発表者氏名	論文タイトル名	発表雑誌	巻号	ﾍﾟｰｼﾞ	出版年
120) Nagao Y, Tanaka K, Kobayashi K, Kumashiro R, Sata M	Analysis of approach to therapy for chronic liver disease in an HCV hyperendemic area of Japan	Hepatol Res	28	30-35	2004
121) Kawaguchi T, Yoshida T, Harada M, Hisamoto T , Nagao Y, Ide T, Taniguchi E, Kumemura H, Hanada S, Maeyama M, Baba S, Koga H, Kumashiro R, Ueno T, Ogata H, Yoshimura A, Sata M	Hepatitis C virus down-regulates insulin receptor substrates 1 and 2 through up-regulation of suppressor of cytokine signaling 3	Am J Pathol	165	1499-1508	2004
122) 長尾由実子、佐田通夫	ウイルス性肝炎（上）-基礎・臨床研究の進歩-１Ｃ型肝炎ウイルス（HCV）HCV感染に起因する肝外病変　肝外病変の主要病態とその対処法　その他の肝外病変	日本臨床	62	561-568	2004
123) 長尾由実子、千葉逸朗、佐田通夫	歯学部並びに歯科衛生士学校の学生を対象に実施したＢ型及びＣ型肝炎に対しての意識調査	感染症学雑誌	78	554-565	2004
124) Nagao Y, Kawaguchi T, Ide T, Kumashiro R, Sata M	Exacerbation of oral erosive lichen planus by combination of interferon and ribavirin therapy for chronic hepatitis C	Int J Mol Med	15	237-241	2005
125) Kawaguchi T, Nagao Y, Tanaka K, Ide T, Harada M, Kumashiro R, Sata M	Causal relationship between hepatitis C virus core and the development of type 2 diabetes mellitus in a hepatitis C virus hyperendemic area: a pilot study.	Int J Mol Med	16	109-114	2005
126) Nagao Y, Kawaguchi T, Tanaka K, Kumashiro R, Sata M	Extrahepatic manifestations and insulin resistance in an HCV hyperendemic area.	Int J Mol Med	16	291-296	2005
127) 長尾由実子, 佐田通夫	HCVの肝外病変	医学のあゆみ	215	212-213	2005
128) 佐田通夫, 長尾由実子, 田中一雄	ウイルス肝炎からの発癌とその予防 HBc抗体は，HCV関連肝癌の発症に関与する：　HCV高感染地区で得られた知見	犬山シンポジウム記録		51-54	2005

発表者氏名	論文タイトル名	発表雑誌	巻号	ﾍﾟｰｼﾞ	出版年
129) Tanaka K, Nagao Y, Ide T, Kumashiro R, Sata M.	Antibody to hepatitis B core antigen is associated with the development of hepatocellular carcinoma in hepatitis C virus-infected persons: a 12-year prospective study.	Int J Mol Med	17	827-832	2006
130) Ohtsubo K, Oku E, Imamura R, Seki R, Hashiguchi M, Osaki K, Yakushiji K, Yoshimoto K, Ogata H, Nagamatsu H, Ando E, Shimamatsu K, Okamura T, Sata M	Simultaneous hepatic relapse of non-Hodgkin's lymphoma and hepatocellular carcinoma in a patient with hepatitis C virus-related cirrhosis.	Acta Haematol	116	266-271	2006
131) Wang Y, Takao Y, Harada M, Yutani S, Ide T, Sata M, Itoh K, Yamada A	New epitope peptides derived from hepatitis C virus (HCV) 2a which have the capacity to induce cytotoxic T lymphocytes in HLA-A2+ HCV-infected patients.	Microbiol Immunol	50(11)	857-865	2006
132) Murashima S, Tanaka M, Haramaki M, Yutani S, Nakashima Y, Harada K, Ide T, Kumashiro R, Sata M	A decrease in AFP level related to administration of interferon in patients with chronic hepatitis C and a high level of AFP.	Dig Dis Sci	51(4)	808-812	2006
133) 長尾由実子, 佐田通夫	肝癌の発症予防–その対策と治療–	筑紫医師会報	30(3)	41-45	2006
134) 長尾由実子, 佐田通夫, 鈴木史雄, 野林晴彦, 川上裕	C型肝炎ウイルス持続感染者に対する薬物療法-インターフェロン療法の普及とその現状-	政策研ニュース	19	21-23	2006
135) 長尾由実子、佐田通夫、鈴木史雄、野林晴彦、川上裕	優れた薬物療法のさらなる普及をめざして –C型肝炎ウイルス感染者におけるインターフェロン療法の受療の現状と考察–	リサーチペーパーシリーズ	32	1-81	2006
136) Homma M, Matsuzaki Y, Inoue Y,Shibata M, Mitamura K,Tanaka N,Kohda Y	Marked Elevation of Erythrocyte Ribavirin Levels in Interferon and Ribavirin-Induced Anemia	Clinical Gastroen-terology And Hepatology	2	337-339	2004
137) Hakamada T,Funatsuki K,Morita H, Ugajin T,Nakamura I,Ishiko H,Matsuzaki Y,Tanaka N, Imawari M	Identificatoin of noval hepatitis C virus-specific cytotoxic T lymphocyte epitopes by ELISpot assay using peptides with human leukocyte anitigen-A 2402-binding motifs	Jounal of General Virology	85	1521-1531	2004

発表者氏名	論文タイトル名	発表雑誌	巻号	ﾍﾟｰｼﾞ	出版年
138) 松崎靖司　他	肝硬変・肝細胞癌への進行を防ぐために慢性C型肝疾患患者のフォローアップ戦略	消化器の臨床	別冊8(2)	209-217	2005
139) Chiba T,Tokuuye K,Matsuzaki Y,Sugahara S, Chuganji Y, Kagei K, Shoda J,Hata M, Abei M,Igaki H, Tanaka N,Akine Y	Proton Beam Therapy for Hepatocellular Carcinoma:A Retrospective Review of 162 Patients	Clin Cancer Res 2005	11(10)	3799-3805	2005
140) Miyazaki T,Karube M,Matsuzaki Y,Ikegami T,Doy M,Tanaka N,Bouscarel B	Taurine inhibits oxidative damage and prevents fibrosis in carbon tetrachloride-induced hepatic fibrosis	Jounal of Hepatology	43	117-125	2005
141) Ikegami T,Matsuzaki Y,Fukushima S, Shoda J,Olivier JL,Bouscarel B,Tanaka N	Suppressive Effect of Ursodeoxycholic Acid on Type IIA Phospholipase A2 Expression in HepG2 cells	Hepatology	41(4)	896-905	2005
142) Matsuzaki Y	Alcohol abuse and occult HBV-a risk factor for hepatocellular carcinoma(Editorial)	Hepatol Res	31	69-72	2005
143) 池上正、松崎靖司	基礎知識　薬剤師から専門家への質問　病期の進展度と肝炎の活動度は何が違います？また、どの検査データからわかるのでしょうか？	薬局	57(12)	14-18	2006
144) 松崎靖司　他	非切除治療の適応と、その進め方　放射線治療(陽子線治療)をどう行うか 現況と展望	臨床腫瘍ﾌﾟﾗｸﾃｨｽ	2(4)	391-397	2006
145) 松崎靖司、徳植公一	肝細胞癌に対する陽子線、炭素線照射療法–重荷電粒子線療法の現状と適応–	肝胆膵	53(5)	895-901	2006
146) Inoue Y, Homma M, Matsuzaki Y, et al	Erythrocyte ribavirin concentration for assessing hemoglobin reduction in interferon and ribavirin combination therapy.	Hepatol. Res.	34(1)	23-27	2006

IV. 研究成果の刊行物

【書　　籍】

INTERNATIONAL KILMER CONFERENCE PROCEEDINGS

Volume VIII

Editors:

John B. Kowalski, Ph.D.
Robert F. Morrissey, Ph.D.
Johnson & Johnson
Sterilization Science & Technology
U.S.A.

