

Comparative Study of Hepatocellular Carcinoma in Shikoku, Japan: a Study of 198 Autopsy Cases in Tokushima and Ehime Prefectures

GO AKAGI (deceased),^{*1} Keizo FURUYA,^{*1} Hisashi OTSUKA,^{*1, *4} Shigeru TAO^{*2} and SHOZO MORIWAKI^{*3}

^{*1}Second Department of Pathology, School of Medicine, The University of Tokushima, Tokushima 770,

^{*2}Laboratory of Pathology, Ehime Prefectural Central Hospital, Kasugacho 83, Matsuyama 790 and

^{*3}Department of Pathology and Clinical Research, Shikoku Cancer Center Hospital, Horinouchi 13, Matsuyama 790

A total of 198 cases with hepatocellular carcinoma (HCC) autopsied in two different areas in Shikoku, Tokushima and Ehime, was examined clinicopathologically. The incidence of HBsAg-positives in overall HCC cases was 49.0%, being higher in Tokushima (52.4%) than in Ehime (43.1%). The difference seemed to be caused by the high incidence in female cases in Tokushima (46.7% in Tokushima vs. 23.1% in Ehime). The mean age of HCC cases with HBsAg (53.9 years) is younger than that of cases without HBsAg (58.8 years). The incidence of HBsAg-positive HCC cases in Shikoku decreased step by step toward older age groups from 63.4% in 41-50, 59.5% in 51-60, 34.6% in 61-70, to 15.8% in over-71 age groups, and has been decreasing gradually with the passage of time from 57.1% in 1960-1971, 50.0% in 1972-1976, to 40.8% in 1977-1981. The incidences of HBsAg-negatives in all autopsy cases increased from 2.0% in 1960-1971 to 3.3% in 1977-1981 ($P < 0.05$) although the incidences of HBsAg-positives showed almost the same level. Both in Tokushima and Ehime, the incidences of HCC associated with cirrhosis and HCC with HBsAg were smaller in grade IV cases, and the incidence of HBsAg-positive HCC was high in cases with macronodular type of cirrhosis.

Key words: Hepatocellular carcinoma — Liver cirrhosis — Hepatitis B surface antigen

In Japan the association of liver cirrhosis and HCC is as frequent as in other Asian countries¹⁾ and a high incidence of hepatitis B virus (HBV) infection in patients with these hepatic diseases has been noted.^{2, 3)} However, the incidences of hepatocellular carcinoma (HCC) differ considerably in different areas of Japan, and are generally higher in the west of Japan than in the east.⁴⁾ Shikoku Island in Southwest Japan is one of the areas where the incidence of HCC is high according to the mortality statistics of Japan. The death rate of liver cancer per one hundred thousand population in 1977-1981 is 17-23 (20.0 on average) in Tokushima and 14-18 (16.3 on average) in Ehime.⁵⁾ The high incidence of HCC in Tokushima is presumed to be a result of high prevalence of persistent infection of HBV, which has been suggested to be one of the important etiologic factors in HCC devel-

opment.²⁾ In the present study, cases with HCC autopsied in two different areas of Shikoku Island, Tokushima in the east and Ehime in the west, were examined to clarify the relation of HBV infection to HCC and to allow comparative analysis of clinicopathologic data of HCC in the two areas.

MATERIALS AND METHODS

One hundred and twenty-six cases of HCC in the autopsy files of The University of Tokushima and four hospitals in Tokushima Prefecture, and 72 cases of HCC autopsied at the National Hospital Shikoku Cancer Center, Matsuyama, Ehime Prefecture, and Ehime Prefectural Central Hospital were reviewed (Table I). These 198 cases of HCC were found in 3664 autopsies (1960-1981): 2529 in Tokushima and 1135 in Ehime. Histologic analysis was made on stained sections of both neoplastic and noncancerous liver tissues of each case. For detection of hepatitis B surface antigen (HBsAg) in nonneoplastic liver tissue, paraffin sections were stained by Shikata's orcein method and aldehyde-fuchsin stain was also employed when necessary as described in our previous study.²⁾ The liver cir-

^{*4} To whom all correspondence should be addressed.

rhosis was classified into 3 types, i.e. macronodular, micronodular and mixed, according to the criteria proposed by Anthony *et al.*,⁶⁾ and for histologic grading of HCC the classification of Edmondson and Steiner (grade I to IV) was adopted.⁷⁾ Data were analyzed statistically using the chi-square test and Student's *t*-test.

