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Trends in the total numbers of HBV and HCV carriers in Japan from 2000 to 2011

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Summary

We estimated the total number of undiagnosed HBV and HCV carriers and patients with hepatitis virus-related disease in Japan according to 6 different groups classified by their natural histories during 2011. In 2011, the total number of carriers and patients infected with HBV or HCV was estimated according to 6 groups using government reports and reports from the hepatitis epidemiology research group of The Ministry of Health, Labor and Welfare in Japan. In 2011, the total number of hepatitis virus carriers was estimated to be 2 090 128-2 840 128 in which the estimated number of undiagnosed HCV and HBV carriers was 776 826 (HBV: 481 470; HCV: 295 356). The total number of treated patients, as either inpatients or outpatients, was estimated to be 811588 (HBV: 303 366; HCV: 520 600) in 2011. It is presumed that many carriers shirk consultation for many reasons, such as patients' misunderstanding, lack of awareness and forgetfulness of their positive status. The numbers of infected patients who did not seek treatment increased gradually to 501 714-1 251 714 (HBV: 333 791-483 791; HCV: 167 923-767 923) in 2011. Compared to 2000, the number of undiagnosed carriers was significantly reduced in 2011 probably because of the well-organized, effective national hepatitis virus screening system that has been launched by the Japanese government since 2002. Moreover, the increase in the number of untreated persons who are aware of their positive status shows that more effort should be invested in improving the referral system from screening centres to core hospitals.

KEYWORDS
hepatitis B, hepatitis C, hepatitis virus carriers, undiagnosed carriers and patients in Japan

1 | INTRODUCTION

According to the World Health Organization (WHO) Global Hepatitis report in 2017, approximately 257 million people or 3.5% of the global population are living with chronic hepatitis B virus (HBV) infection, whereas 71 million people or 1% of the global population are living with chronic hepatitis C virus (HCV) infection.[1] Apart from that, viral hepatitis accounted for 1.34 million deaths in 2015, among which 887 000 deaths were due to HBV-related liver complications and 399 000 deaths were due to HCV-related liver complications.[2,3] Left untreated, HBV and HCV infections can lead to liver cirrhosis (LC) (720 000 deaths) and hepatocellular carcinoma (HCC) (470 000 deaths). These long-term complications are life-threatening and accounted for 96% of deaths due to viral hepatitis.[1]

Abbreviation: CR, complete response; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICD, International Classification of Diseases; IFN, interferon; LC, liver cirrhosis; MHLW, Ministry of Health, Labor, and Welfare; WHO, World Health Organization

Principal investigator: Junko Tanaka

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Compared to the WHO Global Hepatitis report on viral hepatitis, the number of deaths due to HCC had been increasing in Japan since 1975. This number of deaths started to increase consistently until it reached its peak of 34 637 per year in 2002, but it decreased gradually until it reached <30 000 per year in 2014.[4] Although mortality has been decreasing annually, HCC still ranks as the fourth common cause of death due to malignancy in men and the sixth common cause of death in women in Japan.[5] By its aetiology, HBV contributes 53% and HCV 25% to liver cancer worldwide. But, this is inverted in Japan, where it is estimated that the contribution of HCV is 66%.[6] These figures indicate the importance of managing infected people to meet the WHO goal of eliminating viral hepatitis by 2030.[1]

Since 2000, the Japanese government has pursued an aetiology-based hepatitis and HCC control health policy and strategy based on large-scale epidemiologic or clinico-pathological studies.[7] In accordance with the national health policy, the hepatitis epidemiological research groups of The Ministry of Health, Labor, and Welfare (MHLW) in Japan estimate the number of undiagnosed hepatitis virus carriers and patients with hepatitis virus-related disease with respect to sex-specific and age-specific groups using the data collected by the Japanese Red Cross Blood Center in the same year.[8,9] MHLW declared that the estimated number of hepatitis virus carriers and patients with hepatitis virus-related disease was about 3.0-3.7 million persons in 2000. This declaration was based on an estimation of undiagnosed carriers aged between approximately 15 and 69 years in 2000.[8] Based on this estimation, the countermeasures for viral hepatitis infection control and prevention were started and focused on screening.

As a part of the countermeasure system, it is important to estimate the numbers of hepatitis virus carriers and patients in 2011, using results from large-scale epidemiological studies and national reports to determine the actual trends in the numbers of carriers from 2000 to 2011.

The aim of this study was to determine the trend of total numbers of HBV and HCV carriers over the last 11 years by each liver disease state (AC, CH, LC and HCC) and different states of HBV and HCV carriers linked to the society (undiagnosed carrier, diagnosed carriers who are consulting at the hospital, diagnosed carriers who are not consulting at the hospital, newly infected carrier, cured person and death from 2000 to 2011), and according to this figure we can evaluate the effectiveness of the countermeasure against hepatitis and we can also adopt new strategies based on the outcome of current interventions.

2 | MATERIALS AND METHODS

In this study, we estimated the number of hepatitis virus carriers and patients with hepatitis virus-related disease with respect to sex-specific and age-specific groups in Japan.

2.1 | Classification of 6 groups of hepatitis virus carriers in Japan

A carrier state can be further subdivided into 6 groups as follows.

