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Epidemiology of viral hepatitis C: Road to elimination in Japan

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Abstract: Although HCV infection was the main cause of HCC in Japan contributing 70% over two decades after its first cloning in 1989, it was markedly decreased to 49% in 2013 and expected to decrease continuously. Based on blood donor national database, the new incident cases were 0.4/100,000 person-years, the prevalence was 0.13% and the total number was 890,902-1,302,179 in 2015. Establishment of blood donor screening with anti-HCV measurement and nucleic acid test introduced by Japanese Red Cross as pioneer, high-level medical and surgical care, and the government's policy under the Basic Act on Hepatitis Control have changed its epidemiology and outbreak trend and also enforced the disruption of potential transmission cascades. HCV prevalence among the younger generation was extremely low in all regions, and the predominant age for HCC has shifted to over 60 years old population. Considering such changes, HCV induced HCC occurrence is supposed to be ultimately suppressed in the near future. However, taking into account society changes, regulating intravenous drugs users and monitoring high-risk groups such as tattoos, and men who have sex with men are indeed required in Japan. Understanding the epidemiological changes in HCV is important in assigning, modifying, and designating effective response systems. Selective or national action plans, strategic approaches, and cooperation between government sectors have a positive impact on HCV prevention and control. A dramatic decrease in total number of HCV carriers, increase in number of people treated with highly effective DAA, and subsequent high SVR indicates Japan might achieve WHO's target of HCV elimination by 2030.

***Keywords*:** disease burden, elimination, countermeasure, Japan

Introduction

Hepatitis C virus (HCV) is a positive sense, single-stranded RNA virus sharing the same family of *Flaviviridae* with yellow fever virus, West Nile virus and Dengue virus (*1,2*). HCV has accounted for a major public health burden worldwide and the World Health Organization (WHO) reported that an estimated 71 million people have chronic HCV infection with an attributable death of 399,000 people due to HCV related liver cirrhosis (LC) and hepatocellular carcinoma (HCC) in 2016 (*3*). Moreover, HCV is the major cause of HCC and has contributed to 70-80% of LC and 15% of HCC worldwide (*4*). Therefore, WHO set a global elimination target of viral hepatitis B and C by 2030. Concerning HCV, three major terminal points were set as follows: 80% increase of those eligible to be treated, 90% reduction in incidence of new infection and 65% reduction in HCV-related mortality.

HCV was discovered as the cause of non-A, non-B hepatitis and it was first cloned in 1989 (*1,5*). HCV particles are 50-80 nm in diameter and the HCV genomes comprised of 5'-3' single stranded RNA of 9.6 kilo base pairs bearing ten different open reading frames (ORF) encoding for the production of core, E1, E2, p7, NS2, NS3, NS4A, NS4B, NS5A and NS5B (*6*). HCV isolates can be classified into seven genotypes (1 to 7) and a number of subtypes and its various geographical distribution (*7*). The virulence, transmissibility and sensitivity to antiviral therapy might be greatly influenced by its genotypes. The dominant genotype of HCV in Japan is genotype 1b followed by genotype 2a and 2b (*8-10*). At times, HCV genotype 2b comes across over genotype 1b among those born after 1970 while genotype 2a is constantly found in all age groups in Japan (*8,9,11*). A similar pattern of genotype distribution was also found in hemodialysis patients and a change in genotype distribution from genotype 1b to 2a/2b was also reported among those who started dialysis after 1991 (*12*). In this review article, we would like to express the epidemiology of HCV in Japan.

Countermeasures against HCV in Japan

After cloning of HCV, the diagnostic assays and the treatment for HCV have been gradually developed.

