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Abstract

To better understand the spread of hepatitis C virus (HCV) infection, we studied the association of HCV infection with similarly transmissible hepatitis B virus (HBV) infection and with hepatitis A virus (HAV) infection, which is supposed to be related to a nosocomial transmission of HCV. This was done by studying the presence or absence of antibodies to these viruses, as well as hepatitis B surface antigen, in a population of 1,398 inhabitants with abnormal liver function tests or history of liver disease and/or blood transfusion. This group was drawn from a group of 7,905 examinees screened for liver disease in 26 districts of Okayama prefecture, Japan. The prevalence of antibody-positive cases increased with age for those viruses. Small but significantly increased odds ratios were obtained among anti-HCV antibodies (HCVAb), anti-hepatitis B core antibodies (HBcAb) and anti-hepatitis A antibodies (HAVAb). After adjusting odds ratios by logistic regression analysis, a significant association was present only between HCVAb and HBcAb. The distribution of age-adjusted prevalences (AAP) of HCVAb in 26 districts was significantly wider than those of HBcAb or HAVAb. The district-based AAP of HCVAb, but not of HBcAb and HAVAb, correlated significantly with the district-based prevalence of infectious hepatitis having a tendency of chronicity reported in 1953-1955. Adjusted odds ratios calculated by logistic regression analysis of the virus markers showed that HCVAb was significantly associated with a past history of blood transfusion. Thus, the spread of HCV infection is speculated to have been triggered by blood transfusion, particularly from paid donors initially, followed by transmission by nosocomial or close person-to-person contact.

KEYWORDS: hepatitis A, hepatitis B, hepatitis C, seroepidemiology, route of infection, blood exposure

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To better understand the spread of hepatitis C virus (HCV) infection, we studied the association of HCV infection with similarly transmissible hepatitis B virus (HBV) infection and with hepatitis A virus (HAV) infection, which is supposed to be related to a nosocomial transmission of HCV. This was done by studying the presence or absence of antibodies to these viruses, as well as hepatitis B surface antigen, in a population of 1,398 inhabitants with abnormal liver function tests or history of liver disease and/or blood transfusion. This group was drawn from a group of 7,905 examinees screened for liver disease in 26 districts of Okayama prefecture, Japan. The prevalence of antibody-positive cases increased with age for those viruses. Small but significantly increased odds ratios were obtained among anti-HCV antibodies (HCVAb), anti-hepatitis B core antibodies (HBcAb) and anti-hepatitis A antibodies (HAVAb). After adjusting odds ratios by logistic regression analysis, a significant association was present only between HCVAb and HBcAb. The distribution of age-adjusted prevalences (AAP) of HCVAb in 26 districts was significantly wider than those of HBcAb or HAVAb. The district-based AAP of HCVAb, but not of HBcAb and HAVAb, correlated significantly with the district-based prevalence of infectious hepatitis having a tendency of chronicity reported in 1953-1955. Adjusted odds ratios calculated by logistic regression analysis of the virus markers showed that HCVAb was significantly associated with a past history of blood transfusion. Thus, the spread of HCV infection is speculated to have been triggered by blood transfusion, particularly from paid donors initially, followed by transmission by nosocomial or close person-to-person contact.

Key words: hepatitis A, hepatitis B, hepatitis C, seroepidemiology, route of infection, blood exposure

The hepatitis C virus (HCV) is a major public health problem worldwide, and the prevalence of HCV infection is estimated to be 0.2 to 3.9% (1-4) of blood donors or healthy individuals in developed countries including Japan. HCV infection readily progresses to chronic hepatitis and cirrhosis, ultimately developing into hepatocellular carcinoma at a high rate (5). The most common risk factor for HCV infection is blood transfusion performed before the Japanese Red Cross instituted screening of donor blood for anti-HCV antibodies (HCVAb) in November 1989 (6). Blood transfusion is still the highest risk factor in developing countries (7). However, less than half the subjects with positive HCVAb have a history of blood transfusion and the rest have only indirect evidence of exposure to blood, such as surgery, acupuncture or tattoos (1, 2, 6, 8-11), or even no identifiable risk factor except having stayed for more than 3 months in endemic countries during childhood (1).

