In this study, the most frequent HCV RNA was genotype 6 (54.5%), followed by genotype 1b (27.3%). Genotypes 6 and 1 were also reported in Cambodian persons.[16] Furthermore, viral RNA was detected in 39.3% of anti-HCV positive samples. In Japan, where genotype 1b is predominant,[6] 70% of the individuals with anti-HCV are assumed to have an ongoing infection with HCV RNA.[17,18] The lower proportion of HCV RNA among anti-HCV positive persons in Cambodia compared to that in Japan was possibly caused by the difference of genotype. It is known that response to interferon-based therapy varies according to HCV genotypes. Compared to other HCV genotypes, the response rate to the therapy in genotype 1 is lower,[19,20] and that in genotype 6 may be at an intermediate level.[19,20] Another possibility is host-oriented factors such as their own immunity or food intake in Cambodian people.

Additionally, from our multivariate analysis, participants aged of 60 years or older had high risk for anti-HCV positivity (adjusted OR, 16.8) and HCV RNA positivity (adjusted OR, 15.0). High risk of HCV infection may be attributed to unsafe blood transfusion or other insufficiently sterilized medical manipulations in the past. Other possibilities may be cohort effect or age effect.

Furthermore, our multivariate analysis found that the history of blood transfusion is a potential risk factor for HCV RNA positivity in Cambodia (adjusted OR, 30.8). Although all Cambodian blood donors now are requested to be screened for HIV, HBV, HCV and syphilis according to the Ministry of Health, it is a necessary to perform the screening procedure more rigorously to avoid infections from contaminated blood.

In conclusion, our results of HBV and HCV seroprevalence, genotypic distribution and multivariate analysis for risk factors supposed that horizontal HBV transmission may be frequent in Cambodia. Particularly, operation and blood transfusion were identified as the risk factor for HBV and HCV infection, respectively. Therefore, for reducing HBV and HCV infections, it is necessary to launch a HB vaccination program for adults and to improve blood safety and sterilization in hospital in Cambodia.

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REFERENCES

1 World Health Organization. Prevention and control of viral hepatitis infection: framework for global action. Available at: http://www.who.int/csr/disease/hepatitis/Framework/en/. Accessed June 22, 2013.
2 World Health Organization. Hepatitis B (Factsheet No. 204). Available at: http://www.who.int/mediacentre/factsheets/fs204/en/. Accessed June 22, 2013.
3 Clements CJ, Baoping Y, Crouch A *et al.* Progress in the control of hepatitis B infection in the Western Pacific Region. *Vaccine* 2006; **24**: 1975–82.
4 Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. *Vaccine* 2012; **30**: 2212–9.
5 World Health Organization. Hepatitis C (Factsheet No.164). Available at: http://www.who.int/mediacentre/factsheets/fs164/en/. Accessed June 22, 2013.
6 Chen DS, Locarnini S, Wait S *et al.* Report from a viral hepatitis policy forum on implementing the WHO framework for global action on viral hepatitis in North Asia. *J Hepatol* 2013; **59**: 1073–80.
7 World Health Organization. International agency for research on cancer. GLOBOCAN 2012. Available at: http://globocan.iarc.fr/Pages/fact_sheets_population.aspx. Accessed February 1, 2014.
8 National Institute of Statistics, Ministry of Planning Phnom Penh, Cambodia. Genaral population census of Cambodia 2008. Available at: http://camnut.weebly.com/uploads/2/0/3/8/20389289/2009_census_2008.pdf Accessed January 11, 2014.
9 Sa-Nguanmoo P, Tangkijvanich P, Thawornsuk N *et al.* Molecular epidemiological study of hepatitis B virus among migrant workers from Cambodia, Laos, and Myanmar to Thailand. *J Med Virol* 2010; **82**: 1341–9.
10 Ol HS, Bjoerkvoll B, Sothy S *et al.* Prevalence of hepatitis B and hepatitis C virus infections in potential blood donors in rural Cambodia. *Southeast Asian J Trop Med Public Health* 2009; **40**: 963–71.
11 Thuring EG, Joller-Jemelka HI, Sareth H, Sokhan U, Reth C, Grob P. Prevalence of markers of hepatitis viruses A, B, C and of HIV in healthy individuals and patients of a Cambodian province. *Southeast Asian J Trop Med Public Health* 1993; **24**: 239–49.
12 Reekie J, Gidding HF, Kaldor JM, Liu B. Country of birth and other factors associated with hepatitis B prevalence in a population with high levels of immigration. *J Gastroenterol Hepatol* 2013; **28**: 1539–44.
13 Caruana SR, Kelly HA, De Silva SL *et al.* Knowledge about hepatitis and previous exposure to hepatitis viruses in immigrants and refugees from the Mekong Region. *Aust N Z J Public Health* 2005; **29**: 64–8.
14 Huy TT, Sall AA, Reynes JM, Abe K. Complete genomic sequence and phylogenetic relatedness of hepatitis

B virus isolates in Cambodia. *Virus Genes* 2008; **36**: 299–305.
15 Sato T, Do SH, Asao T *et al.* Estimating numbers of persons with persistent hepatitis B virus infection transmitted vertically and horizontally in the birth cohort during 1950–1985 in Japan. *Hepatol Res* 2014; [Epub ahead of print].
16 Akkarathamrongsin S, Praianantathavorn K, Hacharoen N, Theamboonlers A, Tangkijvanich P, Poovorawan Y. Seroprevalence and genotype of hepatitis C virus among immigrant workers from Cambodia and Myanmar in Thailand. *Intervirology* 2011; **54**: 10–6.
17 Tanaka J, Kumagai J, Katayama K *et al.* Sex- and age-specific carriers of hepatitis B and C viruses in Japan estimated by the prevalence in the 3,485,648 first-time blood donors during 1995–2000. *Intervirology* 2004; **47**: 32–40.
18 Moriya T, Koyama T, Tanaka J, Mishiro S, Yoshizawa H. Epidemiology of hepatitis C virus in japan. *Intervirology* 1999; **42**: 153–8.
19 Nguyen MH, Keeffe EB. Prevalence and treatment of hepatitis C virus genotypes 4, 5, and 6. *Clin Gastroenterol Hepatol* 2005; **3**: S97–S101.
20 Fung J, Lai CL, Hung I *et al.* Chronic hepatitis C virus genotype 6 infection: response to pegylated interferon and ribavirin. *J Infect Dis* 2008; **198**: 808–12.

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Original Article

High prevalences of hepatitis B and C virus infections among adults living in Binh Thuan province, Vietnam

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Aim: Vietnam is one of the countries with the highest mortality from liver cancer, which is mostly attributed to hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. For planning preventive strategies against these infections, we investigated prevalences of HBV and HCV infections among adults living in Binh Thuan, Vietnam.

Methods: Our study consisted of a serological survey for HBV and HCV infections and a questionnaire survey on their risk factors. The sample size was calculated based on anticipated rate of hepatitis B surface antigen (HBsAg). Subjects were randomly sampled using a multistage method. Confirmation and family-tree surveys were conducted to examine persistent HBV infection and intrafamilial HBV transmission, respectively.

Results: A total of 509 adults, comprised of 230 men (45.2%) and 279 women (54.8%), were enrolled. Prevalences of HBsAg, hepatitis B surface antibody and hepatitis B core antibody were 15.3%, 60.3% and 71.7%, respectively. Most HBV DNA positive sera were classified as genotype B (75.3%) and C (11.7%). Of HBsAg positive subjects, 96.7% were persistently infected and one acutely HBV infected person was identified. Family-tree surveys suggested that horizontal extrafamilial HBV transmission might have been frequent. Prevalences of anti-HCV and HCV RNA were 3.4% and 1.8%, respectively. HCV genotype 6a was prominent (55.6%).

Conclusion: In Binh Thuan, prevalences of HBV and HCV infections are high, HBV genotype B and HCV genotype 6a are predominant, and horizontal HBV transmission may still occur. Therefore, raising the coverage of a universal HBV vaccination program may be an effective liver cancer control in Vietnam.

Key words: general population, hepatitis B virus, hepatitis C virus, seroepidemiology, Vietnam

INTRODUCTION

HEPATITIS B VIRUS (HBV) and hepatitis C virus (HCV) infections have been considered the most important etiology of hepatocellular carcinoma (HCC), which is the third most common cause of cancer death among men globally.[1] Worldwide, nearly 2 billion people have been exposed to HBV[2] and 170 million people are chronically infected with HCV.[3] In the Asia–Pacific region, HBV is the leading cause of chronic hepatitis which can evolve into liver cirrhosis and HCC.[4]

Liver cancer has been the most frequent cause of cancer death in Vietnam.[5] According to Globocan 2012, Vietnam is one of the countries with the highest age-standardized mortality of liver cancer of 23.7 (per 100 000 population).[5] Approximately 90% of patients with HCC had evidence of HBV[6] and approximately one-seventh of them were related to HCV.[6] Meanwhile, prevalences of chronic HBV and HCV infections in Vietnam were estimated to be approximately 12.0% and 2.0%, respectively.[6] Particularly, chronic HBV infection was predicted to remain endemic in the next decade, despite the achievement of the universal infant HBV vaccination program.[7] However, data on prevalences of

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HBV and HCV infections among the general population in Vietnam are limited. There have been few population-based studies conducted in North Vietnam in the last 6 years, while nationwide researches have not been performed. Therefore, we investigated HBV and HCV infections for seroprevalence, genotypic distribution and risk factors among the adults living in Binh Thuan, a province located in South Vietnam. Our population-based study is hoped to provide updated and additional information for planning preventive strategies against HBV and HCV infections in Vietnam.

