

# Chronic Japanese schistosomiasis and hepatocellular carcinoma: ten years of follow-up in Yamanashi Prefecture, Japan

Fumiyoshi Iida,<sup>1</sup> Ryuichi Iida,<sup>2</sup> Hiroshi Kamijo,<sup>3</sup> Kazuhiko Takaso,<sup>4</sup> Yoshiki Miyazaki,<sup>5</sup> Wataru Funabashi,<sup>6</sup> Kazuko Tsuchiya,<sup>7</sup> & Yoshiro Matsumoto<sup>8</sup>

In a preliminary study carried out in the study area we found that 19.1% (173/907) of patients with chronic liver disease and 51% (35/68) of hepatocellular carcinoma cases were infected with Japanese schistosomiasis. Analysis of data from 571 autopsies revealed a similarly high incidence of schistosomiasis among cases of hepatoma and other liver diseases. A prospective case-control study conducted over 10 years showed that hepatoma developed in 5.4% (26/484) of chronic schistosomiasis cases and in 7.5% (23/307) of patients with chronic liver disease (hepatitis, cirrhosis, etc). The difference was not statistically significant ( $P = 0.228$ ). A high incidence of hepatitis C virus (HCV) antibody (HCVAb) was found in the schistosomiasis group (36.5%; 95% CI = 44.9–28.1%) and in the chronic liver disease group (56.0%), 39% of whom had chronic hepatitis ( $P = 0.028$ ). Various factors that might have contributed to the development of hepatoma and schistosomiasis were investigated, but no evidence of a significant correlation between schistosomiasis and hepatoma was found. The high incidence of HCVAb was considered to have been responsible for the development of hepatocellular carcinoma in chronic schistosomiasis patients. The role of HBV infection in the development of hepatoma in schistosomiasis patients was not confirmed after an assay for HCVAb was included in the study.

Voir page 580 le résumé en français. En la página 580 figura un resumen en español.

## Introduction

In Yamanashi Prefecture, Japanese schistosomiasis used to be endemic around the tributaries of the Fuji river, i.e. the Kamanashi, Arakawa and Fuefuki rivers, an area of 19 000 hectares (Fig. 1). However, no new cases have been reported since 1982, and in 1996 the local government declared that the disease had been completely eradicated.

Yamanashi Prefecture has the highest incidences of liver cirrhosis and liver carcinoma in eastern Japan, although rates are higher in western Japan. Inaba reported a high mortality from liver

cirrhosis and liver carcinoma in the areas endemic for schistosomiasis in Yamanashi (1), and Nakashima et al. pointed out that the incidence of liver carcinoma was unusually high in patients with chronic schistosomiasis (2). The present study was carried out to determine the occurrence of liver carcinoma among patients with chronic schistosomiasis and to identify the factors contributing to this complication.

## Materials and methods

### Case records of patients with chronic schistosomiasis and chronic liver diseases

**Preliminary investigation.** We began the preliminary investigation in 1983 by analysing data on 907 cases of chronic liver disease collected from 51 (11.9%) of the 429 medical and surgical institutions in Yamanashi Prefecture.

**Prospective case-control study.** Over the 3-year period from 1985 to 1987, a total of 484 cases of chronic schistosomiasis and 307 cases of chronic liver disease (791 cases in all) were recorded. The patients were followed up over the next 10 years until the end of 1996, with particular attention to the development of liver carcinoma and to the cause(s) of death (Table 1).

**Criteria for chronic schistosomiasis.** The livers of patients were examined by ultrasonographic (Fig. 2) and computer tomographic (Fig. 3) methods. Patients whose livers showed signs of schistosomia-

<sup>1</sup> Honorary Director and Surgeon, Yamanashi Kosei Hospital, and President of the Yamanashi Medical Association, 2-32-11 Marunouchi, Kofu City, Japan 400. Requests for reprints should be sent to this author.

<sup>2</sup> Director and Internist, Yamanashi Health Insurance Hospital, Kofu City, Japan.

<sup>3</sup> Director and Internist, Koma Kyoritsu Hospital, Kushigata, Yamanashi, Japan.

<sup>4</sup> Department of Medicine, Yamanashi Prefectural Central Hospital, Kofu City, Japan.