In Japan, screening of antibodies to HCV (anti-HCV) by first generation recombinant enzyme linked immunosorbent assay (ELISA) was started among blood donors since November 1989 (*13*) and replaced by second generation passive hemagglutination (PHA) in April 1992 (*14*). Until 2007, the Japanese Red Cross Society (JRC) used either PHA method (second generation) (HCV-PHA "Dynabot") or PA method (Ortho HCV Ab PA Test II) and substituted with CLEIA method (chemiluminescent enzyme immunoassay, Lumipulse Presto Ortho HCV, Fujirebio Ltd.) in 2008 and CLIA method (chemiluminescent immunoassay, Abbott Architect) in 2018 respectively. JRC uses unique reagents and diagnostic criteria for HCV screening uniformly throughout the country. Moreover, nucleic acid testing (NAT) to screen for HCV RNA was added to HCV screening as a parallel test in October 1999 by JRC (*14,15*).

Later, the Ministry of Health, Labour and Welfare (MHLW) of Japan introduced the initial 5-year project (2002-2006) for the national screening of HBV and HCV among all residents at and over 40 years old (*16*). Later, the aforementioned screening systems are continuing with their prosperity. The screening system for HCV uses the combination of anti-HCV measurement and HCV RNA detection using NAT at the same time. The screening is targeted to explore asymptomatic cases in the general population. It is a unique and effective screening strategy having the benefit of early diagnosis of HCV infection.

Since 2004, JRC implemented the look-back system, in which all collected blood products were partly stored for 10 years with the aim to reconfirm the components of blood products when a blood donor tested positive for infection has a previous record of blood donation and if that blood product was already sent to medical institutions according to the guidelines for look-back system on blood products (*17*).

Aiming to improve the medical care service for liver disease, the regional core specialty hospitals for liver disease were established in all prefectures of Japan in 2007 under the notification of the Health Bureau of the MHLW (*18*). All the core hospitals conduct the following activities: *i*) provision of general medical information on liver disease, *ii*) gathering and sharing information on medical institutions in the prefecture, *iii*) organizing workshops and lectures to medical personnel and health education to local residents, and providing consultation support on liver disease, and *iv*) setting up a forum for consultation with specialist medical institutions on liver disease. In 2008, the medical expense subsidy system was installed in Japan and then the Basic Act on Hepatitis Measures has been formulated since 2010 (*16*).

Interferon-based treatment of HCV infection was started in 1992. The interferon free first-generation Direct Acting Antiviral (DAAs) were introduced in 2014 and then the second generation DAAs have been phasing in since 2015. The development of oral drug DAAs, which have very high sustained virologic response to HCV (SVR), has led to a marked improvement in the treatment of HCV since 2014 (*16*). The evolution of HCV and its countermeasures over the past 30 years in Japan in terms of basic medical, clinical and epidemiological aspects is very impressive (Figure 1).

Natural history of HCV simulated by Markov Model

The natural history of chronic HCV infection was clarified for the first time in 2003 using a Markov model based on clinical cohort data composed of a group of patients who were found to be infected at the time of blood donation and were followed up for a long time at the liver disease hospitals in the 1990s (*19*). Using medical records of a total 942 HCV carriers among blood donors from 1990 to 1999, the natural history of HCV infection was simulated by the Markov Model. The hypothetical cohort demonstrated that among 40 year old males who were diagnosed as asymptomatic HCV carriers, 2.62% of them remain unchanged in their liver disease state but 48.4% developed into chronic hepatitis (CH), 14.6% into LC and 34.4% into HCC at 30 years after initial diagnosis and without any treatment. In contrast to males, the rates were 1.85%, 45.4%, 32.8% and 20.0% respectively in females of the same age group (*19*).