METHODS

Study design

WE CONDUCTED A cross-sectional study among adults aged 20 years or older in Binh Thuan province. Based on the anticipated hepatitis B surface antigen (HBsAg) rate of 20.0%, confidence level of 95% and precision of 5%, sample size was determined to be 510. Participants were included by multistage sampling. First, La Gi town was one of three cities/towns/districts randomly chosen from 10 cities/towns/districts of Binh Thuan province. Except La Gi town, in two of three areas it is difficult to conduct this survey. Second, three wards, including Binh Tan, Phuoc Hoi and Phuoc Loc, were randomly selected from nine wards/communes of La Gi town. Finally, participants were enrolled from the lists of residents aged 20 years or older in three selected wards by systematic random sampling.

Additionally, approximately 6 months after the initial survey, all initial participants in Binh Tan ward were recruited to the confirmation survey for differentiating acute from persistent HBV infection among HBsAg positive individuals, as well as detecting incident HBsAg positive cases and HCV infections among susceptible persons.

In addition, for investigating the intrafamilial transmission of HBV infection, all participants who were persistently infected HBV, named "index persons", identified in our confirmation survey as well as their family members were invited to participate in the family-tree survey.

Ethical issues

This study was approved by the Ethics Committee for Epidemiological Research of Hiroshima University in Japan and Binh Thuan Provincial Department of Health in Vietnam. Informed consents were provided by all participants.

Questionnaire survey

An unsigned questionnaire was used to obtain data on characteristics of participants such as age, sex, occupation and potential risk factors including current health status, family history of liver diseases, history of hospitalization, surgery, blood transfusion, dental procedure, injections, acupuncture, tattoos, skin-piercings, sharing of razors, manicure service and skin-cutting cures.

Serological testing

Approximately 10 mL of blood was drawn from each participant. After centrifugation, sera were kept at −30°C and transported to Hiroshima University. All sera were tested for HBsAg, hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb) and HBV DNA. HBsAg was detected using a reversed passive hemagglutination assay (Mycell II HBsAg; Institute of Immunology, Tokyo, Japan). A chemiluminescence immunoassay was used to detect HBsAb (Architect Osabu; Abbott, Tokyo, Japan) and HBcAb (Architect HBc II; Abbott). HBV DNA was detected by real-time polymerase chain reaction (PCR) (TaqMan Fast Universal PCR Master Mix (2X); Applied Biosystems, Foster City, CA, USA) and the cut-off point for HBV DNA was more than 10^2 copies. HBV genotyping was performed by enzyme immunoassay (Immunis HBV genotype EIA; Institute of Immunology), and some samples which could not be determined by enzyme immunoassay were identified by direct sequencing (BigDye Terminator v3.1 Cycle Sequencing Kit; Applied Biosystems). HBV exposure was defined as the seropositivity for HBsAg and/or HBcAb.

For HCV infection, HCV antibody (anti-HCV) and HCV RNA were detected by particle agglutination assay (Ortho HCV Ab PA test II; Ortho-Clinical Diagnostics, Tokyo, Japan) and real-time PCR (TaqMan Fast Virus 1-Step Master Mix; Applied Biosystems), respectively. HCV infection was defined as the seropositivity for anti-HCV.

Statistical analysis

Data were analyzed using JMP version 7.0.2 (SAS Institute, Cary, NC, USA). The proportions were estimated with 95% confidence intervals (95% CI). The χ^2-test or Fisher's exact test were used as appropriate to compare the proportions between different groups. Risk factors for HBV and HCV infections were determined by calculating odds ratios (OR) and 95% CI using univariate and multivariate logistic regression analyses with the stepwise method in which factors were retained if they

Table 1 Demographic characteristics of participants ($n = 509$)

Characteristics	Total		Men		Women	
	n	%	*n*	%	*n*	%
Age (years)						
20–29	130	25.5	65	12.8	65	12.8
30–39	106	20.8	53	10.4	53	10.4
40–49	126	24.8	53	10.4	73	14.3
≥50	147	28.9	59	11.6	88	17.3
Occupation						
Farmer	75	14.7	35	15.2	40	14.3
Fisherman	23	4.5	23	10.0	0	0
Health-care worker	19	3.7	4	1.7	15	5.4
Housewife	112	22.0	0	0	112	40.1
Officer	128	25.2	79	34.4	49	17.6
Trader	66	13.0	18	7.8	48	17.2
Worker	86	16.9	71	30.9	15	5.4
Total	509	100.0	230	45.2	279	54.8

reached the 0.25 level of significance. A *P*-value less than 0.05 was considered statistically significant.

RESULTS

Characteristics of participants

IN 2012, 509 participants, comprised of 230 men (45.2%) and 279 women (54.8%), were enrolled in the study (Table 1). Age distribution ranged 20–81 years old (average age, 40.8 ± 1.1 years).

Among 169 initial subjects in Binh Tan ward, 152 (89.9%) participated in the confirmation survey. There was no significant difference in sex and age between subjects participating in the initial survey and those in the confirmation survey.

For family-tree surveys, four among 29 participants who were identified to be persistently infected with HBV agreed to participate. In total, 26 participants including four index persons and their 22 family members (parents, spouse or siblings of index persons) were studied. Their age ranged 23–75 years old and the male-to-female ratio was 1:1.36.

Questionnaire survey

Overall, 20.0% of participants had a family history of liver disease. Most participants were exposed to injections (78.4%), while fewer participants had history of surgery (18.9%), blood transfusion (6.1%) and tattoos (6.7%) (Fig. 1).

Serological analyses

Prevalences of HBsAg, HBsAb and HBcAb among participants were 15.3% (95% CI, 12.2–18.5%), 60.3% (95% CI, 56.0–64.6%) and 71.7% (95% CI, 67.8–75.6%), respectively. Based on different profiles of HBV markers, prevalence of HBsAg positivity was 15.3% (78/509), while prevalence of HBV exposure (positive for HBsAg and/or HBcAb) was 71.7% (365/509). Among

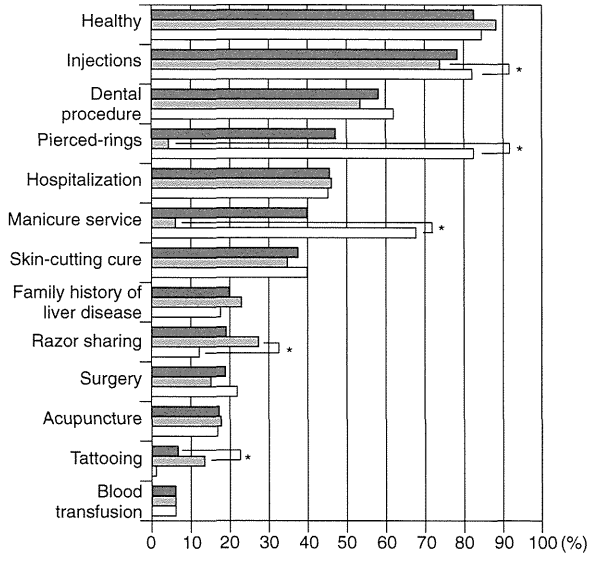

Figure 1 Potential risk factors among male and female participants in the sero-epidemiological study in Binh Thuan, Vietnam in 2012 ($n = 509$). Differences in percentages of "yes" answer between sexes were tested by χ^2-test or Fisher's exact test as appropriate, and significant differences are indicated by asterisks. ■, Total ($n = 509$); ▨, male ($n = 230$); □, female ($n = 279$).

the 77 HBV DNA positive samples, 58 (75.3%) were classified as genotype B, nine (11.7%) as genotype C, four (5.2%) as genotype D and the remaining six (7.8%) as unidentifiable.

Generally, prevalences of these HBV markers in men and women were not significantly different (Fig. 2). Conversely, the rates of HBcAb positivity and HBsAb positivity tended to increase with age, while the HBsAg positive rate was inclined to decrease with age (Fig. 2). In univariate analysis, HBsAg seropositivity was related to age of 50 years or over (OR = 0.3; 95% CI, 0.1–0.6; $P < 0.001$) and family history of liver disease (OR = 3.1; 95% CI, 1.9–5.3; $P < 0.0001$), while HBV exposure was associated with age of 40–49 years (OR, 1.8; 95% CI = 1.0–3.0; $P < 0.05$) and age of 50 years or over (OR, 1.8; 95% CI = 1.1–3.1; $P < 0.05$) (Table 2). Multivariate analysis identified that HBsAg seropositivity was related to age of 50 years or over (adjusted OR = 0.3; 95% CI, 0.1–0.6, $P < 0.001$), fishermen (adjusted OR, 3.5; 95% CI = 1.1–10.1; $P < 0.05$) and family history of liver disease (adjusted OR = 3.0; 95% CI, 1.7–5.2; $P < 0.0001$), whereas HBV exposure was still associated with age of 40–49 years (adjusted OR = 1.8; 95% CI, 1.0–3.1; $P < 0.05$) and age of 50 years or over (adjusted OR = 1.8; 95% CI, 1.1–3.1; $P < 0.05$) (Table 2).

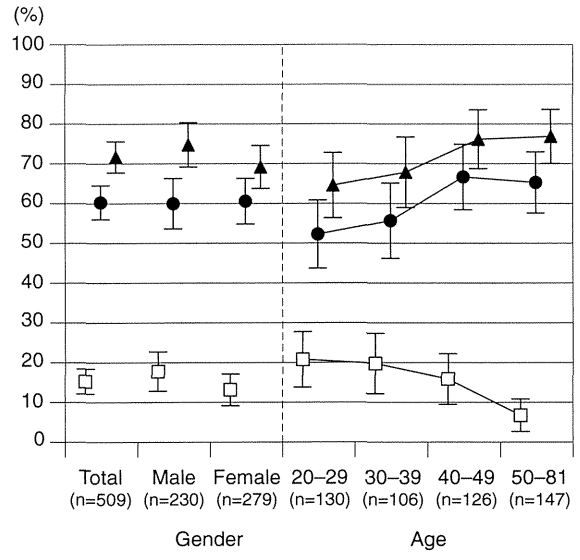

Figure 2 Prevalences of hepatitis B virus markers among adults living in Binh Thuan province, Vietnam. Sex- and age-specific prevalence of hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb) and hepatitis B core antibody (HBcAb) are shown with 95% confidence intervals. –□–, HBsAg; –●–, HBsAb; –▲–, HBcAb.