Johnson & Johnson

Eighth International Kilmer Memorial Conference

Osaka, Japan
2003

Endorsed by
Japanese Ministry of Health, Labor, and Welfare
Japanese Society of Medical Instrumentation

ISBN 0-921317-57-3

Polyscience Publications Inc.
Laval, Canada

Printed in Canada

A National Project for the Management of Viral Hepatitis toward Prevention of Hepatocellular Carcinoma in Japan

Hiroshi Yoshizawa, M.D. and Junko Tanaka, Ph.D.

Hiroshima University Graduate School of Biomedical Sciences, Japan

Introduction

In Japan, deaths due to hepatocellular carcinoma (HCC) numbered 9,442 in 1970 and increased by 3.7-fold to 34,637 in 2002. HCC ranks third among malignancies in Japan, next only to lung cancer (56,405) and stomach cancer (49,213). Approximately 93% of HCC is caused by hepatitis viruses, including hepatitis B virus (HBV) and hepatitis C virus (HCV); the etiology is unknown for the remainder of cases [26]. Although cases of HCC due to HBV infection have been constant since 1970, those attributed to HCV infection keep increasing and amounted to 81% in 2002.

By far the majority of HCC cases develop in the background of fibrosis and cirrhosis in the liver as sequelae of chronic necro-inflammation induced by HBV or HCV infection. Most cases of HCC caused by persistent HBV infection present in individuals in their early 50's, while HCC caused by persistent HCV infection present somewhat later in the late 50's to early 60's [26]. These distributions reflect carriers of HBV and HCV who cluster in the cancer-baring ages (40's, 50's, and 70's) in Japan.

To cope with escalating rates of HCC due to hepatitis virus infections, a national project was started in Japan in April 2002, targeting individuals aged 40 years or older. It is based on information regarding seroepidemiology of persistent HCV infection combined with epidemiological profiles of HCC. Additionally, it is aided by recent remarkable advances in the diagnosis of HCC by means of imaging modalities, such as ultrasonography, computed tomography, and angiography, as well as tumor markers like alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA-II: also known as DCP [des-γ-carboxyl prothrombin]). An increased life expectancy of patients with HCC by virtue of markedly improved treatments would make this project rewarding as well.

In this review, we will focus on: (1) the seroepidemiology of persistent HCV infection and HCC induced by this infection; (2) present status and achievements of a national program in the management of HCV infection aimed at preventing HCC; and (3) imminent issues that have surfaced during the first year of national screening and recommendations for going forward.

Shifting Patterns of HCC in Japan during the Past 50 Years

In Japan, the outbreak of HCV infection occurred some 50 years ago during the chaos that surrounded the termination of World War II [26]. The Japanese are now facing long-term ramifications of this HCV epidemic as seen by the surge in deaths due to HCC in recent years which as shown in Figure 1, is breathtakingly evident. Mortality attributable to HCC started to increase in 1975, and numbers 27.1/100,000 population per year at the latest survey in 2001. An abrupt rise in the number of HCC cases in 1993 is attributed to changes in the diagnostic criteria identified by the WHO International Classification of Diseases (ICD), from ICD9 to ICD10 in that year. Men suffered from HCC 2.3 times more frequently than women at the last survey. Furthermore, deaths due to HCC in men have almost quadrupled in remarkable contrast to those in women where the death rate has doubled. Thus, the speed at which HCC has increased in men is twice that seen in women.

