

このパンフレットは、B型肝炎ウイルスキャリアーの診断とフォローアップについて概説し、初診時検査項目を具体的に示した。さらに、二次医療機関への紹介につて解説し、二次医療機関と担当医の一覧を示してある。

図3 B型肝炎ウイルスキャリアー一次医療機関用の啓発・普及用パンフレット

C型肝炎ウイルスキャリアー用と同様にB型肝炎ウイルスキャリアーの診断とフォローアップについて概説し、初診時検査項目を具体的に示した。さらに、二次医療機関への紹介につて解説し、二次医療機関と担当医の一覧を示してある。

加により、県内の各医療圏域ごとに合計14回の講演を行った。対象は医師、保健師である。合計14回の講演に合計1,284名の医師、保健師が参加した。この際、配付資料として、患者用配付資料である、「肝がんの発生予防に資するC型肝炎検診の効率的な実施に関する研究班」により作成された「C型肝炎ウイルス検査を受けられる方に」、改訂第2版、「B型肝炎ウイルス検査を受けられる方に」を広く配布し、患者に対する普及・啓発活動に利用できるようにした。これらの資料を別添の図1「C型肝炎ウイルス検査を受けられる方に」、改訂第2版、図2、「B型肝炎ウイルス検査を受けられる方に」に提示した。

### ① 一次、二次医療機関向けの普及・啓発パンフレットの改訂

改訂の要点は以下の4点である。①開業医など一般医家向けに要点を強調、②手帳の改訂と併せて検査項目の改訂、③キャリア用健康管理手帳によるモニタリングの重要性を強調、④2次医療機

関名簿の改訂。なお、C型肝炎ウイルスキャリアー診療の手引き-二次医療機関用-改訂第2版には、健康管理手帳が公費負担で行われ、広島県地对協慢性肝疾患対策専門委員会により推進されているものであることを記し、返信はがきの投函による調査への協力の重要性を強調した。

### ② 県内各医療圏毎の二次医療機関の見直し

2次医療機関の専門医の移動などにより必要となった専門医名簿の改訂を行った。今後も診療実施状況などにより適宜変更していく予定であり、このことはパンフレットにも盛り込んである。

### ③ 患者フォロー用肝炎健康管理手帳の改訂

手帳を以下の点について改訂を行った。①開業医など一般医家向けにより使いやすいものに改訂、②診療の手引きと併せて検査項目の改訂、③キャリア用健康管理手帳によるモニタリングの重要性を強調。また、B型肝炎ウイルスキャリアー用の手帳についても同様のものを作成し、肝炎ウイルスキャリアーの診療に利用可能とした(図3)。

## おわりに

平成14～15年度の取り組みにおいて、C型肝炎ウイルス感染陽性者のフォローアップは、一次医療機関と二次医療機関の双方において患者の診療を行っていくというコンセプトを徹底するために、一次、二次医療機関用のパンフレットの作成とその改訂、C型肝炎ウイルスキャリア用健康管理手帳の作成と改訂を行った。さらにB型肝炎ウイルスキャリア用の健康管理手帳も作成した。これらの使用が適切に行われるように、講演会による説明も行った。講演会への参加者が千人以上という実績に見られるように、肝炎対策活動に対する関心の高まりが認められた。さらに、一次、二次医療機関向けの普及・啓発用パンフレットの改訂を行い、再配布することしたので、より多くの医療機関において、国策としての肝炎対策、広

島県での取り組みに対する理解が深まることが期待される。今後、改訂されたC型肝炎ウイルスキャリア用健康管理手帳やB型肝炎ウイルスキャリア用健康管理手帳の利用状況をフォローアップしていくことにより、われわれの構築したネットワークの実効性の評価が可能となっている。さらに将来的には、二次医療機関において、厚生労働省により示されたC型慢性肝炎のガイドラインに沿った治療が有効に実施されているかどうかを検証する必要がある。これらの活動が有効に実施されれば、抗ウイルス療法を受けないままに肝細胞癌を発症するような症例、進行肝細胞癌が初診時に発見されるような症例が減少していくことが期待される。

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

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## 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.