1. undiagnosed carriers who are unaware of their infection;
2. patients who are known carriers and have been already hospitalized as inpatients or have been receiving medical treatment as outpatients;
3. unconsulted or ceased carriers who have been aware of being infected but have not consulted any medical facility, or have stopped receiving medical treatment;
4. newly infected carriers from 2000 to 2011;
5. cured individuals from 2000 to 2011; and
6. deaths due to all causes from 2000 to 2011.

2.2 | Estimates for the number of undiagnosed carriers

The number of undiagnosed HBV and HCV carriers who were unaware of their infection in 2000 and 2011 was estimated by calculating the sum of products of sex-specific, age-specific and area-specific prevalence among 3 485 648 and 2 720 727 first-time blood donors 1996-2000 and 2007-2011(Appendix 3, 4),[8,10] respectively, with total population.

$$\Sigma_{i,j,k}\, r_{ijk} \times P_{ijk},$$

where i, j, k denote the index area (i = 1 for Hokkaido, i = 2 for Tohoku, i = 3 for Kanto, i = 4 for Hokuriku/Tokai, i = 5 for Kinki, i = 6 for Chugoku, i = 7 for Shikoku, and i = 8 for Kyusyu), sex (j = 1 for men and j = 2 for women) and age group (k = 1 for 15-19 years, k = 2 for 20-24 years, k = 3 for 25-29 years, k = 4 for 30-34 years, k = 5 for 35-39 years, k = 6 for 40-44 years, k = 7 for 45-49 years, k = 8 for 50-54 years, k = 9 for 55-59 years, k = 10 for 60-64 years and k = 11 for 65-69 years). Symbols r_{ijk} and P_{ijk} denote the carrier rate and total population among the group of area i, sex j, and age k. We assumed that the carrier rate among people aged 70 and older would be the same as that for those aged 60-69 years. (Figure 1).

We also assumed all people whose hepatitis B surface antigen became positive were HBV carriers. At the same time, 70% of those with anti-HCV positivity were assumed to be HCV carriers. The number of undiagnosed carriers based on a clinical diagnosis (asymptomatic carrier, chronic hepatitis, LC and HCC) was estimated as a proportion with respect to the per cent distribution of each clinical diagnosis.

2.2.1 | Distribution pattern of the clinical diagnosis of undiagnosed HCV carriers in 2000

The distribution pattern of clinical diagnosis of 906 HCV carriers among blood donors in Hiroshima[11,12] (Appendix 1) was used as a baseline.

2.2.2 | Distribution pattern of the clinical diagnosis of undiagnosed HCV carriers in 2011

The distribution pattern of the clinical diagnosis of undiagnosed HCV carriers in 2011 was estimated for 11 years using the Markov