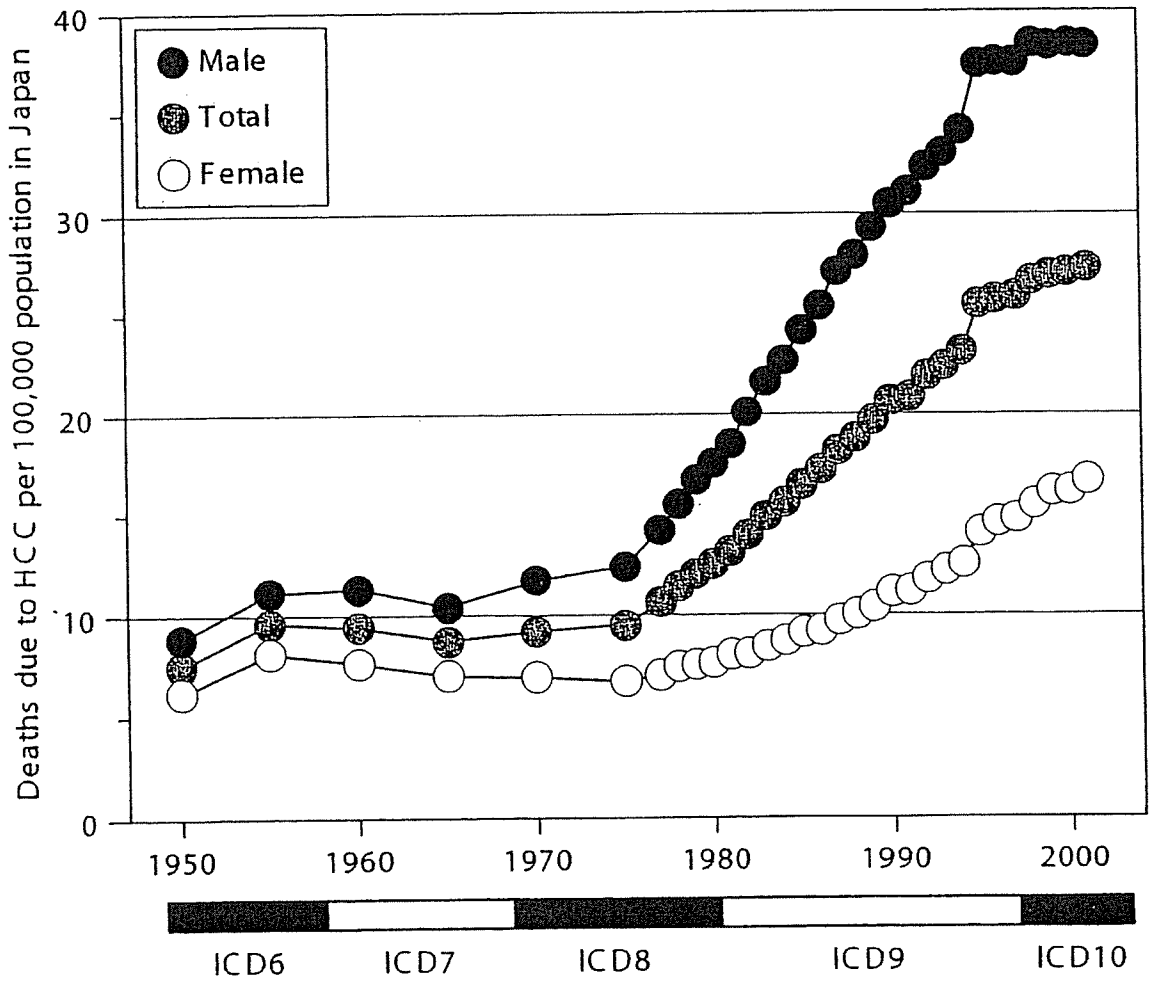

Figure 1. Increasing deaths due to HCC in Japan during the past 50 years (modified from Reference 26 with addition of recent data).

Shifting causes of deaths due to HCC during the past 20 years are illustrated in Figure 2. Unlike most countries in Asia and Africa where persistent HBV infection has been the leading cause of HCC, deaths due to HBV infection have stayed almost the same throughout the past 2 decades. HCC categorized as due to Non-A, Non-B viral infection surfaced at the same time but kept increasing. As the serological diagnosis of HCV infection became feasible in 1990 [13] in the immediate wake of the landmark discovery of HCC by Choo *et al.* in 1989 [4], most HCC of a Non-A, Non-B etiology has turned out to be induced by persistent HCV infection. There remain, however, approximately 10% of HCC cases in Japan for which etiology is not ascribed to persistent infection with HBV or HCV, and henceforth these cases are classified as Non-A, Non-B, Non-C.

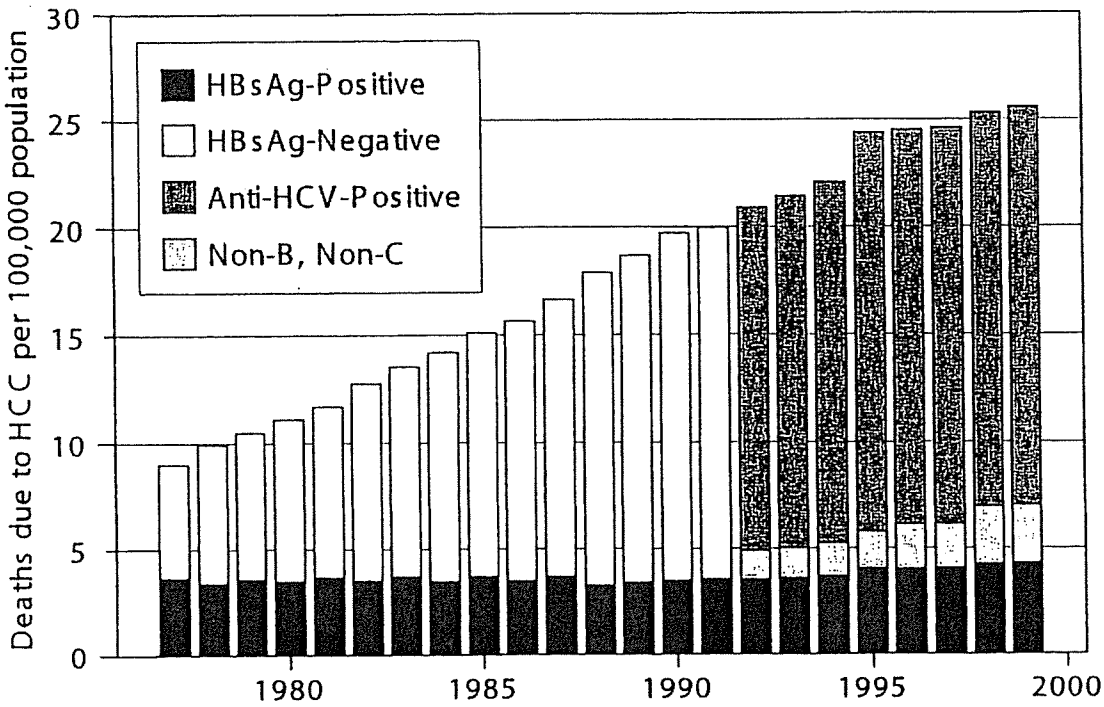

Figure 2. Causes of HCC shifting with time in Japan (modified from Reference 26 with addition of recent data).

Due to an iatrogenic nature of the transmission of HCV, its distribution in the world is extremely uneven [5]. Even in the same country, HCV tends to prevail more in inhabitants of urban districts compared to rural regions. Even in Japan, there are marked differences in the prevalence of persistent HCV infection. An increasing gradient in the frequency of HCC from northeast to southwest along the axis of the Japanese Islands was noted some time ago. Thus, deaths due to HCC in excess of 30/100,000 population per year occur only in southeastern prefectures, represented by those in Shikoku and Kyushu Islands. Yamanashi

in the eastern part of Japan is a single exception with 31.7 deaths of HCC per 100,000 population per year. The mass treatment of *Scistosomiasis japonicum* with intravenous injection since 1982 is implicated in the local spread of HCV there. As the incidence of HCC increased, over time the distribution of HCC has become more diffused over Japan.

Figure 3 compares the distribution of HCC in men between the mid-1970s and the new millennium. The distribution of HCC was fairly even throughout Japan in 1995, although scattered districts with a high rate of deaths due to HCC stood out in the south coast of Kyushu Island. Although the hardest hit areas have remained the same throughout the last 30 years, the distribution became more uneven in the survey taken in 2001. Thus, northern Kyushu, Hiroshima in the west of Honshu Island, and districts surrounding Setonaikai basin with Osaka on the coast of Honshu, as well as Yamanashi in the center of Honshu, became most strongly infiltrated with HCC.