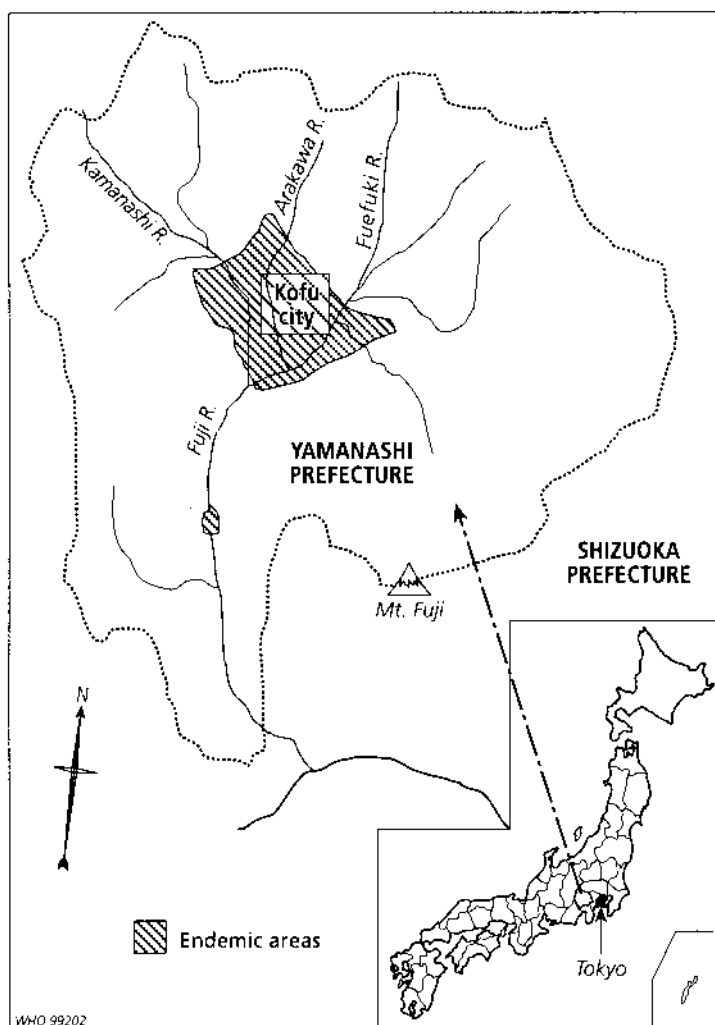
<sup>5</sup> Instructor, First Department of Medicine, Yamanashi Medical College, Tamaho, Yamanashi, Japan.

<sup>6</sup> Director and Surgeon, National Kofu Hospital, Kofu City, Japan.

<sup>7</sup> Director and Internist, Kofu Kyoritsu Hospital, Kofu City, Japan.

<sup>8</sup> Professor, First Department of Surgery, Yamanashi Medical College, Tamaho, Yamanashi, Japan.

Fig. 1. Map showing areas where *Schistosoma japonica* infection was endemic in Yamanashi Prefecture, Japan



sis, had a past history of treatment for schistosomiasis, and/or a positive skin test for Japanese schistosomiasis, were assigned to the schistosomiasis (S) group.

In the prospective case-control study, histological evidence of schistosome ova (Fig. 4) in the liver or intestine was a further criterion for inclusion in the S group.

**Patients with chronic liver disease.** Patients with serum biochemical abnormalities indicative of liver disease, including hepatitis or liver cirrhosis, and/or clinical evidence of hepatomegaly or ultrasonographic proof of a liver disorder, were assigned to the liver disease (L) group. Histopathological confirmation of liver disease (chronic hepatitis, liver cirrhosis, etc.) was added as a basic criterion for inclusion in this group in the prospective case-control study.

### Age distribution of the patients

The age distribution in the schistosomiasis group was asymmetric, with the peak incidence being among individuals aged 50–59 years, skewed to the older side. The age distribution in the liver disease group was also asymmetric with the peak incidence being among those aged 40–49 years but skewed to the younger side. Liver cirrhosis was evenly distributed in both groups, but chronic hepatitis was more common in the L group (39% of 307 cases).

### Follow-up studies on the development of hepatocellular carcinoma

Registered patients were followed up every year and the incidence of hepatoma, deaths and other relevant data were collected from the hospital records.

Table 1. Characteristics of the study patients over the period 1987–96

No. of years followed up	1	2	3	4	5	6	7	8	9	10	Total cases
Preliminary results summarized in	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	—
No. of chronic schistosomiasis patients (S)	458	484	435	388	374	361	354	349	341	333	—
No. of control liver disease patients (L)	266	307	286	260	255	249	246	238	234	233	—
Total number of registered patients	724	791	721	648	629	610	600	587	575	566	—
No. of patients reviewed	342	393	357	327	262	223	222	203	191	170	—
No. of patients with known prognosis	353	447	487	425	302	260	241	231	218	212	—
No. of new hepatoma cases in S group <sup>a, c</sup>	1	3	5	1	3	4	4	3	0	2	26
No. of new hepatoma cases in L group <sup>b, c</sup>	2	2	1	8	0	1	1	4	1	3	23
Total no. of new hepatoma cases in both groups	3	5	6	9	3	5	5	7	1	5	49

<sup>a</sup> S group = chronic schistosomiasis group; 484 initially registered.

<sup>b</sup> L group = control liver diseases group; 307 initially registered.

<sup>c</sup> Incidence of hepatocellular carcinoma in S and L groups = 5.4% (26/484) vs 7.5% (23/307) in 10 years,  $P = 0.227$ .

### Hepatocellular carcinoma and schistosomiasis in autopsied patients

The results of 571 autopsies performed in Yamanashi Prefecture between 1979 and 1982 were analysed to determine whether there was any evidence for the co-occurrence of schistosomiasis and any disease, including hepatocellular carcinoma.

### Serological tests for hepatitis B and C virus infections

The presence of the hepatitis B surface antigen (HBsAg) and its antibody (HBsAb) were determined using enzyme immunoassay (EIA). From 1991 onwards, passive haemagglutination tests for antibody to hepatitis C virus (HCV) were carried out using a commercial kit (Abbott HCV PHA, 2nd generation, Abbott Laboratories, Abbott Park, IL, USA).

### Statistical analysis

Differences in the incidence of Japanese schistosomiasis between the two study groups were analysed using the  $\chi^2$  test or Fisher's exact method, and the difference in the cumulative incidence was analysed using the generalized Wilcoxon test (3).

