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Case-Control Study of Hepatocellular Carcinoma among Koreans Living in Osaka, Japan

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Mortality rates from liver cancer among Koreans living in Osaka are 2–3 times higher than those among Japanese. Our previous study revealed that chronic hepatitis B virus (HBV) infection and excessive alcohol drinking are two major risk factors for hepatocellular carcinoma (HCC) among Koreans in Osaka, although more than 70% of the HCC cases were negative for hepatitis B surface antigen (HBsAg). Using a recently developed immunoassay for detecting serum hepatitis C virus antibody (HCV-Ab), the role of HCV infection was evaluated in a case-control study. The case group consisted of 90 Korean patients who were admitted to Kyowa Hospital in Osaka, and were newly diagnosed as HCC during the period from January 1989 to December 1992. The control group consisted of 249 Korean patients admitted to Kyowa Hospital during the same period and matched in age groups to the HCC cases. Seventy-four and 16.7% of cases were positive for HCV-Ab and HBsAg, respectively. Besides, 41.1% of cases were heavy drinkers. Multiple logistic regression analysis revealed that the adjusted relative risk was 92.4 for HCV-Ab positive and 58.2 for HBsAg positive, as compared with both HCV-Ab and HBsAg negative. Elevated risk was also demonstrated for males with a history of heavy drinking. There was no significant association between the risk of HCC and a history of blood transfusion or cigarette smoking. It was concluded that chronic HCV infection plays a major role in the etiology of HCC among Koreans living in Osaka, in addition to HBV and heavy drinking.

Key words: Hepatocellular carcinoma — Korean population in Osaka — Case-control study — Drinking — Smoking

Several reports[1, 2] have indicated that mortality rates from liver cancer among Koreans living in Osaka are 2–3 times higher than those among Japanese. Koreans constitute the largest ethnic minority of residents in Osaka.[3] Our previous case-control study[4, 5] revealed that chronic hepatitis B virus (HBV) infection and excessive alcohol drinking were two major risk factors of hepatocellular carcinoma (HCC) among Koreans in Osaka. More than 70% of the HCC cases were, however, negative for hepatitis B surface antigen (HBsAg) in the previous study. We have, therefore, evaluated the role of hepatitis C virus (HCV) infection in the etiology of HCC among Koreans in Osaka, using a recently developed immunoassay for detecting serum hepatitis C virus antibody (HCV-Ab).

SUBJECTS AND METHODS

Cases and controls Cases comprised 90 Korean patients (68 males and 22 females) who were admitted to Kyowa Hospital in Osaka, and were newly diagnosed as HCC on the basis of clinical and/or pathological examinations during the period from January 1989 to December 1992.

The controls were selected from Korean patients who were admitted to Kyowa Hospital during the same period and were matched in age groups (40–89 years old) to the HCC cases; however, patients who had a primary diagnosis of liver disease, or any smoking- or alcohol-related disease, such as ischemic heart disease, lung cancer, peptic ulcer, or pancreatitis, were excluded. A total of 5,641 patients were admitted to Kyowa Hospital in 1989–92, and 69.3% of them were Koreans. Two hundred and forty-nine (109 males and 140 females) eligible controls were obtained. Primary diagnosis of controls was classified as injury and poisoning (ICD-9th: 800–999) in 68; diseases of the musculoskeletal system and connective tissue (710–739) in 53; diseases of the digestive system (520–579) in 46; diseases of the genitourinary system (580–629) in 39; symptoms, signs and ill-defined conditions (780–799) in 12; neoplasms (140–239) in 11; and others in 20.

Data collection and analysis All study subjects had been interviewed to obtain histories of cigarette smoking, alcohol drinking, and blood transfusion by the hospital nurses at admission as a routine practice. Smokers were defined as those who had smoked at least one cigarette per day for ten years or more, and were classified according to the average number of cigarettes consumed per day. Drinkers were defined as those who had consumed at least one "go (180 ml)" of sake (or equivalent to 27 ml of ethanol) per day for ten years or more. Drinkers were also classified according to the average amount of sake

(or sake equivalents) consumed per day. Recorded consumption of alcoholic beverages other than sake was converted into sake equivalents according to ethanol content.