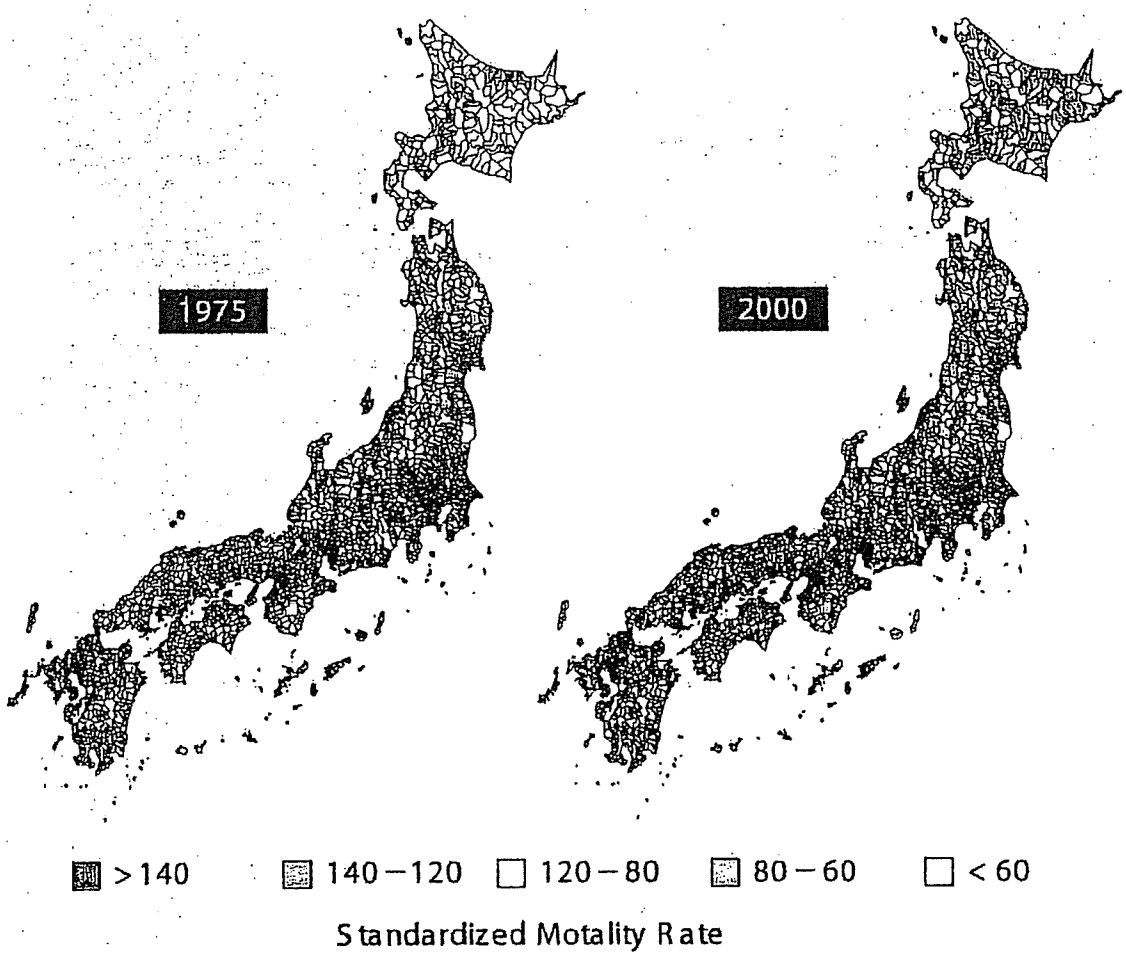

Figure 3. Changes in the distribution of deaths due to HCC in men during the past 30 years in Japan. These maps were produced by Dr. Yoshihiko Mirua of Saitama Prefectural University.

Prevalence of Persistent HCV Infection in Japan

Volunteer blood donors are the best population for estimating the prevalence of persistent infections with any microbe, including HBV and HCV, although they may not faithfully mirror national sex and age distributions. Since blood donors found to have ongoing HBV or HCV infection in previous donations have been deferred from future donation, first-time blood donors need to be tested for avoiding sampling and selection biases. Figure 4 illustrates the age-specific prevalence of antibody to HCV (anti-HCV) in 3,485,648 Japanese individuals who donated blood for the first time during a 6-year period from January 1995 to December 2000 [23]. For convenience of comparison, the ages of blood donors were extrapolated to those in the year 2000. The prevalence of anti-HCV was very low in the blood donors younger than 30 years, but stayed rather high, around 1.5%, in those up to 45 years of age, and started to increase at the age of 50. From that point on, anti-HCV prevalence increased almost exponentially and exceeded 10% among cohorts in their late 60's.

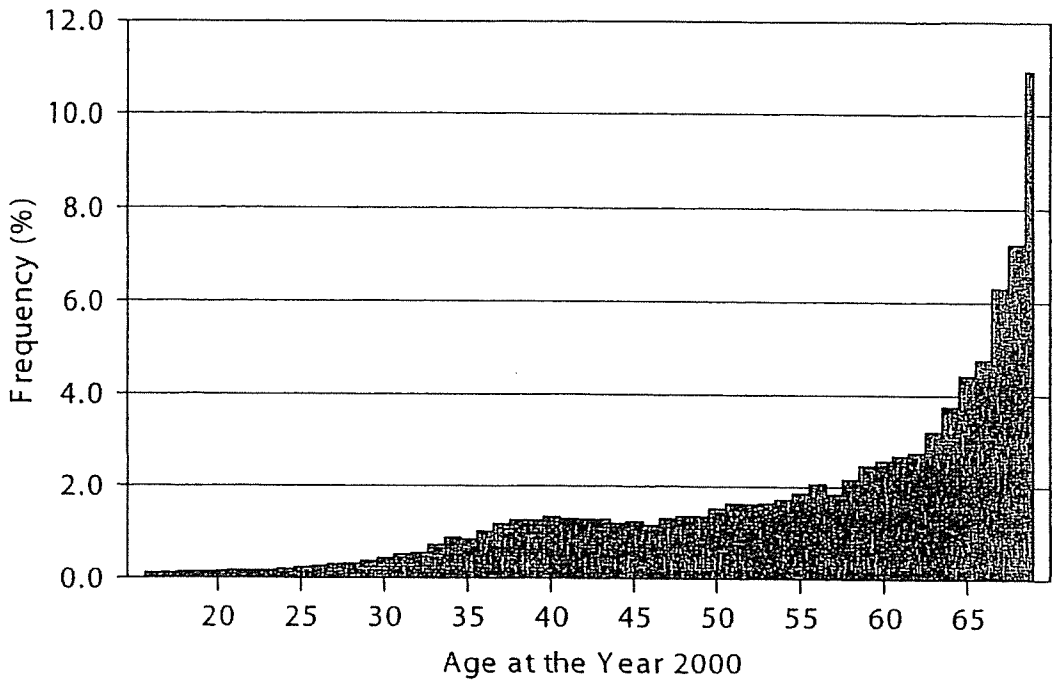

Figure 4. Age-specific prevalence of anti-HCV in a large-scale survey on the first-time blood donors in Japan (reproduced from Reference 23 with permission).

Figure 5 depicts age-specific distributions of anti-HCV in first-time blood donors across the Japanese Islands [23]. Although the pattern of increasing prevalence of anti-HCV with age was maintained in the first-time blood donors at each of the 8 jurisdictions of Japanese Red Cross Blood Centers, there were some differences in the magnitude of HCV diffusion that are reflected in the prevalence of anti-HCV among them. This is most evident in the highest prevalence group –

blood donors in their 60's – where anti-HCV prevalence rates ranged widely from 2.3% in the Chubu/Tokai district to 5.0% in the Chugoku district. Anti-HCV prevalence rates in this age group were also high in the Kyushu, Kinki, and Shikoku districts. These differences in HCV infection are mirrored in the distribution of deaths due to HCC in Japan in recent years (Figure 3).