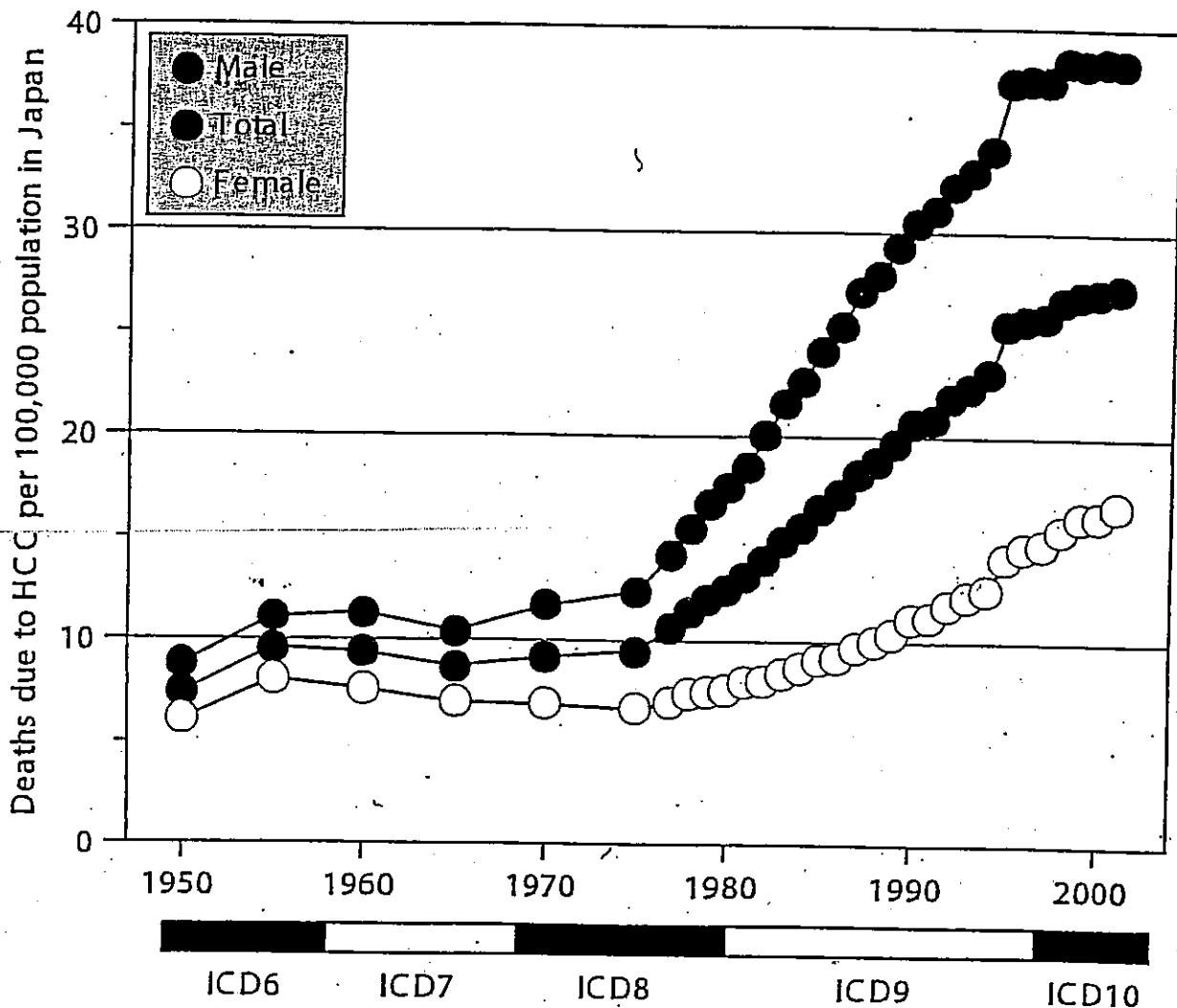
By far the majority of HCC cases develop in the background of fibrosis and cirrhosis in the liver as sequelae of chronic necro-inflammation induced by HBV or HCV infection. Most cases of HCC caused by persistent HBV infection present in individuals in their early 50's, while HCC caused by persistent 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-bearing 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- $\gamma$ -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.

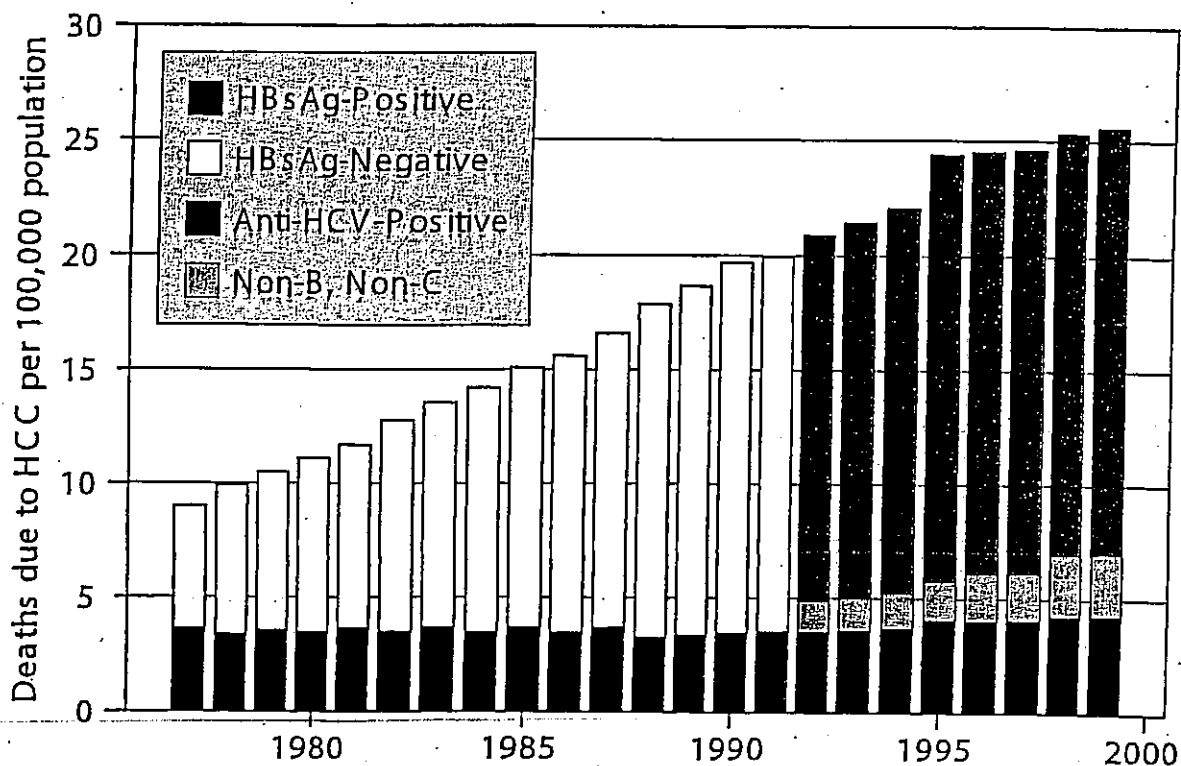
### Shifting Patterns of HCC in Japan during the Past 50 Years

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.

