

# Trends in Hepatocellular Carcinoma Incidences in Japan Between 1996 and 2019

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# Abstract

**Background:** While the proportion of hepatocellular carcinoma (HCC) cases with non-viral etiology continues to increase in Japan, the epidemiological trends in the sex and age distribution of new HCC cases remain unclear. This study examines the epidemiological trends, including the distribution of sex, age, and disease etiology, in HCC incidence over 24 years.

**Methods:** Data of 20,547 newly diagnosed HCC patients in 1996–2019 at 19 institutions participating in the Liver Cancer Study Group of Kyushu were analyzed in this prospective study. We divided the study period into four 6-year quarters. HCC etiology was categorized as hepatitis B virus (HBV) infection, HBV+hepatitis C virus (HCV) infection, HCV infection, and both negative (non-BC).

**Results:** The incidences of HCC per quarter of the study period were 4,311 (21.0%), 5,505 (26.8%), 5,776 (28.1%), and 4,955 (24.1%) cases, sequentially. Overall, 14,020 (68.2%) patients were male. The number of HCC cases in patients  $\leq 50$  years, 60–69 years, 70–79 years, and  $\geq 80$  years were 3,711 (18.1%), 6,652 (32.4%), 7,448 (36.2%), and 2,736 (13.3%), respectively. The average age of newly diagnosed patients increased in each quarter. HCC was associated with HBV, HBV+HCV, and HCV infections and non-BC in 2,997 (14.6%), 187 (0.9%), and 12,019 (58.5%), and 5,344 (26.0%) cases, respectively. The number of HCV-associated cases decreased in each quarter, while that of non-BC-associated cases increased.

**Conclusions:** HCC incidence tends to increase in the elderly and in non-BC patients; in contrast, HCC incidence due to HCV tends to decrease. In countries where HCV infection is likely the predominant cause of HCC, similar trends in HCC incidence are anticipated in the future.

## Introduction

In 2018, liver cancer was the sixth most commonly diagnosed cancer and the fourth leading cause of cancer-related deaths worldwide, following lung, colorectal, and stomach cancers, with an estimated 841,000 new cases and 782,000 deaths annually.(1–4) Primary liver cancer includes hepatocellular carcinoma (HCC, comprising 75–85% of cases) and intrahepatic cholangiocarcinoma (comprising 10–15% of cases), as well as some rare disease types.(1, 2) The main risk factors for HCC, are chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), high alcohol intake, obesity, and type 2 diabetes.(1, 2, 5–10)

Globally, HBV infection is the leading cause of incident liver cancer and associated mortality, followed by alcohol consumption, HCV infection, and other causes, which account for 33%, 30%, 21%, and 16% of the total burden of this disease, respectively.(2) The major risk factors associated with HCC vary between regions. In areas considered “high-risk” for HCC, for example, China and East Africa, the critical disease determinant is chronic HBV infection; in contrast, in countries such as Egypt or Japan, HCV infection is likely the predominant cause.(1, 2) Recent developments in HCV treatment suggest that a large proportion of liver cancer cases can be prevented.(1, 11, 12) An interferon (IFN)-free direct-acting antiviral agent (DAA, daclatasvir plus asunaprevir) was approved for use in Japanese patients with HCV infection in July

2014. Therefore, high rates of sustained virological response (SVR) have been achieved in patients with chronic HCV infection.(13–16) Recently, DAAs have been introduced as an easy and safe antiviral oral therapy for HCV infection.(16)

In Japan, viral hepatitis remains the leading cause of HCC; however, the decrease in the prevalence of HCV-related HCC has changed the distribution of the disease etiology.(7) Specifically, while the proportion of HCC cases with non-viral etiology continues to increase in Japan,(17) epidemiological trends in sex and age distribution of new HCC cases remain unclear. Therefore, this study aimed to examine the epidemiological trends in HCC incidence in Japan over the past 24 years (1996–2019).