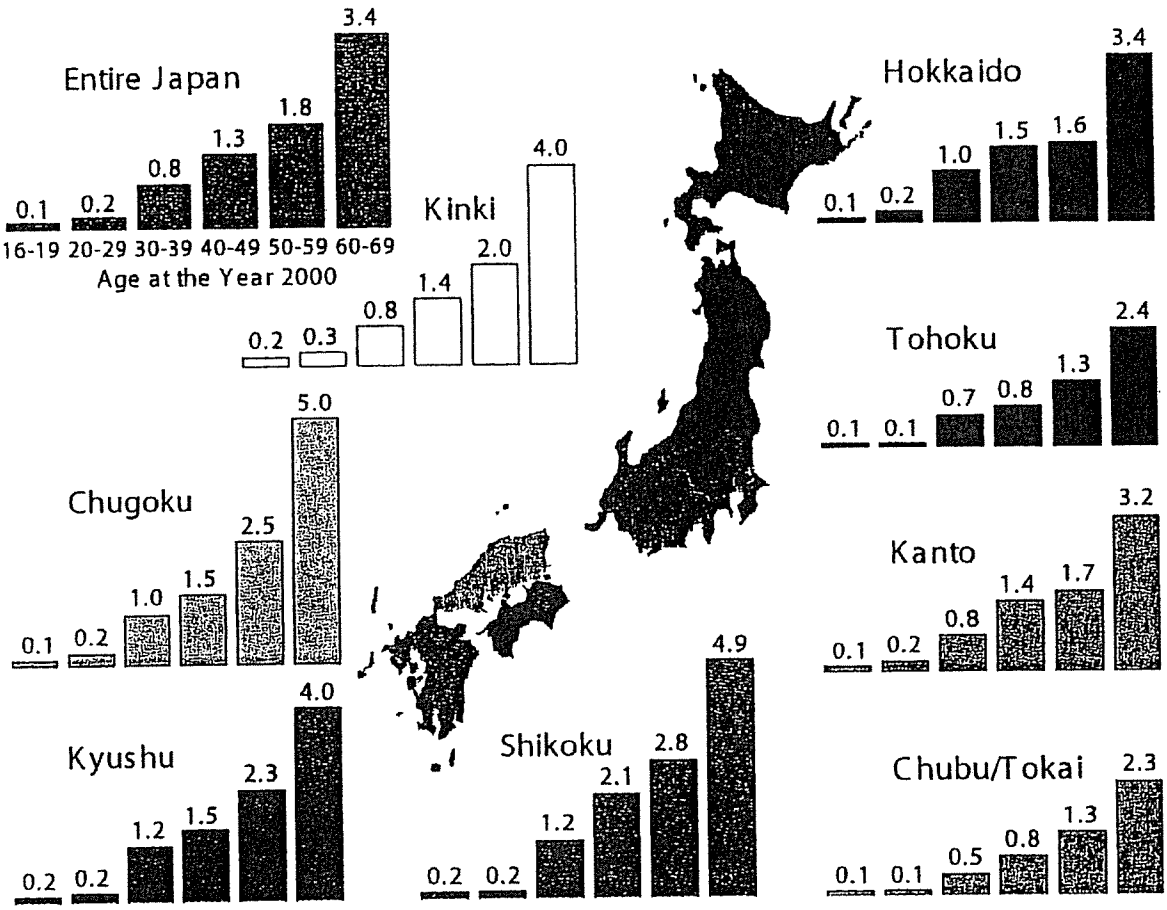

Figure 5. Age-specific distributions of anti-HCV in the first-time blood donors at the 8 jurisdictions of Japanese Red Cross Blood Centers (reproduced from Reference 23 with permission).

The pattern of age-specific anti-HCV in Japan reflects the exposure to HCV in the past and suggests that de novo HCV infection would be rare. This has been proven in prospective studies on different populations in various districts in Japan [26]. The incidence of HCV infection in blood donors was very low and ranged from 1.8/100,000 person-years in Hiroshima during 1988-1992 to 3.4/100,000 person-years in Osaka during 1992-1997. The incidence of HCV infection was also low in company employees (0 in 3,079 during 1992-1995) as well as among patients in mental health institutions and elderly in nursing homes (combined: 0 in 678 during 1992-1995) who are at increased risk for viral infections. Hence, horizontal transmission of HCV has been contained in Japan and only rarely are there new cases nowadays.

With regards to perinatal HCV transmission, only 2 of the 86 babies (2.3%) born to carrier mothers were infected [15]. This incidence is on par with that of mother-to-baby transmission of HBV of less than 3 to 4% for babies born to mothers expressing hepatitis B e antigen in serum [11,17]. The rarity of mother-to-baby transmission of HCV is reflected in the extremely low prevalence of anti-HCV in infancy; it was detected in merely 240 of the 400,000 (0.06%) children aged less than 6 years [26]. Hence, there are no pressing needs for taking measures to cope with the mother-to-baby transmission of HCV.

The incidence of post-transfusion HCV infection has decreased to practically nil since screening of blood donors by the second-generation immunoassay for anti-HCV was introduced in 1992 [26]. The remaining risk has been reduced further by the introduction of nucleic acid amplification testing (NAT) that has been in place since October 1999 [16]. HCV rarely, if ever, transmits by sexual contact, unlike HBV for which this mode of transmission occurs frequently. Fortunately, illicit intravenous drug use is still very infrequent among the Japanese youth. Each of these factors have contributed to a very low incidence of new HCV infection in Japan, which is exceptional for developed countries.

Clinical Courses of HCV Infection

The prevalence of anti-HCV in first-time blood donors increases sharply with age (Figures 4 and 5) [23], which represents the long-term sequelae of exposure to HCV in the distant past that was accelerated by a number of factors [26]. Insofar as *de novo* HCV infection is contained in Japan, the age-specific prevalence of anti-HCV will keep shifting toward the elderly in the future. Because HCC in Japan occurs predominantly in HCV carriers older than 50 years of age, deaths due to HCV-associated HCC will likely plateau around 2000–2010 and decrease thereafter.

We are left with an estimated 880,000 HCV carriers older than 40 years [23], however, who are at increased risk of developing HCC. How soon and how often this group develops HCC is our utmost concern. Figure 6 illustrates clinical diagnoses among the 912 HCV carriers who were identified at the time of blood donation in Hiroshima. Surprisingly, approximately two-thirds of them have already developed chronic hepatitis and only one-third were without clinical liver disease. Furthermore, liver cirrhosis was detected in 5 carriers (0.5%) and HCC in 1 (0.1%). In a prospective study, 362 of this cohort received a second medical examination at least 5 years later (average 8.2 years [range: 5.0 to 10.3 years]) (Figure 7). Clinical diagnoses remained unchanged in most of this group. However, 4 men and 1 woman had developed HCC at the ages of 62, 63, 64, 68, and 67 years, respectively. In addition, liver cirrhosis had emerged in 11 of the 214 (5.1%) blood donors who were originally found to have chronic hepatitis, and in 2 of the 144 (1.4%) who were without clinical illness at the outset. Notably, HCV infection resolved through the use of interferon therapy in 42 blood donors who had presented with chronic hepatitis C.

