptomatic carriers at the first examination. As a positive result, HCV infection had resolved by interferon (IFN) therapy in 42 blood donors with chronic hepatitis C; they would never have received IFN, if the HCV infection had not been found at the time when they wished to donate blood. In addition, 6 of the 146 (4%) asymptomatic carriers cleared HCV infection during 5 years or longer. Five subjects resolved the infection by IFN, and the remaining one spontaneously; he might have been acutely infected with HCV and clearing it when he visited the blood center for donation.

Simulating the Natural History of HCV Infection in Asymptomatic Carriers by the Markov Model

The prospective study on blood donors who were found with HCV has unfolded liver disease advancing in some of them [19]. In order to plan the strategy to deal with inapparent HCV infection, it is necessary to foresee when and what will happen how frequently in asymptomatic carriers. However, the natural history of HCV infection is hard to define. As is evident in their wish to donate blood, subjects found with HCV infection were utterly unaware of it. The time when HCV infection was contracted is unknown in most carriers, except in those with

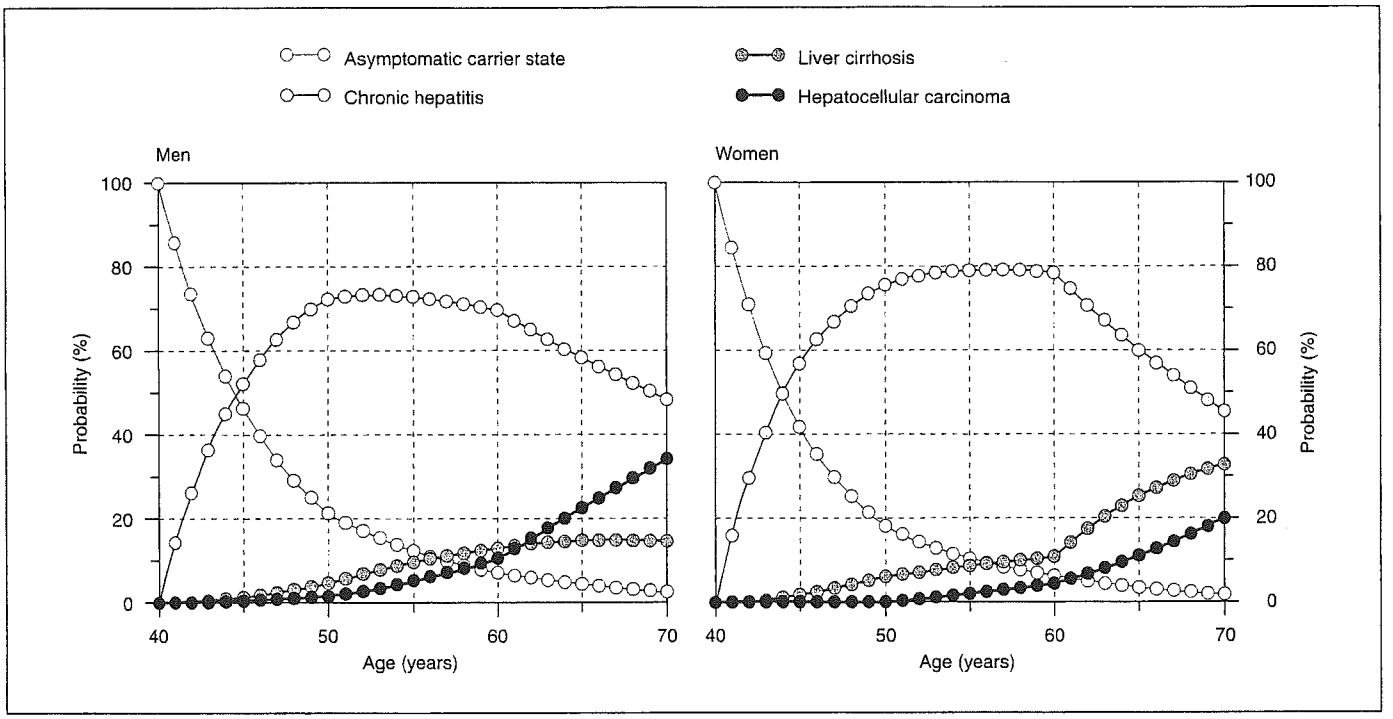

Fig. 6. Simulation of clinical courses of imaginary cohorts of 40-year-old male and female asymptomatic HCV carriers during 30 years by the Markov model [modified from ref. 21].

