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Blood Transfusion, Alcohol Consumption, and Cigarette Smoking in Causation of Hepatocellular Carcinoma: A Case-Control Study in Fukuoka, Japan

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In the present study, we investigated the association between hepatocellular carcinoma (HCC) and hepatitis B virus infection (HBV), blood transfusion and drinking and smoking habits by comparing 124 HCC cases and 250 controls. We confirmed a very high relative risk (RR), i.e. 31.0 ($P<0.001$), among persons who were positive for serum hepatitis B surface antigen (HBsAg). However, the prevalence of serum HBsAg positives among our cases was only 21%, about half of those reported earlier, indicating a role of other etiological factors. Those who have a history of blood transfusion showed a significantly elevated RR of 3.0 ($P<0.001$) or 4.9 ($P<0.001$), and most of them (85%) were non-carriers of HBV. Thus, the past history of blood transfusion is an important risk factor among the Japanese. Unidentified non-A, non-B hepatitis viruses in transfused blood probably play a significant role in causing HCC. We estimated that 15% of male HCCs were attributable to blood transfusion. A positive relationship between alcohol consumption and HCC was detected, particularly among HBsAg-negative subjects with no history of blood transfusion who had drunk heavily in their younger years. RR estimates were not great (e.g., heavy drinkers: 2.5), but a substantial proportion of HCC may be attributed to drinking because of common drinking habits among Japanese males. Smoking was also found to have a positive association, but the relationship at a young age was less clear, and further investigation is needed to clarify the etiological role of smoking.

Key words: Hepatocellular carcinoma — Hepatitis B virus — Blood transfusion — Alcohol — Smoking

It is noteworthy that the incidence of and mortality from liver cancer among the male population in Japan has been increasing sharply since about 1975, although such an increase was not observed among the female population.[1,2] In 1985, liver cancer was the third most common cause of cancer deaths among male Japanese, following gastric and lung cancers. The majority of liver cancers among the Japanese are hepatocellular carcinoma (HCC),[3] which is known to have a strong relationship with chronic hepatitis B virus (HBV) infection.[4,5] However, the prevalence of chronic HBV infection has been declining rapidly among HCC patients (about 40% in 1968–77,[6] about 30% in 1982–83[3]). Therefore, the etiology of the increase in liver cancers among Japanese males must be investigated to examine the involvement of other factors in addition to chronic HBV infection.

Blood transfusion has been suspected as a risk factor for HCC from clinical data.[7–9] However, most studies were limited to studies among cases, and analytical studies comparing cases and controls are needed to clarify the role of blood transfusion. Another suspected risk factor is the drinking habits of Japanese males.[10,11] It is well-known that heavy alcohol consumption affects liver function and may perhaps lead to HCC. Again, most studies have assessed drinking habits among cases only, and more analytical studies comparing cases and controls are required to elucidate the role of alcohol consumption in the causation of HCC. In this connection, it is of interest to note that the annual ethanol consumption per capita has increased about 3-fold from 1955 to 1984 in Japan.[12] Besides drinking, several studies in recent years have suggested a positive relationship between smoking and HCC.[13–16]

This paper describes a case-control study of HCC in relation to these potential etiological factors in Fukuoka, Japan, where HCC risk is one of the highest in this country.[1]

Materials and Methods

The present study included 124 cases with HCC who were admitted to the 3rd Internal Medicine and 2nd Surgery Departments of Kyushu University Hospital. Cases were eligible if the following criteria were met: a) incident cases diagnosed initially within one year prior to identification; b) aged 40 to 69; patients aged 70 or more and those under 40 were excluded since the former may lack reliability in their responses about their past history, and the latter present a practical difficulty in obtaining adequate controls in the health centers (of course, the vast majority of cases were more than 40 years of age); c) residents in Fukuoka or Saga Prefecture and of Japanese nationality; this is to minimize biased information relating to regions or race. The cases were identified between December 1985 and December 1987 by a weekly review of the list of hospitalized patients and the admission reports and by contact with physicians. During that period, 214 patients with HCC were identified, of whom 71 were ineligible according to the above criteria (criterion a, 27; b, 34; c, 10). Of the remaining 143 cases, 10 were discharged before contact, 6 were too sick to be interviewed, 1 refused to be interviewed, and 1 could not be interviewed due to the refusal of the physician in charge. Finally, 125 cases were interviewed, but one of them was excluded since his responses were of doubtful reliability due to underlying dementia.