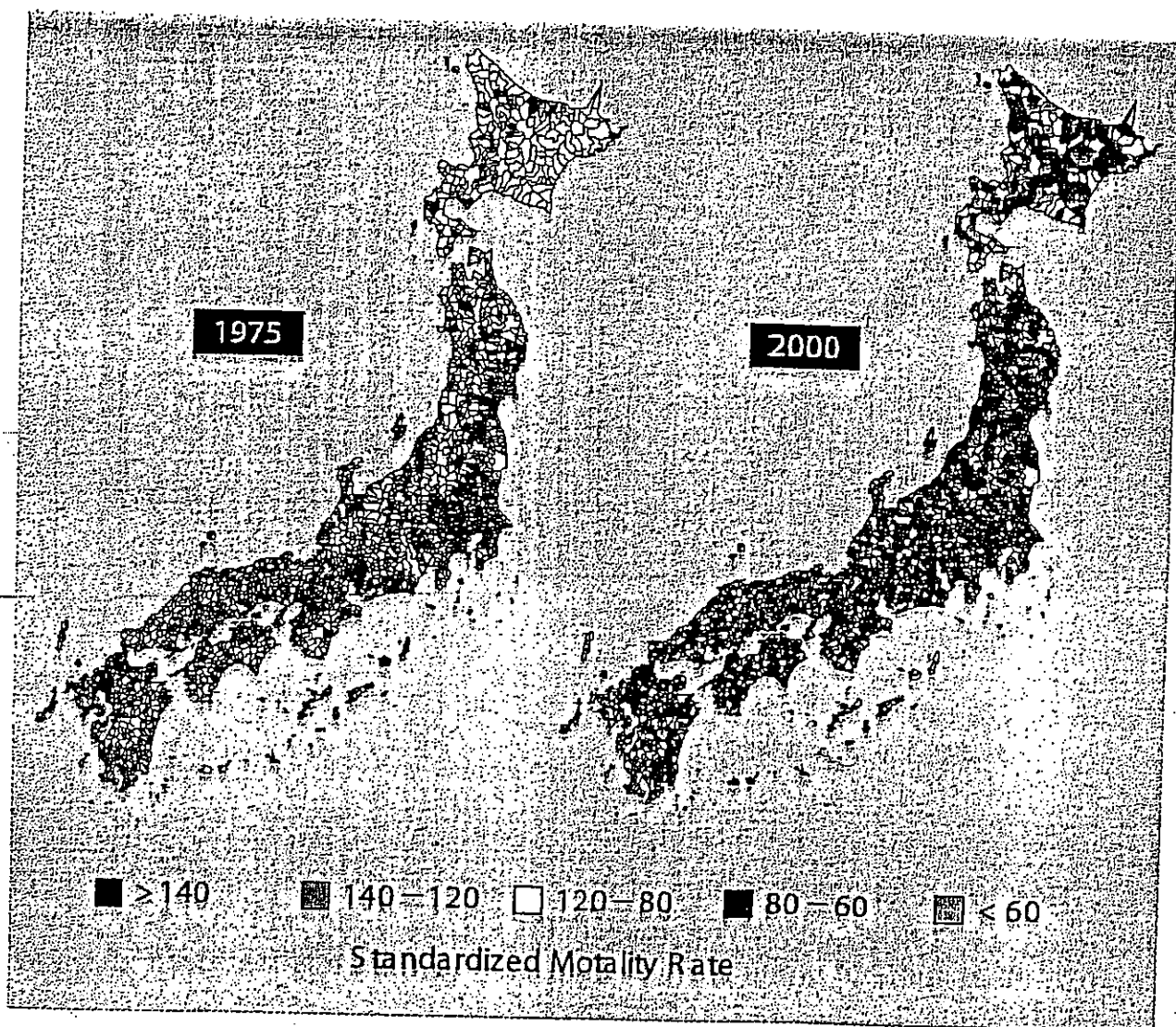


**Figure 2.** Causes of HCC shifting with time in Japan (modified from Reference 26 with addition of recent data).

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.

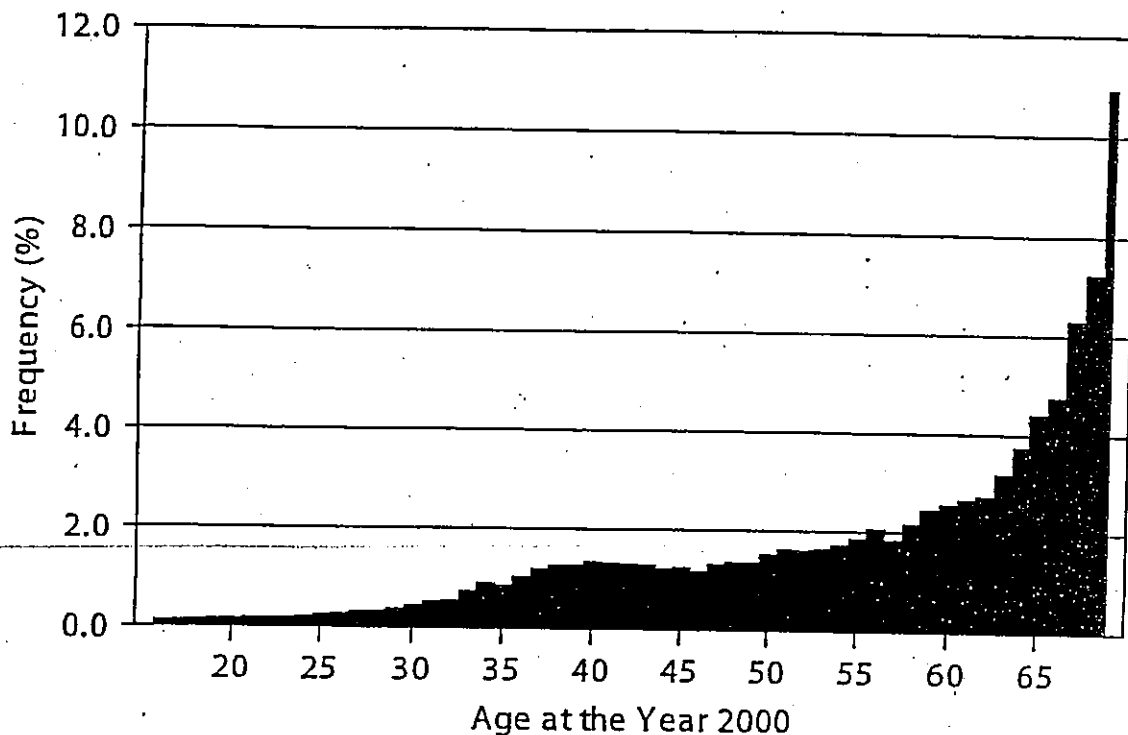


**Figure 3.** Changes in the distribution of deaths due to HCC in men during the past 30 years in Japan. These maps were produced by Dr. Yoshihiko Mirua of Saitama Prefectural University.