## Results

### Frequency of hepatocellular carcinoma in chronic schistosomiasis patients

#### Preliminary investigations

*Schistosomiasis, hepatitis B virus infection and hepatoma.* Analysis of 907 cases of chronic liver

Fig. 2. Ultrasonogram of the liver of a patient with chronic schistosomiasis. Arrows indicate high echogenic pattern ("tortoise shell")

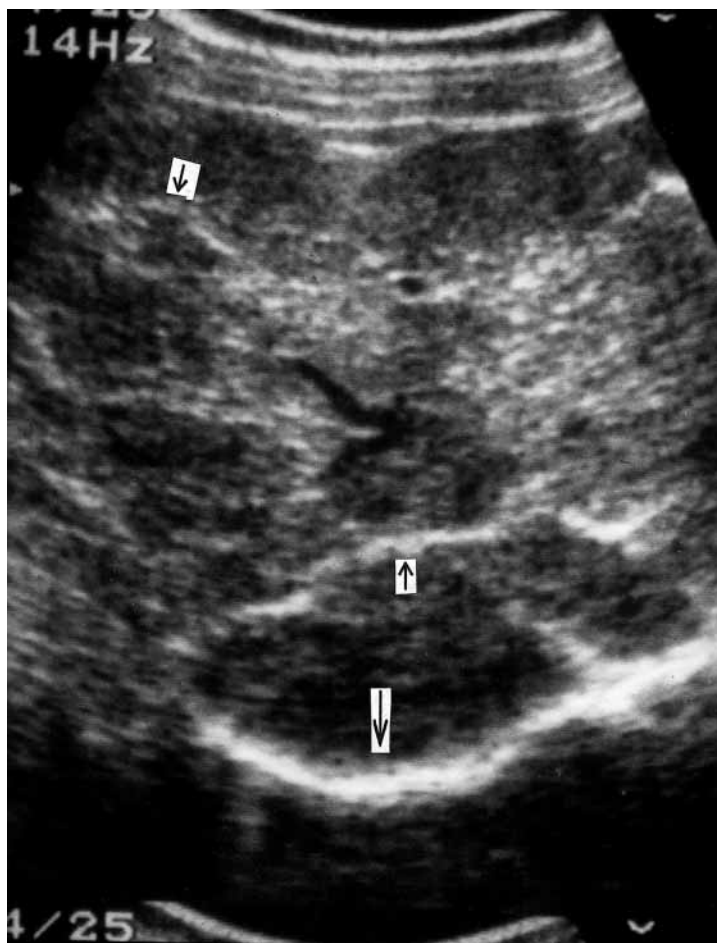


Fig. 3. Computer tomogram of the liver of a patient with chronic schistosomiasis.