Of the 124 patients, HCC diagnoses were confirmed histologically in 45 cases. For the remaining 79 cases, 75 were diagnosed as suffering from HCC from findings in angiography, and in 4 the diagnosis was clinically established from the results of examinations such as ultrasonography, computed tomography, and serum alpha-fetoprotein. Among the cases, 99 (80%) were diagnosed as having cirrhosis, of whom 40 were determined from histology, one from findings at laparoscopy, and the others from clinical and laboratory data.

Table I. Distribution of Cases and Controls by Sex and Age

Ages	Males		Females	
	Cases	Controls	Cases	Controls
40–49	8	26	4	9
50–59	51	84	12	32
60–69	40	71	9	28
Total	99	181	25	69
Mean age (years)	57.4	55.9	55.7	56.9

The controls consisted of 250 persons aged 40 to 69, resident in Fukuoka City, who visited Hakata Public Health Center located near Kyushu University Hospital between January 1986 and December 1987 to undergo health examinations. Controls were selected so that their distributions by sex and age were as similar as possible to those of the cases. Those who suffered from chronic liver diseases such as chronic hepatitis and cirrhosis, or from whom a blood specimen could not be obtained, were excluded. The distribution of cases and controls by sex and age is shown in Table I. Cases and controls were comparable in terms of years of schooling and occupation.

Subjects were interviewed in person by one trained interviewer in the hospital wards or at the health center. In order to obtain accurate information, all interviews were tape-recorded and checked against questionnaires by both the interviewer and one of the authors (K.T.). Besides the history of blood transfusion and other relevant characteristics, detailed drinking and smoking histories for the whole life were obtained. As for drinking habits, subjects were classified into non-drinkers and drinkers. In the present study, drinkers were defined as those who had drunk at least one or more units of alcoholic beverages per day, once a week or more, for at least one year. The unit ("drink" in the present study) corresponds to the amount of alcoholic beverage containing 23 ml of ethanol, nearly the equivalent to 150 ml of sake, 90 ml of shochu (a distilled alcoholic beverage made in Japan), 450 ml of beer, and 60 ml of hard liquor. Among the drinkers, those who had stopped drinking one or more years prior to the interview were considered ex-drinkers. The drinkers were also classified according to their cumulative alcohol consumption by "drink-years." This measure was obtained by multiplying the daily consumption of each type of alcoholic beverage expressed in "drinks" by the number of years of consumption and then by adding all types of beverages and different periods of life. As for smoking habits, smokers were defined as those who had smoked every day, at least one pack per week, for at least one year. The smokers were classified into ex-smokers and current smokers in the same way as used for drinking habit. They were also classified according to the cumulative amount of smoking expressed in pack-years.

Information about serum hepatitis B surface antigen (HBsAg) was obtained from medical records for cases; all cases were tested for serum HBsAg by radioimmunoassay (RIA) or reversed passive hemagglutination (RPHA). Sera were obtained from 250 controls, and tested for HBsAg by RPHA. Among the subjects with a history of blood transfusion, 19 cases and 24 controls whose sera

were available were tested for serum antibodies to hepatitis B core antigen (anti-HBc) by RIA. The presence of a positive serum HBsAg in a person without symptoms of acute hepatitis within the last few months is usually considered to indicate a chronic HBV carrier state.

The statistical analysis was done by modeling the data through unconditional logistic regression for controlling confounding factors such as sex, age, and other important variables, using the SAS statistical package.[17,18] The natural antilogarithm of regression coefficients of indicator variables was interpreted as the relative risk (RR) for HCC, and the 95% confidence interval (CI) was similarly obtained from the regression coefficient and its standard error. Trends in the relationships with drinking and smoking habits were evaluated by using the variables scored according to the levels of these habits. All reported P values are two-tailed.

Results

Table II presents the distribution of cases and controls and RR according to serum HBsAg. The prevalence of serum HBsAg positives was 21% in cases for both sexes combined, and only 1.2% in controls. The adjusted RR of HCC among HBsAg-positive subjects as compared with HBsAg-negatives was 31.0 ($P<0.001$), indicating a strong relationship between chronic HBV infection and HCC. The serum HBsAg positives were less frequent among male cases (18%) than among female cases (32%).