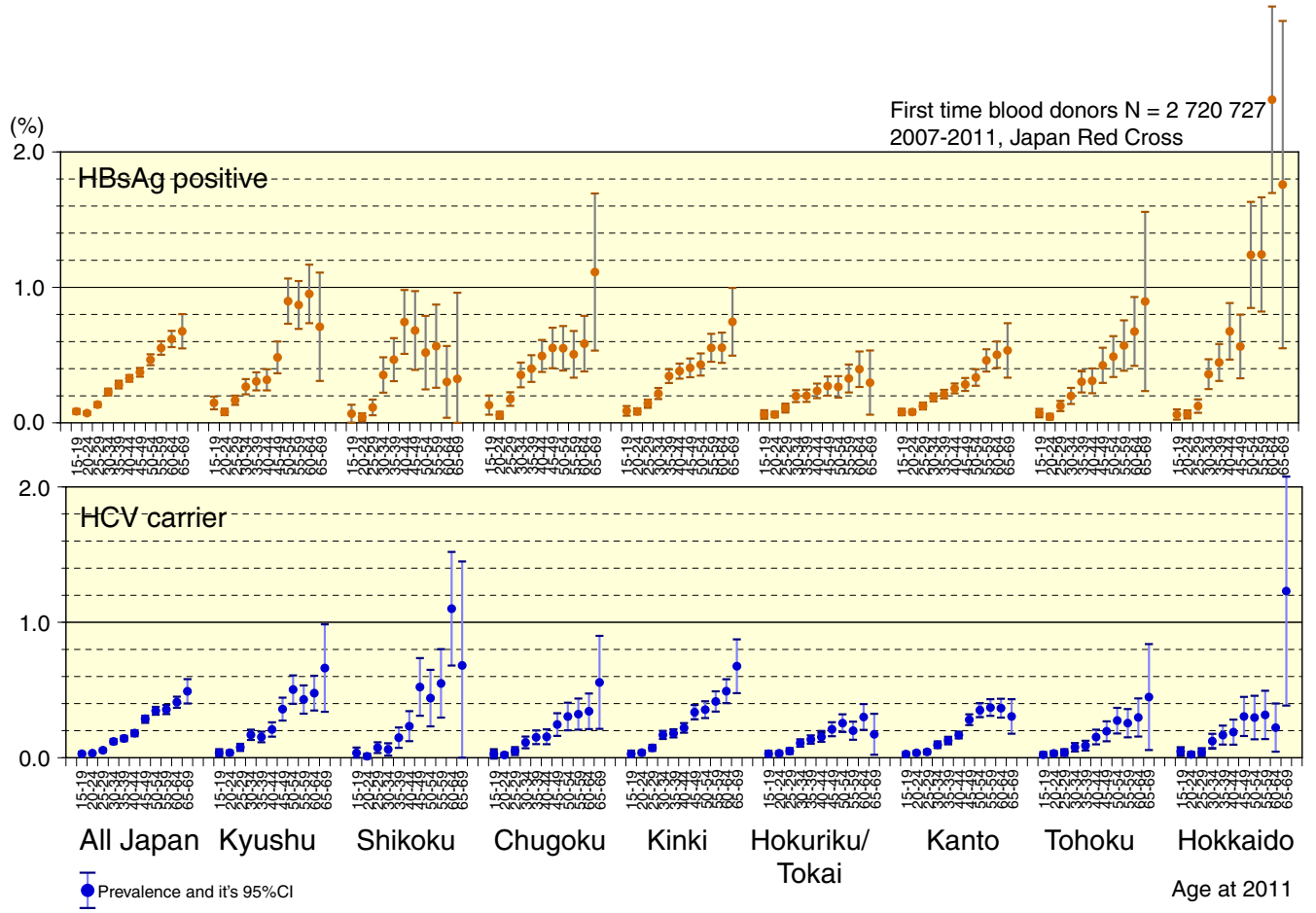

FIGURE 1 Area- and age-specific HBsAg-positive and HCV carrier rate among first-time blood donors during 2007-2011. Age-specific HBsAg-positive and HCV carrier rate by all Japan, and 8 areas are shown in figure. Error bar means 95% CI of prevalence

model simulation based on the initial distribution of HCV in 2000 (Appendix 1). The transition probabilities were estimated based on 699 HCV carriers in Hiroshima who were firstly diagnosed at the time of their blood donation.[13,14]

2.2.3 | Distribution pattern of the clinical diagnosis of undiagnosed HBV carriers in 2000

The distribution pattern of the clinical diagnosis of undiagnosed HBV carriers in 2000 was estimated for 19, 30 and 45 years using the Markov model simulation, in which the time for initial distribution of HBV in all asymptomatic carriers was assumed (Appendix 1). Additionally, the transition probabilities were determined among 938 HBV carriers who were followed up at Narao Hospital.[13]

2.2.4 | Distribution pattern of the clinical diagnosis of undiagnosed HBV carriers in 2011

The distribution pattern of the clinical diagnosis of undiagnosed HBV carriers in 2011 was estimated for 11 years using the Markov model simulation based on the initial distribution of HBV in 2000 (Appendix 1). The transition probabilities were assumed based on 938 HBV carriers who underwent follow-up at Narao Hospital.[13]

2.3 | Estimates for the number of patients

2.3.1 | Patients with HBV- and HCV-related disease in 2000

Patients with hepatitis-related disease in 2000 were included in the patient survey.[15] The following International Classification of Diseases (ICD) codes were used to categorize the differential diagnosis of liver disease: C22, malignant neoplasm of the liver and intrahepatic bile ducts (HCC); K73, chronic hepatitis; K74.3-74.6, LC; B16-17.0, B18.0-B18.1, viral hepatitis B, except acute hepatitis B; and B17.1, B18.2, viral hepatitis C, except acute hepatitis C.

Proportions of HBV and HCV carriers among each liver disease were assumed to be 13:65 for LC[16] and 17:72 for malignant neoplasm of the liver and intrahepatic bile ducts.[17] We assumed a proportion of 13:65 for chronic hepatitis, which was the same as LC. In this study, viral hepatitis B and C were assumed as chronic hepatitis B and C, respectively.

TABLE 1 Estimated number of persons with persistent HCV or HBV infection at 2000

At 2000	Total	AC	CH	LC	HCC
HBV (L-U)	1 317 752-1 467 752	1 120 344-1 259 811	139 677-143 676	33 387-35 387	24 345-28 878
Undiagnosed (L-U)	1 217 752-1 367 752	1 120 344-1 259 811	68 677-72 676	15 987-17 987	12 745-17 278
Under 39 y	253 551	232 691	19 594	1064	203
40-64 y	714 201	655 209	42 417	11 590	4985
Over 65 y (L-U)	250 000-400 000	232 444-371 911	6666-10 665	3333-5333	7557-12 090
Patients	100 000	0	71 000	17 400	11 600
HCV (L-U)	1 694 954-2 194 954	464 373-672 238	1 088 401-1 363 682	87 609-98 845	54 571-60 189
Undiagnosed (L-U)	1 184 954-1 684 954	464 373-672 238	706 401-981 682	10 809-22 045	3371-8989
Under 39 y	125 663	50 852	74 811	0	0
40-64 y	759 291	288 802	466 422	4068	0
Over 65 y (L-U)	300 000-800 000	124 719-332 584	165 169-440 449	6742-17 978	3371-8989
Patients	510 000	0	382 000	76 800	51 200
Total(L-U)	3 012 706-3 662 706	1 584 717-1 932 049	1 228 079-1 507 358	120 097-134 233	78 916-89067
Undiagnosed (L-U)	2 402 706-3 052 706	1 584 717-1 932 049	775 079-1 054 358	26 797-40 033	16 116-26 267
Under 39 y	379 214	283 543	94 405	1064	203
40-64 y	1 473 492	944 011	508 839	15 658	4985
Over 65 y (L-U)	550 000-1 200 000	357 163-704 495	171 835-451 114	10 075-23 311	10 928-21 079
Patients	610 000	0	453 000	94 200	62 800

(L-U): Range from lower estimate to upper estimate.

