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A Hospital-based Case-Control Study on Hepatocellular Carcinoma in Fukuoka and Saga Prefectures, Northern Kyushu, Japan

Katsuhiro Fukuda,[1] Akira Shibata,[1] Itsuyo Hirohata,[1] Kyuichi Tanikawa,[2] Genjiro Yamaguchi[2] and Misa Ishii[2]

[1]Department of Public Health and [2]Second Department of Internal Medicine, Kurume University School of Medicine, 67, Asahi-machi, Kurume 830

Three hundred and sixty-eight case-control sets (male 287 pairs; female 81 sets) were collected for a hospital-based case-control study of primary hepatocellular carcinoma (HCC) conducted in Northern Kyushu, Japan. All incident cases of HCC were collected weekly from the inpatients (aged 40–69) of the Second Department of Internal Medicine, Kurume University Hospital between April, 1986 and May, 1992. One control for a male case and 4 controls for a female case were sampled, being matched to a case on age (same 5-year age class), sex, residence (prefecture) and time of hospitalization (within 2 months after a case interview) from the inpatients of two general hospitals in Kurume. Information was collected by interview in person by a well-trained interviewer and from a review of hospital records by the authors. Multivariate analyses based on a conditional logistic regression model without an interaction term revealed that hepatitis B surface antigen (HBsAg) positive status (odds ratio (OR) = 8.67; 95% confidence interval (95%CI) = 2.54–29.57), history of blood transfusion over 10 years previously (2.40; 1.26–4.56), parental history of hepatic diseases (2.31; 1.11–4.80) and heavy alcohol drinking (60≦ drink-years) by age 40 (3.23; 1.61–6.51) were statistically significant risk factors of male HCC. Univariate analysis for females also showed an elevated OR of HBsAg (7.58; 1.96–29.35). Although the sample size was limited, univariate analysis indicated that anti-hepatitis C virus antibody by c100-3 antigen positive status had a statistically significant OR for HCC in both sexes.

Key words: Hepatitis B — Hepatitis C — Blood transfusion — Alcohol drinking — Parental hepatic disease

The etiology of primary hepatocellular carcinoma (HCC) has been extensively examined during the last decade and hepatitis B or C virus, blood transfusion, heavy alcohol drinking, and other factors have been identified as risk factors for HCC. However, exposure to these risk factors varies depending on time, place, and social background of the population at risk. Several epidemiologic studies of HCC etiology among Japanese have been conducted.[1–10]

This paper reports the results of a hospital-based case-control study conducted in Fukuoka and Saga Prefectures, Northern Kyushu, Japan.

MATERIALS AND METHODS

The study was initiated in April, 1986. Incident cases of HCC, who were 1) Japanese, 2) aged 40–69, 3) residents of either Fukuoka or Saga prefecture, and with a confirmed diagnosis of HCC were identified once a week through the inpatient records of the Second Department of Internal Medicine, Kurume University Hospital. HCC patients whose diagnosis was made within 1 year prior to admission were also regarded as eligible. Their hospital controls, who were not affected by chronic hepatitis or by hepatic cirrhosis, matched for age (within the same 5-year age class), sex, residence (prefecture) and time of hospitalization (within 2 months after a case interview) were obtained from inpatients of the two university-affiliated general hospitals in Kurume. One control was selected for each case, but 4 controls have been sampled for each female case since July, 1989.

Hospital records were reviewed to obtain ultrasonographic, angiographic, and histological findings, as well as hepatitis B surface antigen (HBsAg) status by reversed passive hemagglutination or enzyme immuno assay and anti-hepatitis C virus antibody by c100-3 antigen (anti-HCV) status, which was available only for subjects acquired during the later part of 1990 and thereafter.

Information on their past history of treated diseases including blood transfusion, parental and spouse's history of hepatic diseases (the latter item was introduced in 1989), longest occupation, lifetime experiences of cigarette smoking and alcohol drinking, and dietary habits for the period prior to the diagnosis were obtained through interviews in person by a well-trained interviewer using a structured questionnaire. The interviews

Abbreviations: HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; anti-HCV, anti-hepatitis C virus antibody; OR, odds ratio; 95%CI, 95% confidence interval.