Arrows indicate high density fibrotic lesions

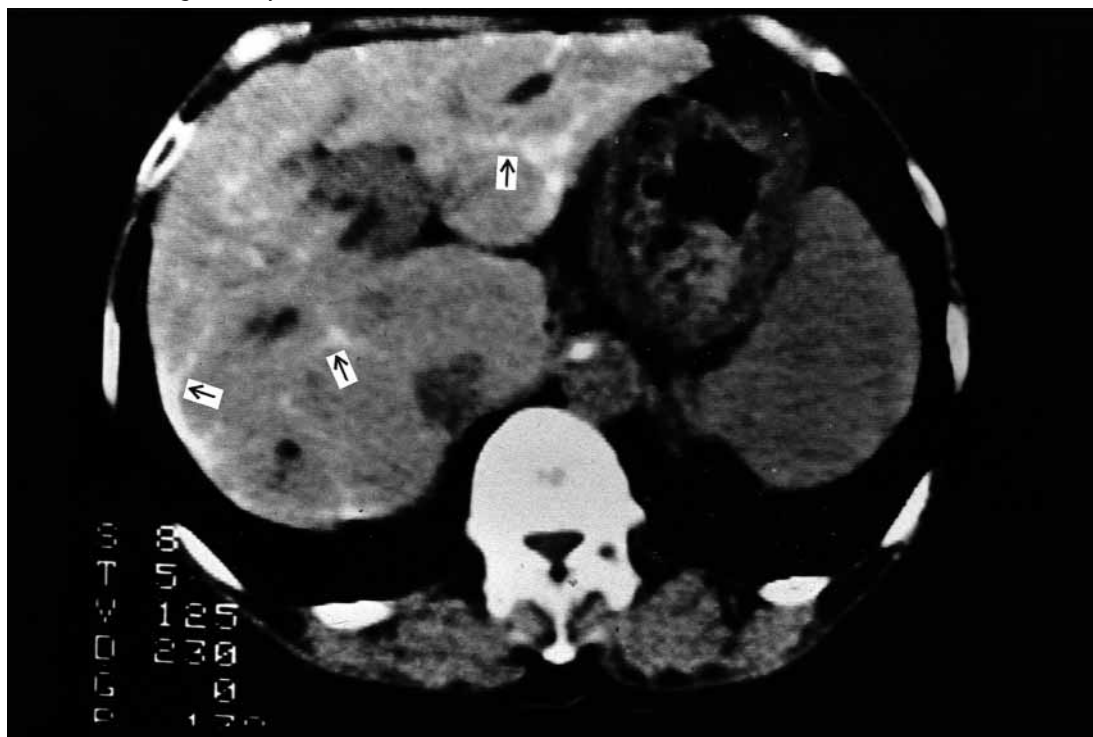
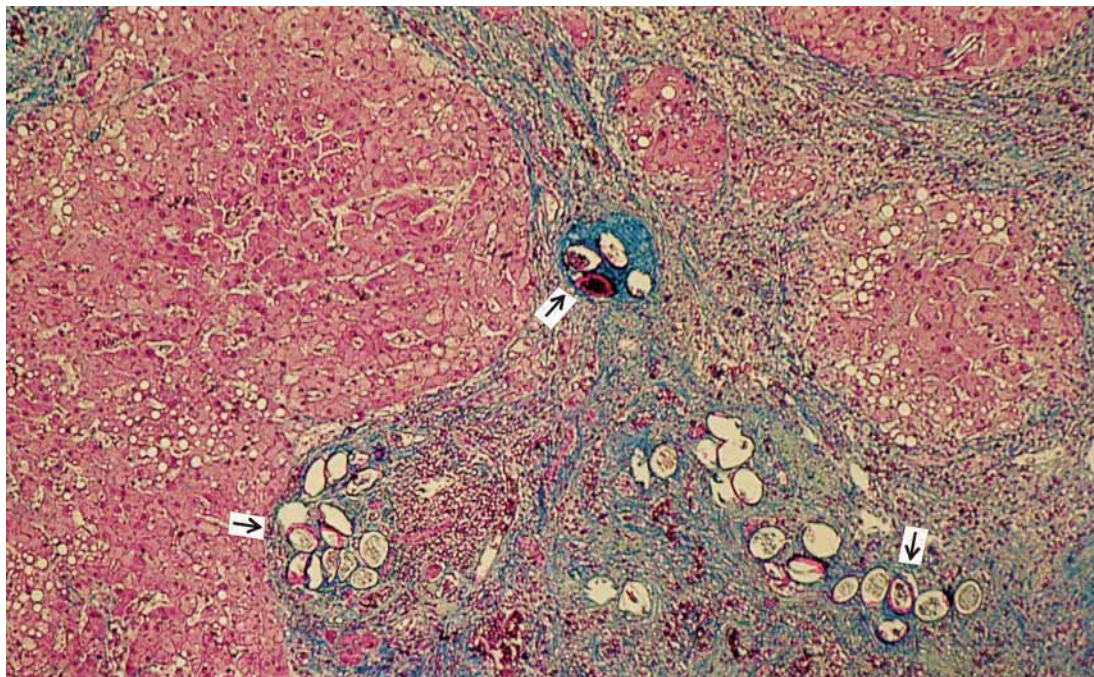


Fig. 4. **Fibrosis and clusters of schistosome ova in the dilated portal area of the liver of a patient with schistosomiasis.** Arrows indicate clusters of ova, mostly dead or calcified



disease in 1983 in the study area revealed that 19.1% (173/907) were complicated by schistosomiasis, which was most significantly correlated with hepatoma (51%, 35/68) and liver cirrhosis (48%, 71/148), but less so with chronic hepatitis (20%, 17/90) and other liver diseases (8.3%, 50/601,  $P < 0.001$ ). HBsAg was associated with hepatoma (29%, 20/68), chronic hepatitis (28%, 25/90), liver cirrhosis (31%, 35/113) and other liver diseases (14.9%, 90/601) in that order ( $P < 0.01$ ). Chronic schistosomiasis was closely associated with hepatoma and liver cirrhosis, and HBsAg with hepatoma, chronic hepatitis and liver cirrhosis. Neither a history of blood transfusion nor the amount of alcohol consumed daily was significantly associated with liver carcinoma.

**Hepatocellular carcinoma and schistosomiasis in autopsied patients.** Analysis of the findings from 571 autopsies revealed that 39% (21/54) of liver carcinoma cases were complicated by schistosomiasis. However, 14.6% (21/144) of the cases with chronic schistosomiasis, compared with 7.7% (33/427) of the patients without the disease, were complicated by hepatoma ( $P = 0.015$ ).

These preliminary investigations revealed that chronic schistosomiasis was more significantly associated with liver carcinoma and cirrhosis of the liver.

### Prospective case-control study of hepatocellular carcinoma in schistosomiasis patients

#### *Development of liver carcinoma in the study groups.*

By the end of the study in 1996, liver carcinoma had developed in 5.4% (26/484) of patients in the S group and in 7.5% (23/307) of those in the L group (not

significant,  $P = 0.23$ , Table 1). The cumulative incidences of liver carcinoma per 1000 patients in the two groups are shown in Fig. 5, but did not differ significantly ( $P = 0.5$ ).

### Causes of hepatocellular carcinoma in the study groups

#### **Incidence of HCV antibody (HCVAb)**

A total of 235 cases recruited to the study between 1985 and 1987 were tested. In the S group, 46 (36.5%) of 126 cases were positive, compared with 61 (56.0%) of 109 cases in the L group ( $P = 0.028$ ). This could have arisen because 39% of the L group patients had chronic hepatitis. However, the high incidence of HCVAb in the S group (36.5%, 95% confidence interval (CI) = 28.1–44.9%) is noteworthy and is discussed below.