Since hepatitis C is originally a blood-borne infection like hepatitis B, a close association should exist between HCVAb and antibodies to the hepatitis B core antigen (HBcAb), which is a measure of past and current hepatitis B virus (HBV) infection and has a higher sensitivity than antibodies to the hepatitis B surface antigen (HBsAb) (12). In some similar studies, however, HCVAb was compared with HBsAb or even with hepatitis B surface

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antigen (HBsAg) (13). The present study was initiated on a district-based population to analyze the association of HCVAb with not only HBcAb but also with anti-hepatitis A virus (HAV) antibodies (HAVAb) in an attempt to examine nosocomial infection associated with HAV infection as suggested by Naito *et al.* (14). Also, we compared the present district-based figures for HCVAb with those for infectious (or epidemic) hepatitis in Okayama prefecture during 1953 to 1955 (15, 16) to shed light on chronological trends in the spread of HCV infection.

Subjects and Methods

Demographic profiles. The subjects of the present study were 1,398 inhabitants (752 males and 646 females with a male to female ratio of 1.2) with abnormal liver function tests and/or past and family histories of liver disease and/or blood transfusions and were referred to as further examinees. The subjects were drawn from 7,905 inhabitants (2,376 males and 5,529 females; male to female ratio, 0.43) of Okayama Prefecture, Japan, who underwent a periodic mass screening for liver diseases. The further examinees were 17.7 % of the total screened inhabitants. This mass screening was organized by the Agricultural Cooperative Association of Okayama Prefecture for residents over 40 years of age as recommended by the Ministry of Health and Welfare of Japan and was carried out by the Okayama Health Foundation from April 1992 to March 1993. The thresholds of screening tests for liver diseases were aspartate aminotransferase (AST) $>$ 30 IU/l, alanine aminotransferase (ALT) $>$ 30 IU/l and γ-glutamyltransferase (GGT) $>$ 50 mIU/ml. They were from 26 districts (9 cities and 17 counties) covering most of the areas in Okayama prefecture. The average number of examinees per district was 304, ranging from 66 to 647, with an average number of further examinees per district at 54, ranging from 6 to 113.

The prevalence of infectious hepatitis in corresponding districts of Okayama prefecture from 1953 to 1955 was calculated by dividing the number of patients who visited clinics (16) with the population of the corresponding districts in 1954 and expressed as cases per 1,000 inhabitants.

Assays of virus markers. Sera of all the further examinees who were suspected of having liver injury were analyzed for HCVAb by enzyme immunoassay (EIA) with an Abbott HCV EIA 2nd Generation kit (Dainabot Co., Ltd., Tokyo), for HBsAg by EIA with an HBsAg Dainapack (Dainabot Co., Ltd.), for HBcAb by EIA with a Hepatitis B Virus Core Antigen (Recombinant) CORAB kit (Dainabot Co., Ltd.) and for HAVAb by EIA with an EIA kit, IMx HAVAB Assay System (Dainabot Co., Ltd.).

Statistical analysis. Association among virus markers and associated parameters was analyzed by calculating adjusted odds ratios and 95 % confidence intervals (95 % CI) with a logistic regression model. Predicting variables entered into the logistic equations were sex, age groups (younger than 40, 40 to 49, 50 to 59, 60 to 69 and older than 69 years of age), and the virus markers except the one selected as the dependent variable. HBsAg was not entered into the equations as there was a strong correlation between HBsAg and HBcAb. The cutoff level for HBcAb was arbitrarily set at 50 %, yielding some HBcAb-negative cases despite the presence of HBsAg. Risk factors of HCV, HBV and HAV infection were also analyzed by calculating adjusted odds ratio with the logistic regression model. Predicting variables entered into the equations for the logistic model of risk analysis were sex, age groups (younger than 40, 40 to 49, 50 to 59, 60 to 69 and older than 69 years of age), past histories of blood transfusion and liver diseases, and family history of the liver diseases.