2.3.2 | Patients with HBV- and HCV-related disease aged ≤64 years in 2011

Patients aged <64 years were included in the estimation of the number of hepatitis virus-related diseases using medical receipts for insurance claims as follows.[10] We collected the medical claims related to hepatitis virus-related diseases from a database of 582 922-787 075 employees and their family members and summarized the diagnosis individually. Then, we estimated the sex-specific and age-specific 1-year prevalence of each hepatitis virus-related disease. Finally, we estimated the number of patients by the sum of the products of the sex-specific and age-specific 1-year prevalence and total population in Japan.

2.3.3 | Patients with HBV- and HCV-related disease aged ≥65 years and older in 2011

The number of patients aged ≥65 years was included in the patient survey in 2011.[15] The number of patients aged ≥65 years with a malignant neoplasm of the liver and intrahepatic bile ducts, chronic hepatitis and LC was calculated based on each age-specific group.

Proportions of HBV and HCV among each liver disease were assumed to be 14:71 for LC and chronic hepatitis[19] and 17:72 for a malignant neoplasm of the liver and intrahepatic bile ducts.[17] We assumed that chronic viral hepatitis B (ICD code: B18.0-18.1) and C (ICD code: B18.2) were chronic hepatitis B and C, respectively. The proportion of patients aged ≥65 years among all patients with viral hepatitis B and C was the same as that for those with chronic hepatitis.

2.4 | Estimates for the number of unconsulted or ceased carriers in 2011

This was estimated by subtracting the numbers of the 4 groups (undiagnosed carriers, patients, cured carriers and deaths) in 2011 from the total of number of carriers (undiagnosed carriers and patients) in 2000.

2.5 | Estimates for the number of new infections from 2000 to 2011

These incidences were estimated by summing the product of sex-specific and age-specific incidence rates among 219 292 and 218 797 blood donors during 1994-2004 in Hiroshima with respect to the total population[20]:

$$\Sigma_{j,k}\, ir_{jk} \times P_{jk},$$

where j, k denote the index of sex and age groups. Symbols ir_{jk} and P_{jk} denote the incidence rate and total population among the groups of sex j and age k, respectively.

2.6 | Estimates for the number cured from 2000 to 2011

We assumed that no one with HBV infection was completely cured. For HCV, this statistical report was used for the number of interferon (IFN) treatments: "Issued record of application for government-subsidized medical expense of hepatitis IFN

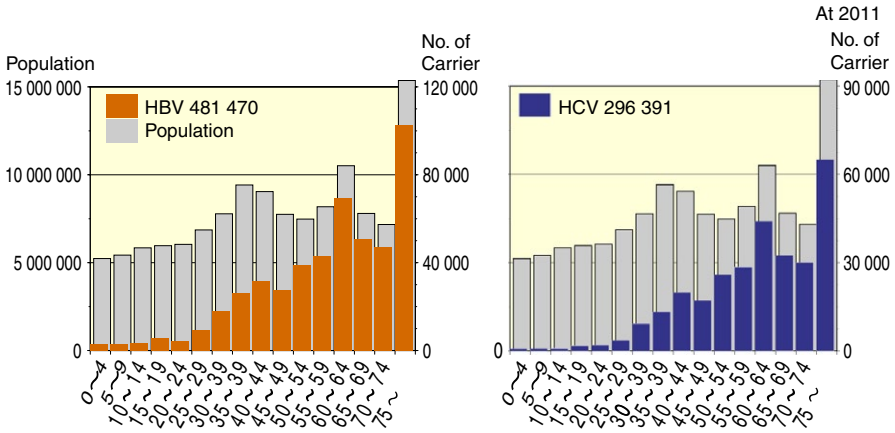

FIGURE 2 Age distribution of estimated number of undiagnosed HBV and HCV carriers in 2011. Estimated numbers of undiagnosed HBV and HCV carriers are shown with population distribution

treatment" in 2008-2011.[21] (Appendix 2). The complete response (CR) rate was assumed as 60% (distributions of genotypes 1b and 2 were assumed as 70% and 30%, respectively). CR rates for patients with genotype 1b and genotype 2 were 50% and 80%, respectively. The number of cured persons by government-subsidized medical care in 2000-2011 was estimated by the product of the number of IFN treatments in 2008-2011, CR rate and (11/4) which is used to estimate the total number of application forms for medical expenses recorded 4 years to 11 years. Furthermore, the total number of cured persons was estimated to be 1.0-1.5 times the number of cured persons by government-subsidized medical care, with the assumption that the proportion of elderly people in the medical system was 0-33.3%.