Based on the cumulative probabilities for developing

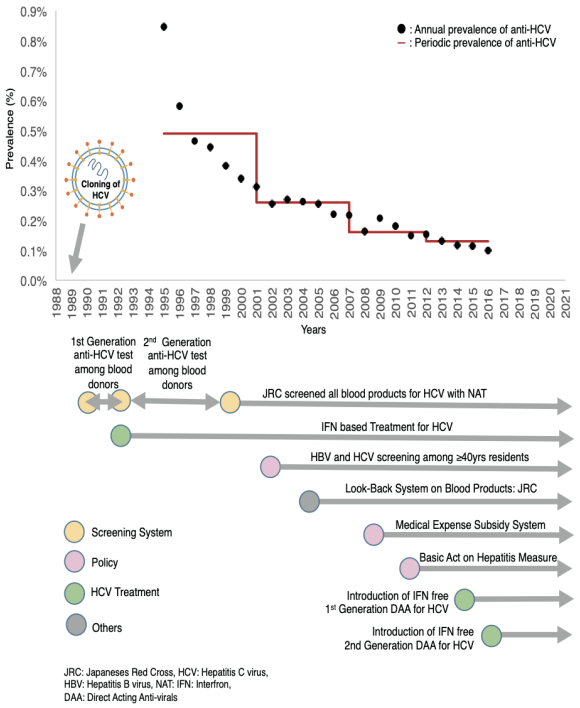

Figure 1. HCV prevalence trend among first time blood donors and its corresponding countermeasure in Japan. In the figure, the red line shows the prevalence of anti-HCV among first time blood donors since 1995. The decreasing trend was illustrated by line and each countermeasure was stated with corresponding arrow indicating the implemented year.

LC and HCC, 43.8% of 40 year old male initially diagnosed as CH remains unchanged as CH, but 15.0% developed into LC and 41.1% into HCC when they were 70 years old. Meanwhile, the rates were 38.9%, 32.7% and 22.0% respectively in females of the same age group (*19*) (Figure 2).

Based on the aforementioned results, it was clarified that the liver disease state progresses in those chronically infected with HCV even if the person is asymptomatic. Moreover, the turnover rate to HCC is increased with age. On the other hand, it is important to find a person who is chronically infected with HCV at an early stage before symptoms appear (necessity of hepatitis virus screening) and provide effective treatment to prevent the onset of carcinogenesis, and most importantly to treat HCC at its dominant age of carcinogenesis. This is part of the evidence that led to the introduction of hepatitis virus testing for all Japanese residents aged 40 and over.

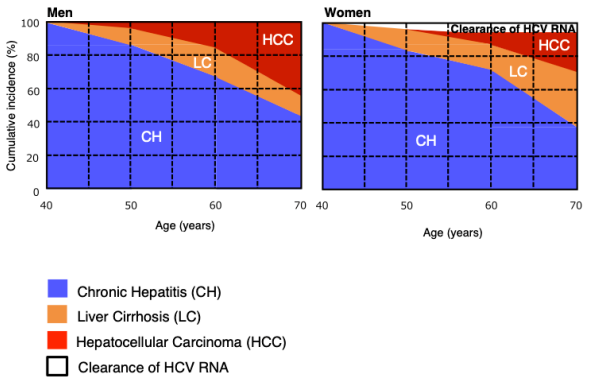

Figure 2. Natural course of HCV infection in hypothetical cohorts aged 40 years until they reach 70 years of age. It shows the transition probabilities and the natural course of HCV infection in those who were diagnosed with HCV induced chronic hepatitis at the age of 40 and then turned into 70 years old. The starting point is defined at 40 years old who were first diagnosed as chronic hepatitis.

Prevalence of HCV in Japan

A study of anti-HCV prevalence among blood donors during 1995-2000 included 3,485,648 first time blood donors in Japan and the prevalence was reported to be 0.49%. Females had higher prevalence than males (0.48% *vs.* 0.50%) (*20*). Anti-HCV positive rate is high in the west regions (Chugoku, Shikoku, Kinki and Kyushu regions) ranging from 0.6-0.7% and lower in the east regions (Tohoku, Kanto and Chubu regions) ranging from 0.3 to 0.4% except Hokkaido (0.6%) (*20*).

The prevalence also differed by age and sex, females had higher prevalence than males until 35 years old but the reciprocal was found after 35 years old having lower prevalence in females (*21*). Anti-HCV positive rate of the elderly is extremely high at 1.28-3.38%, and the same tendency is shown in all regions. In Japan, 89-93% of anti-HCV positive people are over 40 years old in 2000.