RESULTS

Numbers of cases of HCC during the 22-year period from 1960 to 1981 in Tokushima and Ehime Prefecture are shown in Table I. The incidences of HCC associated with cirrhosis (HCC+LC) were 86.5% (109/126) in Tokushima and 79.2% (57/72) in Ehime. Male-to-female ratio of HCC+LC was 4.0:1 in Tokushima and 6.1:1 in Ehime, although no definite sex preference was seen in cases of HCC without cirrhosis (HCC-LC), especially in Tokushima (1.1:1). Male preponder-

ance was more conspicuous in Ehime than in Tokushima in both groups of HCC+LC and HCC-LC, i.e. the proportion of female HCC cases was relatively high in Tokushima.

The incidences of HBsAg-positive cases in HCC of both prefectures are compared in Table II. The incidence of HBsAg-positive cases was higher in Tokushima (52.4%) than in Ehime (43.1%). The incidence of HBsAg-positives was significantly different between HCC+LC (53.0%) and HCC-LC (28.1%) ($P < 0.05$). In Tokushima, the incidence of HBsAg-positive HCC cases was relatively high in females (46.7%) and the sex difference was small. In Ehime, on the other hand, a definite sex difference in the incidence was seen (47.5% in male and 23.1% in female).

The mean age of HCC cases with HBsAg (53.9 ± 10.0 years) was about five years younger than that in cases without HBsAg

Table I. Autopsy Cases of HCC in Tokushima and Ehime (1960-1981)

Area		No. of cases (%)	Males (%)	Females (%)	M/F
Tokushima	HCC+LC	109 (86.5)	87 (90.6)	22 (73.3)	4.0:1
	HCC-LC	17 (13.5)	9 (9.4)	8 (26.7)	1.1:1
	Total	126 (100.0)	96 (100.0)	30 (100.0)	3.2:1
Ehime	HCC+LC	57 (79.2)	49 (83.1)	8 (61.5)	6.1:1
	HCC-LC	15 (20.8)	10 (16.9)	5 (38.5)	2.0:1
	Total	72 (100.0)	59 (100.0)	13 (100.0)	4.5:1
Both area	HCC+LC	166 (83.8)	136 (87.7)	30 (69.8)	4.5:1
	HCC-LC	32 (16.2)	19 (12.3)	13 (30.2)	1.5:1
	Total	198 (100.0)	155 (100.0)	43 (100.0)	3.6:1

HCC, Hepatocellular carcinoma; +LC, with liver cirrhosis; -LC, without liver cirrhosis.

Table II. Incidence of HBsAg-positive Cases in HCC in Tokushima and Ehime

Area		No. of cases	No. of HBsAg ⁺ (%)	Males (%)	Females (%)
Tokushima	HCC+LC	109	60/109 (55.0) ^{a)}	48/87 (55.2) ^{a)}	12/22 (54.5) ^{a)}
	HCC-LC	17	6/17 (35.3)	4/9 (44.4)	2/8 (25.0)
	Total	126	66/126 (52.4)	52/96 (54.2)	14/30 (46.7)
Ehime	HCC+LC	57	31/57 (43.1)	26/49 (53.1)	2/8 (25.0)
	HCC-LC	15	3/15 (20.0)	2/10 (20.0)	1/5 (20.0)
	Total	72	31/72 (43.1)	28/59 (47.5)	3/13 (23.1)
Both area	HCC+LC	166	88/166 (53.0) ^{a)}	74/136 (54.4)	14/30 (46.7)
	HCC-LC	32	9/32 (28.1) ^{b)}	6/19 (31.6)	3/13 (23.1)
	Total	198	97/198 (49.0)	80/155 (51.6)	17/43 (39.5)

Significantly different in *a* vs. *b* ($P < 0.05$).

c) No. of HBsAg-positives/No. of HCC cases (%).

(58.8±12.7 years) in overall cases ($P<0.01$) (Table III). In Tokushima, the mean age of female HCC cases with HBsAg was 5 years younger than that of male, and also 10 years younger than that of HCC female cases without HBsAg, although no sex preference was seen in HBsAg-negative cases of HCC. In Ehime, the difference in mean age of HBsAg-positive and negative cases was smaller than in Tokushima in both sexes.

The age distribution of HCC is shown in Table III. Both in Tokushima and Ehime, HBsAg-positive cases of HCC showed a peak in the 51–60 age group. On the other hand, HBsAg-negative cases tended to be in broader age distribution, between 51 and 70 years in Tokushima and between 51 and 80 years in Ehime.