Notably, of the 31 HBsAg positive participants at the initial survey, 30 persons participated in the confirmation survey. Of the 30 participants, 29 (96.7%) remained positive for HBsAg, indicating persistent infection, whereas the remaining one became negative for HBsAg and positive for HBsAb, implying an acute infection at the initial survey. No HBsAg positive case was observed among subjects who were negative for all HBV markers at the initial survey, resulting in an incidence rate of 0 (95% CI, 0–29.5/100 person-years).

Additionally, in family-tree surveys, four index persons were positive for both HBsAg and HBcAb, whereas HBsAg was detected in eight of 22 family members. In total, 12 HBsAg positives among 26 persons in four families and the prevalence of HBsAg was 46.2% (95% CI, 27.0–65.3%). In family 1, the index person was the mother and only the oldest child was positive for HBcAb, while four younger children were negative for HBcAb (Fig. 3a). In families 2 and 3, the parents of the index persons were negative for HBsAg. However, HBsAg was detected in two index persons' older sisters in family 2, and four index persons' siblings in family 3 (Fig. 3b,c). The index person in family 4, the father, and his two sons were positive for HBsAg (Fig. 3d).

For HCV infection, 17 (3.3%; 95% CI, 1.8–4.9%) of the 509 participants were positive for anti-HCV, while HCV RNA was detected in nine (1.8%; 95% CI, 0.6–2.9%). Five (55.6%) of them were classified as genotype 6a. Each of the remaining four belonged to genotype 1b (11.1%), 2a (11.1%), 3a (11.1%) and 6e (11.1%), respectively. Differences in anti-HCV and HCV RNA rates between sexes were not significant (Fig. 4). Although anti-HCV and HCV RNA rates tended to increase with age (Fig. 4), only age of 50 years or over was related to seropositivity for anti-HCV in univariate analysis (OR = 8.4; 95% CI, 1.2–67.3; $P < 0.05$) and in multivariate analysis (adjusted OR = 6.4; 95% CI, 1.1–120.6; $P < 0.05$) (Table 3). In 150 participants who were initially negative for HCV infection, nobody was positive for anti-HCV or HCV RNA in the confirmation survey, resulting in a HCV incidence of 0 (95% CI, 0–4.9/100 person-years).

DISCUSSION

WE FOUND IN this survey that prevalence of HBsAg among the adults living in Binh Thuan, located in South Vietnam, was 15.3%. In North Vietnam, HBsAg rates of 18.8%,[8] 19.0%[9] and 8.8%[10] were reported. Despite the discrepancies due to the

Table 2 Univariate and multivariate analysis of risk factors for HBV infection among adults living in Binh Thuan province, Vietnam ($n = 509$)

		n	%	HBsAg seropositivity						HBV exposure†					
				Univariate analysis‡			Multivariate analysis§			Univariate analysis‡			Multivariate analysis¶		
				OR	95% CI	*P*	AOR	95% CI	*P*	OR	95% CI	*P*	AOR	95% CI	*P*
Sex	Female	230	54.8	1.0			1.0			1.0			1.0		
	Male	279	45.2	1.4	0.9–2.3	0.1548	1.0	0.6–1.8	0.9050	1.3	0.9–1.9	0.1622	1.3	0.8–2.0	0.1575
Age group (years)	20–29	130	25.5	1.0			1.0			1.0			1.0		
	30–39	106	20.8	0.9	0.5–1.8	0.8557	0.8	0.4–1.6	0.5564	1.2	0.7–2.0	0.5932	1.1	0.6–1.9	0.9420
	40–49	126	24.8	0.7	0.4–1.4	0.3117	0.7	0.4–1.4	0.2893	1.8	1.0–3.0	**0.0427**	1.8	1.0–3.1	**0.0416**
	50 and over	147	28.9	0.3	0.1–0.6	**0.0006**	0.3	0.1–0.6	**0.0009**	1.8	1.1–3.1	**0.0247**	1.8	1.1–3.1	**0.0258**
Occupation	Worker	86	16.9	1.0			1.0			1.0			1.0		
	Farmer	75	14.7	1.0	0.4–2.3	0.9363	–			1.7	0.9–3.4	0.1321	–		
	Fisherman	23	4.5	2.5	0.8–7.1	0.0918	3.5	1.1–10.1	**0.0223**	1.9	0.7–5.7	0.2304	–		
	Health-care worker	19	3.7	1.1	0.3–4.1	0.9411	–			0.6	0.2–1.6	0.3081	0.4	0.2–1.3	0.1333
	Housewife	112	22.0	0.8	0.4–1.8	0.5949	–			1.5	0.8–2.7	0.2191	–		
	Officer	128	25.2	1.2	0.6–2.6	0.5844	–			1.4	0.8–2.6	0.2396	–		
	Trader	66	13.0	0.7	0.2–1.8	0.4149	–			1.5	0.8–3.1	0.2276	–		
Unhealthy status	No	439	86.3	1.0						1.0					
	Yes	70	13.7	1.0	0.5–2.1	0.9223	–			1.0	0.7–1.7	0.9552	–		
Family history of liver disease	No	407	80.0	1.0			1.0			1.0			1.0		
	Yes	102	20.0	3.1	1.9–5.3	**<0.0001**	3.0	1.7–5.2	**<0.0001**	1.5	0.9–2.4	0.1499	1.5	0.9–2.6	0.1182
Hospitalization	No	277	54.4	1.0			1.0			1.0					
	Yes	232	45.6	0.7	0.4–1.2	0.1702	0.7	0.4–1.2	0.1535	1.2	0.8–1.7	0.4727	–		
Surgery	No	413	81.1	1.0						1.0					
	Yes	96	18.9	0.6	0.3–1.3	0.2431	–			1.0	0.6–1.7	0.9681	–		
Blood transfusion	No	478	93.9	1.0			1.0			1.0					
	Yes	31	6.1	1.7	0.7–4.0	0.2471	2.4	0.9–6.2	0.0714	1.7	0.7–4.2	0.2543	–		
Dental procedure	No	213	41.9	1.0			1.0			1.0					
	Yes	296	58.1	0.7	0.4–1.1	0.1127	0.8	0.5–1.3	0.3084	0.9	0.6–1.3	0.5156	–		
Injections	No	110	21.6	1.0						1.0					
	Yes	399	78.4	0.9	0.5–1.6	0.7325	–			1.0	0.6–1.6	0.9771	–		
Acupuncture	No	421	82.7	1.0						1.0					
	Yes	88	17.3	0.9	0.4–1.6	0.6289	–			1.1	0.6–1.8	0.8157	–		
Tattoos	No	475	93.3	1.0						1.0					
	Yes	34	6.7	1.2	0.5–3.0	0.6971	–			1.3	0.6–3.0	0.5234	–		
Piercings	No	269	52.9	1.0						1.0					
	Yes	240	47.1	0.7	0.4–1.1	0.0948	–			0.8	0.5–1.2	0.2290	–		
Sharing of razors	No	412	80.9	1.0						1.0					
	Yes	97	19.1	1.3	0.7–2.4	0.3259	–			1.0	0.6–1.7	0.9118	–		
Manicure service	No	306	60.1	1.0						1.0					
	Yes	203	39.9	1.1	0.7–1.7	0.8226	–			0.8	0.6–1.2	0.3584	–		
Skin-cutting cures	No	318	62.5	1.0						1.0					
	Yes	191	37.5	0.9	0.5–1.4	0.5642	–			1.0	0.7–1.5	0.9943	–		

†Hepatitis B virus (HBV) exposure: seropositivity for hepatitis B surface antigen and/or hepatitis B core antibody.

‡χ^2-Test or Fisher's exact test.

§Logistic regression analysis with the stepwise method: $R^2 = 0.0932$, model *P*-value < **0.0001**, $n = 509$.

¶Logistic regression analysis with the stepwise method: $R^2 = 0.0236$, model *P*-value = **0.0262**, $n = 509$.

Bold text represents statistical significance.

AOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

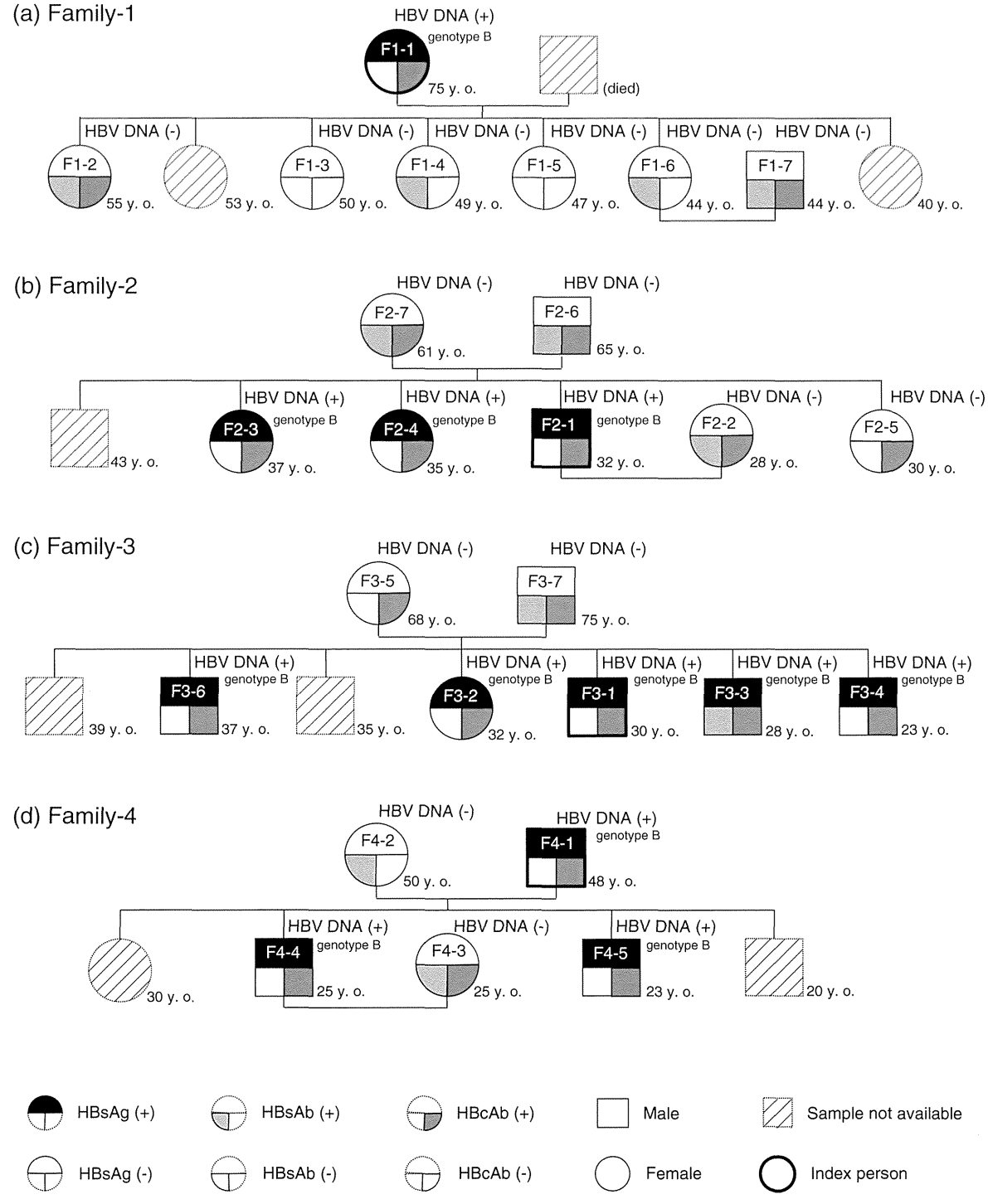

Figure 3 Trees of four families, including 26 subjects participating in the family-tree survey. Sex, age and results of hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb) and hepatitis B virus (HBV) DNA testings of each subject are shown. (a) Family (F)1; (b) F2; (c) F3; (d) F4. y. o., years old.

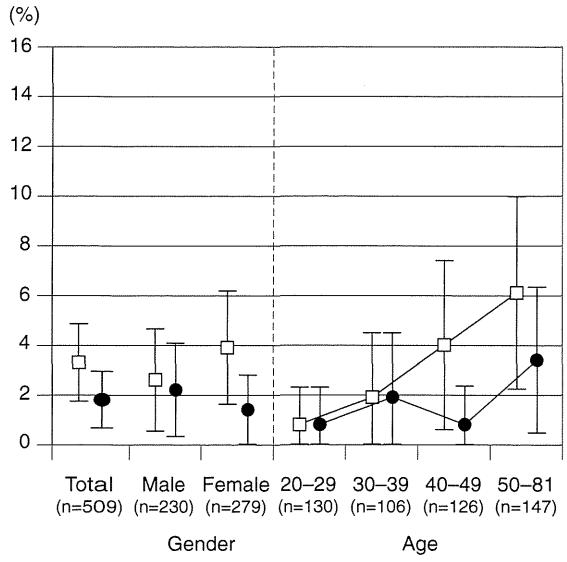

Figure 4 Prevalences of anti-hepatitis C virus (HCV) and HCV RNA among adults living in Binh Thuan province, Vietnam. Sex- and age-specific prevalence of anti-HCV and HCV RNA are shown with 95% confidence intervals. -□-, anti-HCV; -●-, HCV RNA.

differences in study areas, study periods of time, study methods and size, we can verify a high prevalence of HBsAg in Vietnam. According to conventional classification,[2] Vietnam remains an endemic country of HBV infection. Additionally, compared to other Southeast Asian nations[4,11] and Japan,[12] Vietnam is one of the countries with the highest HBsAg seroprevalence. We observed that 71.7% of participants in our study were positive for HBcAb, the same high prevalence of 65.2–79.2%[8,9] reported in North Vietnam. By comparing the prevalence of HBsAg and HBcAb in our study, we assumed that the horizontal infection may have occurred more frequently in adults or after childhood than by vertical transmission. Additionally, although the prevalence of HBsAb was high at 60.3% (307/509), only 62 (12.2%) participants were positive for HBsAb but negative for HBcAb. We supposed that their HBsAb seropositivity might not be related to the universal HBV vaccine program, because all participants had been born at least 10 years before the universal HBV vaccine program for infants was introduced in Binh Thuan in 2002. These 62 participants might have been vaccinated by themselves or might have been infected in the past with a low titer of HBcAb now.

Generally, genotypes B and C are most prevalent in Asian countries, while genotypes A and D are common in Europe and the USA.[13] Our study among the general population found that the most popular HBV genotype is B (75.3%), followed by C (11.7%). Comparable HBV genotype distribution of genotypes B and C were also observed in Vietnam.[14,15] However, genotype C was reported to predominate over genotype B.[16,17] These conflicts may be due to different study populations; genotype B was common among asymptomatic HBV infected cases, whereas genotype C was prominent in patients with liver cirrhosis and HCC.[18]

From the result of logistic regression analysis in our study, we did not find any sex difference in HBsAg positive risk and HBV exposure risk, the same result as in other surveys in Vietnam.[9,10] However, a prevalence study in Japan reported that HBsAg positive rate among men was higher than that among women.[12] Moreover, we observed that persons aged 50 years or over had lower risk for HBsAg positivity than those aged 20–29 years. The same tendency was reviewed by Custer *et al.* in Southeast Asia.[11] The low HBsAg rates among older age groups might have been observed from two hypotheses: (i) the loss of HBsAg which was reported in the natural course of HBV carriers in Japan;[19] and (ii) the cohort effect in Vietnam, such as the Vietnam War (1954–1975).

Hence, the evidences of age-dependent increase of HBcAb positive rate possibly imply ongoing horizontal transmission of HBV among Vietnamese adults. However, other reasons such as the differences in the historical background at different ages should be additionally investigated.

Notably, from our analysis we observed that family history of liver disease was a significant risk factor for HBsAg positivity (adjusted OR = 3.0). Therefore, family history of liver disease is considered an important predictor for HBV infection.

To our knowledge, this is the first study showing evidence of common HBV acquisition in early childhood in Vietnam through confirmation survey; most of the HBsAg positive adults were confirmed to be persistently infected. Additionally, we identified the case of acute HBV infection. At initial survey, this person was positive for HBsAg and HBcAb, and negative for HBsAb. Approximately 6 months later, at confirmation survey, the person became negative for HBsAg and positive for HBsAb and HBcAb. Hence, we suggest that ongoing HBV horizontal transmission in adulthood now occurs in Vietnam.

Furthermore, serological profiles in our family-tree surveys showed possibilities of different routes of HBV spread in Vietnam. Because taking blood samples at the same time for all members, particularly for children,

Table 3 Univariate and multivariate analysis of risk factors for HCV infection among adults living in Binh Thuan province, Vietnam ($n = 509$)