### Prevalence of Persistent HCV Infection in Japan

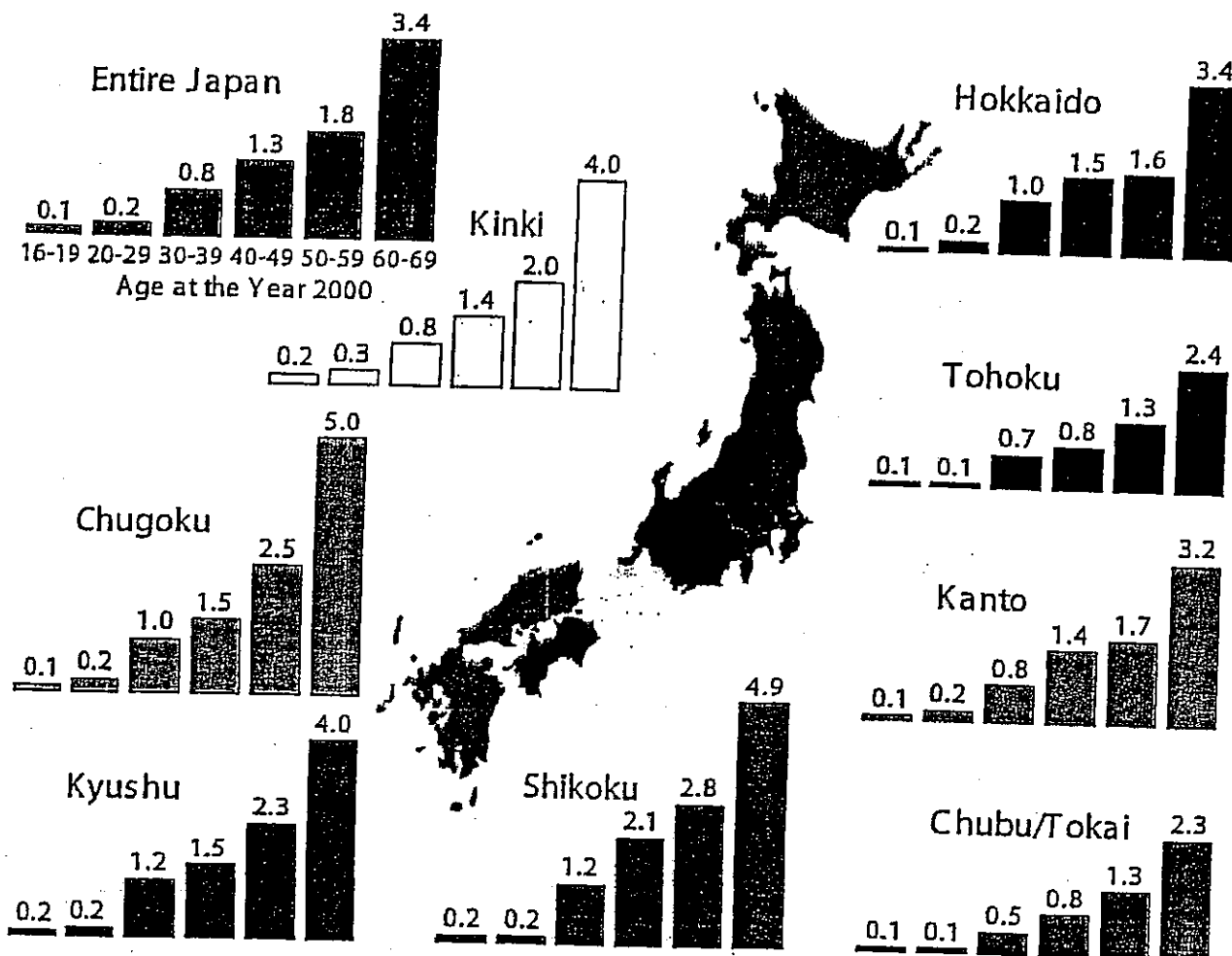
Volunteer blood donors are the best population for estimating the prevalence of persistent infections with any microbe, including HBV and HCV, although they may not faithfully mirror national sex and age distributions. Since blood donors found to have ongoing HBV or HCV infection in previous donations 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.