The Epidemiological Research Group on the Burden of Viral Hepatitis and Measures for its Elimination (VH-Epi) conducted the study about HCV among first time blood donors in collaboration with the Japanese Red Cross Society (*20,22,23*). The overall anti-HCV prevalence among first-time blood donors was 0.49% (95% CI: 0.48-0.50%) during 1995-2000 (*20*), 0.26% during 2001-2006 (*23*) and 0.16% during 2007-2011 (*22*). The prevalence was found to be less than 1% in all age groups of both sexes (*22*) while it was as low as 0.13% (95% CI: 0.13-0.14%) in the 2012-2016 population (Figure 3) (*24*). Moreover, the prevalence among first-time blood donors in all of Japan during 2012-2016 were divided into the eight main regions of Japan and shown in Figure 3. Age dependent prevalence was reported, with higher prevalence of HCV infection in older age groups and low prevalence in the generation born in the 1990s. Although prevalence among older generation during 2012-2016 was reportedly higher than young generation, it was found to be lower than the same age group of the previous study during 1995-2000. Although the data contained those who were born before 2000, no administrative or clinical cases of widespread infection were reported in the population born after 2000 and it is suggested that HCV infection rate among the general population born after 2000 remains low. To explore prevalence among those born after 2000, a further study is needed.

Incidence of HCV in Japan

New incident cases of HCV in Japan are obligated to report to the Infectious Disease Surveillance of National Institute of Infectious Disease as a Type 5 infectious disease so that such information can be obtained in Japan.

As HCV infection is somehow asymptomatic and subclinical, it is important to monitor the persistence of HCV infection in combination with surveillance through notification under the Infectious Disease Control Law. Additionally, the epidemiological survey on specific populations is also considered necessary to be conducted regularly.

Since the early 1990s, the VH-Epi has conducted and reported on several database-oriented surveys with the cooperation of JRC in order to clarify the new incidence of HCV regionally and on a nationwide scale, the results are shown as follows.

The incidence of HCV among 448,020 individuals who donated 2,676,738 blood units in Osaka during 1992-1997 was reported to be 3.8 per 100,000 person-years (*25*). The highest incidence rate of HCV was found in younger blood donors (16-24 years old: 8.89) compared to older blood donors (35-49 years old: 1.81). In Hiroshima, the incidence study on HCV among blood donors has been started since 1994 (*26*). This study included 218,797 individuals who donated 1,207,773 blood units at regional JRC Blood Center in Hiroshima

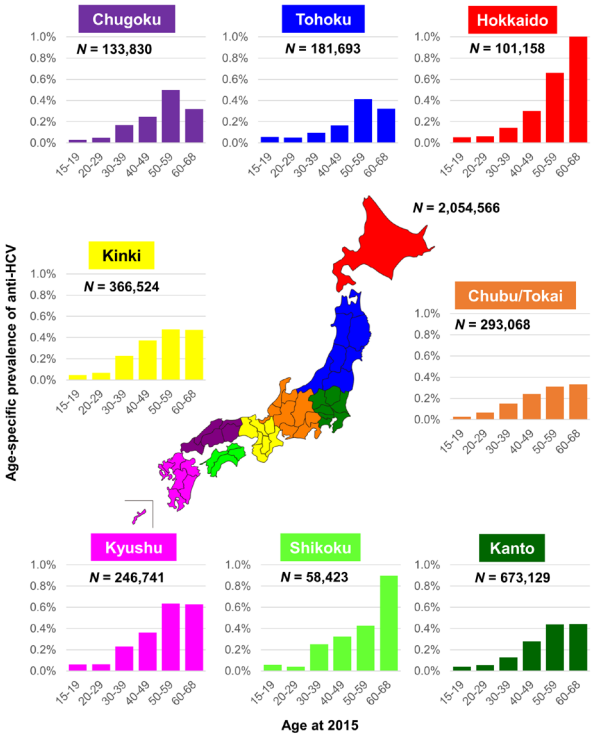

Figure 3. Age-specific prevalence of anti-HCV among first-time blood donors during 2012-2016. In this figure, Japan is geographically divided into eight main regions and the age specific prevalence of anti-HCV is shown for each region in the bar graph and each color in the map represents its corresponding region.