Prevalences of HCVAb, HBcAb and HAVAb were compared among 26 districts by calculating the age-adjusted prevalence (AAP) from the standardized prevalence ratio (SPR). This was done by taking the age distributions of the prevalences of virus markers among all the further examinees as expected age distributions. The district-based AAP was statistically evaluated by the Chi square test.

The correlation between the population-adjusted number of patients (patients who visited clinics and were diagnosed as having acute hepatitis divided by the population of the district at that time and expressed as cases per 1,000 inhabitants) with infectious (or epidemic) hepatitis in the period from 1953 to 1955 and the prevalence of HCV, HBV and HAV in the period from 1992 to 1993 was also compared for corresponding districts. This was possible since the ratios of further examinees to total examinees did not vary widely.

All the statistical evaluations were made with computer packages of Microsoft Excel Version 5.0 and SPSS Version 8.0 (SPSS Inc. Chicago, IL, USA).

Table 1 Age distribution of hepatitis virus markers among 1398 screened subjects

Age (years)	Male	Female	F/M	HCVAb (%)	HBsAg (%)	HBcAb (%)	HAVAb (%)
≤ 39	46	14	0.3	1.7	5.0	15.0	6.7
40 – 49	69	60	0.9	9.3	7.0	31.8	31.0
50 – 59	163	202	1.2	11.2	2.7	27.9	68.8
60 – 69	348	295	0.8	17.9	3.0	36.9	81.6
70 ≤	126	75	0.6	15.9	2.5	48.8	90.5
Total	752	646	0.9	14.4	3.3	34.9	71.7

HCVAb: Anti-hepatitis C virus antibodies; HBsAg: Hepatitis B surface antigen; HBcAb: Anti-hepatitis B core antibodies; HAVAb: Anti-hepatitis A antibodies.

Table 2 Adjusted odds ratios for age strata and prevalences of HCVAb, HBcAb and HAVAb calculated by logistic regression analysis

	HCVAb		HBcAb		HAVAb	
	OR	[95% CI]	OR	[95% CI]	OR	[95% CI]
Sex	0.7*	[0.5-0.9]	1.2	[0.9-1.5]	1.0	[0.8-1.3]
Age (years)						
< 40	0.1*	[0.02-0.95]	0.4*	[0.2-0.8]	0.02*	[0.01-0.05]
40 – 49	0.6	[0.3-1.1]	0.9	[0.6-1.4]	0.1*	[0.1-0.2]
50 – 59	0.6*	[0.4-0.9]	0.7*	[0.5-0.95]	0.5*	[0.4-0.7]
60 – 69	1.0		1.0		1.0	
70 ≤	0.8	[0.5-1.3]	1.6*	[1.2-2.2]	2.1*	[1.3-3.6]
HCVAb	/		1.9*	[1.4-2.5]	1.4	[0.9-2.1]
HBcAb	1.9*	[1.4-2.5]	/		1.2	[0.9-1.6]
HAVAb	1.4	[0.9-2.1]	1.2	[0.9-1.6]	/	
Predictive probability	85.6		65.7		78.9	

HCVAb; HBcAb; HAVAb: See legend to Table 1.
OR: Odds ratio; CI: Confidence interval.
*$P < 0.05$.

Results

The age distributions of the prevalences of virus marker-positive subjects and genders among the further examinees are shown in Table 1. Higher prevalences of HCVAb, HBcAb and HAVAb were found in the 60s to 70s age groups. This tendency was more marked in HCV than in HBcAb, suggesting that a differential cohort effect contributes to the increased prevalence with age. On the other hand, the prevalence of HBsAg-positive subjects was higher in younger generations. Since the number of asymptomatic carriers of HCV in a healthy population is relatively small in comparison to those who have abnormal liver function tests, the minimum prevalence of HCVAb for the ages studied in Okayama prefecture was calculated by dividing the number of further examinees positive for HCVAb by the number of total examinees and was found to be 2.5 %. The prevalence of HAVAb in Okayama prefecture should be close to the average percentage of HAVAb-positive further examinees (71.7 %) as acute hepatitis cases were not likely to be included in this study. The percentage of HBsAg-positive further examinees (3.3 %) was much smaller than that of HBcAb-positive ones (34.9 %); thus, the positive HBcAb could be regarded as indicating a past history of exposure to HBV rather than the carrier state of HBV.