a history of transfusion or blood products by which they may have been infected. Since it takes decades until cirrhosis and HCC develop after HCV infection, doctors can hardly see through the entire history of their patients. Furthermore, it is unethical and not permitted to observe patients without any treatment at present.

The Markov model is powerful for simulating the natural history of chronic disease [20]. First, probabilities of transitions between any two clinical states within a cycle (usually a year) are assessed by the observation of a limited number of patients who have been followed regularly and rigorously for only a few to several years. Then, the natural history through many years is simulated in imaginary cohorts by integrating all probabilities for each transition per year that are multiplied successively for years elapsed. We have simulated the natural history of HCV infection in men and women by the Markov model [21]. Probabilities for transition per year between any of four clinical states (the asymptomatic carrier state, chronic hepatitis, cirrhosis and HCC) were calculated on 2,251 person-years from 942 patients with HCV infection who had been rigorously examined at least every year. HCC or death was defined as the absorbing state from where no transitions occur.

Based on the transition matrix constructed, the cumulative probability for developing chronic hepatitis, cirrhosis and HCC during 30 years was simulated on a hypothetical cohort of men and women who are found to be asymptomatic HCV carriers at the age of 40 (fig. 6). Of male asymptomatic carriers who enter their fifties, chronic hepatitis is estimated to develop in 72.4%, cirrhosis in 4.6% and HCC in 1.5%; 10.6% are expected to have HCC when they become 60 years old. In contrast, of female asymptomatic carriers who enter their fifties, chronic hepatitis is estimated to develop in 75.9% and liver cirrhosis in 6.2%, but HCC in none. HCC is expected to elicit only in 4.5% of female asymptomatic carriers at the age of 60, with a probability much less than 10.6% in male asymptomatic carriers. There is a steep rise in the cumulative probability for developing HCC in males in their sixties, and it reaches 34.4% at the age of 70, which is higher than that for liver cirrhosis at 14.6%. Although the cumulative probability for developing HCC increases in females reaching 70 years of age, it remains 20.0% and is much lower than that for liver cirrhosis at 32.8%.

The ability of this Markov model in predicting the clinical outcome of HCV infection was evaluated by comparing the results of 5-year follow-ups in 70 men and 83

women with those simulated by it [21]. The results were in good agreement, thereby attesting to the reliability of this model in predicting the natural history of HCV infection in asymptomatic carriers and patients with chronic hepatitis.

Efficient Screening of Individuals with Persistent HCV Infection in the General Population

There are two groups of individuals who test positive for anti-HCV. Subjects in the first group have ongoing infection with HCV RNA in serum, while those in the second group already have cleared infection without serum HCV RNA. Hence, nucleic acids need to be extracted from sera of subjects with anti-HCV, amplified by polymerase chain reaction, also known as nucleic acid amplification test (NAT), with primers deduced from the nucleotide sequence commonly expressed by HCV isolates of any genotypes, and examined for amplification products. However, this is by no means easy, demanding high cost, labor and equipment. Hence, polymerase chain reaction for detecting HCV RNA is not suitable for mass screening of ongoing HCV infection on a national scale.

We have invented a method to efficiently and sensitively screen ongoing HCV infections at low costs. The method takes advantage of the titer of anti-HCV that is higher in individuals with ongoing infection than in those who have cleared HCV infection. The bottom of anti-HCV titers over which HCV RNA can coexist and the ceiling below which HCV RNA is absent can be determined on the panel of anti-HCV-positive sera with or without HCV RNA; however, there is an inevitable grey zone in between. The flow chart depicted in figure 7 retains the benefit of this method, compensates for uncertainties given rise to by the grey zone and avoids missing rare sera with low-titered anti-HCV accompanied by HCV RNA.