HBsAg was tested by means of a reversed passive hemagglutination (RPHA) method. HCV-Ab was tested by using an enzyme-linked immunosorbent assay (ELISA, Ortho) method.

Multiple logistic regression analysis was employed to estimate relative risks of HCC adjusted for age (3 categories: 40–59, 60–69, 70–89 years old), sex, and other confounding factors. The statistical test for difference in age at diagnosis was based on the t test. All reported P values were two-tailed. These analyses were conducted with a statistical package, STATA (Computing Resource Center, California).

Table I. Age and Sex Distributions of Cases and Controls

Age	Males		Females	
	Cases No. (%)	Controls No. (%)	Cases No. (%)	Controls No. (%)
40–49	5 (7.4)	20 (18.4)	0 (0.0)	16 (11.4)
50–59	14 (20.6)	19 (17.4)	1 (4.6)	21 (15.0)
60–69	29 (42.7)	27 (24.8)	8 (36.4)	26 (18.6)
70–79	15 (22.1)	32 (29.4)	12 (54.6)	49 (35.0)
80–89	5 (7.4)	11 (10.1)	1 (4.6)	28 (20.0)
Total	68 (100)	109 (100)	22 (100)	140 (100)

RESULTS

Table I shows the age and sex distributions of HCC cases and controls. The average age of cases was 63.7 (standard deviation: 10.0) years old for males and 71.6 (6.9) for females, while the average age of controls was 63.9 (12.9) for males and 68.4 (12.7) for females.

Table II indicates the distributions of HBsAg, HCV-Ab, history of blood transfusion, and smoking and drinking habits, together with odds ratios of HCC for males. Sixteen percent of cases were positive for HBsAg, while only 3.6% of controls were positive. Prevalence of HCV-Ab among cases was 74.4%, much higher than that among controls (8.0%). Only one female case was positive for both HBsAg and HCV-Ab. Eleven percent of cases and 7.6% of controls had a history of blood transfusion. Smoking and drinking habits were very different between males and females. For males, 66.2% of cases and 63.3% of controls were smokers. For females, 13.6% of cases and 22.2% of controls were smokers. As for drinking, 80.9% of cases and 67.0% of controls were drinkers among males, while 9.1% of cases and 25.0% of controls were drinkers among females. Fifty-four percent of male cases had a history of heavy drinking (consumed at least 3 "go"s of sake a day for 10 years).

Table III shows the age-specific distributions of HBsAg positives and of HCV-Ab positives between cases and controls. The average age of HCV-Ab-positive cases

Table II. Distributions of HBsAg, HCV-Ab, History of Blood Transfusion, Smoking and Drinking Habits

Factor	Males			Females	
	Cases No. (%)	Controls No. (%)	OR (95% CI)[a]	Cases No. (%)	Controls No. (%)
HBsAg					
(+)	11 (16.2)	6 (5.5)	3.31 (1.16–9.43)	4 (18.2)	3 (2.1)
(−)	57 (83.8)	103 (94.5)	1.00	18 (81.8)	137 (97.9)
HCV-Ab					
(+)	51 (75.0)	12 (11.0)	24.2 (10.8–54.7)	16 (72.7)	8 (5.7)
(−)	17 (25.0)	97 (89.0)	1.00	6 (27.3)	132 (94.3)
Transfusion					
(+)	7 (10.3)	10 (9.2)	1.14 (0.41–3.14)	3 (13.6)	9 (6.4)
(−)	61 (89.7)	99 (90.8)	1.00	19 (86.4)	131 (93.6)
Smoking[b]					
>20	13 (19.1)	24 (22.0)	0.94 (0.40–2.20)	0 (0.0)	5 (3.6)
1–20	32 (47.1)	45 (41.3)	1.24 (0.62–2.45)	3 (13.6)	26 (18.6)
None	23 (33.8)	40 (36.7)	1.00	19 (86.4)	109 (77.9)
Drinking[c]					
≥3	37 (54.4)	22 (20.2)	4.66 (2.04–10.6)	0 (0.0)	2 (1.4)
1–2	18 (26.5)	51 (46.8)	0.98 (0.43–2.24)	2 (9.1)	33 (23.6)
None	13 (19.1)	36 (33.0)	1.00	20 (90.9)	105 (75.0)

a) Odds ratios and their 95% confidence intervals.
b) No. of cigarettes/day.
c) "Go"s of sake/day.