When odds ratios among HCVAb, HBsAg, HBcAb and HAVAb were calculated without adjusting for age, there was a weak but significant association not only

Table 3 Adjusted odds ratios for age strata and risk factors of hepatitis C virus, hepatitis B virus and hepatitis A virus infection calculated by logistic regression analysis

	HCVAb		HBcAb		HAVAb	
	OR	[95% CI]	OR	[95% CI]	OR	[95% CI]
Sex	0.8	[0.6-1.0]	1.2	[0.9-1.5]	1.0	[0.7-1.3]
Age (years)						
< 40	0.1*	[0.01-0.7]	0.3*	[0.1-0.6]	0.01*	[0.01-0.05]
40 – 49	0.5*	[0.3-0.9]	0.8	[0.5-1.2]	0.1*	[0.1-0.2]
50 – 59	0.6*	[0.4-0.9]	0.7*	[0.5-0.9]	0.5*	[0.4-0.7]
60 – 69	1.0		1.0		1.0	
70 ≤	0.9	[0.6-1.4]	1.6*	[1.2-2.2]	2.2*	[1.3-3.6]
Blood transfusion	1.9*	[1.2-3.1]	1.1	[0.7-1.6]	1.1	[0.7-1.8]
Pasthistory of liver disease	1.9*	[1.3-2.7]	1.4	[1.0-1.8]	0.9	[0.6-1.3]
Family history of liver disease	2.6*	[1.1-6.4]	3.7*	[1.6-8.8]	1.1	[0.4-3.2]
Predictive probability	85.6		66.3		78.9	

HCVAb; HBcAb; HAVAb; OR; CI: See legends to Tables 1 and 2.
*$P < 0.05$.

between HCVAb and HBcAb with an odds ratio of 2.0 (CI: 1.5-2.7), but also between HCVAb and HAVAb with an odds ratio of 1.9 (CI: 1.3-2.8). Associations were also observed between HAVAb and HBcAb with an odds ratio of 1.5 (CI: 1.2-2.0) and between HAVAb and HBsAg with an odds ratio of 0.6 (CI: 0.3-0.99). HBsAg and HBcAb had a high odds ratio of 8.2 (CI: 4.4-15.4), thus HBsAg was eliminated in the logistic regression analysis. As for the adjusted odds ratio, the association of HAVAb with HCVAb or HBcAb became insignificant, leaving a significant odds ratio only between HCVAb and HBcAb (Table 2). There was a sex difference in the prevalence of HCVAb, with a higher rate in females.

A similar logistic regression analysis of risk factors of HCV, HBV and HAV infection (Table 3) was performed. Blood transfusion, and past history and/or family history of liver disease were all risk factors of HCV infection, while only family history of liver disease was noted as a risk factor or associated risk factor of HBV infection, although only 15.4 % of HCVAb-positive cases had a history of blood transfusion. For HBV infection, a family history of liver disease was the only associated risk factor. These risk factors were unrelated to HAV infection. The distribution of blood transfusion dates differed widely, 27.0 % of subjects having received blood transfusion before the commencement of screening donor blood for HBsAg in April 1972 and 80.3 % before commencement of screening for HCVAb in November 1989 (24).

SPR and AAP of HCVAb, HBcAb and HAVAb among the further examinees in 26 different districts of Okayama prefecture are presented in Table 4. AAP of virus marker-positive cases varied widely from one district to another, particularly in HCVAb, with a coefficient of variation as high as 44.7 %, followed by 28.8 % for HBcAb and 12.8 % for HAVAb. Significantly higher prevalence was present in districts E, F, K and Y for HCVAb, in districts K, T and X for HBcAb and in no districts for HAVAb. Districts with higher prevalences of HCVAb were not necessarily associated with those with higher prevalences of HBcAb.