In Table II, the association between a history of blood transfusion and HCC is also presented. Eleven cases (10 males and 1 female) with a history of blood transfusion due to liver diseases, e.g. due to surgery for esophageal varices of liver cirrhosis etc., were included in the group with no history of blood transfusion. Those who had experienced blood transfusion and those who had received blood transfusion 10 or more years prior to the interview showed significantly elevated RR for HCC of 3.0 ($P<0.001$) and 4.9 ($P<0.001$), respectively. The mean duration between blood transfusion and the time of interview was 28.8 years in the 27 cases, which was significantly longer than the 19.0 years observed in the 24 controls ($P<0.01$). Of these transfused subjects, only 4 cases and none of the controls were HBsAg-positive, suggesting that viruses other than HBV (non-A, non-B hepatitis viruses) were probably responsible for the increased risks for HCC. The presence of serum anti-HBc could also be examined in 19 out of 27 cases and all 24 controls with a positive history of blood transfusion. Twelve cases and 11 controls were positive for serum anti-HBc, and 4 cases were also HBsAg-positive with high titers of anti-HBc; the remaining 8 cases and all the 11 controls were HBsAg-negative with low titers of anti-HBc, suggesting resolved HBV infections.

Table III shows the distribution of cases and controls according to drinking and smoking habits. A noticeable finding was that ex-drinkers were more frequent among the cases (about 40% in males) than among the con-

Table II. Distribution of Cases and Controls and Relative Risks According to Serum HBsAg and History of Blood Transfusion

Factor		Males			Females			Both sexes
		Cases	Controls	RR[a]	Cases	Controls	RR[a]	RR[b] (95% CI)
HBsAg	Negative	81	178	1.0	17	69	1.0	1.0
	Positive	18	3	15.7	8	0	—	31.0(8.8–109.8)
History of blood transfusion[c]	No[d]	78	166	1.0	19	60	1.0	1.0
	Yes	21	15	2.8	6	9	2.2	3.0(1.6–5.8)
History of blood transfusion 10 or more years earlier	No	79	172	1.0	20	62	1.0	1.0
	Yes	20	9	4.5	5	7	2.3	4.9(2.4–10.0)

a) RR adjusted for age.
b) RR adjusted for sex, age, drinking, smoking, and either history of blood transfusion or HBsAg.
c) History of blood transfusion other than accompanying liver diseases.
d) Including 10 male cases and 1 female case with a history of blood transfusion due to liver diseases (see text).

Table III. Distribution of Cases and Controls According to Drinking and Smoking Habits

Factor	Males		Females	
	Cases No. (%)	Controls No. (%)	Cases No. (%)	Controls No. (%)
Drinking habit				
Non-drinker	22 (22.2)	41 (22.7)	18 (72.0)	59 (85.5)
Ex-drinker	39 (39.4)	20 (11.0)	6 (24.0)	7 (10.1)
Current drinker	38 (38.4)	120 (66.3)	1 (4.0)	3 (4.3)
Smoking habit				
Non-smoker	10 (10.1)	29 (16.0)	18 (72.0)	55 (79.7)
Ex-smoker	29 (29.3)	46 (25.4)	3 (12.0)	3 (4.3)
Current smoker	60 (60.6)	106 (58.6)	4 (16.0)	11 (15.9)

Table IV. Relative Risks (with 95% Confidence Intervals) for HCC According to Cumulative Alcohol Consumption through Whole Life and until Age 40 among All Subjects and Also among HBsAg-negative Subjects with No History of Blood Transfusion

Cumulative alcohol consumption (drink-years[c])	All subjects[a]		HBsAg(−) and no history of blood transfusion[b]	
	Whole life	Until age 40	Whole life	Until age 40
Non-drinker	1.0	1.0	1.0	1.0
1–29	1.1 (0.5–2.3)	1.2 (0.6–2.4)	1.3 (0.5–3.2)	1.7 (0.8–3.8)
30–59	0.5 (0.2–1.3)	1.9 (0.9–4.2)	0.8 (0.3–2.4)	2.3 (0.9–5.7)
60+	1.7 (0.9–3.5)	1.9 (0.8–4.4)	2.3 (1.0–5.2)	2.5 (1.0–6.5)
Trend χ^2	2.02	3.57	3.97	4.42
P value	0.16	0.06	0.05	0.04

a) RR adjusted for sex, age, HBsAg, history of blood transfusion, and smoking in analyzing all subjects.
b) RR adjusted for sex, age, and smoking in analyzing HBsAg-negative subjects with no history of blood transfusion.
c) See the text.

trols (about 10% in males), and consequently the percentage of current drinkers among the cases was lower than that among the controls. Of the 45 ex-drinkers among the cases, 29 (64%) reported that they had stopped drinking due to liver disease with a mean duration of having given up drinking of 5.9 years. In all cases, the average number of years of suffering from liver disease prior to the onset of HCC was 10.4 years. In contrast to drinking habit, there were no marked differences in the distribution of ex-smokers and current smokers between the cases and the controls, although the prevalence of ex-smokers among the female cases was somewhat higher than that among the female controls.