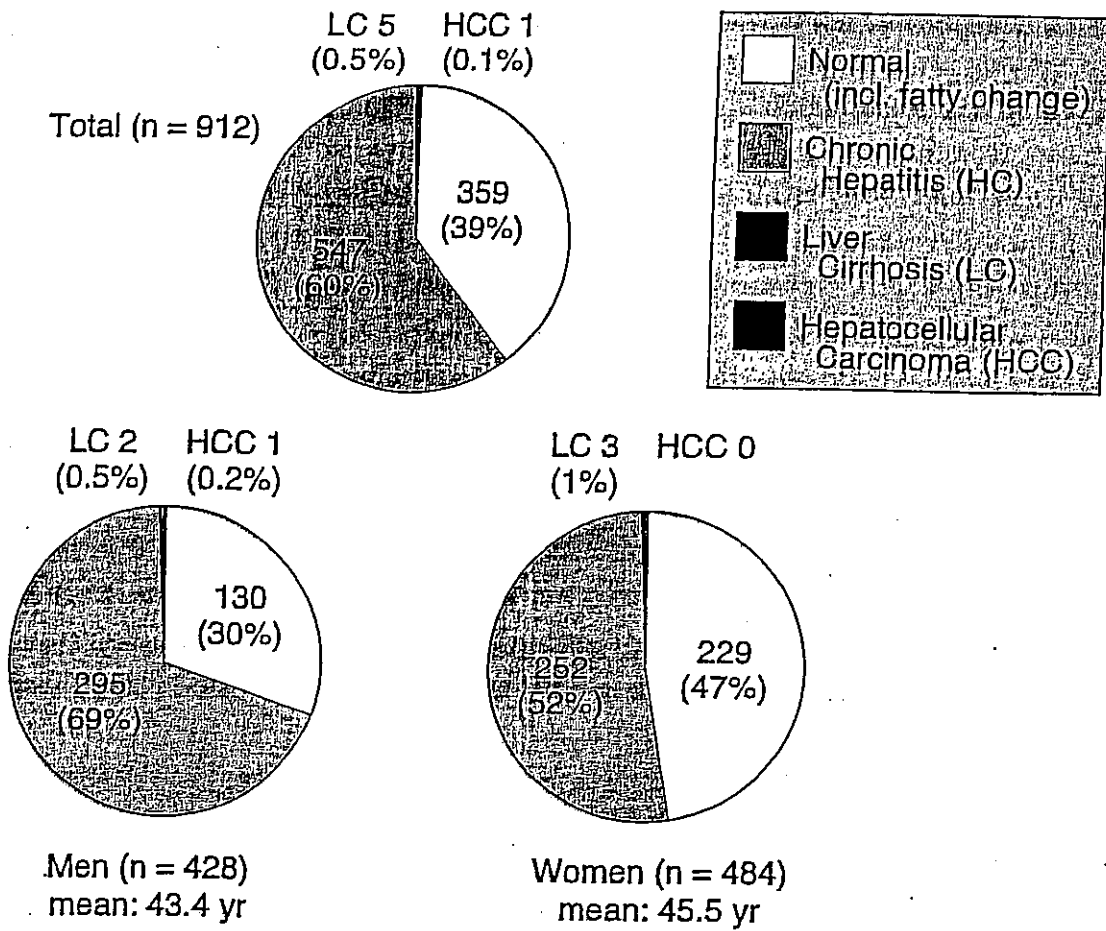


Figure 6. Distribution of liver disease in blood donors in Hiroshima who were found positive for anti-HCV.

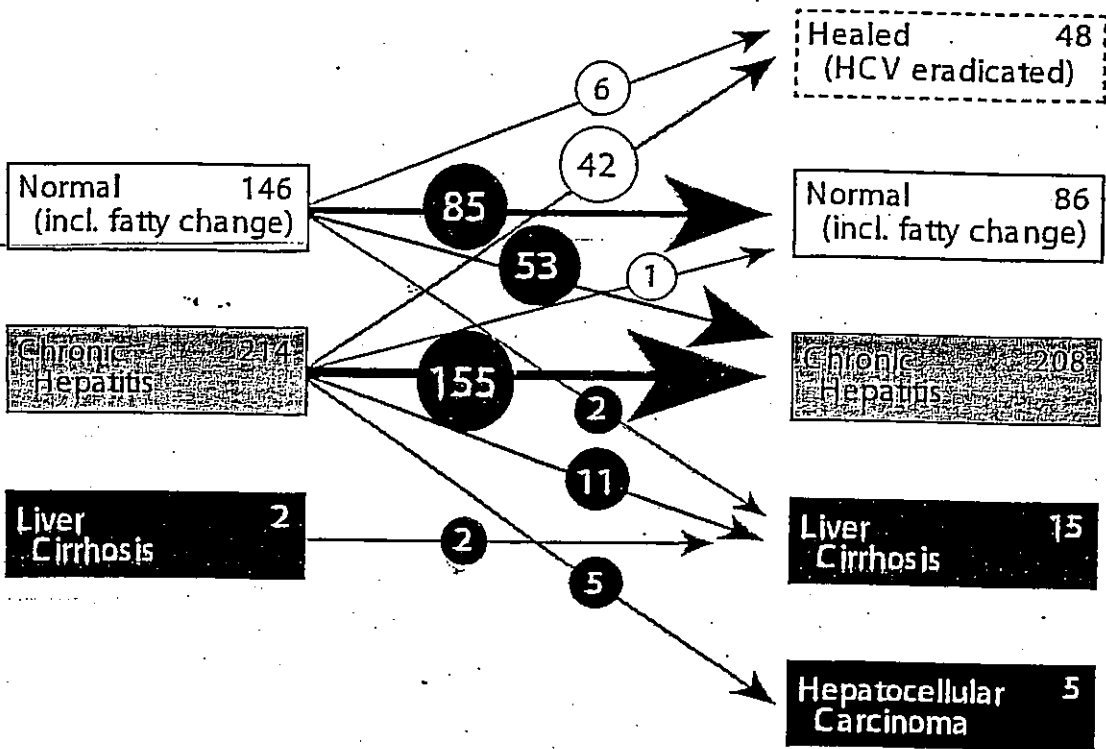


Figure 7. Evolution of liver disease in blood donors with anti-HCV in Hiroshima during follow-up for at least 5 years.

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.