		n	%	Anti-HCV seropositivity						HCV RNA seropositivity					
				Univariate analysis†			Multivariate analysis‡			Univariate analysis†			Multivariate analysis§		
				OR	95% CI	*P*	AOR	95% CI	*P*	OR	95% CI	*P*	AOR	95% CI	*P*
Sex	Female	230	54.8	1.0			1.0			1.0			1.0		
	Male	279	45.2	1.5	0.6–2.4	0.1548	1.2	0.4–3.6	0.6974	1.5	0.4–5.8	0.5283	1.6	0.4–6.8	0.4677
Age group (years)	20–29	130	25.5	1.0			1.0			1.0			1.0		
	30–39	106	20.8	2.5	0.2–27.7	0.4459	2.1	0.2–45.7	0.5537	2.5	0.2–27.7	0.4459	2.5	0.2–53.8	0.4606
	40–49	126	24.8	5.3	0.6–46.3	0.0908	4.4	0.7–85.8	0.1839	1.0	0.1–16.7	0.9823	1.1	0.0–27.4	0.9602
	50 and over	147	28.9	8.4	1.1–67.3	**0.0171**	6.4	1.1–120.6	**0.0322**	4.5	0.5–39.4	0.1331	4.8	0.8–92.4	0.1569
Occupation	Worker	86	16.9	1.0			1.0			1.0					
	Farmer	75	14.7	0.8	0.2–2.8	0.6665	–			0.6	0.1–3.2	0.5072	–		
	Fisherman	23	4.5	0	–	0.1925	–			0	–	0.2920	–		
	Health-care worker	19	3.7	0	–	0.2357	–			0	–	0.3378	–		
	Housewife	112	22.0	0.5	0.1–1.8	0.2781	–			0.4	0.1–2.1	0.2437	–		
	Officer	128	25.2	0.1	0.0–0.9	**0.0125**	0.2	0.0–1.2	0.1649	0	–	**0.0138**	–		
	Trader	66	13.0	0.4	0.1–2.1	0.2801	–			0.3	0.1–2.9	0.2826	–		
Unhealthy status	No	439	86.3	1.0						1.0					
	Yes	70	13.7	1.4	0.4–4.9	0.6353	–			0.8	0.1–6.3	0.8164	–		
Family history of liver disease	No	407	80.0	1.0						1.0					
	Yes	102	20.0	1.2	0.4–3.9	0.7146	–			1.1	0.2–5.6	0.8689	–		
Hospitalization	No	277	54.4	1.0						1.0					
	Yes	232	45.6	1.1	0.4–2.8	0.9009	–			1.5	0.4–5.7	0.5443	–		
Surgery	No	413	81.1	1.0						1.0					
	Yes	96	18.9	1.8	0.6–5.3	0.2580	–			2.2	0.5–8.9	0.2628	–		
Blood transfusion	No	478	93.9	1.0						1.0					
	Yes	31	6.1	1.0	0.1–7.5	0.9709	–			0	–	0.4408	–		
Dental procedure	No	213	41.9	1.0						1.0					
	Yes	296	58.1	1.3	0.5–3.7	0.5775	–			1.5	0.4–5.9	0.6014	–		
Injections	No	110	21.6	1.0						1.0					
	Yes	399	78.4	0.5	0.2–1.4	0.1633	–			0.5	0.1–2.2	0.3886	–		
Acupuncture	No	421	82.7	1.0						1.0					
	Yes	88	17.3	1.0	0.3–3.6	0.9683	–			0.6	0.1–4.8	0.6210	–		
Tattoos	No	475	93.3	1.0						1.0					
	Yes	34	6.7	0.9	0.1–6.8	0.8934	–			1.8	0.2–14.6	0.5911	–		
Piercings	No	269	52.9	1.0						1.0					
	Yes	240	47.1	2.1	0.8–5.8	0.1403	–			0.9	0.2–3.4	0.8696	–		
Sharing of razors	No	412	80.9	1.0						1.0					
	Yes	97	19.1	0.3	0–2.0	0.1595	0.2	0.0–1.3	0.1755	0.5	0.1–4.3	0.5403	–		
Manicure service	No	306	60.1	1.0						1.0					
	Yes	203	39.9	1.1	0.4–2.8	0.9117	–			0.8	0.2–3.0	0.6856	–		
Skin-cutting cures	No	318	62.5	1.0						1.0					
	Yes	191	37.5	0.9	0.3–2.5	0.8468	–			1.3	0.4–5.1	0.6653	–		

†χ^2-Test or Fisher's exact test.

‡Logistic regression analysis with the stepwise method: $R^2 = 0.0862$; model *P*-value = **0.0455**, $n = 509$.

§Logistic regression analysis with the stepwise method: $R^2 = 0.0457$, model *P*-value = 0.3883, $n = 509$.

Bold text represents statistical significance.

AOR, adjusted odds ratio; CI, confidence interval; HCV, hepatitis C virus; OR, odds ratio.

within a family is considered an unusual event in Vietnam, only four families of which a member was a health-care worker agreed to participate in family-tree survey. In family 1, there was no evidence of vertical HBV transmission as the mother was persistently HBV infected but none of her children were positive for HBsAg. In families 2 and 3, because the parents were negative for HBsAg, it was not obvious that children were infected from their parents. There was another possibility that the HBsAg positive children might have been horizontally infected from other persons who were persistently infected with HBV and had a close relationship with the children. In family 4, there was no evidence of vertical transmission because the mother was negative for HBsAg. These children might have been horizontally infected from their father or from other persons who were persistently infected with HBV and had a close relationship with them. We could not identify the transmission mode by using only genotyping results because all HBV DNA positive subjects in our family-tree surveys were infected with HBV genotype B. A recent study among HBV carriers in the birth cohort during 1950–1985 in Japan estimated that horizontal transmission was approximately sesquialterally as frequent as vertical transmission.[20] Therefore, it is possible that for the first time our family-tree survey has supposed that not only perinatal vertical transmission or intrafamilial horizontal spread but also horizontal infection of HBV from an extrafamilial source such as babysitter or kindergarten classmate in early childhood are important in Vietnam. Hence, preventive strategies for horizontal HBV transmission should be properly considered, along with the universal HBV vaccination for infants.

Regarding HCV infection, we revealed the anti-HCV seroprevalence of 3.3% (95% CI, 1.8–4.9%), higher than anti-HCV rate of 1.0% reported in North Vietnam.[21] Particularly, our study is the first population-based investigation of HCV RNA prevalence in Vietnam, observing a HCV RNA positive rate of 1.8% (95% CI, 0.6–2.9%), much higher than the HCV carrier rate in Japan.[22] Thus, in our study, 52.9% of anti-HCV positive individuals were seropositive for HCV RNA. This proportion was as high as 100.0% (3/3) in participants aged 20–39 years but declined to 42.9% (6/14) in participants aged 40 years or older, suggesting that the periods of infection were also different. Additionally, we identified that HCV genotype 6a was the most frequent (55.6%). In Vietnam, the predominance of HCV genotype 6a was also reported in blood donors[23] although HCV genotype 1b was more frequent among patients with liver disease.[24] The discrepancy regarding HCV genotypic distribution may be explained by the fact that infection with HCV genotype 1b is more related with progressive liver diseases in comparison with other HCV genotypes.[25] Therefore, our results supposed that HCV genotype 6a was prominent among the general population.

From logistic regression analysis, we did not find any sex difference in the risk of anti-HCV seropositivity as well as in the risk of HCV RNA seropositivity. However, our multivariate analysis revealed that age of 50 years or over had a higher risk of anti-HCV seropositivity (adjusted OR = 6.4). High risk of anti-HCV seropositivity among the elderly may be attributed to unsafe blood transfusion and other insufficiently sterilized medical manipulations in the past.

With participants randomly sampled from the whole community, we provided sufficiently reliable results of seroprevalences of HBV and HCV infections. Overall, the high prevalence of HBcAb compared to that of HBsAg supposed that horizontal transmission was more frequent than expected. Another critical strength of this study is that results of both confirmation survey and family-tree surveys (in the former we could find one acutely HBV infected person among a small cohort during a short follow-up period, and in the latter all of children may not be vertically HBV infected) more strongly supported the importance of ongoing horizontal transmission.

Hence, to reduce the burden of HCC and other chronic liver diseases, it is crucial to raise the coverage of the universal infant HBV vaccination and launch a HBV vaccination program for adults in Vietnam. Other measures for preventing HBV and HCV parenteral transmission such as blood safety and sterilization in medical settings should be further improved.

ACKNOWLEDGMENTS

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REFERENCES

1 Raza SA, Clifford GM, Franceschi S. Worldwide variation in the relative importance of hepatitis B and hepatitis C

viruses in hepatocellular carcinoma: a systematic review. *Br J Cancer* 2007; **96**: 1127–34.
2 World Health Organization. Hepatitis B. 2002. Available at: http://www.who.int/csr/disease/hepatitis/HepatitisB_whocdscsrlyo2002_2.pdf?ua=1. Accessed January 31, 2014.
3 World Health Organization. Hepatitis C. 2003. Available at: http://www.who.int/csr/disease/hepatitis/Hepc.pdf. Accessed January 31, 2014.
4 Merican I, Guan R, Amarapuka D *et al.* Chronic hepatitis B virus infection in Asian countries. *J Gastroenterol Hepatol* 2000; **15**: 1356–61.
5 World Health Organization. International agency for research on cancer. Globocan 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide 2012. Available at: http://globocan.iarc.fr/Pages/fact_sheets_population.aspx. Accessed January 31, 2014.
6 Gish RG, Bui TD, Nguyen CT *et al.* Liver disease in Viet Nam: screening, surveillance, management and education: a 5-year plan and call to action. *J Gastroenterol Hepatol* 2012; **27**: 238–47.
7 Nguyen VT, Law MG, Dore GJ. An enormous hepatitis B virus-related liver disease burden projected in Vietnam by 2025. *Liver Int* 2008; **28**: 525–31.
8 Hipgrave DB, Nguyen TV, Vu MH *et al.* Hepatitis B infection in rural Vietnam and the implications for a national program of infant immunization. *Am J Trop Med Hyg* 2003; **69**: 288–94.
9 Nguyen VT, McLaws ML, Dore GJ. Highly endemic hepatitis B infection in rural Vietnam. *J Gastroenterol Hepatol* 2007; **22**: 2093–100.
10 Duong TH, Nguyen PH, Henley K, Peters M. Risk factors for hepatitis B infection in rural Vietnam. *Asian Pac J Cancer Prev* 2009; **10**: 97–102.
11 Custer B, Sullivan SD, Hazlet TK, Iloeje U, Veenstra DL, Kowdley KV. Global epidemiology of hepatitis B virus. *J Clin Gastroenterol* 2004; **38**: S158–68.
12 Tanaka J, Kumagai J, Katayama K *et al.* Sex- and age-specific carriers of hepatitis B and C viruses in Japan estimated by the prevalence in the 3,485,648 first-time blood donors during 1995–2000. *Intervirology* 2004; **47**: 32–40.
13 Kurbanov F, Tanaka Y, Mizokami M. Geographical and genetic diversity of the human hepatitis B virus. *Hepatol Res* 2010; **40**: 14–30.
14 Hayashi K, Katano Y, Chuong TX *et al.* Prevalence of hepatitis B virus subgenotypes and basal core promoter, precore variants in patients with acute hepatitis B in central Vietnam. *Intervirology* 2009; **52**: 22–8.
15 Huy TT, Ushijima H, Quang VX *et al.* Characteristics of core promoter and precore stop codon mutants of hepatitis B virus in Vietnam. *J Med Virol* 2004; **74**: 228–36.
16 Toan NL, Song LH, Kremsner PG *et al.* Impact of the hepatitis B virus genotype and genotype mixtures on the course of liver disease in Vietnam. *Hepatology* 2006; **43**: 1375–84.
17 Tran HT, Ushijima H, Quang VX *et al.* Prevalence of hepatitis virus types B through E and genotypic distribution of HBV and HCV in Ho Chi Minh City, Vietnam. *Hepatol Res* 2003; **26**: 275–80.
18 Kao J, Cheng D. HBV genotypes: epidemiology and implications regarding natural history. *Curr Hepat Rep* 2006; **5**: 5–13.
19 Kobayashi M, Hosaka T, Suzuki F *et al.* Seroclearance rate of hepatitis B surface antigen in 2,112 patients with chronic hepatitis in Japan during long-term follow-up. *J Gastroenterol* 2014; **49**: 538–46.
20 Sato T, Do SH, Asao T *et al.* Estimating numbers of persons with persistent hepatitis B virus infection transmitted vertically and horizontally in the birth cohort during 1950–1985 in Japan. *Hepatol Res* 2014; [Epub ahead of print].
21 Nguyen VT, McLaws ML, Dore GJ. Prevalence and risk factors for hepatitis C infection in rural north Vietnam. *Hepatol Int* 2007; **1**: 387–93.
22 Tanaka J, Koyama T, Mizui M *et al.* Total numbers of undiagnosed carriers of hepatitis C and B viruses in Japan estimated by age- and area-specific prevalence on the national scale. *Intervirology* 2011; **54**: 185–95.
23 Pham DA, Leuangwutiwong P, Jittmittraphap A, Luplertlop N, Bach HK, Akkarathamrongsin S. Theamboonlers A and Poovorawan Y. High prevalence of hepatitis C virus genotype 6 in Vietnam. *Asian Pac J Allerry Immunol* 2009; **27**: 153–60.
24 Nguyen TB, Pham HV. Apply the direct sequencing of the qPCR products to do the HCV genotyping. *Y Hoc TP Ho Chi Minh* 2009; **13**: 243–9.
25 Zein NN. Clinical significance of hepatitis C virus genotypes. *Clin Microbiol Rev* 2000; **13**: 223–35.