were tape-recorded and checked against the questionnaires by the authors. Occupations were classified according to the system used in the 1990 Population Census of Japan.[11] Since the use of tobacco products other than cigarettes is very limited in Japan, smokers were defined as those who had smoked cigarettes every day, at least 1 pack (20 cigarettes) a week, for 1 year or longer. Non-smokers were defined as those who had never smoked, had smoked less than 1 pack a week, or for less than 1 year. Age at starting and stopping smoking and the daily amount of cigarettes smoked at any stage of the smoking habit were collected and the lifetime amount of smoking was quantified by using the accumulated Brinkman-Coates[12] index. A detailed drinking history, such as age at starting and stopping drinking, and the kinds and amount of alcoholic beverages consumed during all stages of the drinking habit, were obtained for their lifetime. The daily amount of alcohol intake was graded by a "drink," defined as the amount of alcoholic beverage containing 23 ml of ethanol. The accumulated amount of alcohol intake was quantified by using a "drink-years" index which was the figure obtained by multiplying the number of "drinks" for all types of beverages by the number of years of their consumption. Drinkers were defined as those who had consumed any alcoholic beverages more than once a week, at least one "drink" a week for 1 year or longer. Non-drinkers were defined as those who had never drunk or those who had drunk less than once a week, less than one drink a week and/or for less than 1 year. The dietary information focused on the usual dietary habits during the previous 1 to 2 years. Subjects were asked about their frequency of intake of the 12 food items listed in Table VI.

Case-control comparison by item was performed by either the Wilcoxon matched-pairs signed-ranks test, the McNemar's test, or a univariate analysis based on a conditional logistic regression model. Multivariate analysis based on a conditional logistic model without an interaction term was performed by sex to elucidate the relationship between items and HCC, and the existence of a dose-response relationship was also assessed using the same model for items which have more than two categories. Correlation between items shown in an M×N table was analyzed by using the chi-square test.

RESULTS

Between April, 1986 and May, 1992, 1,125 HCC patients were hospitalized in Kurume University Hospital. Seven hundred and fifty of them were excluded because their age was outside the eligible range, or they were not residents of eligible Prefectures, or they had been diagnosed over 1 year prior to admission. Three cases refused to be interviewed and 4 cases provided incomplete medical or interview data. Among potential controls, no one refused interview but 3 provided incomplete medical or interview data. Finally, 368 case-control sets (male 287 1:1 case-control pairs; female 41 1:1 pairs, 3 1:3 sets, and 37 1:4 sets) were completed.

Age at the time of investigation and sex distribution are shown in Table I; as regards age, late fifties and early sixties were the most prevalent among males and females, respectively. Diagnosis of HCC was based on histological findings (75.3% for males; 81.5% for females), angiographic results (20.6% for males; 13.6% for females), or other findings. Further, 10.5% of male and 11.1% of female cases were HBsAg-positive and the majority of controls were HBsAg-negative, as shown in Table II. Among the subjects with known anti-HCV status, 82.9% (=58/70) of male and 82.8%(=24/29) of female cases were anti-HCV-positive, and 8.7%(=4/46) of male and 5.9%(=4/68) of female controls were anti-HCV-positive. The 10 most prevalent diseases which had been treated, based on the multiple responses at the time of

Table I. Age and Sex Distribution of Study Subjects at Time of Investigation

Age	Male[a]	Female[b]	
		Case	Control
40–44	8 (2.8)	1 (1.2)	4 (2.0)
45–49	14 (4.9)	3 (3.7)	9 (4.5)
50–54	47 (16.4)	11 (13.6)	22 (11.1)
55–59	89 (31.0)	12 (14.8)	30 (15.2)
60–64	87 (30.3)	33 (40.7)	77 (38.9)
65–69	42 (14.6)	21 (25.9)	56 (28.3)
Total	287 (100.0)	81 (99.9)	198 (100.0)

a) No difference between case and control.
b) Frequency shown without preserving matching.

Table II. Status of Hepatitis B Surface Antigen and Anti-hepatitis C Virus Antibody by c100-3 Antigen

	Male		Female[a]	
	Case	Control	Case	Control
A. Hepatitis B surface antigen				
−	255 (88.9)	273(95.1)	72 (88.9)	194 (98.0)
+	30 (10.5)	3 (1.0)	9 (11.1)	3 (1.5)
±	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	1 (0.3)	11 (3.8)	0 (0.0)	1 (0.5)
B. Anti-hepatitis C virus antibody				
−	12 (4.2)	42(14.6)	5 (6.2)	64 (32.3)
+	58 (20.2)	4 (1.4)	24 (29.6)	4 (2.0)
Unknown	217 (75.6)	241(84.0)	52 (64.2)	130 (65.7)
Total	287(100.0)	287(99.9)	81(100.0)	198(100.0)

a) Frequency shown without preserving matching.