2.7 | Estimates for the number of deaths from 2000 to 2011

Numbers of deaths from 2000 to 2011 were estimated using the all-cause mortality and survival rates by the total population and number of deaths available by vital statistics in 2000 and 2005[5] as follows. Let i be the index of groups (i = 1 for carriers younger than 39-year-old in 2000; i = 2 for 40- to 64-year-old carriers in 2000; i = 3 for 65 years and older carriers in 2000; i = 4 for 40-year-old and older patients in 2000), and let j be the kind of virus (j = 1 for HBV; j = 2 for HCV). Let $m_{i,2000}$ and $m_{i,2005}$ be mortality in 2000 and 2005. Using the number of $(i, j)^{th}$ groups in 2000 ($P_{i,j,2000}$), the estimated numbers of deaths until 2011 are calculated by the following formula:

$$P_{i,j,2000}(1-(1-m_{i,2000})^5(1-m_{i,2005})^6).$$

In this estimation, we assumed the following: the age range for all patients is more than 40 years, and the risk ratio of persistent infection of HBV or HCV is 1.

2.8 | Ethical Consideration

No ethical issues occurred in this study, because only census data and published data were used as the data source.

3 | RESULTS

The number of hepatitis virus carriers and patients with hepatitis virus-related disease among the 6 different groups in 2011 was calculated based on an estimate of 3.01-3.66 million carriers in 2000.

The total estimated number of HBV- and HCV-infected persons, including both diagnosed and undiagnosed carriers, in 2000 was 3 012 706-3 662 706 (HBV: 1 317 752-1 467 752; HCV: 1 694 954-2 194 954), but this number decreased to 2 090 128-2 840 128 (HBV: 1 118 627-1 268 627; HCV 983 879-1 583 879) in 2011. (Tables 1 and 2).

Then, the patients were subdivided into 4 main groups based on age-specific and sex-specific stratification to determine the trend of the natural course of the infection. The numbers of HCV and HBV undiagnosed carriers were estimated to be 2 402 706-3 052 706 (HBV: 1 217 752-1 367 752; HCV: 1 184 954-1 684 954) in 2000 and 776 826 (HBV: 481 470; HCV: 295 356) in 2011. (Figures 2 and 3) However, the numbers of patients were estimated to be 610 000 (HBV: 100 000; HCV: 510 000) in 2000 and 811 588 (HBV: 303 366; HCV: 520 600) in 2011. Furthermore, it is presumed that the number of carriers belonging to the unconsulted or ceased carriers group who did not receive a consultation had increased gradually up to 501 714-1 251 714 (HBV: 333 791-483 791; HCV: 167 923-767 923) in 2011 (Tables 2).

The number of deaths from 2000 to 2011 was estimated to be 375 777-610 200 (HBV carriers: 145 027-199 125; HCV carriers: 750-411 075) (Tables 2). The total number of newly infected persons was 54 645 (HBV infection: 21 184; HCV infection: 33 460) (Tables 2). The total number of cured persons after successful anti-HCV therapy was estimated as 200 000-300 000 (Tables 2). The numbers of carriers by different provisional diagnoses are listed in Tables 1 and 2.

4 | DISCUSSION

In Japan, various national strategies to trace the number of infected person were introduced only after discovery of the specific virus and techniques to detect the virus in humans as early as the 1980s. After 1986, screening for pregnant women was introduced to prevent