In order to examine the chronological relationship between the present district-based AAP of virus markers during 1992-1993 and the previous district-based prevalence of infectious hepatitis during 1953 to 1955, the correlation between them was tentatively analyzed and the results are given in Table 5. A significant positive correlation was found between HCVAb and infectious hepatitis with a tendency toward chronicity at that time, but not between HCVAb and the other virus markers.

Discussion

Although the present study was conducted on a limited population at a high risk for hepatitis C, the positive rate of HCVAb in a population with normal liver function tests and without histories of risk factor for HCV infection is

Table 4 Comparison of prevalences of HCVAb, HBcAb and HAVAb in 26 districts

Districts	Number	HCVAb			HBcAb			HAVAb		
		SPR	AAP	χ^2	SPR	AAP	χ^2	SPR	AAP	χ^2
A	46	1.0	0.14	0.0	1.1	0.38	0.1	1.1	0.81	0.5
B	40	1.0	0.14	0.0	0.7	0.24	1.3	1.0	0.69	0.1
C	103	1.2	0.17	0.6	1.1	0.38	0.3	1.0	0.69	0.1
D	13	1.1	0.16	0.0	1.1	0.38	0.0	1.2	0.88	0.5
E	73	2.2	0.31	14.3**	0.8	0.28	1.0	1.0	0.71	0.0
F	29	2.1	0.30	5.5*	1.2	0.43	0.7	1.0	0.73	0.0
G	56	0.9	0.12	0.2	0.6	0.20	3.8	0.7	0.53	2.7
H	21	0.6	0.08	0.7	1.3	0.46	0.9	1.1	0.78	0.1
I	39	0.6	0.08	1.1	0.9	0.31	0.2	0.9	0.62	0.5
J	72	1.1	0.15	0.1	1.2	0.42	1.0	1.0	0.72	0.0
K	31	2.0	0.28	4.1*	0.4	0.15	3.8*	0.9	0.68	0.1
L	36	0.8	0.11	0.2	0.9	0.32	0.1	0.9	0.68	0.1
M	44	0.6	0.09	0.9	1.4	0.50	2.9	0.9	0.64	0.4
N	88	1.0	0.14	0.0	0.9	0.30	0.5	1.0	0.70	0.0
O	113	1.1	0.16	0.2	0.8	0.28	1.3	0.9	0.68	0.2
P	40	1.1	0.16	0.1	0.9	0.31	0.1	1.3	0.93	2.3
Q	111	0.9	0.13	0.1	1.1	0.38	0.4	1.1	0.79	0.8
R	35	1.4	0.20	0.7	1.1	0.39	0.2	1.2	0.89	1.3
S	40	0.8	0.11	0.3	0.8	0.28	0.5	1.0	0.72	0.0
T	105	0.8	0.11	0.8	1.4	0.47	4.7*	1.1	0.77	0.4
U	31	0.9	0.13	0.0	0.6	0.20	2.0	0.8	0.58	0.7
V	6	1.3	0.19	0.1	1.1	0.39	0.0	1.1	0.81	0.1
W	52	1.1	0.15	0.0	1.1	0.37	0.1	0.9	0.68	0.1
X	32	0.4	0.06	1.7	1.6	0.57	4.8*	1.1	0.78	0.2
Y	99	0.4	0.06	4.7*	1.1	0.38	0.3	0.9	0.68	0.2
Z	43	0.5	0.07	1.6	0.6	0.21	2.3	1.1	0.77	0.2
Mean ± SD		1.0	0.15 ± 0.067		1.0	0.35 ± 0.101		1.0	0.72 ± 0.092	
CV			44.7%			28.8%			12.8%	

HCVAb; HBcAb; HAVAb: See legend to Table 1.
SPR: Standardized prevalence ratio; AAP: Age-adjusted prevalence; SD: Standard deviation; CV: Coefficient of variation.
*$P < 0.05$; **$P < 0.01$.