First, sera of examinees are tested for anti-HCV, and those which are negative are regarded without HCV RNA and not tested further. The anti-HCV immunoassay has been calibrated for three categories of positive results: (1) high titers for the presence of HCV RNA, (2) low titers that can be very rarely accompanied by HCV RNA and (3) medium titers in the grey zone that may or may not co-occur with HCV RNA. Sera with high-titered anti-HCV are deemed to contain HCV RNA and are not examined any further. Although extremely exceptional sera with high-titered anti-HCV do not contain HCV RNA,

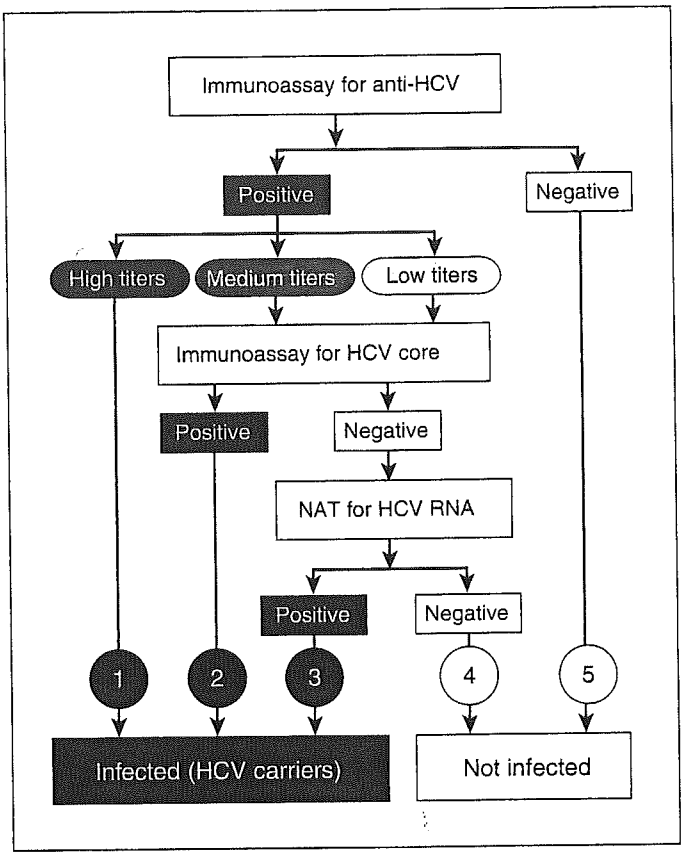

Fig. 7. Strategy for the national screening for persistent HCV infection in Japan with immunoassays for anti-HCV as well as HCV core protein combined with NAT.

we consider false-positive results far more acceptable than false-negative results in judging HCV infection and staying on the safe side. Sera with medium-titered or low-titered anti-HCV are then screened by immunoassay for HCV core antigen; it is easier and less costly than NAT for HCV RNA. If HCV core antigen is detected in the test serum, it indicates ongoing HCV infection, which is theoretically justifiable, and is not tested by NAT. Finally, NAT is performed on all sera with low- and medium-titered anti-HCV, including those that are negative for HCV core antigen. All sera fall into one of the five categories at the bottom of figure 7, of which three (1–3) indicate the presence of ongoing HCV infection and the remaining two (4 and 5) the lack of it. Examinees receive this chart with a mark on one of the categories 1–5 to let them know where they stand.