was about 12 years older than that of HBsAg-positive cases (67.6 years vs. 55.3 years). The difference was statistically significant ($P=0.0001$). As for controls, prevalences of HBsAg among younger age groups (40–69 years old) were higher than those among older age groups (70 years old or over), while prevalences of HCV-Ab were remarkably high among older age groups (60 years old or more).

Table IV shows adjusted odds ratios of HCC. Since there was only one case who was positive for both HBsAg and HCV-Ab, we excluded this case from multiple logistic regression analyses. Using subjects with neither HBsAg nor HCV-Ab as a referent, we estimated age and sex adjusted odds ratio as 33.2 for subjects with HBsAg, and 65.3 for subjects with HCV-Ab. Age and sex adjusted odds ratio was estimated as 1.29 for those who had a history of blood transfusion. Analysis of the relationship between the risk of HCC and smoking or drinking was restricted to male study subjects. Heavy drinkers, who had consumed at least 3 "go"s of sake a day for 10 years, showed 4.69 times higher risk of HCC in comparison with the risk for non-drinkers.

Odds ratios adjusted for age, sex, and other possible confounding factors (HBsAg, HCV-Ab, history of blood transfusion, smoking and drinking) were estimated, together with their 95% confidence intervals. Significantly elevated risks were demonstrated for the following 3 factors; HBsAg (58.2), HCV-Ab (92.4), and a history of heavy drinking (27.5, only for males). Odds ratios for these 3 factors, particularly for a history of heavy drinking, increased after adjustment for confounders. A dose-response relationship between the risk of HCC and drinking was also demonstrated (linear trend; $P<0.001$). There was no significant association between the risk of HCC and a history of blood transfusion or cigarette smoking.

Table III. Age-specific Distributions of HBsAg and HCV-Ab between Cases and Controls

Age	Cases			Controls		
	No. of subjects	HBsAg (+) No. (%)	HCV-Ab (+) No. (%)	No. of subjects	HBsAg (+) No. (%)	HCV-Ab (+) No. (%)
40–49	5	4 (80.0)	1 (20.0)	36	3 (8.3)	0 (0.0)
50–59	15	6 (40.0)	8 (53.3)	40	2 (5.0)	2 (5.0)
60–69	37	4 (10.8)	30 (81.1)	53	4 (7.6)	7 (13.2)
70–79	27	1 (3.7)	22 (81.5)	81	0 (0.0)	6 (7.4)
80–89	6	0 (0.0)	6 (100)	39	0 (0.0)	5 (12.8)
Total	90	15 (16.7)	67 (74.4)	249	9 (3.6)	20 (8.0)

Table IV. Adjusted Odds Ratios and Their 95% Confidence Intervals

Factor		OR[a]	OR[b]	95% CI[b]	*P*-value
Both sexes					
HBsAg(+), HCV-Ab(−)		33.2	58.2	15.3–221	<0.001
HBsAg(−), HCV-Ab(+)		65.3	92.4	33.8–252	<0.001
HBsAg(−), HCV-Ab(−)		1.00	1.00		
Transfusion	(+)	1.29	0.48	0.14–1.62	0.08
	(−)	1.00	1.00		
Males only					
Smoking[c]	>20	0.95	0.35	0.07–1.63	0.10[e]
	1–20	1.35	0.65	0.18–2.42	
	None	1.00	1.00		
Drinking[d]	≥3	4.69	27.5	4.16–182	<0.001[e]
	1–2	0.92	1.14	0.28–4.69	
	None	1.00	1.00		

a) Odds ratios adjusted for age and sex.
b) Odds ratios and their 95% confidence intervals, adjusted for age, sex and other confounders (HBsAg, HCV-Ab, transfusion, smoking, drinking).
c) No. of cigarettes/day.
d) "Go"s of sake/day.
e) Test for linear trend.