## Experimental Procedures

This prospective study was approved by the Ethics Committee of the National Hospital Organization Nagasaki Medical Center (no. 2020053), and was conducted according to the guidelines of the 1975 Declaration of Helsinki.(18)

We included only those newly diagnosed HCC patients in this study diagnosed at one of the 19 participating institutions of the Liver Cancer Study Group of Kyushu between 1996 and 2019 (24 years). The distribution of factors such as sex, age, and disease etiology was examined among the new HCC cases. The study period was divided into four quarters of six years each: 1996–2001 (first quarter), 2002–2007 (second quarter), 2008–2013 (third quarter), and 2014–2019 (fourth quarter).

## Diagnosis

We diagnosed HCC by measuring alpha-fetoprotein and des-gamma-carboxy prothrombin serum levels and via imaging techniques, including ultrasonography, contrast-enhanced computerized tomography, magnetic resonance, and/or tumor biopsies.

## Etiology

The etiology of HCC was categorized as follows: HBsAg positive and HCV-antibody negative (HBV), both HBsAg and HCV-antibody positive (HBV + HCV), HBsAg negative and HCV-antibody positive (HCV), and both HBsAg and HCV-antibody negative (non-BC).

## Statistical analysis

Inter-quarter differences in sex and disease etiology frequencies were calculated using the chi-square test, and age differences were examined using the one-way analysis of variance (ANOVA) and post-hoc analysis (Bonferroni) methods. All the statistical analyses were performed using JMP software version 15 (SAS Institute, Inc., Cary, NC, USA). *P*-values of < 0.05 were considered significantly different.

## Results

A total of 20,547 patients were newly diagnosed with HCC during 1996–2019 (24 years, Table 1). The number of new HCC cases in the first, second, third, and fourth quarters was 4,311 (21.0%), 5,505 (26.8%), 5,776 (28.1%), and 4,955 (24.1%), respectively (Table 2–4).

Table 1  
Overall patient characteristics (n = 20,547)

Characteristics	Value
Sex (male/female)	14,020 (68.2%)/6,527 (31.8%)
Age (years)	68.6 ± 10.1
Etiology (HBV/ HBV + HCV/ HCV/ non-BC)	2,997 (14.6%)/187 (0.9%)/12,019 (58.5%)/5,344 (26.0%)
Results are expressed as the number (%) or the mean ± standard deviation.	
Abbreviations; non BC=both hepatitis B surface antigen and HCV-antibody negative.	

Table 2  
Sex distribution of new-onset hepatocellular carcinoma cases in each quarter

Sex	First quarter (1996–2001) n = 4,311	Second quarter (2002–2007) n = 5,505	Third quarter (2008–2013) n = 5,776	Fourth quarter (2014–2019) n = 4,955
Male n = 14,020 (68.2%)	3,048 (70.7%)	3,732 (67.8%)	3,842 (66.5%)	3,398 (68.6%)
Female n = 6,527 (31.8%)	1,263 (29.3%)	1,773 (32.2%)	1,934 (33.5%)	1,557 (31.4%)
<i>P</i> -value	-	<i>P</i> = 0.0020 (vs. First quarter)	<i>P</i> = 0.1491 (vs. Second quarter)	<i>P</i> = 0.0231 (vs. Third quarter)
Data are expressed as counts (%).				

Table 3  
Age distribution of new hepatocellular carcinoma cases in each quarter

<b>Age</b>	<b>First quarter (1996–2001) n = 4,311</b>	<b>Second quarter (2002–2007) n = 5,505</b>	<b>Third quarter (2008–2013) n = 5,776</b>	<b>Fourth quarter (2014–2019) n = 4,955</b>
≤ 50 years n = 3,711 (18.1%)	994 (23.0%)	1181 (21.5%)	955 (16.5%)	581 (11.7%)
60–69 years n = 6,652 (32.4%)	1,839 (42.7%)	1697 (30.8%)	1,690 (29.3%)	1,426 (28.8%)
70–79 years n = 7,448 (36.2%)	1,292 (30.0%)	2179 (39.6%)	2227 (38.6%)	1750 (35.3%)
≥ 80 years n = 2,736 (13.3%)	186 (4.3%)	448 (8.1%)	904 (15.6%)	1198 (24.2%)
Mean	65.4 ± 9.2	67.4 ± 9.8	69.5 ± 10.1	71.5 ± 10.1
<i>P</i> -value	-	<i>P</i> < 0.0001 (vs. First quarter)	<i>P</i> < 0.0001 (vs. Second quarter)	<i>P</i> < 0.0001 (vs. Third quarter)
Data are presented as counts (%) or mean ± standard deviation.				