#### **Infection with HCV or HBV and/or alcoholism as risk factors for hepatocellular carcinoma**

Only patients who had been tested for HCVAb were included in this part of the study. Five patients with liver carcinoma who were not included in the analysis of HCVAb were added, and 22 patients with carcinoma of the stomach, colon or other organs at the time of initial recruitment were excluded (18 cases in the S group and 4 cases in the L group). The final number of patients in the S group was 113 and in the L group 105.

**Combined schistosomiasis and HCV infection and development of hepatocellular carcinoma.** A total 13 of 47 (28%) patients with chronic schistosomiasis and who were also HCVAb positive developed hepatocellular carcinoma, compared with

5 (8%) of 66 patients who were HCVAb negative ( $P = 0.004$ ).

Among L group patients without schistosomiasis, 15 (25%) of 61 patients who were HCVAb positive developed hepatocellular carcinoma compared with 4 (9%) of 44 patients who were HCVAb negative ( $P = 0.042$ ). These data indicate that HCV infection was responsible for the development of hepatocellular carcinoma, irrespective of the presence of chronic schistosomiasis (Table 2).

**HCV infection and the development of hepatocellular carcinoma.** Hepatocellular carcinoma developed in 28 (26%) of 108 cases who were HCVAb positive but in only 9 (8%) of the 110 cases who were HCVAb negative ( $P = 0.05$ ). Thus, only a history of HCV infection was highly correlated with the development of liver carcinoma. However, when HCV infection was disregarded, hepatoma developed in 18 (16%) of 113 patients with schistosomiasis and in 19 (18%) of 105 patients with chronic liver diseases but without schistosomiasis ( $P = 0.670$ , Table 2).

**HBV infection and development of hepatocellular carcinoma.** This part of the study involved 73 HCVAb-negative patients who had been controlled for a history of schistosomiasis. A total of 5 of 42 patients (12%) with positive serology for HBV infection developed hepatoma, compared with 4 of 41 patients (10%) with negative serology (not significant,  $P = 0.898$ ). It was also noted that 5 of 9 patients who developed hepatoma were seropositive for HBV compared with 37 of 64 patients who did not (not significant,  $P = 0.898$ , Table 3).

These results indicate that past and/or present infection with HBV had no influence on the development of hepatoma in patients in the absence of HCV infection.

### Combined effect of schistosomiasis, HCV and HBV infections and development of hepatocellular carcinoma

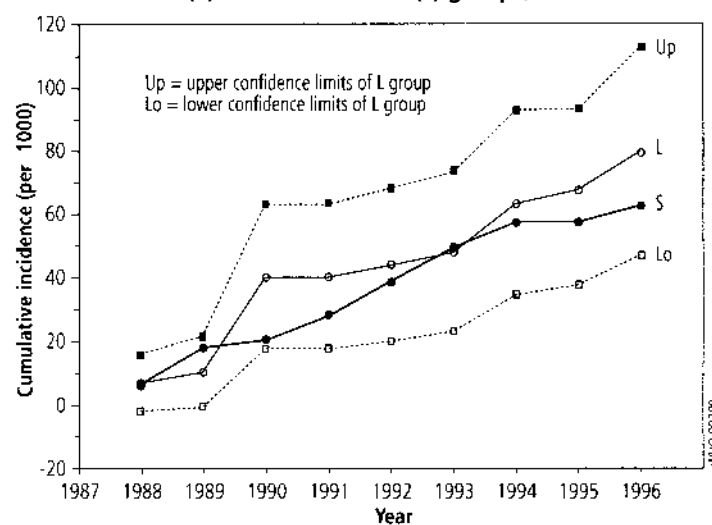
**HCVAb-positive schistosomiasis cases.** Hepatoma developed in 3 of 9 cases positive for HBV infection compared with 8 of 31 patients with negative HBV serology (Fisher's exact probability (FEP) = 0.190, not significant).

**HCVAb-negative schistosomiasis cases.** Hepatoma developed in 2 of 15 cases with positive HBV serology compared with 3 of 18 cases with negative HBV serology (FEP = 0.410, not significant).

**Schistosomiasis-negative, HCVAb-positive cases.** Hepatoma developed in 4 of 22 cases with positive HBV serology versus 9 of 45 cases with negative HBV serology (FEP = 0.431, not significant).

**Cases negative for both schistosomiasis and HCVAb.** Hepatoma developed in 3 of 29 cases with positive HBV serology, compared with 1 of 12 cases with negative HBV serology (FEP = 0.333, not significant). These data further indicate that HBV infection did not influence the development of hepatoma in our study population (Table 4).

Fig. 5. Cumulative incidence of hepatocellular carcinoma in the schistosomiasis (S) and liver disease (L) groups, 1987–96



**Probability of developing hepatocellular carcinoma in the absence of HCVAb, HBsAg and HBsAb.** Hepatoma developed in 3 of 18 patients with schistosomiasis ( $P = 0.167$ , 95% CI = 0–0.339), and in the absence of schistosomiasis in 1 of 12 patients ( $P = 0.083$ , CI = 0–0.239, FEP = 0.469, Table 4).

**HCV infection alone and development of hepatoma.** Irrespective of their history of schistosomiasis or HBV infection, 164 patients were divided into those who were HCVAb positive ( $n = 90$ ) or HCVAb negative ( $n = 74$ ). Hepatocellular carcinoma developed in 24 cases in the former group and 9 cases in the latter group ( $P = 0.02$ ) (Table 4).