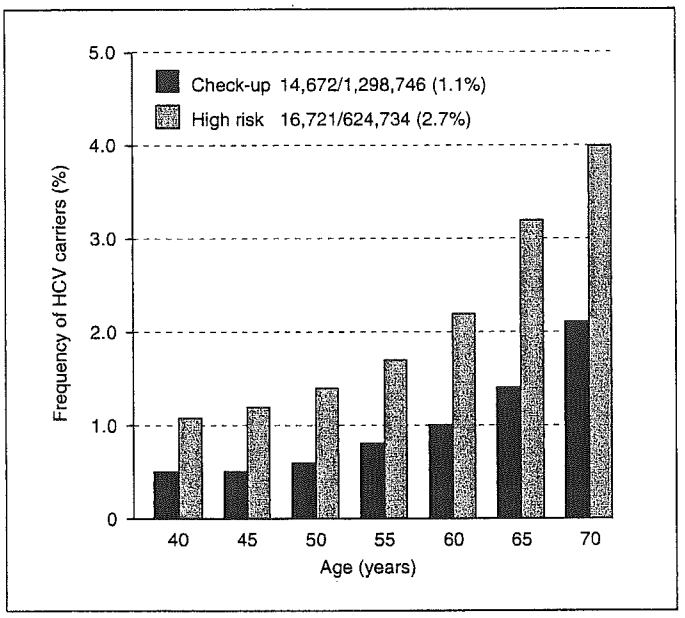

Fig. 8. Age-specific distribution of persistent HCV infection in Japan determined by the national screening during the first fiscal year (April 2002 to March 2003). HCV carriers identified among examinees at regular health check-ups and individuals at high risk, who were stratified by age, are shown separately.

A Nation-Wide Project to Spot HCV Carriers Older than 40 Years in Japan

A 5-year project for screening the Japanese for ongoing HCV and HBV infections on a national scale was launched in April 2002 [19]. It has been performed on two distinct populations. Health check-ups are offered to the Japanese every 5 years when they become 40 years old until they reach 70 years of age. Therefore, by screening health check examinees for 5 years, all carriers of hepatitis viruses who are aged 40 years or older can be identified by March 2007. Thereafter, each year, only individuals who reach 40 years of age need to be screened. This project is based on an extremely low incidence of de novo infection with HCV or HBV in Japan [14], which makes it sufficient to screen for these hepatitis viruses only once in the lifetime.

Subjects who cannot wait for the screening for HCV infection at regular health check-ups, because of an urgent requirement for it, are provided with a chance to receive it at least once. They include individuals at high risk for HCV infection: (1) those who were found with abnormal liver function in the past; (2) those who may have received transfusion with blood or its products before 1992 at a major operation or because of massive hemorrhage at delivery, which had not been screened for anti-HCV by the second-generation immunoassay, and who are not regularly monitored for their liver function; and (3) those in whom liver function tests gave abnormal results at regular examination which they receive in clinics of their companies and institutions. Individuals older than 70 years and off regular health check-ups are tested for virus markers if they wish.

The Ministry of Health, Labour and Welfare of Japan has reported results of the national screening project in the first fiscal year from April 2002 to March 2003. Of the 3,212 municipalities in Japan, 2,997 (93.3%) started this project with a good compliance. The Department of Welfare for the Aged compiled results in the first fiscal year and registered 1,923,480 examinees, of whom 31,393 (1.6%) were found with ongoing HCV infection. There were 1,298,746 examinees at regular health check-ups and 14,672 (1.1%) were found to be HCV carriers. In comparison, of 624,734 high-risk subjects who received tests on other occasions, 16,721 (2.7%) were found with ongoing HCV infection, at a frequency twice as high as that in health check examinees. The results are shown for both groups, stratified by age (fig. 8). HCV carriers were found in 3.2 and 1.3% of the individuals aged 65 at high risk and those examined at check-ups and more often in those aged 70 years, at 4.0 and 2.1%, respectively.

Figure 9 illustrates the results of persistent HCV infection in examinees of regular health check-ups and individuals at high risk from the 48 jurisdictions in Japan. Without exception, the prevalence of persistent HCV infection is higher in individuals at high risk than in health check examinees. Additionally, there is an apparent gradient in the persistent HCV infection from the southwest to the northeast of Japan; the gradient mirrors that of blood donors in the 8 jurisdictions of the Japanese Red Cross Blood Center (fig. 2).