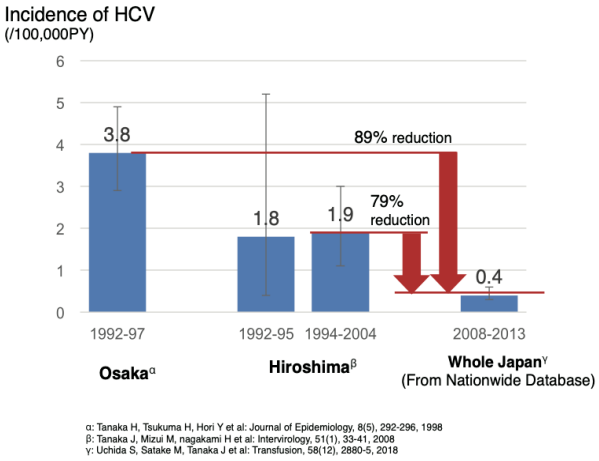

Figure 4. Trend of HCV Incidence among blood donors. This figure represents the incidence rate of anti-HCV among blood donors in Osaka (1992-19797), Hiroshima (1992-1995 and 1994-2004) and all of Japan (2008-2013). The reduction of the incident cases is indicated by the red arrow.

during 1994-2004 (*26*). HCV infection developed in 16 individuals in follow-up visits accounting for an incidence rate of 1.86 per 100,000 person-years (95% CI: 1.06-3.01) (Figure 4). The incidence rate was higher in females than males in the age group over 50 (*26*).

Using the national database of blood donors in Japan, the retrospective cohort study on HCV incidence was conducted in collaboration between the VH-Epi group and JRC to investigate new HCV RNA positivity (new HCV infection) during 2008-2013 (Figure 4) (*27*). The cohort included those who donated blood at least twice during the two-year period from October 2008 to September 2010, 2,341,338 (7,770,533 person-years) and were consecutively "HCV RNA negative and HCV antibody negative" at the first two donations (Figure 4). From the results, the rate of new HCV infections as a whole in Japan is estimated to be 0.40 per 100,000 person-years (95% CI: 0.27-0.57) (*27*), which is considered to be a very low rate and it is an 89% reduction from previous study in Osaka during 1992-1997 (*25*) and a 79% reduction from previous study in Hiroshima during 1994-2004 (*26*).

The incidence of post-transfusion hepatitis in Japan was high (> 50%) in the 1960s when the system was based on the sale of blood but fell sharply to 0.48% in 1992 with introduction of the blood donation system, the elimination of HBsAg-positive or anti-HCV positive blood, the introduction of 400 ml blood collection followed by the introduction of nucleic acid amplification testing. The number of cases of post-transfusion infections (HBV, HCV and HIV) since 2008 were also reported (*24*). The number of cases identified as post-transfusion infection after confirmation of donated blood samples were investigated retrospectively. After the NAT introduction, no cases of HCV infection have been found since 2009 (*24*). Therefore, transfusion associated HCV infection in Japan is considered to be almost under control.

Total number of chronic HCV infections in Japan

Since the introduction of anti-HCV screening system to all blood donors in 1990, the nationwide epidemiological study on HCV infection has been conducted in each period. Such prevalence studies are able to estimate the number of chronic HCV infections in each age group with known age specific anti-HCV or HCV RNA prevalence. The estimated number of chronic HCV infections aged 16-69 years old during 1995-2000 was 884,954 (95% CI: 725,082-1,044,826) in total, 0.46 million in males and 0.42 million in females (*20*). Based on the above mentioned results during 1995-2000, MHLW added additional data covering over 70 years old undiagnosed carriers and patients. Therefore, estimation of chronic HCV infection was expanded, and the total number was estimated to be 1,694,954-2,194,954 including patients engaged in care and undiagnosed carriers as of 2000. Later the medical claim recording system and the health information system were improved after installing the electronic data system in medical institutions and systematic use of International Classification of Disease (ICD) for electronic input of medical data, clinical diagnosis, and its associated