### HBsAg carrier state and the development of hepatoma in patients seronegative for HCVAb

**Chronic schistosomiasis cases seronegative for HCVAb.** One of 7 patients who were seropositive

Table 2. Incidence of hepatocellular carcinoma in relation to the results of HCV antibody (HCVAb) testing

Schistosomiasis status	HCVAb status	No. tested	No. with hepatoma	Incidence	Significance <sup>a</sup>
Present	+	47	13	0.28	$s, P = 0.004$
Present	-	66	5	0.08	
Total		113	18	0.16	
Absent	+	61	15	0.25	$s, P = 0.042$
Absent	-	44	4	0.09	
Total		105	19	0.18	
Yes or no <sup>b</sup>	+	108	28	0.26	$s, P = 0.050$
Yes or no	-	110	9	0.08	
Total		218	37	0.17	
Present	+or-	113	18	0.16	$ns, P = 0.670$
Absent	+or-	105	19	0.18	
Total		218	37	0.17	

<sup>a</sup>  $s$  = significant,  $ns$  = not significant.

<sup>b</sup> Yes or no = present or absent.

Table 3. Evidence of HBV infection and development of hepatocellular carcinoma (HCVAb negative cases)

Evidence of HBV infection	Yes	No	Total	Incidence	Significance <sup>a</sup>
Yes <sup>b</sup>	5	37	42	0.12	ns
No	4	27	31	0.10	FEP= 0.310
Total	9	64	73	0.12	

<sup>a</sup> ns = not significant; FEP = Fisher's exact probability.

<sup>b</sup> HBsAg + ve and/or HBsAb +ve.

Table 4. Incidence of hepatocellular carcinoma in the patients with or without schistosomiasis, HCV or HBV infection

Row	Schistosomiasis	HVCAB	HBV infection	Hepatoma				Significance <sup>a</sup>
				Yes	No	Total	Incidence	
1	+	+	+	3	6	9	0.33	
2	+	+	-	8	23	31	0.26	ns
3	Total			11	29	40	0.28	
4	+	-	+	2	13	15	0.13	
5	+	-	-	3	15	18	0.17	ns
6	Total			5	28	33	0.15	
7	-	+	+	4	18	22	0.18	
8	-	+	-	9	36	45	0.20	ns
9	Total			13	54	67	0.19	
10	-	-	+	3	26	29	0.10	
11	-	-	-	1	11	12	0.08	ns
12	Total			4	37	41	0.10	
13	+	-	-	3	15	18	0.17	
14	-	-	-	1	11	12	0.08	ns
15	Total			4	26	30	0.13	
16 <sup>c</sup>	+or-	+	+or-	24	66	90	0.27	
17 <sup>d</sup>	+or-	-	+or-	9	65	74	0.12	s, P = 0.021
18	Total			33	131	164	0.20	

<sup>a</sup> ns = not significant, by FEP Fisher's exact probability, see text for details.

<sup>b</sup>  $\chi^2$  test.

<sup>c</sup> Row 3 + row 9.

<sup>d</sup> Row 6 + row 12.

for HBsAg, compared with 4 of 49 patients who were seronegative for HBsAg, developed hepatocellular carcinoma (not significant, FEP = 0.113).

**Cases negative for both schistosomiasis and HCVAb.** Three out of 26 patients who were positive for HBsAg, compared with 1 of 18 patients seronegative for HbsAg, developed hepatoma (not significant, FEP = 0.455). Also in this instance, HBsAg carrier status did not influence the development of hepatoma among patients seronegative for HCVAb (Table 5).

**Alcohol intake and the development of hepatoma.** We analysed 90 patients who were positive for HCVAb and who had a known history of alcohol consumption, 38 of whom belonged to the S group and 52 to the L group. In the S group, a total of 13 (34%) patients developed hepatoma, compared with 15 (29%) patients with a negative history of schistosomiasis (not significant,  $P = 0.995$ ). The

amount of alcohol (sake) consumed was not related to the development of hepatoma.

#### Sex difference and hepatocellular carcinoma.

Among the 218 study patients, hepatocellular carcinoma developed in 19 (15%) of 123 males and in 18 (19%) of 95 females (not significant,  $P > 0.05$ ).

## Discussion

The association between hepatocellular carcinoma and schistosomiasis was pointed out already in the 1940s by Warvi (4) among Chinese originating from mainland China, and in the 1950s by Prates (5) among the natives of Mozambique, where both schistosomiasis mansoni and haematobium are endemic. Similar findings were reported by Mott (6) and Edington (7) in the late 1970s. The question may be raised as to whether schistosoma infection alone is

Table 5. Incidence of hepatocellular carcinoma in relation to schistosomiasis and HbsAg carrier status (HCVAb-negative cases)

Row <sup>a</sup>	Schistosomiasis	HBsAg	Hepatoma				Significance
			Yes	No	Total	Incidence	
1	+	+	1	6	7	0.14	ns
2	+	-	4	45	49	0.08	
3	Total		5	51	56	0.09	
4	-	+	3	23	26	0.12	ns
5	-	-	1	17	18	0.06	
6	Total		4	40	44	0.09	
3	+	+or-	5	51	56	0.09	ns
6	-	+or-	4	40	44	0.09	
7	Total		9	91	100	0.09	

<sup>a</sup> Fisher's exact probability (FEP) for row 1 vs. row 4 = 0.190, not significant. FEP for row 2 vs. row 5 = 0.408, not significant.

responsible for the development of hepatocellular carcinoma.