Projection of HCC in Japan to Other Countries toward the Future

The age-specific prevalence of HCV infection in the year 2000 is compared among Japan, Ukraine and the United States (fig. 10a). It is based on 275,868 blood donors in Hiroshima for Japan, 41,021 blood donors in Kiev for Ukraine and data reported by the Center for Disease Control and Prevention for the United States. The age with the highest prevalence of anti-HCV is markedly different among the three countries. The prevalence

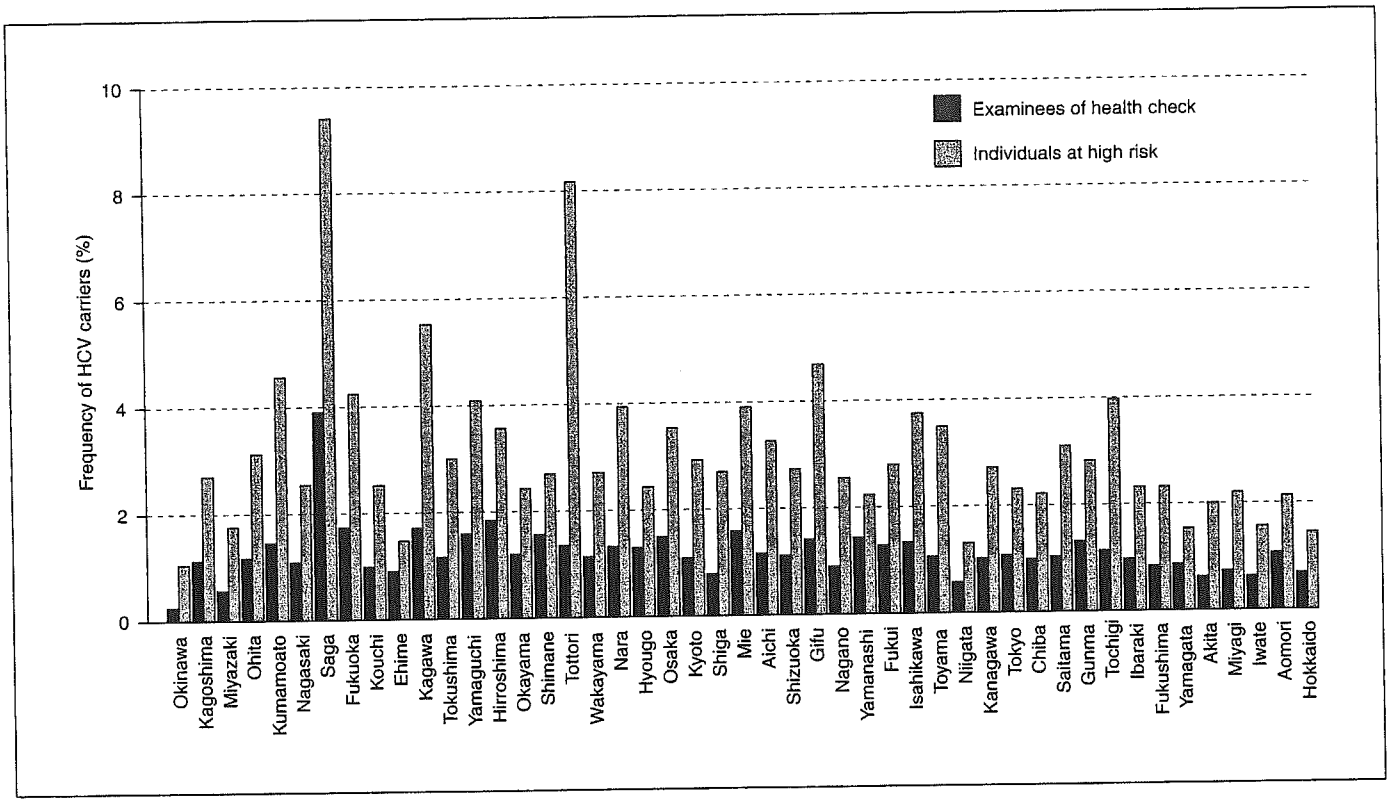

Fig. 9. Distribution of persistent HCV infection in examinees at regular health check-ups and individuals at high risk from the 48 jurisdictions in Japan detected by the national screening during the first fiscal year. The 48 jurisdictions are ordered from southeast on the left to northeast on the right.