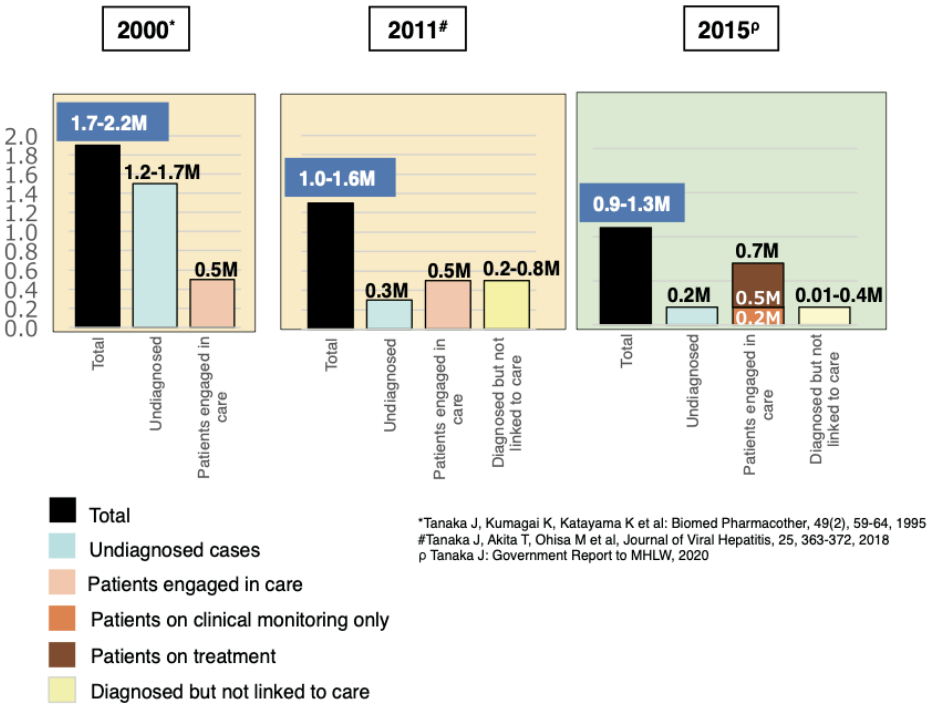

Figure 5. Trend of HCV carriers in Japan during 2000-2015. This figure simply presents the number of HCV carriers by their liver disease status in 2000 and 2011. Each colored bar represents each liver disease status, in order, Total number of HCV carriers, Undiagnosed HCV carriers, Patients taking medical care as in or outpatients at health facilities, and the un-consulted patients who never visit or were lost to follow-up after being diagnosed as HCV carriers. For 2015, the patients are shown in two subcategories: dark brown bar for those taking antiviral treatment and light brown bar for those not taking any antiviral treatment.

records. Considering HCV diagnosed cases but not linked to care, the estimated number of people with chronic HCV infection in the year 2011 was 983,879-1,583,879 (*22*). That number has obviously decreased during 2000-2011 and it is believed to be the impact of the introduction of interferon-based treatment (1992) and NAT to all blood donors (1999) and to all over 40 years old (2002), and installing the medical subsidy system (2008) in Japan. This configuration of the total number of chronic HCV infections allowed us to understand the current HCV burden in Japan. During 2000-2011, the number of HCV new infections was 33,460, the number of cases achieving HCV-RNA clearance was 200,000-300,000 and the number of deaths due to all causes among carriers was 230,750-411,075 (*16,22*) (Figure 5). Based on the analysis of the national database, the total number in 2015 decreased to 890,902-1,302,179, the undiagnosed cases decreased to 224,652, the number diagnosed but not linked to care was 13,061-424,338, those on treatment was 471,986 and those taking clinical monitoring only was 181,203 (*24*).

The VH-Epi is managing many public and national databases such as blood donor data, National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB), infectious disease surveillance system of the National Institute of Infectious Diseases, other national data (demographic, statistics, patient surveys, report on regional public health services and health promotion service, and issued record of application for government subsidized medical expense of hepatitis treatment), *etc.* Based on the abovementioned databases, which cover all of Japan, the VH-Epi, have been conducting complementary verification work with the data obtained from large-scale surveys, *etc.* (survey on the consultation rate after diagnosis, hepatitis virus screening receiving rate survey, pregnant woman survey, serum epidemiological survey in highly invasive areas), and have calculated the number of people chronically infected with hepatitis viruses including HCV in Japan over time.