Table 4  
Distribution of disease etiology among new hepatocellular carcinoma cases in each quarter

<b>Etiology</b>	<b>First quarter (1996–2001) n = 4,311</b>	<b>Second quarter (2002–2007) n = 5,505</b>	<b>Third quarter (2008–2013) n = 5,776</b>	<b>Fourth quarter (2014–2019) n = 4,955</b>
HBV n = 2,997 (14.6%)	579 (13.4%)	853 (15.5%)	889 (15.4%)	676 (13.7%)
HBV + HCV n = 187 (0.9%)	67 (1.6%)	65 (1.2%)	39 (0.7%)	16 (0.3%)
HCV n = 12,019 (58.5%)	3147 (73.0%)	3,636 (66.0%)	3,233 (56.0%)	2,003 (40.4%)
Non-BC n = 5,344 (26.0%)	518 (12.0%)	951 (17.3%)	1,615 (27.9%)	2,260 (45.6%)
<i>P</i> -value	-	<i>P</i> < 0.0001 (vs. First quarter)	<i>P</i> < 0.0001 (vs. Second quarter)	<i>P</i> < 0.0001 (vs. Third quarter)
Data are presented as counts (%).				
Abbreviations; non BC=both hepatitis B surface antigen and HCV-antibody negative.				

## Sex

Overall, 14,020 (68.2%) and 6,527 (31.8%) patients were males and females, respectively (Table 1). The number of cases in men and women per quarter were 3,048 (70.7%) and 3,732 (67.8%); 3,842 (66.5%) and 3,398 (68.6%); 1,263 (29.3%) and 1,773 (32.2%); and, 1,934 (33.5%) and 1,557 (31.4%), respectively (Table 2, Supplemental Fig. 1, 2). There were more female patients in the second quarter than in the first ( $P = 0.0020$ , Table 2); concurrently, there were more male patients in the fourth quarter than in the third ( $P = 0.0231$ , Table 2). Therefore, there was no noticeable change in the sex distribution of HCC incidence throughout the study period (Fig. 1).

## Age

Overall, the patients' mean ( $\pm$  standard deviation, SD) age at diagnosis was  $68.6 \pm 10.1$  years (Table 1). The numbers of HCC cases in patients  $\leq 50$  years, 60–69 years, 70–79 years, and  $\geq 80$  years were 3,711 (18.1%), 6,652 (32.4%), 7,448 (36.2%), and 2,736 (13.3%), respectively (Table 3, Supplemental Fig. 3, 4). The mean ages ( $\pm$  SD) of the patients diagnosed with HCC in the first, second, third, and fourth quarters

were  $65.4 \pm 9.2$ ,  $67.4 \pm 9.8$ ,  $69.5 \pm 10.1$ , and  $71.5 \pm 10.1$  years, respectively, showing an increase over time ( $P < 0.0001$ ,  $P < 0.0001$ , and  $P < 0.0001$ , respectively, Table 3, Fig. 1).

## Etiology

The HCC diagnosis was associated with HBV, HBV + HCV, HCV, and non-BC exposure in 2,997 (14.6%), 187 (0.9%), 12,019 (58.5%), and 5,344 (26.0%) cases, respectively (Table 1). There were 579 (13.4%), 853 (15.5%), 889 (15.4%), and 676 (13.7%) new HCC cases associated with HBV in the first, second, third, and fourth quarters, respectively, showing no change in the overall incidence over time (Table 4, Supplemental Fig. 5, 6). The corresponding values for HCV were 3147 (73.0%), 3636 (66.0%), 3233 (56.0%), and 2003 (40.4%) cases, respectively, showing a decrease over time ( $P < 0.0001$ ,  $P < 0.0001$ , and  $P < 0.0001$ , respectively, Table 4). Finally, the corresponding values for non-BC were 518 (12.0%), 951 (17.3%), 1615 (27.9%), and 2260 (45.6%) cases, respectively, showing an increase over time ( $P < 0.0001$ ,  $P < 0.0001$ , and  $P < 0.0001$ , respectively, Table 4).