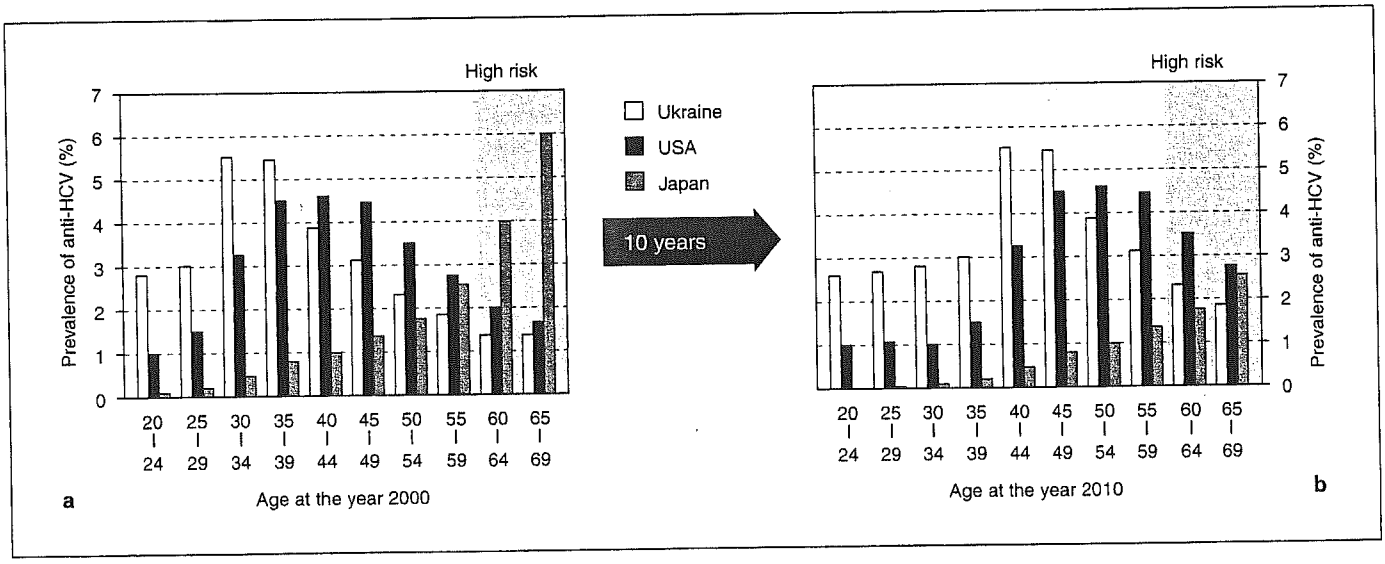

Fig. 10. Age-specific profiles of HCV infection in Japan, the United States and Ukraine. Distributions in the year 2000 (**a**) and those expected in the year 2010 (**b**) are shown.

of anti-HCV steeply increases with age in Japan; the highest is expected in the elderly who scale out of the figure. In contrast, the highest prevalence of anti-HCV is positioned at 40–44 years in the United States, and even younger at 30–35 years in Ukraine.

These wide differences in the age at which anti-HCV peaks among the three countries are attributed to distinct time points when HCV spread extensively among each population. In Japan, HCV infection infiltrated in the subpopulation of younger generations during the 1950s and 1960s in a vicious cycle, but almost completely ceased to occur since 1990 [14]. About two decades later, from the 1970s to the early 1980s, HCV infection widely diffused in the United States; the yearly incidence decreased from 230,000 in the 1980s to 38,000 in the 1990s [22]. More recently, during the late 1980s and the 1990s, HCV infection started to spread in Ukraine and has continued to invade younger generations.