Miyasato (8) demonstrated an additive effect of *S. japonicum* infection on the development of liver carcinoma induced by *N*-2-fluorenylacamide in mice. Also, Amano & Oshima (9) noted a high incidence of liver tumours in ddY mice inoculated with *S. japonicum*.

Concern has been expressed that HBV infection promotes the development of hepatocellular carcinoma among patients with schistosomiasis. Among schistosomiasis patients, high incidences of hepatocellular carcinoma and the HBsAg carrier state have been reported by Iuchi et al. (10), Nakashima et al. (2), Inaba (1), Kojiro et al. (11), Kamo, Kamijo, & Kikuchi (12) and Kitani & Iuchi (13).

Nishioka et al. (14) highlighted that the incidence of hepatocellular carcinoma in Japan had increased from 5.6 per 100 000 population in 1968 to 12.1 per 100 000 in 1985. Hepatocellular carcinoma associated with HBV infection decreased from 40.7% to 24.6% over the same period, while HCV was shown to be a causative agent in 57% of cases of hepatocellular carcinoma.

Our study has shown a high correlation between schistosomiasis and hepatocellular carcinoma, in agreement with reports by other Japanese workers. The incidence of hepatocellular carcinoma among the chronic schistosomiasis group was 5.4 per 1000 over 10 years — close to 7.5 per 1000 in the chronic liver diseases group, 39% of whom had chronic hepatitis.

The role of HBV infection in the development of hepatocellular carcinoma was evident in our preliminary study, which did not investigate HCVAb levels. However, the present study, which did determine HCVAb levels, found no causative association between HBV infection and the development of hepatocellular carcinoma. Nevertheless, there was a significantly higher incidence of hepatocellular carcinoma among individuals who were

HCVAb positive compared with those who were HCVAb negative, both in the schistosomiasis group and control liver diseases group.

The prevalence of HCVAb in Japan is 2.6% among 40–50-year-olds and 3.9% among over-50-year-olds. In Yamanashi Prefecture, 3.6% of males and 1.5% of females aged 40–50 years were HCVAb seropositive, as were 3.6% and 3.9% of males and females aged 50–60 years. These data indicate that the high incidence of HCV infection in schistosomiasis patients, up to 36.5% (95% CI = 28.1–44.9%), was also responsible for the high incidence of hepatocellular carcinoma.

The question of how and when individuals became infected with HCV remains unsolved. Treatment of schistosomiasis with antimony sodium tartrate began in Japan in 1923, and was later employed as a mass treatment for the disease. It has been suggested that this may have provided an opportunity for syringe transmission of hepatitis. It is also suspected that our study population is particularly prone to hepatocellular carcinoma, since this condition developed in 3 of 18 schistosomiasis patients who were seronegative for HCVAb, HBsAg and HBsAb ( $P = 0.167$ , 95% CI = 0.339–0), and in 1 of 12 patients with no history of schistosomiasis or detectable levels of HCVAb, HBsAg or HBsAb ( $P = 0.083$ , 95% CI = 0.239–0). ■

### Acknowledgements

We thank Professor I. Ebisawa, formerly at Toho University School of Medicine, who kindly helped us prepare the manuscript. Both Professor Ebisawa and Professor C. Nishimura, Department of Medical Informatics, helped us in the statistical analysis of our data. This study was initiated and supported by the local Yamanashi Medical Association in honour of its tenth anniversary. The government of Yamanashi Prefecture provided financial support.

## Résumé

### Schistosomiase japonaise chronique et carcinome hépatocellulaire : dix ans de suivi dans la préfecture de Yamanashi (Japon)

Une étude préliminaire effectuée en 1983 dans la préfecture de Yamanashi a révélé que 19,1% (173/907) des malades souffrant d'une maladie hépatique chronique, dont 48% de cirrhoses (71/148) et 51% de carcinomes hépatocellulaires (35/68), présentaient également une schistosomiase. Parmi les malades atteints d'un cancer du foie, 29% (20/68) étaient positifs pour l'HBsAg.

L'analyse des résultats de 571 autopsies pratiquées dans la zone d'étude a montré que 39% (21/54) des malades atteints d'un cancer du foie présentaient également une schistosomiase. Des cancers du foie ont été observés chez 14,6% (21/144) des malades souffrant de schistosomiase chronique contre 7,7% (33/427) chez les malades qui n'étaient pas atteints de cette affection ( $p = 0,015$ ).

Une étude prospective cas-témoins d'une dizaine d'années effectuée à partir de 1986 dans la préfecture de Yamanashi a montré que des cancers du foie s'étaient déclarés chez 5,4% (26/484) des malades souffrant de schistosomiase, contre 7,5% (23/307) des malades

atteints d'une affection hépatique chronique (non significatif,  $p = 0,228$ ).

Une analyse étiologique comportant la détermination des anticorps dirigés contre le virus de l'hépatite C, de l'antigène de surface de l'hépatite B (HBsAg) et des anticorps dirigés contre cet antigène, a montré qu'il y avait 36,5% (46/126, intervalle de confiance à 95% = 44,9-28,1%) de porteurs des anticorps anti-virus C parmi les malades souffrant de schistosomiase. Cette proportion est extrêmement élevée comparativement à celle que l'on relève dans la population générale de la préfecture de Yamanashi (< 4% des personnes âgées de 40 ans).