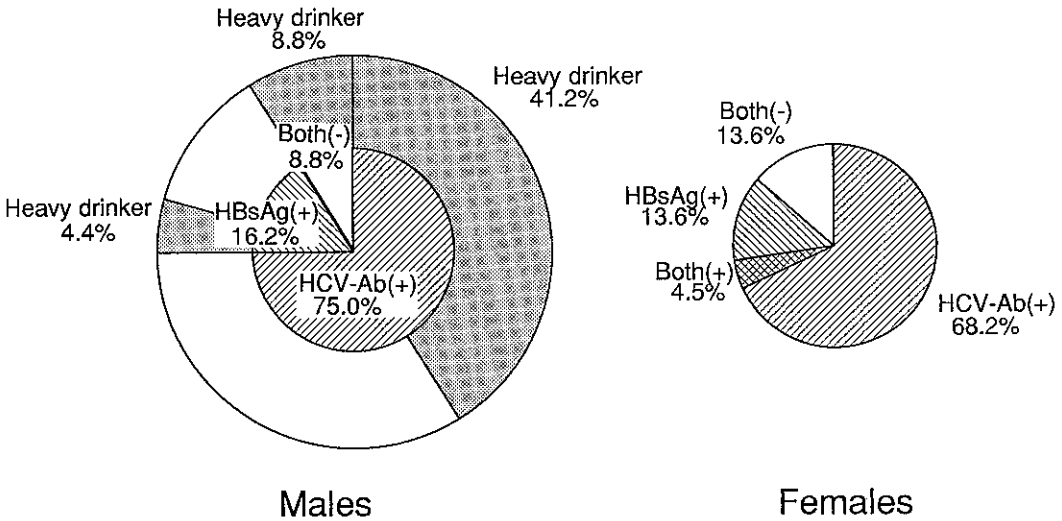

Fig. 1. Distribution of risk factors among HCC cases by sex.

Fig. 1 shows the distributions of these 3 factors among HCC cases according to sex. Distribution of HBsAg and HCV-Ab is presented in the inner circle, and frequencies of heavy drinkers are indicated in the outer circle for males (left side in Fig. 1). Ninety-one percent of male HCC cases were positive for HBsAg or HCV-Ab; besides, half of them were heavy drinkers. The remaining 8.8% of cases, who were negative for both HBsAg and HCV-Ab, were all heavy drinkers. For females (right side in Fig. 1), 86.4% of cases were positive for HBsAg and/or HCV-Ab.

DISCUSSION

The present study has demonstrated that HCV, in addition to HBV and excessive alcohol drinking, is one of the most important risk factors of HCC among Koreans living in Osaka. Because of the rather small sample size, we did not formally calculate the population attributable risk for each of the 3 risk factors. However, we consider that almost 90% of HCC cases among Koreans living in Osaka could be attributed to chronic HBV infection, HCV infection, and/or heavy drinking (Fig. 1).

Several limitations of this study should be mentioned. First, the number of study subjects was very limited, so that point estimates of odds ratios obtained in this study were unstable, showing rather wide confidence intervals (Table IV). Second, information on smoking and drinking habits, as well as history of blood transfusion, was obtained from the computerized hospital data-base, which had been well maintained by the qualified medical record administrators in Kyowa Hospital. Nevertheless, some misclassification or bias might have been introduced not only in data abstracting by these personnel, but also in history taking by nurses and medical doctors. Furthermore, we could not analyze the relationship between the risk of HCC and smoking or drinking, in terms of age at which these had begun, or types of cigarette and alcoholic beverage, because of insufficient information. Thirdly, the use of hospital controls might have underestimated the relationships, particularly the role of smoking, because a number of diseases are related to smoking. Finally, the use of a first generation ELISA for HCV-Ab might have underestimated the role of HCV infection because of possible misclassification.[6] Despite these limitations, we believe that the strong positive association between the risk of HCC and HCV, as well as HBV and excessive alcohol drinking, is likely to be valid.