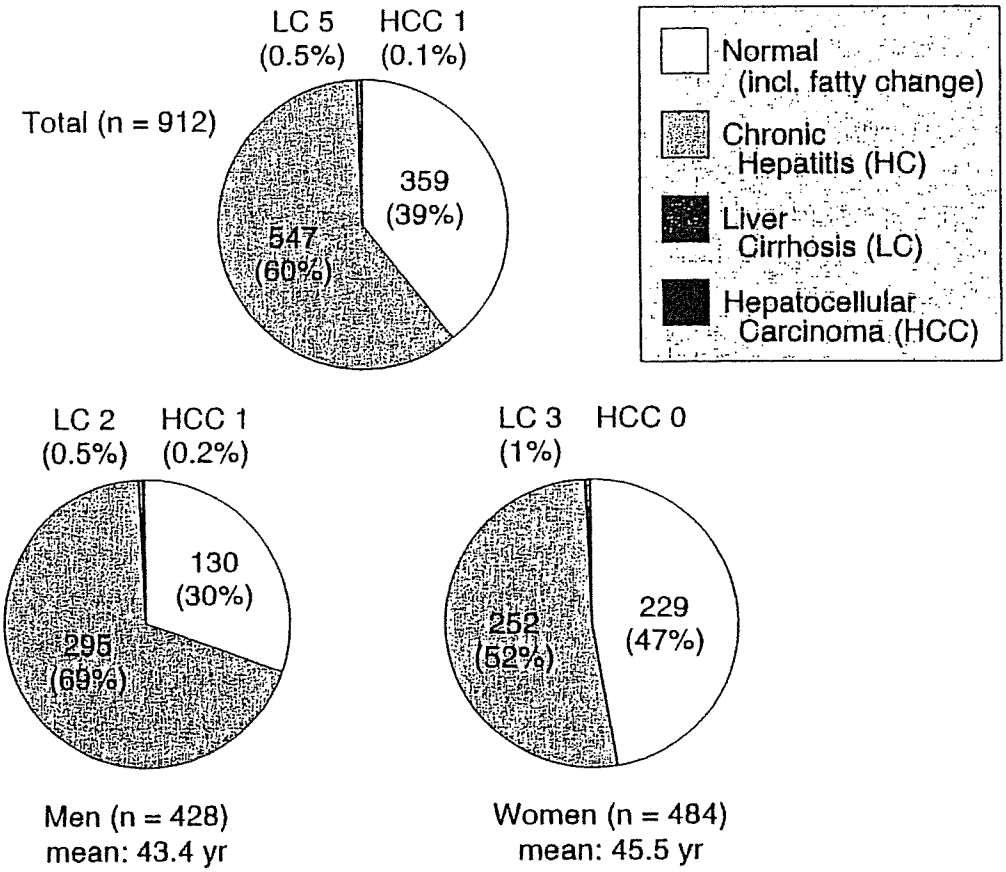

Figure 6. Distribution of liver disease in blood donors in Hiroshima who were found positive for anti-HCV.

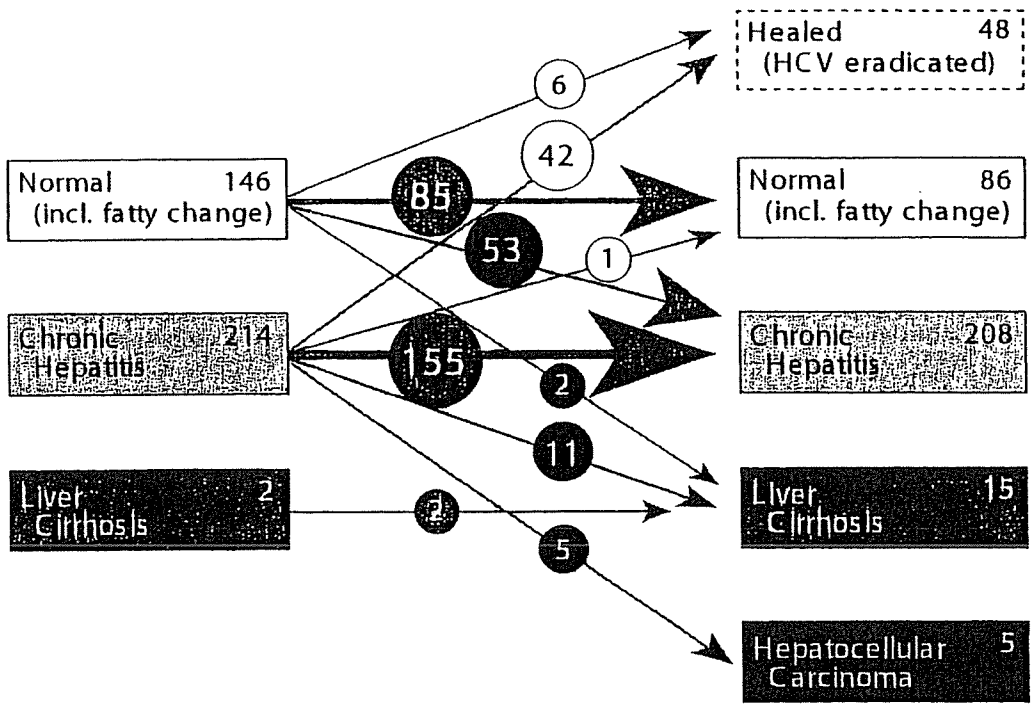

Figure 7. Evolution of liver disease in blood donors with anti-HCV in Hiroshima during follow-up for at least 5 years.

These observations warrant the need for systematically identifying HCV carriers hidden in the general population. These individuals need to be identified, evaluated for the presence of liver disease and the attendant implications for treatment, and then followed closely even if immediate medical intervention is unnecessary. By coordinated efforts of the government, co-medicals, and doctors, it would be reasonably expected that deaths due to HCV-associated HCC will decrease.

The natural history of HCV infection is influenced by many factors and can hardly be generalized [1,19]. It is subject to cohort effects, with the evolution of liver disease faster in patients who visit hospitals [10]. In contrast, children and young women fare much better and infrequently develop clinical disease during long-term follow-up [9,25]. Furthermore, the progression of liver disease is influenced by a number of factors, such as ethnicity, obesity, and alcohol intake. Since it takes decades before liver cirrhosis and HCC to develop in a proportion of HCV carriers, the clinical course is difficult to be seen by a single doctor in the same hospital. In addition, it would be unethical to observe the natural disease course among HCV carriers without offering antiviral treatments of proven efficacy when such individuals are diagnosed with clinical disease.