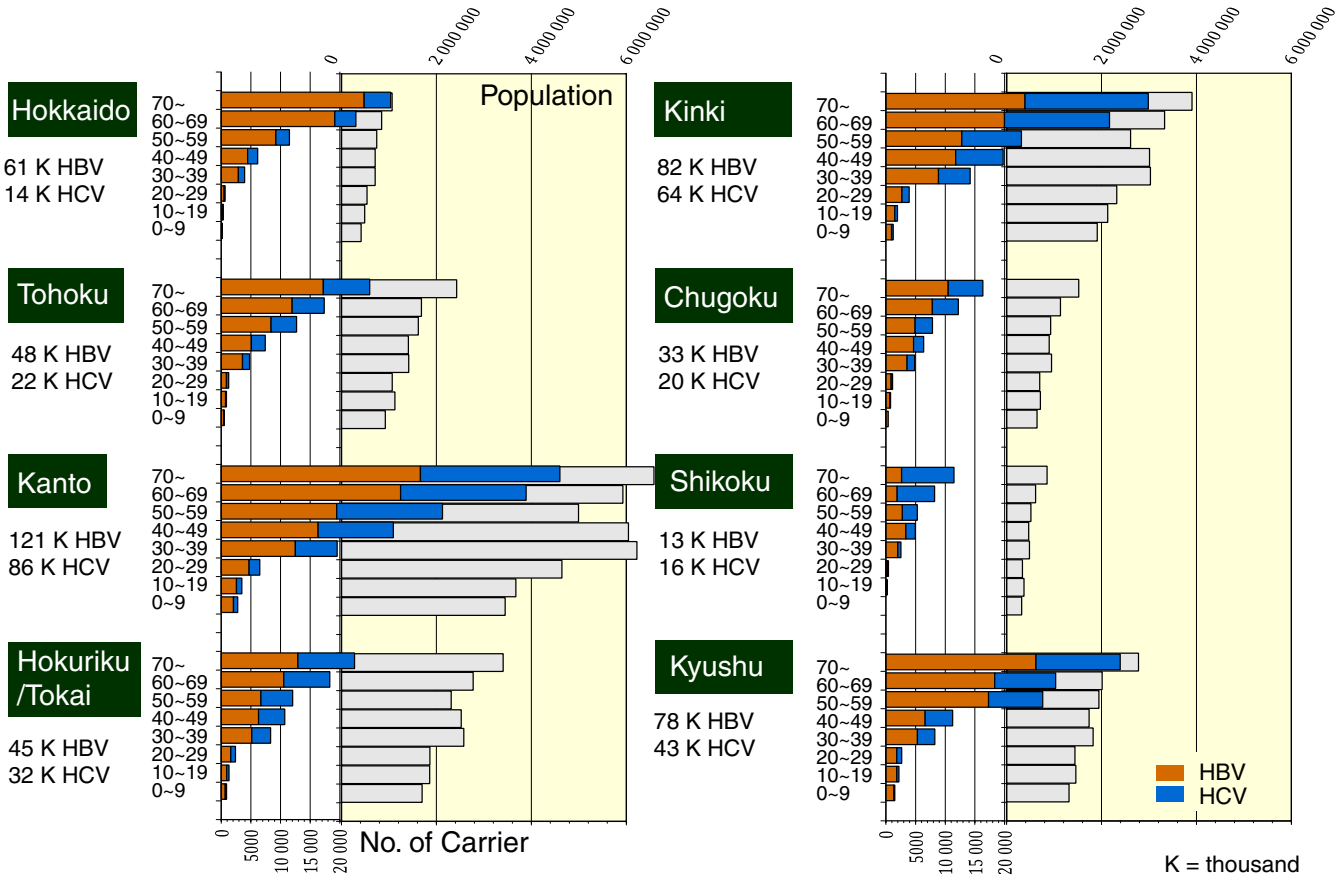

FIGURE 3 Age distribution of estimated number of undiagnosed HBV and HCV carriers by 8 areas in 2011. Estimated numbers of undiagnosed HBV and HCV carriers are shown with population distribution by 8 areas

mother-to-child transmission of HBV, and then, screening of the HCV virus among blood donors was introduced in 1989.[22] Subsequently, many large-scale epidemiological or clinico-pathological studies have been conducted to clearly understand the relationship between persistent infection of hepatitis virus and HCC, natural course of hepatitis virus infection and actual frequency of newly infected people. The nationwide hepatitis virus screening system was first implemented in 2002 funded by the municipal government, which mainly targeted women aged 40 years and older. Since 2007, regional government has established well-coordinated and collaborated hepatitis treatment systems with regional core centres, specialized institutions for hepatitis treatment and primary care doctors.[7] The alleviation of medical costs, ie the medical expense aid system, was launched in 2008.

Moreover, the "Basic Act on Hepatitis Measures" was established to address hepatitis virus infection, and it was adopted by the whole country in 2009.[7] This act is unique and not found in other countries. According to the act, various measures to advance the existing screening system, diagnosis and treatment of liver complication were implemented by various action plans such as hepatitis virus screening for all residents irrespective of age, a medical expense aid system and the establishment of core hospitals for hepatitis treatment in all prefectures.

To get a better control on viral hepatitis, it is important to know the index burden of disease in Japan. Therefore, we have already reported the estimated total number of undiagnosed HBV and HCV carriers in 2000[8] and 2005[9]; they became the baseline evidences for launching new strategy in Japan. Thereafter, the numbers of carriers and patients in 2011 were determined based on the former estimated value in 2000 and the resultant estimate for 2011 was 2 090 128-2 840 128. Within 11 years, the number of undiagnosed carriers decreased from 2.40-3.05 million in 2000 to 0.777 million in 2011. Compared to 2000, significant decrease in numbers of diagnosed patients and undiagnosed carriers in 2011 indicates that hepatitis virus screening and its surveillance were successfully operating and that the current strategic plans and act were very effective for hepatitis virus prevention and control. But other significant outcomes were found in this study.

Firstly, even the number of undiagnosed carrier was greatly reduced, and the number of patients did not increase obviously and was still lower than expected. The number of unconsulted or ceased carriers in 2011 was estimated to be 0.502-1.252 million. This estimate was unexpectedly high because of many reasons such as unawareness of their positive status due to asymptomatic, forgetfulness of their previous experience with testing or their positive status, a misunderstanding or misbelief about the consequences of the infection or the need for follow-up regardless of treatment, a misunderstanding of the doctor's advice, default on treatment or death.