It is very interesting to compare these findings with other case-control studies on risk factors of HCC, in particular, among Japanese in Japan and Koreans in Korea, because of the remarkable differences in the incidence and mortality from liver cancer among the three populations.[1, 2, 7–10] Tanaka *et al.*[11] conducted a case-control study of HCC and found that HCV, as well as HBV and heavy drinking, played a major role in the etiology of HCC in Fukuoka and Saga prefectures, Japan. After adjustment for other possible confounders, the odds ratios were estimated as 52.3 for HCV-Ab positive, 15.3 for HBsAg positive and 2.2 for heavy drinkers. Population attributable risk was furthermore estimated as 62% for HCV-Ab positive and 20% for HBsAg positive. Recently, Shin *et al.*[12] conducted a case-control study in Pusan and reported that HBV played a major role in the etiology of HCC in Korea, while HCV played a minor role and drinking was not sig-

nificantly associated with the risk for HCC. The adjusted odds ratio was reported as 51.5 for HBsAg positive, 23.5 for HCV-Ab positive and 2.1 for heavy drinkers, and the population attributable risk was estimated as 70.1, 20.7 and 10.8%, respectively, in the Pusan study. Smoking was not significantly associated with the risk for HCC in the Fukuoka-Saga[11] and Pusan studies,[12] either.

The reported odds ratios, particularly for HCV-Ab and HBsAg positive, are not necessarily comparable among the three studies. Several points should be kept in mind to understand these discrepancies. First, subjects without HBsAg nor HCV-Ab were used as a referent in the present study. Second, it is reported that the association between the risk of HCC and HBV is stronger among younger age groups, while the association between the risk of HCC and HCV (or non-A, non-B hepatitis virus) is more distinct among older age groups.[13] The mean age of HCC cases was 65.6 years old in the present study, which is the oldest among the three studies. Thirdly, different genotypes of HCV might produce different clinical outcomes,[14] although there is no evidence so far for this. Finally, there might be some variability in susceptibility to hepatocarcinogenesis according to ethnicity, as well as unknown modifiers. Further studies will be needed to confirm and understand these dissimilarities, together with higher odds ratios for heavy drinkers in this study as compared with those reported in the above studies[11, 12] and others.[15, 16]

The prevalence of HBsAg among HCC cases decreased from 28.5% (33/116 cases) in the previous study[4] (1988) to 16.7% (15/90 cases) in the present study. Among female cases, the prevalence of HBsAg decreased remarkably from 42.9% (9/21) to 18.2% (4/22). In contrast, the prevalence of HCV-Ab among HCC cases was found to be very high in the present study (75.0% for males and 72.7% for females). A preliminary study at Kyowa Hospital[10, 17] suggests that prevalence of HCV-Ab among Koreans living in Osaka tends to be higher than that among Japanese in Japan or Koreans in Korea.[18] High prevalence of HCV-Ab has also been reported among Koreans living in Fukuoka, Japan.[19] Oshima *et al.*[20] reported that the prevalence of HBsAg among Korean blood donors was higher than that among Japanese donors. Ubukata *et al.*,[21] furthermore, reported that the proportion of heavy drinkers was higher among Koreans living in Osaka, in comparison with that among Japanese in Osaka.

These observations lead us to conclude that the excess mortality from liver cancer among Koreans living in Osaka could be explained, on the whole, by the high prevalence of HCV infection, as well as the high percentage of HBV carriers and heavy drinkers, among Koreans in Osaka. The manner of HCV transmission remains unclear, for only 11.1% of the cases had a history of blood transfusion. It is an urgent task, therefore, to clarify the routes of HCV infection, particularly within the Korean population in Japan.

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