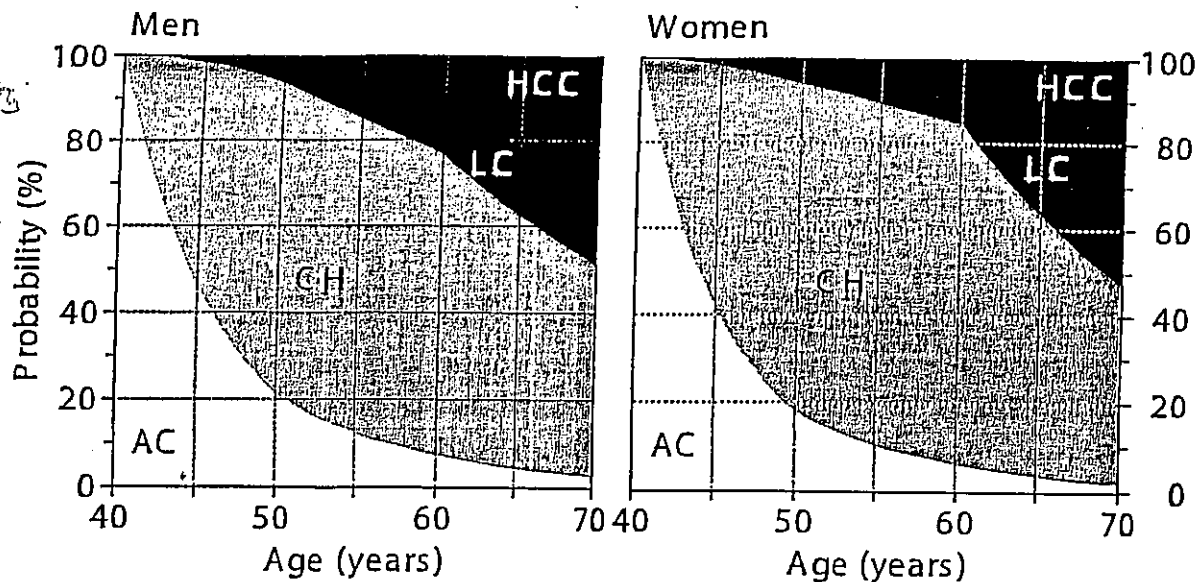
The natural history of HCV infection is influenced by many factors and can hardly be generalized [1,19]. It is subject to cohort effects, with the evolution of liver disease faster in patients who visit hospitals [10]. In contrast, children and young women fare much better and infrequently develop clinical 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.

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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].

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**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)**

<b>1.</b>	<b>Causative Treatment</b> Antivirals such as interferon combined with ribavirin for clearing HCV infection and removing the high risk of developing HCC
<b>2.</b>	<b>Conservative Treatment</b> Anti-inflammatories such as Stronger Neo-Minophagen C as well as ursodeoxycholic acid and phlebotomy for retarding the development of HCC
<b>3.</b>	<b>Early Diagnosis of HCC</b> 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 6<sup>th</sup> 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.

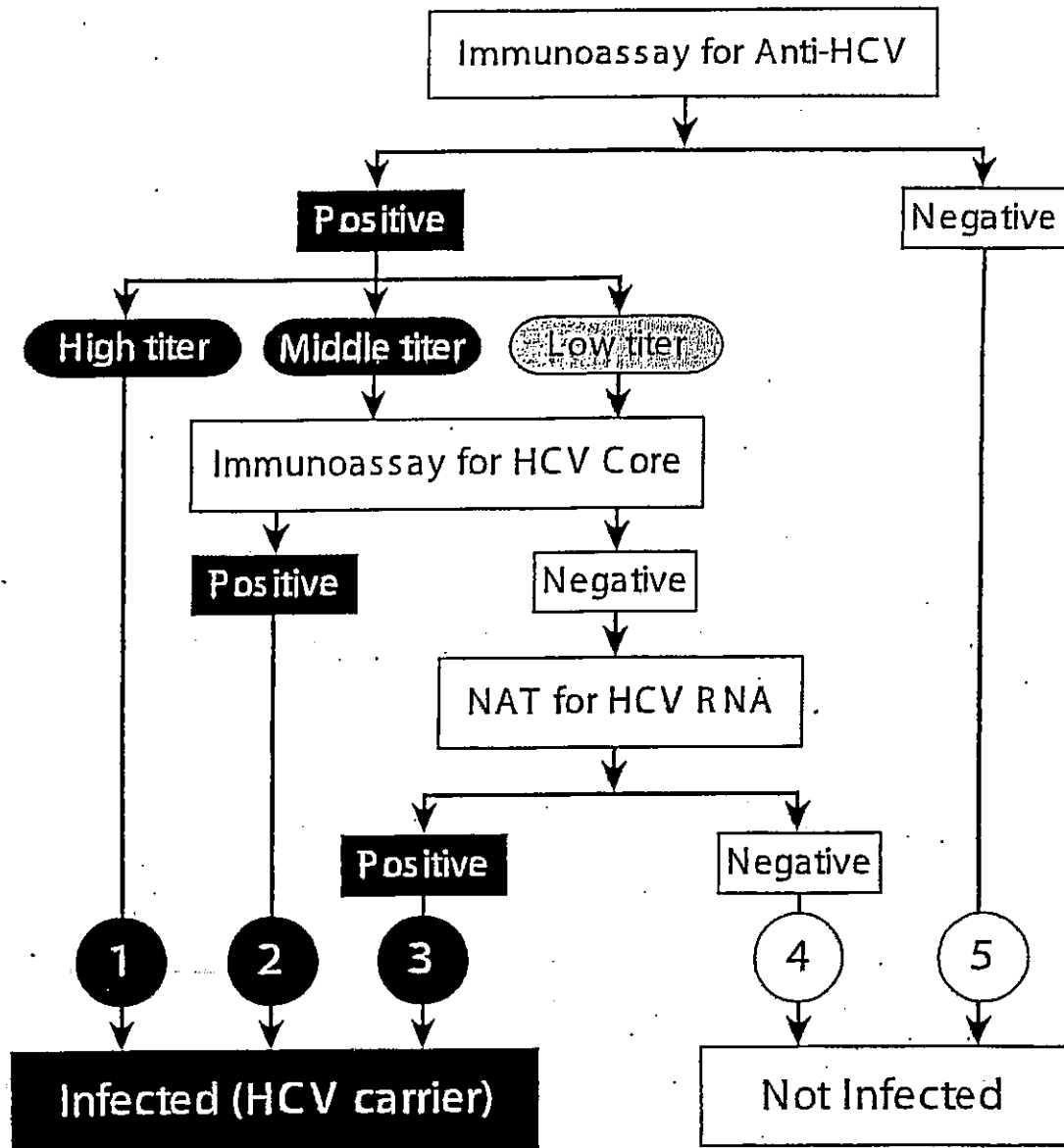
Individuals older than 70 years and not receiving regular health check-ups are also offered testing for viral markers upon request. In addition, individuals testing negative for viral markers but who later produce abnormal liver function test results, with or without clinical symptoms of hepatitis, can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