Secondly, the number of untreated patients coincidently increased to some extent. It is strongly recommended to improve awareness campaign by using mass media outlets, such as television, websites, pamphlets and radio. In addition, the proper and effective referral

TABLE 2 Estimated number of persons with persistent HCV or HBV infection at 2011

At 2011	Total	AC	CH	LC	HCC
HBV (L-U)	1 118 627-1 268 627	470 156 + α1	260 596 + α2	21 167 + α3	32 916 + α4
Undiagnosed	481 470	444 206	23 318	6369	7576
Under 39 y	71 774	65 869	5547	301	57
40-64 y	209 227	191 945	12 426	3395	1460
Over 65 y	200 469	186 392	5345	2673	6059
Patients	303 366	25 950	237 278	14 798	25 340
Under 64 y	257 066	25 950	203 278	9498	18 340
Over 65 y	46 300	0	34 000	5300	7000
Unconsulted or ceased(L-U)	333 791-483 791	α1	α2	α3	α4
HCV (L-U)	983 879-1 583 879	119 741 + β1	600 134 + β2	45 521 + β3	50 560 + β4
Undiagnosed	295 356	117 637	172 696	3591	1432
Under 39 y	32 322	13 080	19 242	0	0
40-64 y	135 544	51 555	83 263	726	0
Over 65 y	127 490	53 002	70 191	2865	1432
Patients	520 600	2104	427 438	41 930	49 128
Under 64 y	319 000	2104	282 438	14 930	19 528
Over 65 y	201 600	0	145 000	27 000	29 600
Unconsulted or ceased(L-U)	167 923-767 923	β1	β2	β3	β4
Total(L-U)	2 090 128-2 840 128	589 687 + γ1	850 554 + γ2	65 780 + γ3	82 392 + γ4
Undiagnosed	776 826	561 843	196 014	9960	9008
Under 39 y	104 096	78 949	24 789	301	57
40-64 y	344 771	243 500	95 689	4121	1460
Over 65 y	327 959	239 394	75 536	5538	7491
Patients*	811 588	27 844	654 540	55 820	73 384
Under 64 y	563 688	27 844	475 540	23 520	36 784
Over 65 y	247 900	0	179 000	32 300	36 600
Unconsulted or ceased(L-U)	501 714-1 251 714	γ1	γ2	γ3	γ4
Since 2000					
Newly infected	54 645	54 645			
HBV	21 184	21 184			
HCV	33 460	33 460			
Cured HCV	200 000-300 000				
Death	375 777-610 200				
HBV	145 027-199 125				
HCV	230 750-411 075				

(L-U): Range from lower estimate to upper estimate; patient*: Excepted number of patients with HBV and HCV coinfection.

system from the screening centre to the treatment centre (core hospitals) should be upgraded.[7] The follow-up observation of positive carriers throughout their life should be continued by regional health care (a private or primary care doctor). Hence, the operation system of regional core hospital should be upgraded and promoted. Most importantly, the natural disease course should be explained to people, and then, proper counselling and health education should be given to positive carriers after screening. The counselling must encompass how important it is to consult with a hepatologist once and undergo further investigation and a follow-up visit at the designated treatment centre or core hospital. These 2 outcomes are the strong evidence to adopt the new national strategy on viral hepatitis and HCC control in Japan.

In fact, the actual figures of morbidity and mortality of hepatitis virus-related disease can vary by prefecture. In some prefectures (eg the Saga prefecture), the mortality due to HCC is so high that the disease becomes a priority among other public health problems. But

the mortality rate may be low in other prefectures. This proves the possible use of the countermeasure system in determining the actual figure of infection, and it helps develop more effective strategic plans based on the prefecture's own needs. Although the strategic plan can vary by prefecture, it must strictly follow the "Basic Act on Hepatitis Measures." Yearly review and evaluation of the existing system and strategic plans can be performed based on the significant outcomes reported according to these countermeasures, and then, any action plans of public health promotion can be decided.

Although the overall number of viral hepatitis carriers in Japan has decreased to some extent, the frequency of HCC is still high among all cancer-related deaths. Most patients with HCC in Japan have underlying viral hepatitis, in which HCV accounts for two-thirds of the patients while HBV accounts for about 15%. To reduce the disease-specific mortality rate related to hepatitis virus, it is recommended to upgrade the promotion of nationwide screening system including screening at risk person, screening of blood donors, haemodialytic patients, recipient of repeated blood transfusion due to haematological disorders such as thalassaemia, continuous medical education and using of newly discovered effective drugs with standard regime, promoting the referral system and core hospitals.

In addition, prefecture-specific health strategies should be allocated based on the prefecture's basic needs and own resources. The countermeasures should also be continued as parameters or indicators of the efficacy of the selected treatment regime and to observe the natural disease course. The estimation of the total numbers of diagnosed and undiagnosed carriers, and treated patients and unconsulted or ceased carriers in accordance with disease-specific mortality are crucial countermeasures in the prevention and control of hepatitis virus infection. Furthermore, a health policy for the treatment of HBV-positive or HCV-positive carriers through screening should be strengthened to meet the elimination goal of hepatitis virus by 2030.[1]

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CONFLICT OF INTEREST

There is no declaration of interest.