It is of note that the national diffusion of HCV infection is triggered and accelerated by defeats in wars in all the three countries. They are the World War II in Japan, the Vietnam War in the United States and the Afghan War in Ukraine, all of which created a national turmoil and stimulated desperation predominantly in younger generations. What we find in the age-specific distribution of anti-HCV in the three countries at present are long-term sequelae of the wide spread of HCV infection around a major war that are shifting with time.

Age-specific distribution of anti-HCV expected in the year 2010 is depicted by shifting the present profile 10 years toward the future (fig. 10b). In Japan, with essentially no new infections, HCV carriers in their sixties will decrease. On the contrary, many individuals infected with HCV in the United States will go into their sixties along with substantial cases of HCC developing in them. The same will happen in Ukraine after an additional 10 years, which can be projected by the current age-specific prevalence of HCV infection. Should that be the case, these countries are going to follow the profile we have for HCC associated with HCV infection in Japan, with time lags of 10 and 20 years, respectively.

Conclusion

HCC is a rare cancer that is easily preventable. Individuals at high risk for developing HCC are infected with HCV or HBV, of which HCV is more universal, and they are readily identified by viral markers. It is imperative that carriers realize that they are infected with HCV, since the majority are unaware of it. Then, they can consult their present status with hepatologists and receive antiviral treatment for terminating the infection as indicated. HCV carriers who cannot clear infection are regularly followed for liver disease, and those with chronic hepatitis or cirrhosis are screened for HCC at appropriate intervals by noninvasive methods, such as ultrasonography and computed tomography, as well as tumor markers like α-fetoprotein and protein induced by vitamin K absence or antagonist-II. They need to be advised to abstain from alcohol in order to decrease the development of HCC. Antiviral and anti-inflammatory therapies are found effective in decreasing the incidence of HCC, even in patients who fail to clear HCV. Due to an extremely wide variation in the progression of liver disease and the incidence of HCC in HCV carriers, it is imperative to handle the situation on a national basis, as we are conducting in Japan. Efforts will be rewarding, with much less morbidity and mortality caused by HCV infection, and will immensely lessen the economical burden on the nation. Hopefully, interim results of our 5-year national project for spotting HCV carriers in Japan will encourage similar efforts elsewhere in the world where HCV-associated HCC is reasonably expected to increase.

Acknowledgements

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永井書店

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肝臓の臨床最前線

Key words　HBV　HCV　キャリア率　推計キャリア数　肝臓がん

わが国における悪性新生物による死亡を部位別にみると「肝」(肝および肝内胆管の悪性新生物，人口動態統計[1])による死亡実数は，1995年に初めて年間3万人を上回り，2002年には死亡数34,637人と，肺がん(56,405人)，胃癌(49,213人)に次いで第3位の位置を占めるに至っている．また，人口10万人あたりの肝がんによる死亡率の推移をみると，1975年から増加の一途を辿り，2002年には全体では27.5人となり，特に男性では38.7人と女性(16.8人)に比べ2倍以上の高い値を示している(図1)．