The Markov chain model is very instrumental for simulating the natural history of chronic diseases [20], and we have applied it to the natural history of HCV infection [22]. The probability of transition between any 2 of the 4 stages, i.e., asymptomatic carrier state, chronic hepatitis, liver cirrhosis, and HCC or death, were calculated on the basis of 2,251 patient-year data obtained from rigorous medical examinations performed on this group at least once a year. HCC was defined as the absorbing state from which no transitions occur, since it has become infrequent for patients with liver cirrhosis in Japan to die of hepatic decompensation or gastrointestinal bleeding. With use of probability matrices constructed on 6 subsets of individuals with HCV infection (asymptomatic carrier state, chronic hepatitis, and liver cirrhosis in men and women) in their 40's, 50's, and 60's, long-term outcomes of HCV infection were simulated.

The outcomes of men and women who are asymptomatic carriers at the age of 40 years are illustrated in Figure 8. After 30 years, male asymptomatic carriers are expected to remain in the asymptomatic carrier state in 2.6%, evolve into chronic hepatitis in 48.4%, progress to liver cirrhosis in 14.6%, and develop HCC in 34.4%, when they reach 70 years of age. The corresponding rates for these outcomes among female asymptomatic carriers aged 40 years were 1.9%, 43.5%, 32.8%, and 20%, respectively. The validity of these simulations was verified in 153 HCV carriers who were identified among blood donors and followed for 5 years [22].

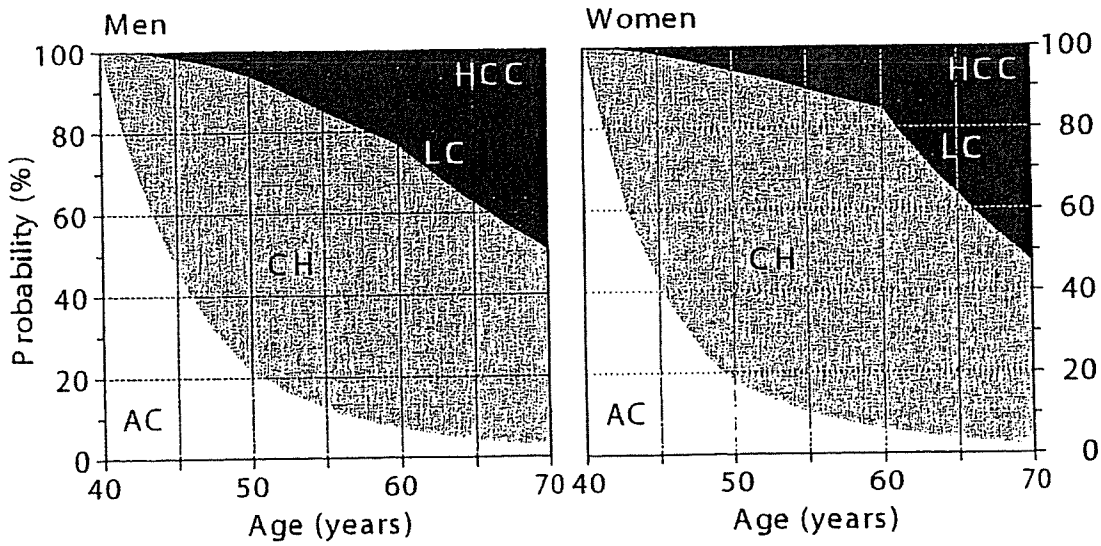

Figure 8. Simulation of clinical courses of 40-year-old male and female asymptomatic carriers of HCV during 30 by the Markov model (reproduced from Reference 22 with permission).

People in Japan, especially the elderly, have been exposed to HBV in the past, although most of them have resolved infection and cleared hepatitis B surface antigen (HBsAg) from the circulation by the present time. HBV remains in the liver, however, even after HBV infection is terminated, accompanied by the seroconversion to antibody to HBsAg in serum [24,27]. Eventually, the antibody to hepatitis B core (anti-HBc) remains as the only serological marker of resolved HBV infection. A high prevalence of anti-HBc in patients with HCV-associated HCC has been reported repeatedly and proposed as evidence for synergetic effects of the past HBV infection on the frequent development of HCC in HCV carriers in Japan [12,18]. The resolved HBV infection common in aged patients with HCV-associated HCC, however, does not contribute to their hepatocarcinogenesis. It represents a cohort effect rather than a casual relationship. In support of this view, anti-HBc was detected significantly more frequently in blood donors of the same age with anti-HCV than without it (56.3% vs. 25.5%, $p<0.001$) [7]. The prevalence of anti-HBc in the Japanese with anti-HCV was no different, however, between those with and without HCC (54.0% vs. 56.3%), thereby indicating that a resolved HBV infection does not contribute to the development of HCC in HCV carriers.

Strategies for Preventing Evolution of Chronic Hepatitis C into HCC

More than 90% of HCC develops in patients with advanced chronic hepatitis and liver cirrhosis, and 80% of it represents the long-term sequel of HCV infection in Japan. Hence, it is very effective to identify HCV carriers in the general population who are at increased risk for developing HCC and to take measures to

prevent the occurrence of this outcome. Three options for preventing HCC among HCV carriers are listed in Table 1. The first choice, of course, is to terminate HCV infection by antiviral therapy, such as interferon with or without ribavirin, in patients for whom such treatment is indicated. The indication is judged from viral factors, such as viral load and genotype, as well as host factors including grade and stage of liver disease. For those who do not respond to antiviral therapies or for whom this therapy is not indicated, and in whom necroinflammation in the liver is active with accompanied by elevated serum transaminase levels, conservative treatments are an option. Stronger Neo-Minophagen C (Minophagen Pharmaceutical Co., Tokyo, Japan) and ursodeoxycholic acid, as well as phlebotomy for decreasing iron loads in the liver, can be given to suppress the inflammation and retard or prevent the progression to fibrosis. Such treatments have proven to be effective in decreasing the development of HCC [2].

Table 1. Three Options for Preventing and Controlling Hepatocellular Carcinoma (HCC) Arising in Carriers of Hepatitis C Virus (HCV)

1.	**Causative Treatment** Antivirals such as interferon combined with ribavirin for clearing HCV infection and removing the high risk of developing HCC
2.	**Conservative Treatment** Anti-inflammatories such as Stronger Neo-Minophagen C as well as ursodeoxycholic acid and phlebotomy for retarding the development of HCC
3.	**Early Diagnosis of HCC** Close surveillance for HCC toward radical treatment enabling a prolonged survival

There is a third option for patients of cancer-bearing ages who cannot receive these 2 therapeutic options for any reason and in whom fibrosis has progressed. These patients need to be followed closely by imaging modalities and tumor markers in serum (AFP and PIVKA-II). Such surveillance helps in an early diagnosis of HCC with the possibility of radical treatment by surgical resection. For those in whom surgery is not indicated, percutaneous ethanol injection therapy (PEIT), percutaneous microwave coagulation therapy (PMCT) and radiofrequency ablation (RFA), as well as transcatheter arterial embolization (TAE) and continuous infusion with anticancer agents through hepatic artery feeding HCC, can be performed.