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特集：C型肝炎治療update

C型肝炎の疫学と対策

田中純子　　片山恵子

I. 総　　論

C型肝炎の疫学と対策

田中純子　片山恵子

Epidemiology of hepatitis C virus infection in Japan

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Abstract

In Japan, a new era of treatment of HCV infection has come.

The issues of hepatitis measures at present are that the HCV carrier in need of treatment is linked to the received treatment properly in conjunction with the improvement of hepatitis screening consultation rate and the promotion of treatment introduction rate with medical institutions consultation rate after hepatitis screening.

Key words: HCV carrier, estimated number of HCV carriers, epidemiology, prevalence, incidence

はじめに

世界保健機関(World Health Organization: WHO)は，C型肝炎ウイルス(hepatitis C virus: HCV)に持続感染している人(HCVキャリア)は世界全体では1.3億–1.5億人であり，年間35万–50万人以上の人々がHCV関連疾患で死亡していると推計している[1]．WHOは，2011年に7月28日を「世界肝炎デー」と定め，肝炎についての啓発をはじめとした世界レベルでのウイルス肝炎の対策，肝炎ウイルス検査の受検勧奨，感染予防対策などを進めている．

我が国では，世界に先駆けて輸血用血液のスクリーニングにC型肝炎ウイルス検査を導入すると同時に，住民を対象とした肝炎ウイルス検査の推進や肝疾患診療ネットワークの構築，新規治療法の開発や医療費助成制度事業などを積極的に実施している．

C型肝炎の治療は，新しい時代を迎えており，HCVの酵素活性に直接作用する直接作用型抗ウイルス薬(direct acting antivirals: DAA)の一種であるプロテアーゼ阻害薬やNS5A阻害薬が認可され，新たなDAAの臨床試験・開発が次々に行われているところである．ペグインターフェロン/リバビリンとDAAの3剤併用療法やDAAのみの経口2剤併用療法は，難治性の遺伝子型1b，高ウイルス量のキャリアに対する著効率も高く，これまでの治療成績と比較すると格段の改善を認めることが期待されている．

新しいHCV感染の治療の時代を迎えた現時点の課題は，治療が必要なキャリアが適切に受療へ結びつくこと，すなわち，肝炎ウイルス検査受診率の向上と併せて，検査後の医療機関受診率と治療導入率の推進といえる．本稿では，

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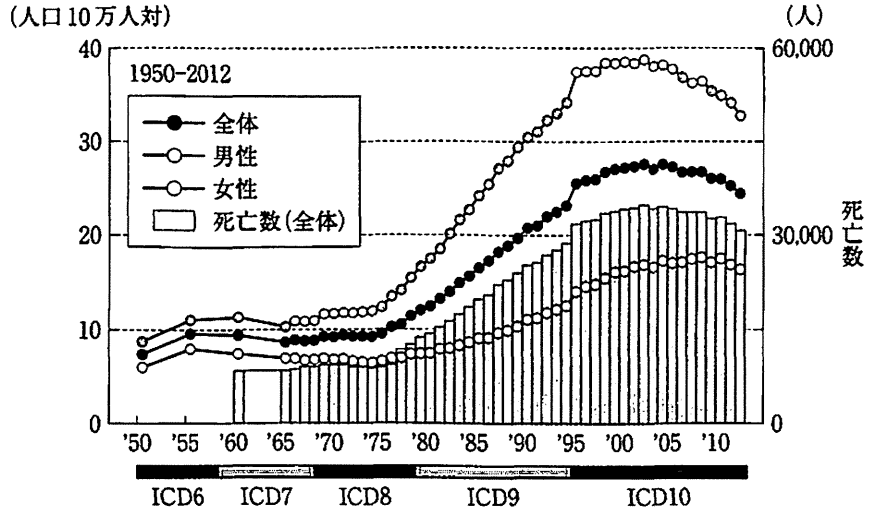

図1 我が国における肝癌による死亡の推移(2014年4月)
人口動態統計より作成.

これまでに得られている疫学調査成績をもとに,C型肝炎の疫学updateを述べてみたい.

1. 肝癌死亡の推移とその成因

我が国の死因の第1位は,1981年以降「悪性新生物」である.最新の人口動態統計報告(2012年)によると[2],悪性新生物による死亡は360,963人,死因の2位は心疾患(198,836人),3位肺炎(123,925人),4位脳血管疾患(121,602人)である.全死亡数1,256,359人のうち64.1%を四大死因が占めている.悪性新生物の部位別に死亡をみると,「肝」(肝および肝内胆管の悪性新生物,2012年)による死亡は,3.1万人(男性20,060人,女性10,630人)と,肺(7.2万人),胃(4.9万人),大腸(4.7万人)についで4番目であり,人口10万人あたりの死亡は24.4人である.

肝癌による死亡は,1950年代はじめから1970年代半ばまで人口10万人あたり10人前後と横ばいで推移した(図1)が,その後急増し2002年(人口10万対27.5)にピークとなった.男性は女性の約2倍の死亡率を示しているが,2002年以後は減少傾向,女性では横ばい状態を保っている.なお,1995年にみられる死亡増加は,ICD10(第10回国際疾病分類)への移行に伴う分類変更によるものである.

時代による高齢化の影響を取り除いた推移を年齢調整死亡率でみると,1995年から男女とも減少傾向が認められ,肝癌のリスクそのものは1970年代並みになったことが確認できるが,依然として肝癌による死亡実数,肝硬変を含む「肝癌および肝疾患」による死亡実数は,それぞれ3万人,5万人を超えている.

我が国の肝癌の病因ウイルス別の成因については,同一の資料と同一の推計方法でこれまで肝炎疫学研究班が行っており,2007年時点までの最新の成績について図2に示す.1970年代後半から現在に至るまで,HBVの持続感染に起因する肝癌の死亡割合は10万人対3-4人と増減なくほぼ一定の値を示しており,極めて特徴的である.1977年の肝癌死亡のうち約41%がHBVに起因すると推定されたが,1985年には約25%,1995年には約17%,2007年には約15%と減少している.一方で,1980年代から2000年代にかけて肝癌による死亡が増加した原因は非A非B型,すなわちHCVの持続感染に起因するものである.

なお,2000年以降の動向をみると肝癌死亡全体の10-20%が非B非C型に由来し増加傾向にあるが,依然として我が国の肝細胞癌死亡の約65%はHCVの持続感染に起因すると推定され,肝癌対策の第一選択としてもC型肝炎ウイルス対策が重要と考えられる.