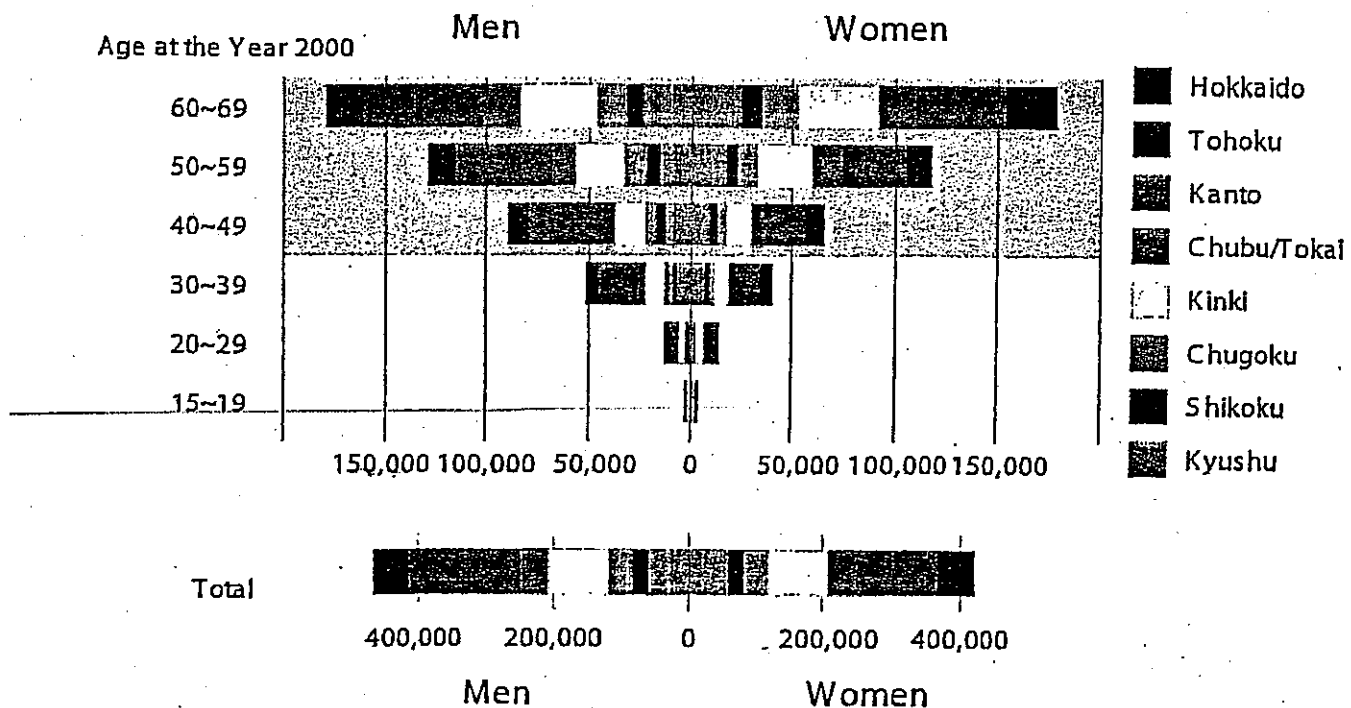
**Figure 9.** Strategy for the national screening for persistent HCV infection with immunoassays for anti-HCV as well as HCV core protein combined with nucleic acid amplification testing (NAT).

**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

624,734 high-risk persons who received tests on other occasions were found to have ongoing HCV infection. This reflects a frequency twice as high as that among those receiving regular health check-ups. HCV carriers were found in 3.2% and 1.3% of the individuals aged 65 to 70 years at high risk and those on check-ups, respectively, and more often in individuals aged 70 years or older (4.0% and 2.1%, respectively).

The numbers of HCV carriers who will be identified during the 5-year project for national screening can be estimated by the prevalence of anti-HCV in first-time blood donors (Figure 4). HCV carrier state is considered to be present on average in 70% of blood donors testing positive for anti-HCV. Sex- and age-specific prevalence rates of anti-HCV were determined individually in 8 jurisdictions of Japanese Red Cross Blood Centers. The estimated total number of HCV carriers in each jurisdiction was obtained by multiplying these prevalence rates by the sizes of the corresponding subpopulations stratified by sex and age extrapolated to reflect the population size in 2000. There are an estimated 850,500 carriers of HCV in Japan who are aged 15 to 69 years, with little difference in numbers between men and women. Targets of the national screening program, who are aged 40 to 70 years, encompass 760,000 HCV carriers and account for 86% of those aged 15 to 65 years (Figure 11).



**Figure 11.** Carriers of HCV stratified by sex and age in Japan estimated by the prevalence of anti-HCV in the first-time blood donors and corresponding subpopulations registered at the Census 2000 (from Reference 23 with permission).

Detection of 29,809 HCV carriers amongst the 1.8 million receiving screening during the first fiscal year may have unfolded only a fraction of persistent HCV infection in the target individuals. Further efforts to get the Japanese populace to be aware of the risk of HCC associated with HCV infection and for orienting them

to receive screening are necessary. High compliance and increased reception rate will only be achieved by concerted efforts among the government, medical community, and public.

### HCV Infections Throughout the World

The age-specific prevalence of HCV infection in the year 2000 is compared between Japan and Kiev, Ukraine as well as with the United States (U.S.) in Figure 12. These data are based on 270,000 blood donors in Hiroshima for Japan, 40,000 blood donors in Kiev for Ukraine, and data reported by the Centers for Disease Control and Prevention for the U.S. The age groups with the highest prevalence of anti-HCV differ markedly among the 3 countries. The prevalence of anti-HCV steeply increases with age in Japan, so that it is the highest in the elderly who scale out of the figure. In contrast, the highest prevalence of anti-HCV occurs in much younger individuals, aged 40 to 44 years, in the U.S., and in those even younger, aged 30 to 35 years, in Ukraine.