Table 5 Correlation coefficients among district-based AAP of positive hepatitis virus markers and district-based prevalence of previous infectious hepatitis with tendency toward chronicity

	IH	IH(CH)	HCVAb	HBsAg	HBcAb	HAVAb
IH	/	0.950***	0.367	−0.232	−0.308	0.298
IH(CH)		/	0.452*	−0.168	−0.315	−0.358
HCVAb			/	0.142	−0.248	0.106
HBsAg				/	0.355	0.236
HBcAb					/	0.381
HAVAb						/

HCVAb; HBcAb; HAVAb: See legend to Table 1.
IH: Total infectious hepatitis cases; IH(CH): Infectious hepatitis cases with tendency toward chronicity based on 1,000 population in 1954.
*$P < 0.05$; ***$P < 0.001$.

assumed to be negligible. Furthermore, since the association among the hepatitis virus antibodies, and not the absolute rate, was studied, the population bias should not be a serious problem in analyzing the obtained results.

We confirmed the presence of highly-endemic areas of HCV infection from SPR of anti-HCV-positive subjects in different districts of Okayama prefecture in Japan. Such areas have been reported not only in Japan (8, 10–12, 14–16) but also in China in certain geographical areas or administrative divisions (17), suggesting the presence of a common route for the spread of HCV infection, which should be identified in order to aid in its prevention. It is not surprising to have found in this study a close association between HCV and HBV infection as revealed by the small but significantly increased odds ratio between their antibodies, as is also documented by others (13), because both of these viruses can be transmitted by exposure to blood. However, the interpretation of this observation is not simple, because only HCVAb, not HBcAb, showed a significant association with a history of blood transfusion. Also, a higher prevalence of HBcAb as compared with HCVAb or HAVAb was found in a younger generation. A possible explanation of these findings may be that HBV is also transmitted by sexual contact, while the spread of HCV by sexual contact is inefficient or controversial (18, 19), although as high a percentage as 53 % is reported for HCVAb in sexually promiscuous individuals (2). The difference in infection rate between HCV and HBV was clearly demonstrated in our separate study in Chiang Mai, Thailand. The prevalence of positive HCVAb in intravenous drug users was 85 % and that in female commercial sex workers and male STD patients was 0–2 %, while the prevalence of HBcAb was similarly high in the three groups, 77, 69 and 64 %, respectively (20). HCV is reported to be transmitted by sexual promiscuity (2), although no such documentation is available in our district and the prevalence of HCVAb was low in younger ages.

Generally less than half the HCVAb-positive cases have a history of blood or blood product transfusion with a considerable variation depending on the subjects analyzed (1, 8). In this study only 15.4 % of HCVAb-positive cases could be accounted for by a history of blood transfusion as a risk factor, this being close to the 18.6 % reported for Fukuoka, Japan (8), even though the prevalence of HCVAb was demonstrated in this study to be closely associated with blood transfusion. A history of surgery is even more important in some studies (8, 9), but not all (10), to explain the high incidence of HCV infection. Recently, identified (1, 21) or unidentified (8, 22) cases of nosocomial exposure as a risk of community-acquired hepatitis C have been reported. The HCV infection associated with medical treatment includes accidental puncture with needle and repeated use of medical equipment with insufficient sterilization, such as needles, syringes or surgical scalpels. Unfortunately, a direct estimate of the percentage of nosocomial exposure in this study is not available. Naito and others (14) have suggested nosocomial or iatrogenic spread of HCV infection at the time of outbreak of hepatitis A in highly-endemic areas. The results of correlation analysis in the present study support their hypothesis for the most part, although the logistic regression analysis weakened the association between HCVAb and HAVAb leaving a significant association only between HCVAb and HBcAb. Studies in smaller endemic areas might reveal association between HCVAb and HAVAb as Naito and others (14) have suggested.