The incidences of HBsAg-positive HCC cases in each decade of life are also shown in

Table III. Overall, the incidence was highest (63.4%) at 41–50 years and decreased step by step toward older age groups: 59.5% at 51–60 years, 34.6% at 61–70 years, and 15.8% in the oldest group.

The incidences of HBsAg-positive cases in HCC cases from 1960 to 1981 are shown in Table IV. In Tokushima, the incidence decreased step by step: 63.6% in 1960–1971, 51.4% in 1972–1976 and 42.2% in 1977–1981. In Ehime, such a tendency was not clear, though the number of cases is too small to estimate exact incidences, especially in 1960–1971. Overall, the incidence decreased gradually from 57.1% (36/63)^a in 1960–1971 to 50.0% (32/64) in 1972–1976, and to 40.8% (29/71)^b in 1977–1981, though the difference between a) and b) was not significant ($0.10 > P > 0.05$). In both prefectures, however, the incidences in older age groups

Table III. The Incidence of HBsAg-positive HCC Cases According to Age Group and Sex and Mean Age of HBsAg-positive and -negative HCC Cases According to Sex

Age group (years)	Tokushima			Ehime			Total
	M	F	M+F	M	F	M+F	M+F
0–40	1/3 (33.3) ^a	1/1 (100)	2/4 (50.0)	4/7 (57.1)	0/1 (0)	4/8 (50.0)	6/12 (50.0)
41–50	14/21 (66.7)	7/10 (70.0)	21/31 (67.7)	4/8 (50.0)	1/2 (50.0)	5/10 (50.0)	26/41 (63.4)
51–60	26/43 (60.5)	4/7 (57.1)	30/50 (60.0)	13/21 (61.9)	1/3 (33.3)	14/24 (58.3)	44/74 (59.5) ^a
61–70	10/20 (50.0)	2/12 (16.7)	12/32 (37.5)	5/17 (29.4)	1/3 (33.3)	6/20 (30.0)	18/52 (34.6) ^a
71–	1/9 (11.1)	0/0 (–)	1/9 (11.1)	2/6 (33.3)	0/4 (0)	2/10 (20.0)	3/19 (15.8)
HBsAg ⁺	54.4±8.7 ^b	49.6±13.2	53.5±9.8	55.3±10.6	58.0±11.0	55.6±10.5	53.9±10.0
HBsAg ⁻	58.8±13.5	59.3±7.8	58.9±12.3	58.0±12.5	61.2±16.4	58.0±12.5	58.8±12.7

M, males; F, females.

a) No. of HBsAg-positives/No. of HCC cases(%). b) Mean age (years)±SD.

Significantly different in c vs. d ($P<0.01$).

Table IV. Changes in the Incidence of HBsAg-positive HCC Cases According to Sex and Age and Incidence of HCC Cases in All Autopsied Cases in Tokushima and Ehime (1960–1981)

Period	No. of HBsAg-positives/No. of HCC cases (%)										HCC in all autopsied cases	
	Tokushima					Ehime					Tokushima	Ehime
	Total	Male	Female	≤60 yr	>60 yr	Total	Male	Female	≤60 yr	>60 yr		
1960–1971	28/44 (63.6) ^a	21/32 (65.6)	7/17 (58.3)	23/32 (71.9)	5/12 (41.7)	8/19 (42.1)	8/17 (47.1)	0/2 (0)	6/13 (46.2)	2/6 (33.3)	44/1008 ^c (4.4)	19/323 ^c (5.9)
1972–1976	19/37 (51.4)	15/28 (53.6)	4/9 (44.4)	14/26 (53.8)	5/11 (45.5)	13/27 (48.1)	12/22 (54.5)	1/5 (20.0)	8/14 (57.1)	5/13 (38.5)	37/667 (5.5)	27/391 (6.9)
1977–1981	19/45 (42.2) ^b	16/36 (44.4)	3/9 (33.3)	16/27 (59.3)	3/18 (16.7)	10/26 (38.5)	8/20 (40.0)	2/6 (33.3)	9/15 (60.0)	1/11 (9.1)	45/854 (5.3)	26/421 (6.2)

Significantly different in a vs. b ($P<0.05$).

c) No. of HCC cases/No. of all autopsied cases (%).