The relationship between HCC and drinking was evaluated on the basis of cumulative alcohol consumption until the age of 40 as well as through the whole life (more specifically, until our interview), since, as stated, drinking habits in the last several years among cases were likely to have changed because of liver disease preceding HCC. Such analyses were performed for all subjects together and separately, only for HBsAg-negative subjects with no history of blood transfusion. This was done in order to evaluate the independent effect of alcohol among such subjects, who are unlikely to be infected with HBV or other transfusion-related viruses. The HBsAg-negative subjects with no history of blood trans-

Table V. Relative Risks (with 95% Confidence Intervals) for HCC According to Cumulative Amount of Smoking through Whole Life and until Age 40 among All Subjects and Also among HBsAg-negative Subjects with No History of Blood Transfusion

Cumulative amount of smoking[c] (pack-years)	All subjects[a]		HBsAg(−) and no history of blood transfusion[b]	
	Whole life	Until age 40	Whole life	Until age 40
Non-smoker	1.0	1.0	1.0	1.0
Low	1.3 (0.6–2.9)	1.3 (0.5–3.1)	1.3 (0.5–3.2)	1.0 (0.3–2.9)
Medium	1.8 (0.8–4.2)	1.1 (0.5–2.4)	2.2 (0.9–5.5)	1.0 (0.4–2.5)
High	2.4 (0.8–7.3)	1.4 (0.6–3.4)	3.8 (1.1–12.5)	1.8 (0.7–4.7)
Trend χ^2	2.91	0.61	5.59	1.99
P value	0.09	0.43	0.02	0.16

a) RR adjusted for sex, age, HBsAg, history of blood transfusion, and drinking in analyzing all subjects.
b) RR adjusted for sex, age, and drinking in analyzing HBsAg-negative subjects with no history of blood transfusion.
c) Levels for cumulative amounts of smoking through whole life expressed in pack-years are as follows: low, 1–24; medium, 25–49; high, 50+. For cumulative amounts of smoking until age 40: low, 1–9; medium 10–19; high, 20+.

fusion included 63 male cases and 163 male controls, and 12 female cases and 60 female controls. The adjusted RR of HCC for four levels of cumulative alcohol consumption as compared with non-drinkers are shown in Table IV. With regard to cumulative alcohol consumptions for the whole life among all subjects, the RR computed were statistically insignificant, and there was no clear dose-response relationship. However, a nearly significant positive trend ($P=0.06$) was detected in the analysis of consumptions until the age of 40. Among HBsAg-negative subjects with no history of blood transfusion, the highest group of alcohol consumption for the whole life showed an elevated RR of 2.3 ($P\fallingdotseq0.05$) with a significant trend ($P\fallingdotseq0.05$), and the association was clearer regarding drinking habits until the age of 40.

In Table V, the association of smoking with HCC is examined according to the cumulative amount of smoking in the same way as drinking, controlling, through logistic regression, alcohol consumption as well as other important variables. A statistically significant relationship was found when the cumulative amount of smoking for the whole life was studied among HBsAg-negative subjects with no history of blood transfusion; this relationship was not clear until the age of 40.

Discussion

This study confirmed the strong relationship between chronic HBV infection and HCC. However, HBV carriers in the present study were far less frequent among HCC cases than has previously been reported in Japan. The Liver Cancer Study Group of Japan reported that about 40% of HCC patients in 1968–77 were HBsAg-positive,[6] while in the present series only 21% of cases were so. These results suggest that risk factors other than chronic HBV infection are playing an increasingly important role in the causation of HCCs in Japan.

A clear association of past history of blood transfusion with HCC was found in the present study. Most HCC patients with a transfusion history were considered non-carriers of HBV on the basis of serum HBsAg and anti-HBc titers. On average, they had received transfusion nearly 30 years prior to the interview. Infections with unknown viruses (more specifically, non-A, non-B hepatitis viruses) through blood transfusions are likely to have produced chronic carrier states, and ultimately such people may have developed HCC many years later. Several follow-up studies of patients with non-A, non-B post-transfusion hepatitis (NANB-PTH) revealed a develop-

ment into chronic hepatitis and liver cirrhosis following NANB-PTH.[19-21] So far, however, progress to HCC has seldom been detected other than in a few case reports.[7-9] This is probably due to a limited follow-up time period.