## Correlation between age and etiology

The mean ages ( $\pm$  SD) of the patients with HCC associated with HBV, HBV + HCV, HCV, and non-BC were  $60.2 \pm 10.9$ ,  $63.6 \pm 10.0$ ,  $69.7 \pm 8.8$ , and  $71.0 \pm 9.9$  years, respectively (Fig. 2). There was a significant association between patient age and disease etiology ( $P < 0.0001$ ,  $P < 0.0001$ , and  $P < 0.0001$ , respectively, Fig. 2).

## Discussion

In the present study, we examined epidemiological trends in HCC incidence, including the distribution of sex, age, and disease etiology over 24 years. Although there was no noticeable change in the sex distribution of HCC incidence throughout the study period, the average age of newly diagnosed HCC patients increased along the quarters. The number of HCV-associated cases decreased over time, while non-BC-associated cases increased over time. Moreover, there was a significant association between patient age and disease etiology.

In July 2014, DAAs were approved for Japanese patients with HCV infection. The development of DAAs has made it easier to treat HCV infections in the elderly and cirrhotic patients, and not only at specialized high-volume centers but also at general practice clinics.<sup>(16)</sup> As a result, the eradication of HCV infection has been reported to reduce HCC risk.<sup>(19)</sup> In the present study, the number of new HCC cases increased from the first to the third quarter (1996–2013), decreasing, after that, from the third to the fourth quarter (2014–2019). This relative reduction in HCC cases observed in the fourth quarter (2014–2019) may be associated with improved management of HCV infections with DAAs.

HCC incidence is 2–3-fold higher among men than women in most regions worldwide, while liver cancer ranks fifth and second in the global number of cases and associated deaths among men, respectively.<sup>(1)</sup> Meanwhile, liver cancer incidence is forecasted to decrease among men in Japan and China and women in Japan and Denmark.<sup>(2)</sup> In the present study, there was no association between sex and HCC incidence

over time. Therefore, while the incidence of HCC is expected to decrease among both men and women in Japan, a sex gap in the burden of this disease remains.

In the present study, patient age among newly diagnosed HCC cases increased over time. Meanwhile, the number of HCV-associated HCC cases decreased over time, in contrast to non-BC-associated cases, which increased over time. Additionally, we observed an association between patients' age and disease etiology. Overall, HBV-associated HCC patients tended to be younger (mean age  $\pm$  SD at onset  $60.2 \pm 10.9$  years) than HCV-associated HCC patients (mean age  $\pm$  SD at onset  $69.7 \pm 8.8$  years). Therefore, it was predicted that the age of new-onset HCC patients would decrease by the decrease in new-onset HCV-associated HCC cases; however, the age of new-onset HCC patients has instead increased. This is because in the present study, the proportion of non-BC-associated HCC cases (mean age  $\pm$  SD at onset  $71.0 \pm 9.9$  years) was higher than that of HCV-associated HCC cases (mean age  $\pm$  SD at onset  $69.7 \pm 8.8$  years), and it continued to increase. In the future, as the incidence of non-BC-associated HCC increases, the age of the incidence of HCC will also increase.