investigation, and the history of blood transfusion are listed in Table III. Hepatic diseases of unknown nature were the most prevalent among cases and peptic ulcer or hypertension among male or female controls, respectively. Blood transfusion was more prevalent among cases than controls. Further, 10.1% of male and 12% of female cases had a parental history of hepatitis, hepatic cirrhosis and some other hepatic diseases, and the comparative figures among controls were 5.8% and 7.5%, respectively. Among the subjects with available history of spouse's hepatic diseases, 9 cases and 8 controls among 110 male case-control sets, and 4 and 22 among 37 female sets had such a history. Approximately 30% of study subjects of both sexes gave "craftsmen, mining, production process and construction workers and laborers" as the longest occupation and "agricultural, forestry and fisheries workers" or "sales workers" was the next most frequent category. Cases tended to have a larger proportion of either smoker or ex-smoker than controls in both sexes as shown in Table IV. Ex-drinkers were more prevalent among cases than controls and relatively larger proportions of heavy drinking were noted among cases

Table III. Distribution of Past History of Treated Diseases and Blood Transfusion

Diseases	Male		Female[a]	
	Case	Control	Case	Control
A. 10 most prevalent diseases treated				
Hepatic diseases of unknown nature	143	6	49	4
Chronic hepatitis	110	0	37	0
Hepatic cirrhosis	61	0	11	0
Acute hepatitis	18	4	2	3
Diabetes	34	36	7	22
Peptic ulcer	33	50	3	12
Hypertension	30	38	15	32
Tuberculosis	27	28	3	11
Heart diseases	9	22	9	13
Lung diseases	7	16	1	9
B. Blood transfusion				
None	210 (73.2)	234 (81.5)	53 (65.4)	151 (76.3)
<10 years previously	27 (9.4)	27 (9.4)	7 (8.6)	29 (14.6)
$10\leqq$	40 (14.0)	18 (6.2)	14 (17.3)	17 (8.6)
Unknown	10 (3.5)	8 (2.8)	7 (8.6)	1 (0.5)
Total	287 (100.0)	287 (100.0)	81 (100.0)	198 (100.0)

a) Frequency shown without preserving matching.

Table IV. Smoking Status and Accumulated Amount of Smoking for Lifetime

	Male		Female[a]	
	Case	Control	Case	Control
A. Smoking status[b]				
Non-smoker	22 (7.7)	30 (10.5)	65 (80.2)	173 (87.4)
Smoker	161 (56.1)	179 (62.4)	10 (12.3)	16 (8.1)
Ex-smoker	104 (36.2)	78 (27.2)	6 (7.4)	9 (4.5)
B. Accumulated amount[c]				
Non-smoker	22 (7.7)	30 (10.5)	65 (80.2)	173 (87.4)
1–499	97 (33.8)	77 (26.8)	11 (13.6)	17 (8.6)
500–999	150 (52.3)	141 (49.1)	5 (6.2)	8 (4.0)
$1000\leqq$	18 (6.3)	39 (13.6)	0 (0.0)	0 (0.0)
Total	287 (100.0)	287 (100.0)	81 (100.0)	198 (100.0)

a) Frequency shown without preserving matching.
b) At the time of investigation.
c) Accumulated amount of smoking in their lifetime for smokers and ex-smokers using the Brinkman-Coates index.

Table V. Drinking Status and Accumulated Amount of Alcohol Intake

	Male		Female[a]	
	Case	Control	Case	Control
A. Drinking status[b]				
Non-drinker	51 (17.8)	79 (27.6)	70 (86.4)	182 (91.9)
Drinker	124 (43.2)	172 (59.9)	4 (4.9)	6 (3.0)
Ex-drinker	112 (39.0)	36 (12.5)	7 (8.6)	10 (5.1)
B. Lifetime intake[c]				
Non-drinker	51 (17.8)	79 (27.5)	70 (86.4)	182 (91.9)
1–29	66 (23.0)	62 (21.6)	4 (4.9)	8 (4.0)
30–59	58 (20.2)	63 (22.0)	2 (2.5)	7 (3.5)
60≦	111 (38.7)	83 (28.9)	5 (6.2)	1 (0.5)
Unknown	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
C. Intake by age 40[c]				
Non-drinker	72 (25.1)	115 (40.1)	73 (90.1)	189 (95.5)
1–29	125 (43.6)	112 (39.0)	2 (2.5)	5 (2.5)
30–59	49 (17.1)	43 (15.0)	2 (2.5)	4 (2.0)
60≦	40 (13.9)	17 (5.9)	4 (4.9)	0 (0.0)
Unknown	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Total	287 (100.0)	287 (100.0)	81 (100.0)	198 (100.0)

a) Frequency shown without preserving matching.
b) At the time of investigation.
c) Drinkers and ex-drinkers combined, using the drink-years index.

than controls as indicated in Table V. Among the 12 food items examined, egg and milk were more frequently consumed by cases than controls as shown in Table VI.