Table V. Relationship between Histologic Grade of HCC and Incidence of Association of Liver Cirrhosis and HBsAg

Grade	Total			Tokushima			Ehime		
	No. of cases	HCC+LC (%)	HBsAg (%)	No. of cases	HCC+LC (%)	HBsAg (%)	No. of cases	HCC+LC (%)	HBsAg (%)
I	10	9 (90.0) ^a	5 (50.0) ^a	7	7 (100)	3 (42.9)	3	2 (66.7)	2 (66.7)
II	97	85 (87.6) ^b	45 (46.4) ^b	66	61 (92.4)	33 (50.0)	31	24 (77.4)	12 (38.7)
III	83	69 (83.1) ^c	45 (54.2) ^d	49	39 (79.6)	28 (57.1)	34	30 (88.2)	17 (50.0)
IV	8	3 (37.5) ^d	2 (25.0) ^h	4	2 (50.0)	2 (50.0)	4	1 (25.0)	0 (0)
Total	198	166 (83.8)	97 (49.0)	126	109 (86.5)	66 (52.4)	72	57 (79.2)	31 (43.1)

Significantly different in *d* vs. *b* ($P < 0.01$), *d* vs. *c* ($P < 0.01$), and *d* vs. mean value of *a*, *b*, and *c* ($P < 0.01$).

No significant difference in *a* vs. *d* ($0.10 > P > 0.05$) or *h* vs. mean value of *e*, *f*, and *g* ($0.50 > P > 0.25$).

Table VI. Incidence of HBsAg-positive Cases According to Type of Cirrhosis in HCC Cases

Type of cirrhosis	Tokushima			Ehime			Total		
	No. of HCC	No. of HBsAg(+) (%)	(%)	No. of HCC	No. of HBsAg(+) (%)	(%)	No. of HCC	No. of HBsAg(+) (%)	(%)
Macronodular	87	54 (62.0)	(62.0)	50	26 (52.0)	(52.0)	137	80 (58.4) ^a	(58.4) ^a
Mixed	13	4 (30.8)	(30.8)	4	1 (25.0)	(25.0)	17	5 (29.4) ^b	(29.4) ^b
Micronodular	9	2 (22.2)	(22.2)	3	1 (33.3)	(33.3)	12	3 (25.0) ^c	(25.0) ^c
Total	109	60 (55.0)	(55.0)	57	28 (49.1)	(49.1)	166	88 (53.0)	(53.0)
Without cirrhosis	17	6 (35.3)	(35.3)	15	3 (20.0)	(20.0)	32	9 (28.1)	(28.1)

Significantly different in *a* vs. mean value of *b* and *c* ($P < 0.01$) and *a* vs. *b* ($P < 0.05$).

No significant difference in *a* vs. *c* ($0.10 > P > 0.05$).

(more than 60 years) tended to decrease dramatically in the recent (1977–1981) period.

The incidences of HCC cases in all autopsies of Tokushima and Ehime in each period are shown in Table IV. In all the cases, the incidences slightly increased from 4.7% (63/1331) in 1960–1971 to 5.8% (135/2333) in 1972–1981. The incidences of HBsAg-negative HCC among all autopsies in each period significantly increased from 2.0% (27/1331) in 1960–1971 to 3.3% (42/1275) in 1977–1981 ($P < 0.05$) although the incidences of HBsAg-positives remained at almost the same level.

The relationship between histologic grade of HCC and liver cirrhosis and HBsAg is shown in Table V. The incidence of HCC+LC in all HCC cases was smaller in grade IV cases than in other grades in both prefectures. Overall, the differences in the incidences between grade II cases (87.6%) and grade IV (37.5%) ($P < 0.01$) and between grade III

(83.1%) and grade IV (37.5%) ($P < 0.01$) were statistically significant. In Tokushima, the incidence of HCC+LC tended to increase in lower grade cases, but such a tendency was not seen in Ehime. The incidence of HBsAg-positive cases in overall HCC cases was also smaller in grade IV cases (25.0%) than in other grades (46.4–54.2%), although no significant differences were seen.

The proportion of macronodular type of cirrhosis in all cirrhotic cases with HCC was very high both in Tokushima (87/109, 79.8%) and Ehime (50/57, 87.8%). The incidences of HBsAg-positive cases in each type of cirrhosis in cases of HCC are shown in Table VI. The incidences of HBsAg-positive cases of HCC with macronodular type of cirrhosis were high both in Tokushima (62%) and in Ehime (52%) compared to those in HCC cases with mixed and micronodular types of cirrhosis and HCC–LC. Overall, the differences in the incidences between HCC cases with macronodular type of cirrhosis and

with other types of cirrhosis were significant ($P < 0.01$ or $P < 0.05$).