The use of DAAs in HCV-infected patients has been shown to lower the risk of liver-related events, including HCC.(20) However, despite an SVR of  $> 95\%$ , the HCC risk in DAA-treated HCV-infected patients—with advanced fibrosis or cirrhosis—was shown to remain between 0.3 and 1.8% per year.(21, 22) The current European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) guidelines recommend lifetime surveillance of HCV-cured patients with cirrhosis. (23, 24) Identifying clinical and molecular markers associated with HCC risk among these patients may improve the treatment effectiveness and resource allocation.(23, 24) Studies on epidemiology and precision medicine may help inform, refine, and customize clinical guidelines for disease surveillance in this context.(25)

In the present study, the average age of patients newly diagnosed with HCC and those newly diagnosed with non-BC-associated HCC increased over time, while the patients newly diagnosed with HCV-associated HCC decreased over time. The increasing age of patients newly diagnosed with non-BC-associated HCC is likely to become a public health concern in the future. Recent studies have reported an association between metabolic syndrome (diabetes and obesity), excessive alcohol consumption (alcoholic fatty liver disease), and high-calorie intake (nonalcoholic fatty liver disease), and HCC risk in countries characterized by Westernized sedentary lifestyles.(26) A detailed understanding of the relevant risk factors is paramount for improving HCC screening, diagnosis, management, and prevention strategies.(26)

This study had some limitations. Firstly, while the hepatic reserve effect in liver carcinogenesis was known, in the present study, we focused mainly on three factors, sex, age, and disease etiology. Secondly, we did not investigate the size or number of HCC incidences, namely, its stages. Future studies investigating the correlation between the HCC stage and sex, age, or disease etiology are required.

In conclusion, the present study suggests that HCC incidence in the elderly and due to non-BC tended to increase, while the incidence of HCV-associated HCC tended to decrease between quarters. In countries

where HCV infection is likely the predominant cause of HCC, like Japan, similar trends in HCC incidence are anticipated in the future.

## **Declarations**

### **Conflict of interest and Ethical Standards:**

The authors have no conflicts of interest to declare.

### **Informed Consent:**

Informed consent was obtained from all individual participants included in the study.

### **Ethical approval:**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Ethics Committee of the National Hospital Organization Nagasaki Medical Center, no. 2020053) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### **Data Availability:**

The data that support the findings of this study are available from the corresponding author, HY, on reasonable request.

### **Animal Research (Ethics):**

Not applicable

### **Consent to Participate (Ethics):**

Informed consent was obtained from all individual participants included in the study.

### **Consent to Publish (Ethics):**

Not applicable

### **Plant Reproducibility:**

Not applicable

### **Clinical Trials Registration:**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Ethics Committee of the National

Hospital Organization Nagasaki Medical Center, no. 2020053) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Author Contribution:**

Masahito Nakano: concept and design, acquisition of data, writing of the manuscript

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Shigemune Bekki: acquisition of data

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### **Conflict of Interest:**

The authors have no conflicts of interest to declare.

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## Figures

Figure 1.