Moreover, the total number of people chronically infected with HCV in Japan was effectively utilized not only by the government but also by companies as baseline data for planning hepatitis countermeasures and treatment strategies.

Contribution of HCV to HCC in Japan

Malignant neoplasms (cancer) have been the major leading cause of death in Japan since 1981, accounting for 27.3% of all deaths (*28*). In 2019, the cancer related mortality was 304.2 per 100,000 population attributing 376,425 deaths and reportedly an increase of 2841 deaths compared to the previous year. The second leading cause was heart disease (15.0%), followed by senility (8.8%), cerebrovascular disease (7.7%) and pneumonia (6.9%). When aspiration pneumonia was removed from the pneumonia category since 2017, the deaths due to

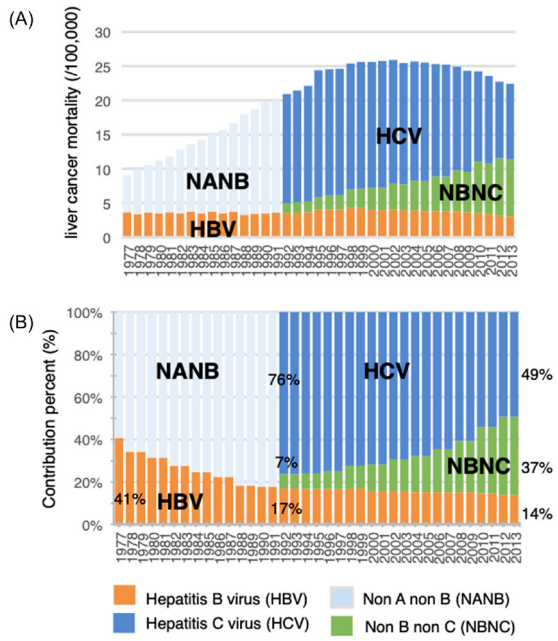

Figure 6. Contribution of HBV, HCV and others to HCC related deaths in Japan. This figure describes the contribution of HBV, HCV and others to HCC related deaths in Japan. The orange bar represents HBV, the green bar HCV, the light blue bar non-A non-B and the dark blue bar non B non C.

pneumonia was downgraded from third to fifth. Out of 376,425 malignant neoplasms, 20.0% originated from lung, 13.7% from colon, 11.4% from stomach, 9.7% from pancreas and 6.7% from liver (5th place for male and 7th place for female).

The VH-Epi has consistently used the same method and the same database to show the proportion of etiological factors contributing to liver cancer mortality since 1980 using the demographic data and the results of the Japan Liver Cancer Study Group. The trends in primary hepatocellular carcinoma (malignant neoplasms of the liver and intrahepatic bile ducts) in Japan are shown in Figure 6. The HCC mortality rate peaked in 2002 and has been decreasing slightly since 2000 for men and since 2010 for women (HCC deaths: 34,637 in 2002 and 25,264 in 2019). Figure 6 shows the causes of HCC by etiological virus. From the late 1970s to 2010, the mortality rate of HCC caused by persistent HBV infection remained almost constant at 3 to 4 per 100,000, but from 2010 to 2013, it showed a slight downward trend (Figure 6A). The proportion of HCV-induced HCC occurrence was 76% in 1992, but this proportion has gradually decreased and was estimated to be 49% in 2013 (Figure 6B). Instead, the proportion of death due to HCC from non-hepatitis B and non-hepatitis C has risen sharply in recent years. The "Basic Plan for the Promotion of Cancer Control" uses the "age-standardized mortality rate under 75 years" (ASR < 75) as an evaluation index for cancer deaths, and it was also calculated for death due to HCC. The number of deaths due to HCC under the age of 75 years has decreased, and those aged 75 years and over tend to account for half of all liver cancer deaths. Next, based on "under-75 age-adjusted mortality rate" for the period 2002-2017, the projection of HCC related mortality was estimated using the same generalized linear model by the National Cancer Centre, it was reported to be 2.7 and 1.9 per 100,000 population in 2025 and 2030, respectively (*24*). From these results, it is suggested that 60% of deaths due to HCC will occur in the people aged 75 and over in the near future and it indicates that the demand for liver cancer treatment for the elderly will increase. Therefore, it is necessary to consider providing liver cancer treatment to the elderly.