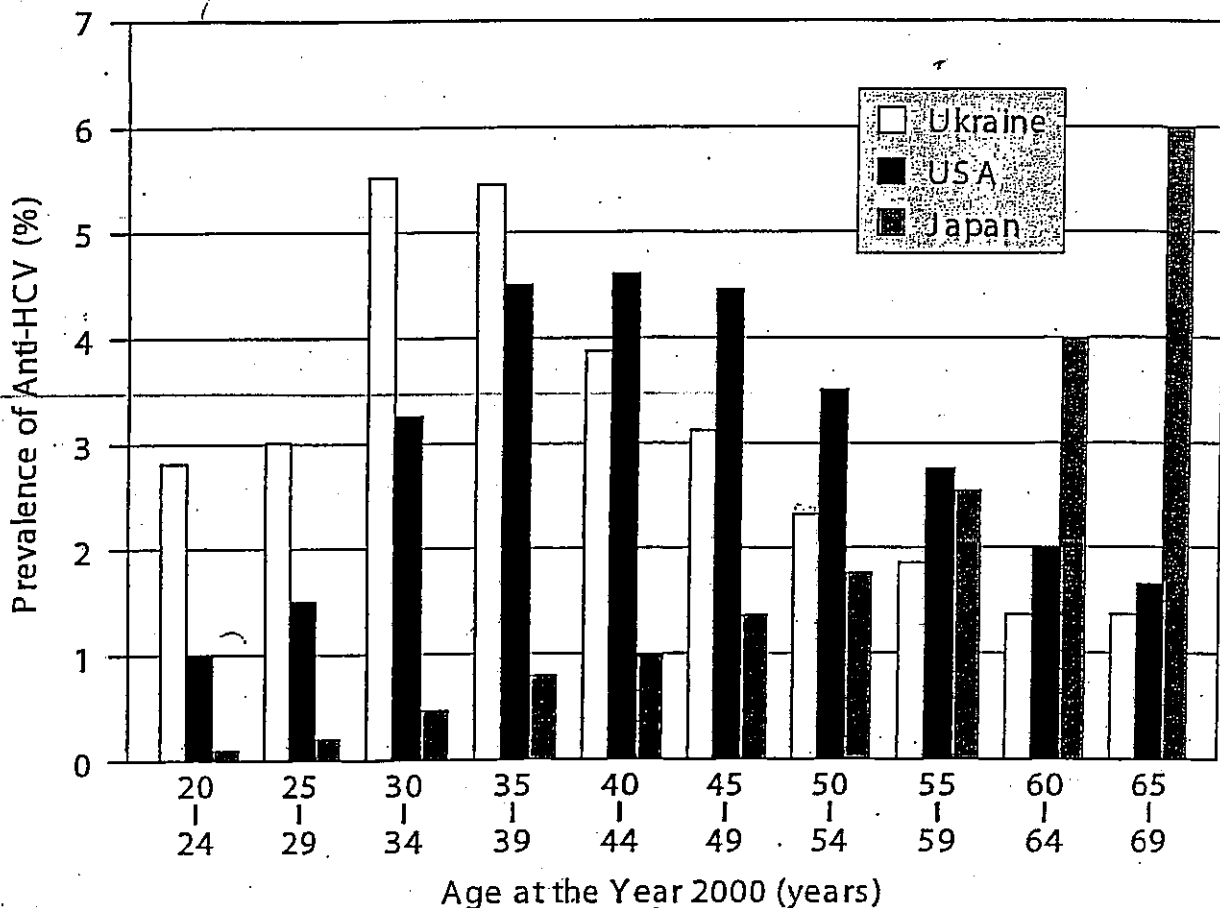


Figure 12. Age-specific profiles of HCV infection in Japan, the Ukraine, and the U.S.

Wide differences in the age at which anti-HCV is most prevalent among the 3 countries are attributed to distinct time points when HCV spread extensively among these populations. In Japan, HCV infection infiltrated the subpopulation of younger generations during the 1950s through 1960 in a vicious cycle [26]. About 2 decades later during the 1970s to early 1980s, HCV infection was widely diffused in the U.S. although it has become less invasive at the present. HCV infection started to spread in the Ukraine since the late 1980s and has continued to involve younger generations. What we witness for the age-specific distribution in the 3 countries at present are long-term sequelae of the shifting peak of age-specific HCV infection with time.

## Conclusions

Today, HCC in Japan preferentially occurs among individuals in their late 50's through early 60's. Fortunately, the life expectancy of patients with HCC has been extended by 6 to 7 years with the advent of efficient treatments. Based on the age-specific distribution of anti-HCV in Japan, deaths due to HCC that have increased continuously until the present will reach a plateau shortly and then start to decrease around 2005–2010. By contrast, in the U.S. the individuals infected with HCV in the past are just now entering the cancer-bearing ages. If appropriate measures are not taken there, the steep increase in deaths due to HCC that we have experienced in Japan since 1975 (Figures 1 and 2) is likely to be reproduced there. The same situation is expected in the Ukraine but the peak is likely to occur some 10 to 15 years later than in the U.S. In addition, the incidence of HCC is increasing already in countries where HCV prevails, including Australia [14], France [3], Italy [21], and Sweden [8], and is expected to double in the U.S. over the next 10 to 20 years [6].

It is our sincere hope to accomplish a major success with screening for hepatitis virus infections through the national project in operation begun in Japan in April 2002. Should our 5-year strategy to cope with HCC induced by persistent hepatitis virus infections prove successful, our experience will likely be valuable to other countries throughout the world where HCV infection prevails.

## Acknowledgments

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