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APPENDIX 1 Age-specific distribution pattern on clinical diagnosis of HCV patients (Mizui[11,12]) HBV estimated by Markov model (Tanaka[13])

	Age	AC (%)	CH (%)	LC (%)	HCC (%)
HCV	≤39	40.4	59.5	0.0	0.0
	40-59	38.0	61.4	0.5	0.0
	≥60	41.6	55.1	2.2	1.1
HBV	≤39	87.8	7.7	0.4	0.0
	40-59	74.0	5.9	1.6	0.2
	≥60	54.2	2.7	1.3	0.5

APPENDIX 2 Number of supporting application for public medical expenses assistance between 2008 ~ 2011 (MHLW[21])

Year	Interferon (IFN)	Nucleic acid analogue	Triple combination (IFN + Ribavirin + Terakuleville)	IFNfree
2008 (H20)	44 731			
2009 (H21)	26 594			
2010 (H22)	28 797	38 038		
2011 (H23)	16 171	New: 11 916	1550	
		Update: 36 766		
Total (2008-2011)	116 293	New: 49 954	1550	
Estimate (2000-2011)	319 806			
Estimate for cure	191 883			

APPENDIX 3 Age-specific prevalence rate of HBsAg among blood donors from 2007 to 2011 (Tanaka[10])

	Total			Men			Women		
Age in 2011	Donors	HBsAg-positive	Prevalence, % (95% CI)	Donors	HBsAg-positive	Prevalence, % (95% CI)	Donors	HBsAg-positive	Prevalence, % (95% CI)
16-19	275 907	233	0.084 (0.074-0.095)	146 229	134	0.092 (0.076-0.107)	129 678	99	0.076 (0.061-0.091)
20-24	870 427	625	0.072 (0.066-0.077)	503 773	373	0.074 (0.067-0.082)	366 654	252	0.069 (0.060-0.077)
25-29	431 363	580	0.134 (0.124-0.145)	275 621	406	0.147 (0.133-0.162)	155 742	174	0.112 (0.095-0.128)
30-34	263 469	600	0.228 (0.210-0.246)	173 371	467	0.269 (0.245-0.294)	90 098	133	0.148 (0.123-0.173)
35-39	249 768	705	0.282 (0.261-0.303)	162 477	552	0.340 (0.311-0.368)	87 291	153	0.175 (0.148-0.203)
40-44	210 825	693	0.329 (0.304-0.353)	131 294	520	0.396 (0.362-0.430)	79 531	173	0.218 (0.185-0.250)
45-49	140 337	524	0.373 (0.341-0.405)	84 149	405	0.481 (0.435-0.528)	56 188	119	0.212 (0.174-0.250)
50-54	109 455	510	0.466 (0.426-0.506)	60 432	346	0.573 (0.512-0.633)	49 023	164	0.335 (0.283-0.386)
55-59	86 364	477	0.552 (0.503-0.602)	44 889	284	0.633 (0.559-0.706)	41 475	193	0.465 (0.400-0.531)
60-64	66 692	413	0.619 (0.560-0.679)	35 001	245	0.700 (0.613-0.787)	31 691	168	0.530 (0.450-0.610)
65-69	16 120	109	0.676 (0.550-0.803)	8645	60	0.694 (0.519-0.869)	7475	49	0.656 (0.473-0.838)
Total	2 720 727	5469	0.201 (0.196-0.206)	1 625 881	3792	0.233 (0.226-0.241)	1 094 846	1677	0.153 (0.146-0.160)

APPENDIX 4 Age-specific prevalence rate of anti-HCV among blood donors from 2007 to 2011 (Tanaka[10])

Age in 2011	Total			Men			Women		
	Donors	Anti-HCV-positive	Prevalence, % (95% CI)	Donors	Anti-HCV-positive	Prevalence, % (95% CI)	Donors	Anti-HCV-positive	Prevalence, % (95% CI)
16-19	275 907	115	0.042 (0.034-0.049)	146 229	60	0.041 (0.031-0.051)	129 678	55	0.042 (0.031-0.054)
20-24	870 427	415	0.048 (0.043-0.052)	503 773	221	0.044 (0.038-0.050)	366 654	194	0.053 (0.045-0.060)
25-29	431 363	339	0.079 (0.070-0.087)	275 621	229	0.083 (0.072-0.094)	155 742	110	0.071 (0.057-0.084)
30-34	263 469	452	0.172 (0.156-0.187)	173 371	346	0.200 (0.179-0.221)	90 098	106	0.118 (0.095-0.140)
35-39	249 768	509	0.204 (0.186-0.221)	162 477	375	0.231 (0.207-0.254)	87 291	134	0.154 (0.128-0.179)
40-44	210 825	547	0.259 (0.238-0.281)	131 294	414	0.315 (0.285-0.346)	79 531	133	0.167 (0.139-0.196)
45-49	140 337	578	0.412 (0.378-0.445)	84 149	436	0.518 (0.470-0.567)	56 188	142	0.253 (0.211-0.294)
50-54	109 455	542	0.495 (0.454-0.537)	60 432	386	0.639 (0.575-0.702)	49 023	156	0.318 (0.268-0.368)
55-59	86 364	439	0.508 (0.461-0.556)	44 889	279	0.622 (0.549-0.694)	41 475	160	0.386 (0.326-0.445)
60-64	66 692	391	0.586 (0.528-0.644)	35 001	232	0.663 (0.578-0.748)	31 691	159	0.502 (0.424-0.580)
65-69	16 120	113	0.701 (0.572-0.830)	8645	67	0.775 (0.590-0.960)	7475	46	0.615 (0.438-0.793)
Total	2 720 727	4440	0.163 (0.158-0.168)	1 625 881	3045	0.187 (0.181-0.194)	1 094 846	1395	0.127 (0.121-0.134)