A notable endemic of hepatitis A was recorded in Okayama in 1980 (23). Similarly, high incidences of hepatitis A in Japan have been reported for 1983 and 1990 (24). These endemics occurred after instituting the screening of donor bloods for HBsAg in April 1972 and before screening for HCVAb in November 1989 (25). However, there was no increase in the incidence of hepatitis C in the same population at the time of hepatitis endemy (4). One explanation for this is that a sufficient supply of disposable syringes and needles was already available at this time. A chronologically significant positive correlation was found between the district-dependent distribution of HCVAb from 1992 to 1993 and that of patients with epidemic hepatitis with a tendency of progressing toward chronic hepatitis from 1953 to 1955. This means that hepatitis C would have already been spread latently in the endemic area before 1953, when the outbreak of infectious hepatitis (presumed to be HAV infection) occurred. Community-acquired hepatitis C is frequently asymptomatic (26), and asymptomatic HCV carriers are apt to have a substantial risk of developing fulminant hepatitis upon superinfection with HAV as observed by Vento *et al.* (27). A similar effect of HAV superinfection on chronic hepatitis B has been reported without excluding HCV infection (28–30). Thus, such patients would initially have a clinical course of acute hepatitis followed by a subsequent course of chronic hepatitis as reported by Inoue (31).

The basal spread of hepatitis C before 1953 is most likely to have been caused by blood transfusion from paid donors during the period of 1948 to 1968 before legislative regulation was implemented (32). This is supported by a comparative study of Fukuoka and Okinawa, where the systems of blood supply for transfusion were entirely different for a similar period of time (8). In the present study, the prevalence of HCVAb was highest in the 60–69 age group and it decreased more rapidly descending age than that of HBcAb, while that of HBsAg was nearly the same, as was report by Nishioka (33). This suggests that the higher prevalence of HCVAb is due not only to a cumulative effect but also due to an apparently higher incidence of HCV infection among those who were born from 1926 to 1930 than those thereafter (33). This may explain the lack of association in HBcAb between the district-based prevalence during the period of 1953 to 1955 and that of the present study. Replacement of HBsAg by HBcAb in the presence of HCV (34) may also have contributed to reducing the figures for HBsAg-positive chronic hepatitis in highly-endemic areas, resulting in the loss of a chronological association between them. The results of this study support the conclusion of previous observations of Kosaka and others that the incidence of serum hepatitis by blood transfusion and the outbreak of infectious hepatitis are independent (16). Different modes of transmission of HBV and HCV have been suggested for the interpretation of differences in the prevalence of these viruses in different geographical areas and administrative divisions in China (17).

The following birth cohort-type effect, namely the age-group data of parallel time shift in age distribution of hepatitis cases presumed to be related to HCV, favors the view that the major spread of HCV infection occurred before 1953: The maximum prevalence of HCVAb in 1992–1993 was observed in a age group of 60–69, while that of hepatitis in a high endemic area studied in 1971 by Hepatitis Epidemiology Research Group of Okayama Public Health Nurse School (personal communication: Sachiko Okuda, Department of Health and Social Welfare, Okayama Prefecture) was reported to be 40–49 years of age; the time difference being 21–22 years with a corresponding age difference of 20 years of age. Similarly, the peak prevalence of epidemic hepatitis with a high rate toward chronicity during 1953 to 1955 was reported to be 21–30 years age (14) with time differences of 41–34 years and an age difference of 40 years as compared with the results in this study. A parallel time shift after 1953 is evident.

In conclusion, the risk of HCV infection appears multifactorial. Iatrogenic spread of HCV infection at the time of hepatitis A endemy, as proposed by Naito *et al.* (14), is reasonable. However, the wider district-dependent variation in the prevalence of HCVAb than that of HAVAb or HBcAb should be explained by different risk factors. One of them would be a basal spread of HCV hepatitis, which is assumed to have been triggered by blood transfusion from paid donors initially, followed by transmission by iatrogenic factors or from person to person by close contact, such as staying in endemic countries for more than 3 months, usually in childhood, as reported by Roudot-Thoraval *et al.* (1). This is supported by the significant association of districts with endemic hepatitis with tendency toward chronicity from 1953 to 1955 and districts with high prevalences of HCVAb from 1992–1993. In order to explain the periodic endemics of HCV in different areas in Japan (35), mutations of HCV gene related to the mode or rate of infection but unrelated to the determinants of antibodies used for detection of HCV at present must be considered even though this is mere conjecture.

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