Univariate analyses between each item and male HCC indicated that HBsAg status (odds ratio (OR)=9.67; 95% confidence interval (95%CI)=2.94–31.73), anti-HCV status (OR=35; $P<0.05$; based on 46 pairs), history of blood transfusion over 10 years previously (2.35; 1.30–4.25), parental history of hepatic diseases (1.93; 1.04–3.61), accumulated amount of alcohol intake for both lifetime (χ^2 for trend=7.68; $P<0.05$) and by age 40 (χ^2 for trend=16.07; $P<0.05$), and frequency of egg (1.85 (5≦versus 4 ≧ in terms of median; 1.32–2.58)) or milk (1.88 (4≦ versus 3≧; 1.33–2.65)) intake were associated with occurrence of HCC. For females, HBsAg status (OR=7.58; 1.96–29.35; based on 80 sets), anti-HCV status (OR=14/0; $P<0.05$ by the McNemar's test; based on the 19 sets, composed of a case and the 1st control) and frequency of milk intake (2.63 (5≦ versus 4≧; 1.46–4.72)) turned out to be associated with HCC.

Multivariate analysis applied simultaneously to the following 5 items, excluding anti-HCV status and accumulated amount of alcohol intake for lifetime revealed that HBsAg positive status, history of blood transfusion over 10 years previously, parental history of hepatic diseases, heavy drinking by age 40, and frequent milk intake were significantly associated with male HCC, and further analysis applied to the same 4 items excluding

Table VI. Median Category[a] of Frequency of Food Intake

Food items	Male		Female	
	Case	Control	Case	Control
Rice	7	7	7	7
Tofu (bean curd)	3	3	3	3
Beans	3	3	3	3
Nuts	2	2	2	2
Fish	4	4	4	4
Fish cooked in oil	3	3	3	3
Meat & poultry	3	3	3	3
Meat & poultry cooked in oil	2	2	2	3
Eggs	5	4[b]	4	4
Milk	4	3[b]	5	3[b]
Fresh vegetables	4	4	4	4
Green-yellow vegetables	4	4	4	5

a) Categories: 1, not eaten; 2, 1–3 times a month; 3, 1–3 times a week; 4, 4–6 times a week; 5, once a day; 6, twice a day; 7, 3 times a day.
b) $P<0.05$ by the Wilcoxon matched-pairs signed ranks test between case and control.

frequency of milk intake showed a similar association (Table VII). Dose-response relation between the accumulated amount of alcohol intake by age 40 and male HCC was also significant (χ^2 for trend=12.73, $P<0.05$).

Correlation analyses between items by chi-square tests showed no statistically significant association between

Table VII. Hepatitis B Surface Antigen, History of Blood Transfusion, Parental History of Hepatic Diseases, Accumulated Amount of Alcohol Intake by Age 40 and Male Hepatocellular Carcinoma[a]

Item	Category	Odds ratio	95% CI[b]
Hepatitis B surface antigen	Negative[d]	1.0	–
	Positive	8.67	2.54–29.57
History of blood transfusion	None[d]	1.0	–
	< 10 years previously	0.93	0.48–1.82
	10≦	2.40	1.26–4.56
Parental history of hepatic diseases	No[d]	1.0	–
	Yes	2.31	1.11–4.80
Accumulated amount of alcohol intake by age 40[c]	Non-drinker[d]	1.0	–
	1–29	1.75	1.12–2.74
	30–59	2.08	1.14–3.79
	60≦	3.23	1.61–6.51

a) Results of multivariate analyses based on a conditional logistic regression model without an interaction term, for 245 case-control sets.
b) 95% confidence interval.
c) Drinkers and ex-drinkers combined, using the drink-years index.
d) Reference category.

items except for a positive association between accumulated amount of alcohol intake and parental history of hepatic diseases among male controls.

DISCUSSION

The Japan Primary Liver Cancer Research Group[13] reported profiles of approximately 9,600 Japanese HCC collected between 1988 and 1989. The most prevalent age groups were late fifties for males and early sixties for females. Proportions of positive HBsAg, anti-HCV or history of blood transfusion were 18.7%, 70.4%, or 20.8% for males, and 15.9%, 68.7% or 27.8% for females. Cases in the present study show less prevalent positive HBsAg and more prevalent positive anti-HCV in both sexes.