With regard to drinking and smoking habits, it may be necessary to examine whether the controls of this study, those who visited a health center to undergo a health examination, were biased in their habits. The possibility exists that they were more conscientious about health and may have included fewer drinkers and smokers than the general population. Referring to available data on these habits among the general population, however, the control group showed little difference. For example, among the inhabitants aged 40 or more of Hisayama Town near Fukuoka City, figures for 1983 show the proportions of non-drinkers, ex-drinkers and current drinkers were 30%, 6% and 64%, respectively, for 993 men, and 92%, 1%, and 7%, respectively, for 1,344 women.[22] The sample survey of smoking habits by Japan Tobacco Inc. reported that, in 1986, the proportions of current smokers among those in their 40's, 50's, and 60's or more were 61.2%, 60.1%, and 51.7%, respectively, for males and 12.3%, 11.0%, and 10.7%, respectively, for females. Applying these rates to our control group, the ratios of observed to expected numbers of current smokers were calculated as 1.0 for males and 1.4 for females. Such data for Fukuoka Prefecture were not available.

We detected a positive association between drinking and HCC. Heavy drinkers showed about 2-fold increase in risk for HCC as compared with non-drinkers. Recent case-control studies in the United States[15, 23] and Japan[10, 24] suggested a positive association of alcohol consumption with HCC, while a study in Greece reported an insignificant effect of alcohol on HCC.[16] In cohort studies, weak or moderately positive relationships between drinking and liver cancer have been demonstrated,[25-29] whereas a recent report in Japan indicated a considerably high risk of liver cancer among heavy drinkers of shochu or strong Japanese spirits.[11] Most of those studies generally support a positive relationship between drinking and HCC, but the risks estimated were far lower than those among HBV carriers.

In addition to drinking, the present study showed a significant association between smoking and HCC among HBsAg-negative subjects with no history of blood transfusion. Trichopoulos *et al.* found, in a case-control study in Greece, an increased risk of HCC among smokers who were negative for serum HBsAg.[13, 16] This positive association was supported by case-control studies reported from Hong Kong[14] and Los Angeles,[15] but was challenged by some other case-control studies.[23, 30] Several cohort studies on the effects of smoking on cancers, although information about HBV infection and drinking was lacking, indicated elevated risks of liver cancer among smokers.[31-33] A cohort study by Hirayama in Japan reported a significant risk increase of liver cancer among smokers after taking drinking habits into consideration.[28] In two other follow-up studies in Japan, however, such an effect was not evident after an adjustment was made for drinking.[11, 29] Thus, there seem to be inconsistent results concerning this association.

In contrast to drinking, smoking habits in younger years were not clearly associated with HCC in this study. These results suggest that the association should be accepted with caution. Most HCC patients in the present study had had liver diseases for many years (an average of 10 years), which appears to have affected their drinking habits more than their smoking. During such a time period, it would be difficult to evaluate the effect of smoking on HCC adjusted for drinking. Analysis at a younger age of life, therefore, may provide a better indication of the role of smoking and HCC. Further investigations are needed to verify the causal association between smoking and HCC.

In considering the recent increase in liver cancer among Japanese males, the population attributable risk (PAR), i.e. the proportion of a disease that can be attributed to an etiological factor, may give some suggestions. It is calculated as follows:

$$\mathrm{PAR}=\frac{b\,(r-1)}{b\,(r-1)+1}\times 100,$$

where r=the relative risk, and b=proportion of the total population with a factor.[17] Assuming that our control group represents the general population of Fukuoka, the PAR of

Table VI. Tentative Estimates of Population Attributable Risks for Male HCCs According to HBV Infection, History of Blood Transfusion, and Drinking and Smoking Habits

Factor	RR[a]	Prevalence among male controls (%)	PAR (%)
HBsAg	17.4	1.7	21.8
History of blood transfusion	3.1	8.3	14.8
Drinking habits[b]	1.4	68.5	21.5
Smoking habits[c]	1.2	82.3	14.1

a) RR were estimated among male subjects alone. In the logistic model, age, HBsAg, history of blood transfusion, and drinking and smoking habits were included. Each RR indicates the risk among the exposed as compared with the non-exposed.
b) Those who had drunk before the age of 40 were regarded as the exposed.
c) Those who had smoked before the age of 40 were regarded as the exposed.

male HCCs for each risk factor in this study can be calculated as presented in Table VI. Blood transfusion may account for 15% of male HCC patients. Among blood donors, there were probably carriers of as-yet unidentified non-A, non-B hepatitis viruses related to HCC, and chronic infections with those viruses may contribute to a substantial proportion of HCC in Fukuoka. The PAR for drinking and smoking habits cannot be accepted immediately, because these estimates are liable to fluctuate according to the change of the RR estimates. However, if alcohol consumption is accepted as an etiological factor of HCC, a substantial proportion of male HCCs could be accounted for by drinking. If so, the increasing consumption of alcohol may be regarded as being partly responsible for the upward trend of HCC among Japanese males.

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