DISCUSSION

A high incidence of HBsAg-positive cases in autopsy materials of HCC in Tokushima in the 20-year period from 1960 to 1979 was described in our previous study.²⁾ In the present study, both in Tokushima, the east part, and in Ehime, the west of Shikoku Island, an intimate association between HCC and HBV infection was noted. However, the incidence of HBsAg-positive cases in HCC has been gradually decreasing in Shikoku. A similar decreasing tendency is also observed in all Japan: 40.7% (266/654) in 1968–1977 and 34.0% (325/954) in 1978–1979.^{3, 8)} Such a decreasing tendency of HBV-positive HCC cases may be due to the improvement of sanitary and nutritional conditions in Japan. However, the incidence of HCC has recently been increasing in Japan: the death rate of liver cancer per one hundred thousand population was 9.2 in 1968–1971, 9.5 in 1972–1976, and 11.9 in 1977–1981.⁵⁾ The death rates in Tokushima and Ehime increased similarly: 15.1 and 13.7 in 1968–1971, 14.5 and 14.0 in 1972–1976, and 20.0 and 16.3 in 1977–1981, respectively.⁵⁾ Some causes of the increase are considered to be (1) persistent infection of HBV²⁾ or its analogues, (2) alcohol consumption,⁹⁻¹¹⁾ (3) cigarette smoking,¹²⁻¹⁵⁾ (4) diet,^{16, 17)} (5) various other environmental carcinogenic agents.^{16, 18)} Although the occurrence of HCC in the present time is still influenced by HBV contamination in the past, as is shown by the similar levels of incidence of HBsAg-positive HCC in all autopsy cases (Table IV), the incidence should decrease in the near future due to preventive treatment for HBV infection between mother and newborn, examination of donor blood, etc. On the other hand, the incidence of HBsAg-negatives has increased significantly (Table IV). The increasing rate may reflect the incidence of non A-non B hepatitis after blood transfusion, since the consumption of blood and refined blood products has been increasing very rapidly.

The incidence of HBsAg-positive HCC cases in all HCC in both prefectures is almost 50%, which is higher than that (36.8%, 1968–1979) in all Japan.^{3, 8)} The high incidence of

HBsAg-positives in female HCC cases (46.7%) in Tokushima might be an important factor in the higher incidence of HBsAg-positive HCC cases in Tokushima than in Ehime. However, it is apparent that the incidence of HBsAg-positive HCC cases is remarkably different in each decade of life. The incidence decreased step by step toward older age groups. This may be related with the younger mean age (53.9 years) of HBsAg-positive HCC cases, with a peak in the 51–60 age group, compared with that (58.8 years) of HBsAg-negatives with broader age distribution (51–70 age group) overall. A similar difference has been observed in other countries.¹⁹⁻²¹⁾ The lower mean age and the narrower age distribution of HBsAg-positive cases may suggest that HBV infection might have occurred at a convergent time in childhood as an etiologic factor for the development of HCC.²⁾

Both the incidences of HCC associated with cirrhosis and HCC with HBsAg were smaller in grade IV cases than in other grades in overall HCC cases. This is consistent with the results of other researchers, and they have suggested that non-cirrhotic HCC has a different pathogenetic background from that of cirrhotic HCC.²²⁻²⁵⁾

The incidence of HCC+LC in overall HCC cases in both prefectures was more than 80%. The incidence in Tokushima was 86.5%, higher than that of all Japan (75.3%, 1853/2460 autopsy cases in 1972 and 1980),⁴⁾ and is similar to that of Kurume (85.5%, 148/173 cases in 1972–1977)²⁶⁾ which is also one of the areas with the highest incidence of HCC in Japan. There were only a few reports on the incidence of HBsAg-positive case in each type of cirrhosis according to the classification of Anthony *et al.*^{27, 28)} The incidence of HBsAg-positive cases (58.4% in both prefectures) in macronodular type of cirrhosis with HCC was higher than those (25.0–29.4%) in other types of cirrhosis with HCC (Table VI). A similar tendency of HBsAg-positive cases was seen in the study of Hirohashi *et al.* in Tokyo: 44.1% (15/34) in macronodular type and 0% (0/3) in micronodular type.²⁸⁾ However, according to the data of Tan *et al.* in Singapore (necropsy materials in 1965–1975), the incidence of HBsAg-positive cases in HCC was higher

(37/57, 74.0%) than that in our cases (49.0%) (Table II) and there was no clear difference between the incidences of HBsAg-positive cases in each type of cirrhosis with HCC: 72.4% (24/33) in macronodular type, 66.7% (2/3) in mixed nodular type and 100% (2/2) in micronodular type.²⁷⁾

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