日本肝癌研究会による調査成績[2]および人口動態統計資料[1]をもとに算出した，成因別にみた肝がん死亡の推移をみると，1978年以降，現在に至るま

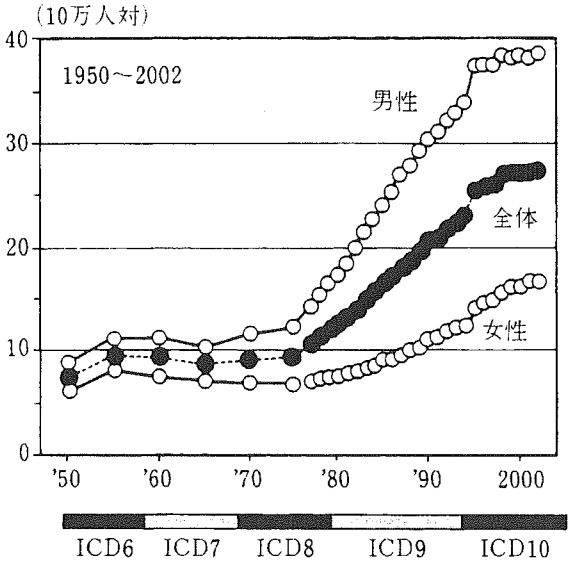

図1　わが国における肝がんによる死亡の推移

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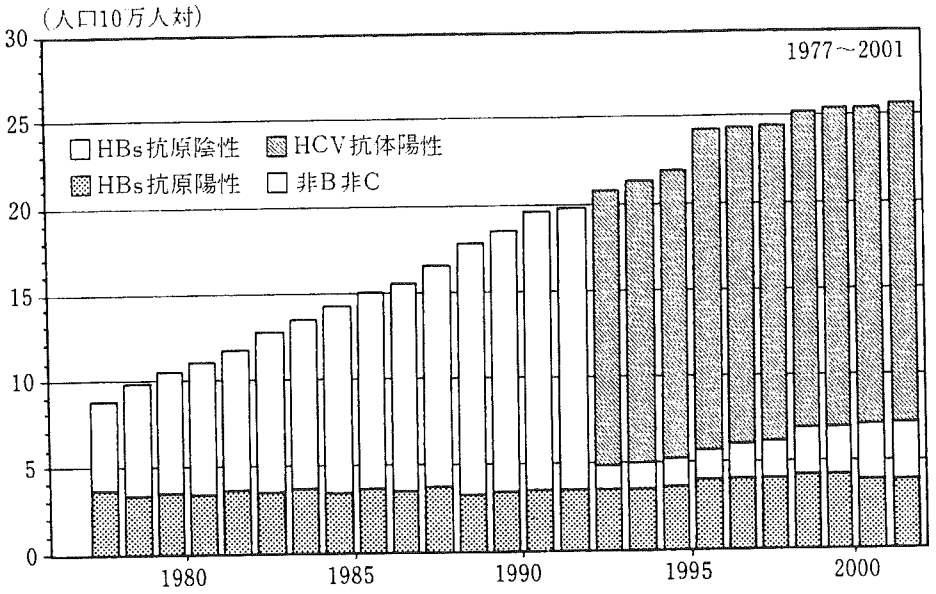

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図2　わが国における成因別肝細胞がん死亡の推移

で，B型肝炎ウイルス(HBV)の持続感染に起因する肝がん(B型の肝がん)は増減がないままで(人口10万人対3～4人)推移しており，わが国で増え続けている肝がんはHBVの持続感染によらない(非A非B型の)肝がんであることが明らかとなっている(図2)．C型肝炎ウイルス(HCV)感染の特異的な診断が可能になった1992年以降についてみると，非A非B型肝がんの95%以上はHCVの持続感染に起因する肝がん(C型の肝がん)であることが明らかになっている．

HBV感染については，その主な感染経路であった母子感染の予防が，1986年出生の児から全国規模で実施に移されたことにより，今年19歳を迎える集団を筆頭とする若年齢層におけるHBVキャリア率はきわめて低い値を示すに至っている[3,4]．

HCV感染については，過去10年余にわたる広汎な血清疫学的調査の結果，新たな感染によるHCVキャリアの発生は特別な場合[5]を除きほぼ止まっている状態にあること[6]，HCVキャリアの母親から出生した児への母子感染率は2.3%程度の低率に止まること[7]等も明らかとなっている．

これらの疫学的背景と近年の肝炎，肝がん治療の急速な進歩を背景に，わが国における肝がん死亡の減少を図る目的で，2002年4月から5年計画で地域住民を対象とした肝炎ウイルス検診(HBV，HCV)が全国規模で開始された．

Ⅰ．地域別にみた肝がん死亡の推移

1993年から2002年までの10年間における悪性新生物の「肝」(肝および肝内胆管の悪性新生物)による死亡率が高い順に10位までの県を表1に示す．

中国・四国・九州地域に位置する県が，10位以内にランクされる地域の7割を占め，近畿以西の