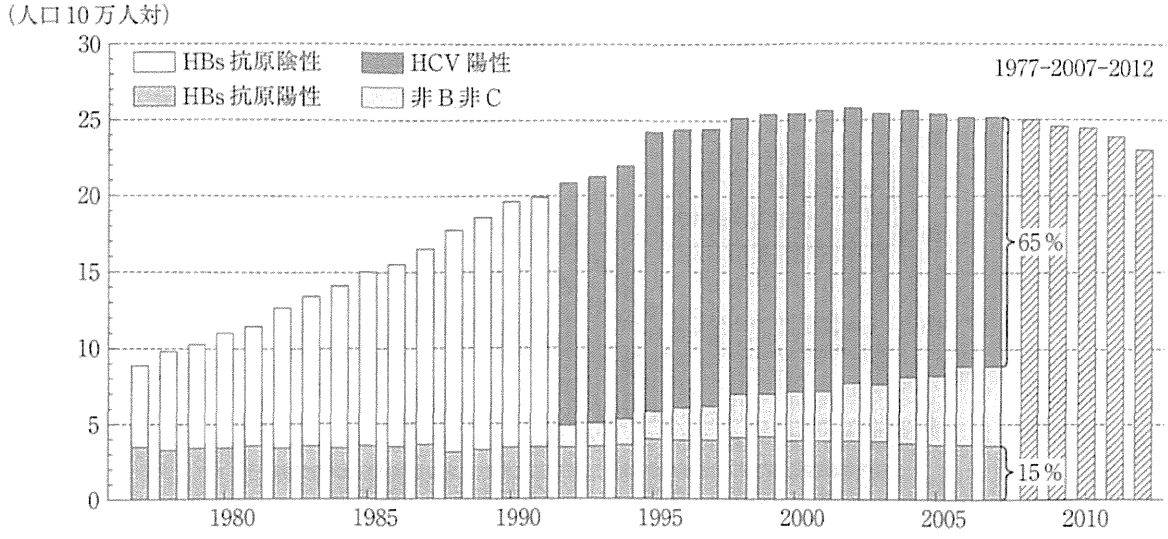

図2 病因別にみた肝細胞癌による死亡の経年的推移
(厚生労働省 肝炎等克服政策研究事業「急性感染も含めた肝炎ウイルス感染状況・長期経過と治療導入対策に関する研究」班)

2. 肝炎ウイルスキャリア数と患者数の動向について

我が国では1989年に輸血用血液のスクリーニングにHCV抗体検査を導入し，世界に先駆けて感染予防対策を講じたが，臨床や検診の場においても，1990年代初めから急速に診断と治療が広がってきた．

1990年代には，住民健診や病院などで行われる肝炎ウイルス検査(診断)の成績や疫学研究報告，臨床病理学的研究報告などから，HCVの持続感染と肝癌の関係，HCV持続感染者の自然病態，HCV新規感染率の状況などが明らかとなった．HCV持続感染者は自覚症状がないまま肝病態が進行することにより，肝癌を高率に発症することなども指摘された．

そこで，自覚症状がなく肝炎ウイルスに持続感染している人(キャリア)がどのくらいいるのかを把握すること，さらに，肝癌へ進行する可能性のある人数規模や地域年齢偏在を把握することは，治療戦略や肝癌対策の基礎資料となる重要な課題であった．しかし，肝炎ウイルスに感染している人のほとんどは自覚症状がなく，肝臓の病態が進行してもなかなか自覚症状が現れないという特性をもっているため，その数を正確に把握することは困難であった．

厚生労働省は，2000年時点の肝炎ウイルスキャリア数全体を，患者を含め300万-370万人(HBV: 110万-140万人，HCV: 190万-230万人)と推定し，検査の推進と医療費助成，治療連携などの肝炎対策を講じてきた．その後，2011年時点における肝炎ウイルスキャリア数の動向についての推計を厚労省肝炎疫学研究班[3]が試みている(第12回厚労省肝炎対策推進協議会)．同研究班では，これまでの疫学的調査成績や患者調査，数理疫学手法などを用い，肝炎ウイルスキャリアの社会での存在状態別の数の把握を行っている．4つの存在状態は以下のとおりである：「①感染を知らないまま潜在しているキャリア」，「②患者としてすでに通院・入院しているキャリア」，「③感染を知ったが受診しないでいる，あるいは継続受診に至っていないキャリア」，「④新規感染によるキャリア」(図3)．

現時点の推計中間報告としては，「①感染を知らないまま潜在しているキャリア」数は，2000年時点の240万-305万人と比較してかなり減少し77.7万人程度になることが明らかとなった．いずれも40歳以上の年齢層が全体の80%以上を占めている(なお，この推計は日本赤十字社の協力の下に，全国で統一された試薬

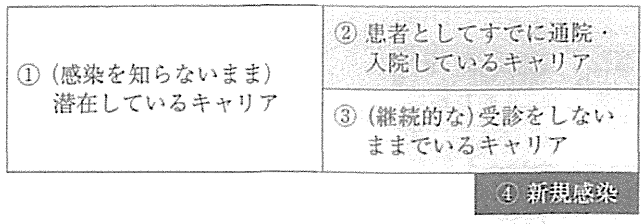

図３　肝炎ウイルスキャリアの社会における存在状態４分類
①②③④分類別の実態把握，実態に即した対策が効果的．
（厚生労働省 肝炎等克服政策研究事業「急性感染も含めた肝炎ウイルス感染状況・長期経過と治療導入対策に関する研究」班）

と診断基準により判定された1995－2006年の約1,000万人の初回供血者集団の資料[4,5]をもとにして行われている）．

2011年には，「①感染を知らないまま潜在しているキャリア」数が減少したと推定されたが，これは1990年代後半から2000年代にかけて，節目検診や無料検査の実施などにより様々な肝炎ウイルス検査の機会（診療，手術時における肝炎ウイルス検査など）が増加したこと，行政・医師会などによる啓発活動の普及により肝炎ウイルス感染の知識が浸透したことで検査が推進され，多くのキャリアの感染が判明したことがその理由と考えられる．老人保健事業や健康増進法による住民検診などの肝炎ウイルス検査報告数[6]を集計すると（図４），40歳以上の約1,300万人が公費助成により肝炎ウイルス検査を受けており，かなりの検査が推進されたことがわかる．

一方，2008年から開始された公費助成による医療費助成交付数をみると，５年間でインターフェロン治療を受けたのは約13万人，核酸アナログの新規導入数は約６万人にすぎず，検査が進み診断はされたものの，いまだ相当数が治療導入に至っていないのではないかと推察される．

そこで，肝炎ウイルス検査で見いだされたキャリアの動向（医療機関受診率）を把握する目的で，検査を受けた住民5,944人を対象とした無記名自記式調査（7自治体：107市町村）の解析を行った[7]ところ，肝炎ウイルス検査で陽性と判定された2,177人のうち，「検査を受けたことを忘れていた」のは14.3％，受検したことは覚えているが結果通知が「陰性」であると間違って認識していたのは9.3％に上った（図５）．したがって，検査で「陽性」と判定されその通知を受け取った場合の医療機関受診率は66.2％と低率となることが明らかとなった．つまり，陽性判定の通知を受け取っても，その1/3は医療機関を受診していないことが明らかとなり，治療導入が進んでいないことが懸念される．医療機関を受診しなかった理由（複数回答）としては，「必要がないと思う」31.7％が３割を占め，「どこを受診するのかわからない」11.9％，「受診する機会がなかった」11.2％が１割強存在したことから，これらの対応策が急務である．

適切な治療導入を進めるためにも，「陽性」判定を通知する際には，医療機関受診の必要性と受診勧奨のための具体的な情報提供をすることが重要であると示唆された．肝炎対策基本法に基づいて告示された「肝炎対策基本指針」において，国は「手術前等に行われる肝炎ウイルス検査の結果の通知について，受検者に適切に説明を行うよう」医療機関に要請している．様々なツール等（肝炎ウイルス検査の記録カード，電子カルテへの記載など）を用いて，検査で「陽性」と判明した受検者が，医療費助成制度を活用し，適切な治療を受けられるしくみを進める必要がある．

3．肝炎ウイルスキャリア率と新規感染率

全国で統一された試薬と診断基準により判定を行っている日本赤十字社の1995－2000年の3,485,648人の５年間の初回供血者集団の資料と2001－06年の６年間の3,748,422人の初回

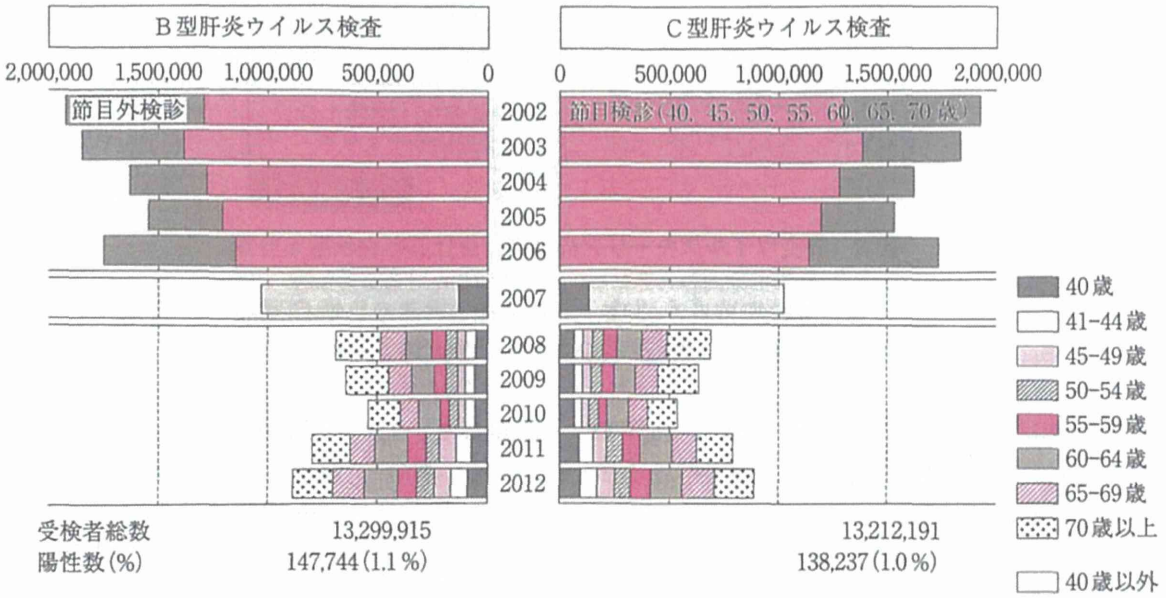

図4 公費助成による肝炎ウイルス検査数(2002-12)
(2014年6月作成)
2002-07年：厚生労働省老健局老人保健課による老人保健法に基づく保健事業における肝炎ウイルス検診実績.
2008-12年：平成20-24年地域保健・健康増進事業報告(健康増進編).