HCV infection among hemodialysis patients

Hemodialysis patients are prone to be infected with blood born infection including HCV infection. The reason behind is not only due to frequent long-term invasive therapeutic procedure but also due to the underlying impaired immune system. In 1990, the anti-HCV prevalence among hemodialysis patients was reportedly high at 23.5% and the blood transfusion history had no association to anti-HCV positivity (*21*). A study from 1999 to 2003 on HCV infection among hemodialysis patients in Hiroshima showed that the HCV RNA positive rate was 15.7% in 1999 and then decreased to 12.9% in 2003 (*29*). The prevalence decreased over 5 years after comprehensive installment of effective infection control measures in hemodialysis centers. The annual incidence of HCV infection was 0.33% *i.e.*, 3 in 1,000 hemodialysis patients were newly infected with HCV infection in a year. A recent study showed that the decreasing trend of both anti-HCV and HCV RNA positivity was found by their dialysis started year (*12*). For those who started dialysis after 2002, anti-HCV prevalence was 9.5% and HCV RNA positivity was 7%. The study also revealed that HCV RNA positivity is the predictive factor for poor prognosis of hemodialysis patients.

The Japanese Society of Dialysis Therapy (JSDT) has also conducted a survey on all 4026 of its institutional members (*30*). Although anti-HCV positive rate among the maintenance dialysis patients (approximately 120,000 patients in 2017) is reported at 5.18%, the rate is already high (3.37%) at the time of new dialysis introduction. Compared to the anti-HCV positive rate of 9.8% obtained from the same survey in 2007 (*31*), the rate has decreased by half over the past 10 years. By the latest 2018 annual report on dialysis patients with viral hepatitis, the prevalence of anti-HCV was 4.7% (*32*) and the positivity of HCV RNA among anti-HCV positives was 37% which was markedly lower than previous report (67% in 2007) (*31*). Moreover, the new treatment guideline for HCV infection especially for dialysis patients infected with HCV has been modified as the 2019 update (*33*) in which the Japan Society of Hepatology (JSH) in joint care with JSDT first recommends DAAs to dialysis

patients. In the future, it will be important to promote awareness of HCV-related guidelines to increase collaboration between nephrologists/dialysis specialists and hepatologists, referral rates to specialists and the uptake of antiviral therapy in order to combat HCV infection in dialysis facilities.

Conclusion

Japan has a vigorous effort on countermeasures against viral hepatitis, from four main aspects. First, the screening system, which was first introduced by JRC among blood donors and later expanded to the over 40 years old general population in all regions after development of anti-HCV measurement and NAT robustly disrupt the transmission cascade, reduce the incident and prevalent cases. Second, widespread screening at the regional and national level provides early diagnosis of asymptomatic carriers, early referral to liver disease specialty hospitals, installment of base specialty hospitals in all prefectures and introduction of highly effective DAAs mightily reduces the total number and contrary increases in number those on treatment, which distinctly reduces HCC occurrence and HCV related deaths. Third, the national policy plays a critical role, the medical subsidy system and the Basic Act on Hepatitis Measure are the very effective tools for promoting care and treatment of HCV and reducing its burden, and consequently accelerating universal health coverage. Last but not least, the cooperation between patients and medical associations is crucial to provide outstanding health care service and to attain the utmost control over HCV. Understanding the epidemiological changes in HCV is important in assigning, modifying, and designating effective response systems. Selective or national action plans, strategic approaches, and cooperation between government sectors have a positive impact on HCV prevention and control. A dramatic decrease in total number of HCV carriers, increase in number of people treated with highly effective DAA, and subsequent high SVR indicates Japan might achieve WHO's target of HCV elimination by 2030.

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