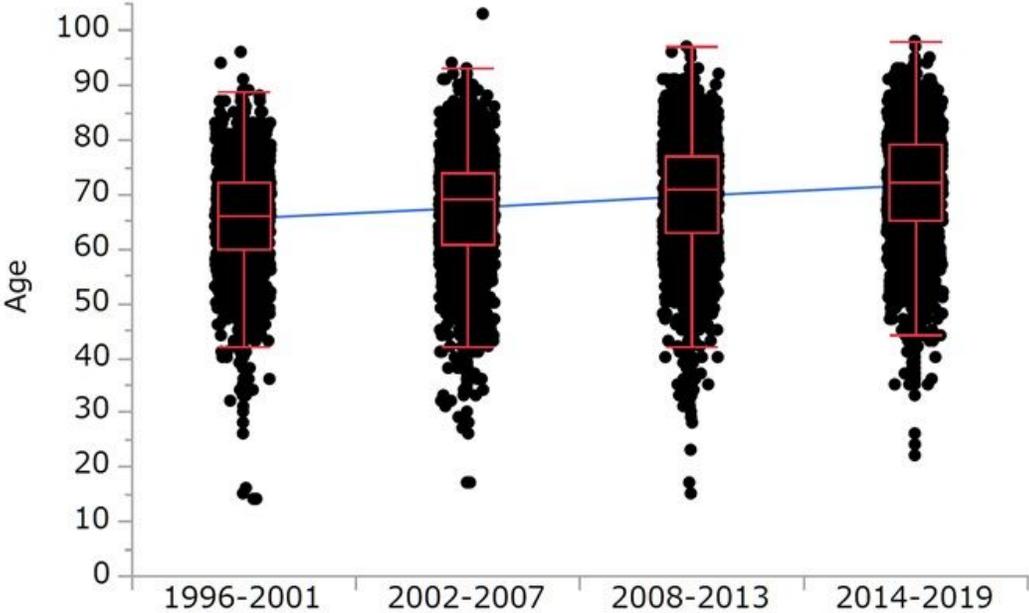
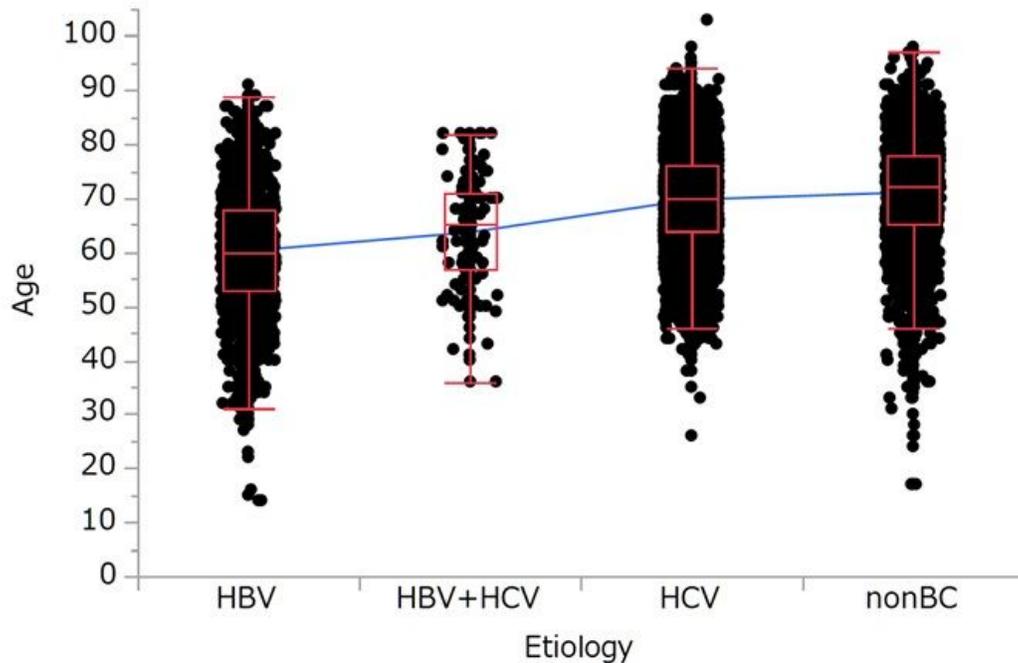


Figure 1

Age distribution of new hepatocellular carcinoma cases.  $65.4 \pm 9.2$  years during 1996–2001 to  $67.4 \pm 9.8$  years during 2002–2007,  $P < 0.0001$ ;  $67.4 \pm 9.8$  years during 2002–2007 to  $69.5 \pm 10.1$  years during 2008–2013,  $P < 0.0001$ ; and  $69.5 \pm 10.1$  years during 2008–2013 to  $71.5 \pm 10.1$  years during 2014–2019,  $P < 0.0001$ , respectively (mean  $\pm$  standard deviation).

# Figure 2.



**Figure 2**

Correlation between patient age and disease etiology.  $60.2 \pm 10.9$  years in HBV to  $63.6 \pm 10.0$  years in HBV+HCV,  $P < 0.0001$ ;  $63.6 \pm 10.0$  years in HBV+HCV to  $69.7 \pm 8.8$  years in HCV,  $P < 0.0001$ ;  $69.7 \pm 8.8$  years in HCV to  $71.0 \pm 9.9$  years in non-BC,  $P < 0.0001$ , respectively (mean  $\pm$  standard deviation).

## Supplementary Files

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- [SupplementalFigure1.tif](#)
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