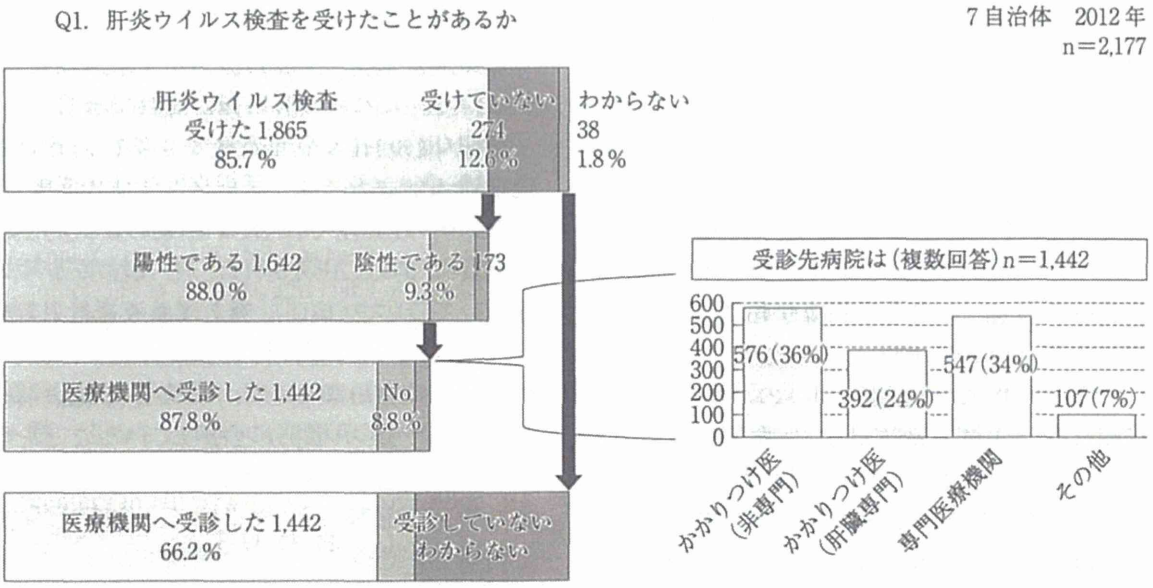

図5 公的補助による肝炎ウイルス検査を受けた後の動向調査(検査で陽性と判定された2,177人)
(厚生労働省 急性感染も含めた肝炎ウイルス感染状況・長期経過と治療導入対策に関する研究)

供血者集団の資料をもとに，いわゆる献血を行う一般健常者集団におけるHCV抗体陽性率の推定を試みた.

HCV抗体陽性率は1995-2000年の5年間の資料では全体で0.49％であったが，2001-06年の6年間では全体で0.26％とHCV抗体陽性率は低下したことが明らかとなった．2つの期間の大規模集団ともに60歳以上の高年齢層では，依然としてHCV抗体陽性率が高い値(1995-2000年：2.0％以上，2001-06年：1.0％以上)

を示したが，20歳以下の若年層ではいずれも極めて低い値を示している．

全国8地域別年齢階級別にみると，西日本地域では平均して高いHCV抗体陽性率[4,5]を示している．しかし，年齢とHCV抗体陽性率の傾向は地域により多少の高低差が認められるものの，年齢が高い集団でHCV抗体陽性率が高い傾向を示すという特徴がいずれの地域にも認められている．

HCVが発見され，輸血用血液のスクリーニングとしてHCV抗体検査が導入された1992年以前には，世界中の輸血後肝炎の主な原因はHCVであったこと，特に米国における輸血後肝炎の90％はHCVによるものであったことをWHOは報告している．我が国においては，核酸増幅検査(nucleic acid amplification test: NAT)導入や様々な感染予防対策により，現時点では輸血に伴うHCV感染はほぼ駆逐されたといえる状況となっている[8]．

HCV新規感染の頻度状況を把握するため，献血者集団を長期間観察し献血時の検査成績からみた調査研究を以下に紹介する．

献血者集団は，ボランティア精神を有し，健康を維持しながら社会生活を送り，定期的に献血を行っている．広島県赤十字血液センターにおける1994年6月～2004年4月までの実供血者418,269人(総献血本数1,409,465本)を対象とした前向き調査[9]では，期間内に複数回献血をした218,797人(861,842人年)のうち，献血時に新たなHCV感染が確認されたのは16例，HCV新規発生率は10万人年あたり1.86人(95％CI: 1.06-3.01人/10万人年)と推定された．1億人に換算すると1年あたり1,000-3,000人程度のHCVの新規感染者が発生していることを示唆している．統計学的な有意差は認められなかったが，女性は2.77人/10万人年と，男性(1.08人/10万人年)よりも高い傾向があった．また，50歳代女性の新規感染率は6.02人(95％CI: 1.64-15.42人/10万人年)と最も高く，ついで20歳代女性は3.21人(95％CI: 0.87-8.22人/10万人年)，30歳代女性が2.31人(95％CI: 0.28-8.35人/10万人年)と女性において高い新規感染率を示す傾向が認められた．

これらの結果から，全体としてのHCV新規発生率は非常に低いと考えられるが，女性，特に50歳代女性での新規感染率が高い理由は不明であり，感染原因を明らかにするための今後の調査が必要と考えられる．

一方，国の感染症サーベイランスに届け出された有症状者の急性C型肝炎報告数は，年間約30-70例と年々減少している．急性C型肝炎の報告数の減少は，罹患が減少していることが原因ではなく，届け出義務の不周知が原因である可能性もある．また，診療報酬(レセプト)を用いた肝炎疫学研究班による推計によると，年間およそ数百の有症状のHCV新規感染者が発生していると推定され，その数にはかなりの開きが認められる．

しかし，現時点に得られている新規感染率調査成績から頻度を計算すると，不顕性および顕性あわせて年間2,000例を超えるHCVの感染者が発生しているとも危惧されることから，感染予防対策の継続と同時に，サーベイランスの届け出義務の徹底と届けられた感染原因の解析が，我が国のHCV感染拡大を未然に防ぐために急務といえる．

なお，一般集団ではHCV感染の新規発生はごくまれであることを示したが，血液を介する感染のハイリスク集団，例えば血液透析患者集団におけるHCV発生率は供血者集団と比較して10^2倍程度高い頻度を示すことが多施設前向き調査成績[10]から明らかとなっていることを付記する．引き続き，感染予防対策は重要である．

おわりに

我が国では，一般集団におけるHCV新規感染が低率であることに加え，コホート効果により低年齢集団の低いHCVキャリア率が高年齢集団にスライドすることにより，全体でのHCVキャリア率がこの20年間に低下しているといえる．さらに，輸血用血液のスクリーニングにHCV抗体検査を取り入れ，世界に先駆けて感染防止対策を講じたこと，HCVキャリアに対する抗ウイルス療法などの治療介入を1990年代当

初から積極的に行ってきたこと，2002年から40歳以上の住民を対象とした肝炎ウイルス検査を全国一斉に導入したことなど，先駆的にHCVキャリア対策，HCV感染対策を行ってきた結果，全体のHCVキャリア率が低下傾向にあると考えられる．日本の疾病対策や臨床医療の効果が確実に現れてきていると考えられる．

ウイルス排除率の高い抗ウイルス薬の導入を迎えた今後の我が国の肝炎対策としては，肝炎ウイルス検査の更なる推進，適切な治療導入対策，治療に至っていないキャリアへの対策が重要である．さらに，手術前検査など様々な機会に行われている肝炎ウイルス検査の結果を受検者に適切に通知し，必要に応じて医療費助成制度を利用するよう勧める仕組みも必要と考えられる．

我が国では，肝炎対策基本法を基にした臨床・基礎・社会医学分野における肝炎・肝癌対策が，国民の健康増進につながるところまできているといえる．

文　献

1) WHO Fact Sheet N0164; Media Centre.
2) 一般財団法人厚生労働統計協会：平成24年人口動態統計上巻，p593，2012.
3) 大規模集団のキャリア率をもとにしたキャリア数推計の試み．平成21，22年度 肝炎等克服緊急対策研究事業 肝炎ウイルス感染状況・長期経過と予後調査及び治療導入対策に関する研究 研究報告書，2010，2011.
4) Tanaka J, et al: Sex- and age-specific carriers of hepatitis B and C viruses in Japan estimated by the prevalence in the 3,485,648 first-time blood donors during 1995-2000. Intervirology **47**(1): 32-40, 2004.
5) Tanaka J, et al: Total numbers of undiagnosed carriers of hepatitis C and B viruses in Japan estimated by age- and area-specific prevalence on the national scale. Intervirology **54**(4): 185-195, 2011.
6) 2002-2007年：厚生労働省老健局老人保健課による老人保健法に基づく保健事業における肝炎ウイルス検診実績．2008-2012年：平成20-24年地域保健・健康増進事業報告(健康増進編).
7) 肝炎ウイルス検査後の意識動向調査の結果報告—2013年度版— 平成25年度 厚生労働科学研究費補助金 肝炎等克服緊急対策研究事業 急性感染も含めた肝炎ウイルス感染状況・長期経過と治療導入対策に関する研究 研究報告書(研究代表者 田中純子)，p197-202，2014.
8) Tani Y, et al; JRC NAT Screening Research Group: Significant background rates of HBV and HCV infections in patients and risks of blood transfusion from donors with low anti-HBc titres or high anti-HBc titres with high anti-HBs titres in Japan: a prospective, individual NAT study of transfusion-transmitted HBV, HCV and HIV infections. Vox Sang **102**(4): 285-293, 2012.
9) Tanaka J, et al: Incidence rates of hepatitis B and C virus infections among blood donors in Hiroshima, Japan, during 10 years from 1994 to 2004. Intervirology **51**: 33-41, 2008.
10) Kumagai J, et al: Hepatitis C virus infection in 2,744 hemodialysis patients followed regularly at nine centers in Hiroshima during November 1999 through February 2003. J Med Virol **76**: 498-502, 2005.