Controls for the present study are taken from hospital inpatients, so we need to evaluate how representative they are of the community population. A mass-screening for hepatic diseases conducted in Saga Prefecture in 1987[14] showed 1.7–1.8% positive HBsAg, 3.6–13.6% positive anti-HCV, and 7.1–7.5% positive history of blood transfusion among approximately 14,600 examinees of both sexes. Comparable figures for the controls were 1–1.5%, 6–9%, and 15–23%, respectively. The present controls might have a larger proportion of history of blood transfusion probably because of being inpatients, but they might be comparable in both HBsAg and anti-HCV positive proportions to the prefecture population. The 1985 National Population Census data[11] indicated 27.8% of residents being employed as "craftsmen, mining, production process and construction workers and laborers" as the largest occupational composition, and 18.5% as "clerical and related workers" as the second largest one among residents aged 15 or over in Fukuoka Prefecture. The census tabulated occupations as at October 1st, 1985 and the present study did so as the occupation of longest duration at the time of investigation, so figures might not be validly comparable with each other. These figures might indicate that the study subjects have a relatively larger composition of "agricultural, forestry and fisheries workers." According to the 1990 National Nutrition Survey in Japan,[15] of which the figures are only valid as national mean values, the proportions of non-smoker, smoker and ex-smoker for males aged 40 to 69 were 25.3%, 53.0% and 21.7%, respectively. The corresponding figures for females were 88.7%, 9.4%, and 1.9%. Smokers seemed to be more prevalent among male controls but little difference was noted for females compared to the national figures. The survey also provided the proportions of drinkers (58.5% for males aged 40 to 69; 6.9% for females aged 40 to 69) but not those of ex-drinkers. The proportion of drinkers among male controls might be comparable to the national figure but that for females seemed to be lower than the national data.

A study on reproducibility of reports of past history, smoking, drinking, and dietary habits obtained by personal interview[16] showed statistically significant positive intraclass correlation coefficients ranging from 0.42 for frequency of fried meat intake to 0.98 for age of stopping smoking. Since the method of data collection was identical to that used in the present study, the reliability of the information collected might be regarded as satisfactory in terms of reproducibility for most of the items. Drinking habit is one of the relatively difficult items to observe

because of its variety and frequent changes over the lifetime. Of various methods for observing drinking habit, quantity-frequency methods might be a method of choice[17] and the one used in the present study is such a method. Disease status often influences an individual's life style and, in the case of HCC, dietary and/or drinking habits are likely to be changed, particularly after the diagnosis, because of encouragement by medical staff to take protein-rich foods and discouragement of drinking. Special attention was paid to collecting information prior to such change of habits by querying subjects on it and by reminding them to provide information relating to the period before any such change. If a tendency for a high correlation between current diet and recalled diet[18] is applicable to the present data, it may account for a higher frequency of milk intake by cases than controls, because it is a part of the recalled diet prior to the diagnosis and also correlates with the current one at the time of interview.

The small sample size meant that multivariate analysis was not applicable to the female data and it was not possible to introduce interaction terms in the multivariate analysis for the male data. The item of anti-HCV status was not included in multivariate analysis because the data were available only for 20% of the male subjects. The item of accumulated amount of alcohol intake for lifetime was also excluded since it correlated with HCC less well than that by age 40.

The proportion of positive HBsAg among Japanese HCC has decreased from 40.7% to 24.6% from 1968 to 1985[19] and the proportion of positive anti-HCV has been noted to show a positive trend with advancing age.[20] Most of the epidemiologic studies on Japanese HCC indicate HBsAg as a risk factor, of which the relative risk ranges from 5.6 to 20.[1-3, 6, 7, 9, 10] The present finding of significant ORs, i.e., 8.7 for males by multivariate analysis and 7.6 for females by univariate analysis are consistent with these figures. Little work has been reported on the association between history of blood transfusion and HCC, but Tanaka *et al.*[9] reported that the relative risk of a positive history of blood transfusion turned out to be not significant after being adjusted for sex, age, occupation, years of education and anti-HCV status. In the present study, the history of transfusion less than 10 years previously did not show a significant OR in multivariate analysis with HBsAg and some other items for the male subjects. Family history (including parental) of liver diseases was reported to be positively associated with HCC,[10] being similar to the result of this study. As to alcohol drinking, 7 of the 10 studies showed a positive association with HCC, and 3 studies[1, 4, 10] reported statistically significant dose-response relations. Although some authors found a statistically significant association between smoking and HCC,[1, 8] most failed to show such a relation. Further study is obviously needed to elucidate the relative magnitude and interactions of hepatitis B or C virus positivity and other factors in the etiology of Japanese HCC.

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