Two major points that should be kept in mind for improving the effectiveness of any project for preventing HCC are: (1) establishment of an effective system to detect HBV or HCV carriers; and (2) systematic and logical management of identified hepatitis virus carriers for prevention and surveillance of HCC as well as prompt treatment of these patients as required.

Methods for Detecting HCV Carriers on the National Scale

The national project for screening Japanese for HBV and HCV infection was launched in April 2002. It is performed on 2 distinct populations. Health check-ups are offered to Japanese citizens every 5 years starting at the age of 40 years until the age of 70 years. By screening at 5-year intervals, all carriers of hepatitis viruses can be identified who are aged 40 years or older. Beginning with the 6th year, only individuals who reach 40 years in that year need to be screened. This project is based on an extremely low incidence of HBV or HCV infection in Japan [26], which makes it sufficient to screen for viral markers only once in a lifetime.

Those who do not receive regular health check-ups are given the opportunity to receive tests at least once. These include individuals at high risk of HCV infection: (1) who were found with abnormal liver function tests in the past; (2) who had a major operation or a history of massive hemorrhage at delivery, and are not receiving regular monitoring for liver function; and (3) in whom liver function tests gave abnormal results at regular health check-ups.

Individuals older than 70 years and not receiving regular health check-ups are also offered testing for viral markers upon request. In addition, individuals testing negative for viral markers but who later produce abnormal liver function test results, with or without clinical symptoms of hepatitis, can consult with their doctors to determine the indication to screening for viral markers.

Anti-HCV is detected in sera from individuals who have ongoing HCV infection as well as from those who have resolved infection. These 2 categories of anti-HCV need to be distinguished from each other. When the national screening was started in April 2002, individuals were screened for anti-HCV, and those with anti-HCV in middle titers only were evaluated for the presence of HCV RNA in serum by NAT to detect ongoing HCV infection. When the ability of this method in efficiently identifying HCV carriers was evaluated in a model area, however, rare persons with low anti-HCV titers tested positive for serum HCV RNA. These individuals would not have undergone NAT evaluation under the original plan.

As a result, a 3-stage screening process has been developed as illustrated in Figure 9: Starting in April 2003, individuals testing positive for anti-HCV in low or middle titers were tested for the HCV core protein, and those with negative results only are tested for HCV RNA by NAT. Individual testing positive for the HCV core protein are deemed carriers.

Testing for HBsAg is performed simultaneously as a serum marker of ongoing HBV infection, for identifying HBV carriers who are at risk of developing HCC as well.

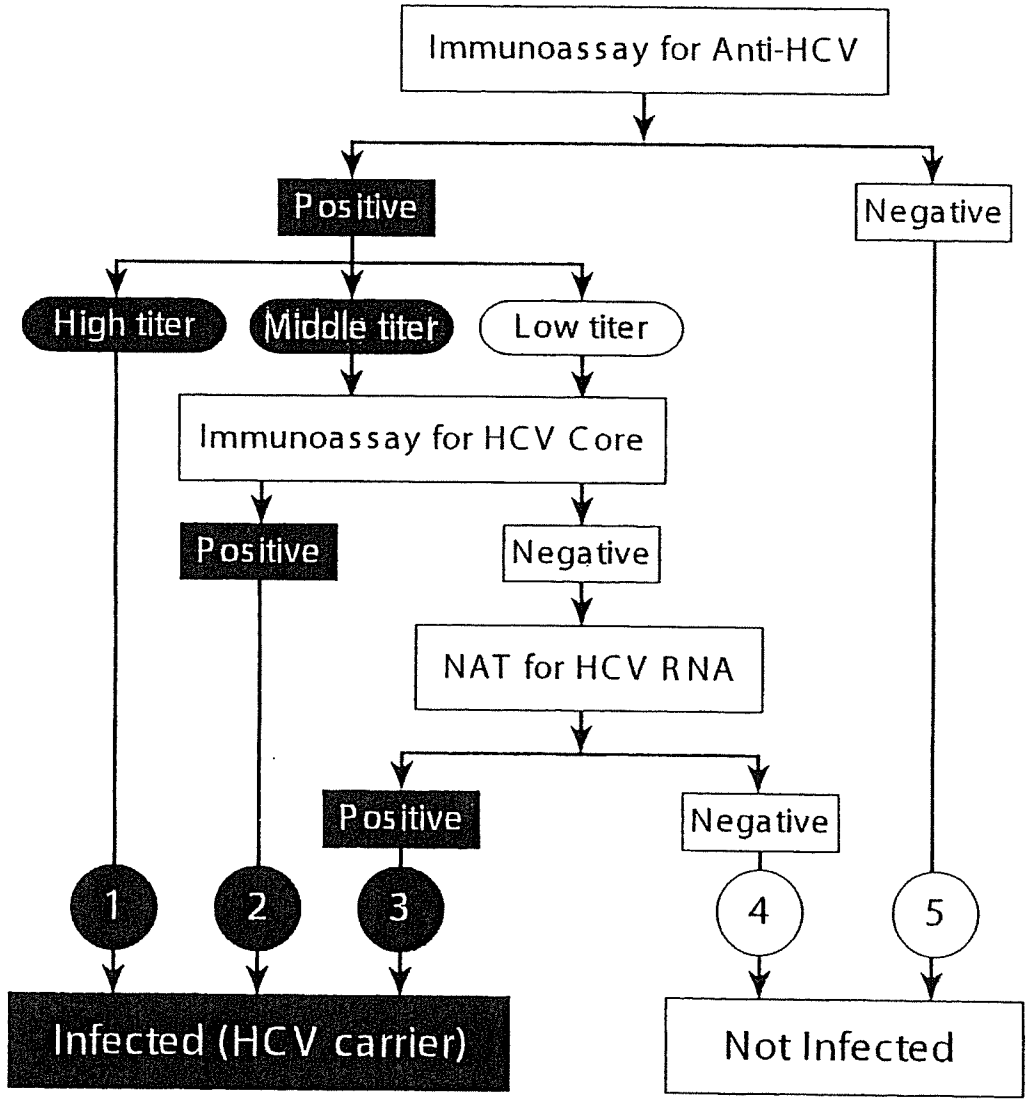

Figure 9. Strategy for the national screening for persistent HCV infection with immunoassays for anti-HCV as well as HCV core protein combined with nucleic acid amplification testing (NAT).

Results of the National Screening Project for Detecting Hepatitis Virus Carriers in the First Fiscal Year (April 2002 – March 2003) and Prospects for the Future

The Japanese Ministry of Health, Labor, and Welfare has reported results of the national screening project in the first fiscal year from April 2002 to March 2003. Of the 3,212 cities and towns in Japan, 2,923 (91%) began HCV screening with good compliance. The Department of Welfare for the Aged compiled results in the first fiscal year and identified 1,923,480 individuals who underwent testing of whom 31,393 (1.6%) were found to have ongoing HCV infection. There were 1,298,746 individuals who received tests at regular health check-ups, and 14,672 (1.1%) of these were found to be HCV carriers. In contrast, 16,721 (2.7%) of the