Nous avons examiné quelques-uns des facteurs pouvant avoir contribué à la formation de cancers du foie, et nous avons étudié en particulier le rôle de la schistosomiase chronique. Seule la présence d'anticorps dirigés contre le virus de l'hépatite C était associée à un accroissement de l'incidence des cancers du foie. Nous n'avons pas constaté que la schistosomiase chronique constitue à elle seule un facteur favorable au cancer du foie.

## Resumen

### Esquistosomiasis japonesa crónica y carcinoma hepatocelular: diez años de seguimiento en la Prefectura de Yamanashi (Japón)

Un estudio preliminar llevado a cabo en 1983 en la Prefectura de Yamanashi reveló que un 19,1% (173/907) de los pacientes con hepatopatía crónica — incluidos el 48% (71/148) de los afectados por cirrosis hepática y el 51% (35/68) de los que sufrían carcinoma hepatocelular — padecían también esquistosomiasis. En total un 29% (20/68) de los pacientes con hepatoma eran HBsAg-positivos.

El análisis de los resultados de 571 autopsias practicadas en la zona estudiada reveló que un 39% (21/54) de los pacientes con hepatoma sufrían también esquistosomiasis. Se observó hepatoma en el 14,6% (21/144) de los pacientes con esquistosomiasis crónica, frente al 7,7% (33/427) de los pacientes sin esquistosomiasis ( $p = 0,015$ ).

Un estudio prospectivo de casos y testigos llevado a cabo en la Prefectura de Yamanashi durante 10 años a partir de 1986 reveló la aparición de hepatoma en un 5,4% (26/484) de los pacientes con esquistosomiasis,

frente a un 7,5% (23/307) en el grupo con hepatopatía crónica (NS,  $p = 0,228$ ).

Los análisis etiológicos realizados, basados en la determinación de los anticuerpos contra el virus de la hepatitis C (anti-VHC), el antígeno de superficie del virus de la hepatitis B (HBsAg) y los anticuerpos contra este último (anti-HBs), revelaron la presencia de anti-VHC en el 36,5% (46/126, IC 95% = 44,9-28,1%) de los casos de esquistosomiasis. Ese porcentaje es muy alto en comparación con el hallado en la población general en la Prefectura de Yamanashi (< 4% entre las personas de 40 años).

Analizamos algunos de los factores que contribuyeron al desarrollo de hepatoma, especialmente el papel de la esquistosomiasis crónica. El único dato asociado a una mayor incidencia de hepatoma fue la presencia de anti-VHC. La esquistosomiasis crónica por sí sola no resultó ser un factor contribuyente.

## References

1. **Inaba Y.** Liver cancer in an endemic area of schistosomiasis japonica in Yamanashi Prefecture, Japan. In: Miller RW et al., eds. *Unusual occurrences as clues to cancer etiology*. Taylor Francis, Tokyo, 1988: 211–218.
2. **Nakashima T et al.** Primary liver cancer coincident with schistosomiasis japonica. *Cancer*, 1975, **36**:1483–1489.
3. **Lawless JF.** *Statistical models and methods for lifetime data*. New York, John Wiley & Sons, 1982: 423–425.
4. **Warvi WN.** Primary neoplasma of the liver. *Archives of pathology*, 1944, **37**: 369–382.
5. **Prates MD.** On the etiology of primary cancer of the liver in the natives of Mozambique. *International journal of cancer*, 1957, **13**: 662–668.
6. **Mott KE.** Possible relationship of schistosoma infection and liver carcinoma. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1978, **72**: 552–553.
7. **Edington GM.** Schistosomiasis and primary liver cell carcinoma. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1979, **73**: 351–352.



8. **Miyasato M.** Experimental study of the influence of *Schistosoma japonicum* infection on carcinogenesis in mice liver treated with *N*-2-fluorenylacetylamide (2-FAA). *Japanese journal of parasitology*, 1984, **33**: 41–48.
9. **Amano T, Oshima T.** Hepatoma formation in ddY mice with chronic schistosomiasis Japonica. *Japanese journal of cancer research*, 1988, **79**: 173–180.
10. **Iuchi M et al.** Primary liver cancer in chronic schistosomiasis, second report. *Acta Hepatologica Japonica*, 1973, **14**: 249–252 (in Japanese).
11. **Kojiro M et al.** Hepatocellular carcinoma and schistosomiasis japonica. *Acta Pathologica Japonica*, 1986, **36**: 525–532.
12. **Kamo E, Kamijo H, Kikuchi S.** Clinical analysis of the etiology of hepatocellular carcinoma and chronic schistosomiasis japonica. *Journal of Yamanashi Medical Association*, 1992, **20**: 21–28 (in Japanese).
13. **Kitani K, Iuchi M.** Schistosomiasis japonica: a vanishing epidemic in Japan. *Journal of gastroenterology and hepatology*, 1990, **5**: 160–172.
14. **Nishioka K et al.** A high prevalence of antibody to the hepatitis C virus in patients with hepatocellular carcinoma in Japan. *Cancer*, 1991, **67**: 429–433.