

# Hepatitis B Virus and Cigarette Smoking: Risk Factors for Hepatocellular Carcinoma in Hong Kong<sup>1</sup>

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## ABSTRACT

One hundred seven Chinese patients with primary hepatocellular carcinoma (PHC) were compared with 107 hospital controls for the presence of hepatitis B surface antigen and smoking, drinking, and dietary habits. Eighty-two % of PHC cases were hepatitis B surface antigen positive compared to 18% of controls (relative risk, 21.3; 95% confidence limits, 10.1 and 45.9). Prior history of jaundice was significantly related to PHC, independent of hepatitis B surface antigen status. There was a significant association between cigarette smoking and PHC negative for hepatitis B surface antigen. The relative risk of hepatitis B surface antigen-negative PHC for heavy smokers (20+ cigarettes/day) was 3.3 compared to light smokers and nonsmokers (95% confidence limits, 1.0 and 13.4). Our data indicated that infection by the hepatitis B virus and cigarette smoking were independent risk factors for PHC.

## INTRODUCTION

The association between HBV<sup>3</sup> and PHC has been studied in many populations (3, 5, 13, 16). Another suspected risk factor for PHC that has been studied repeatedly is exposure to aflatoxins (2, 7, 8, 10-12, 17). Hong Kong is a high-risk area for PHC, yet no controlled study had been conducted there in the past to determine the association between PHC and these possible risk factors. This is a report of a case-control study of PHC in Hong Kong which investigated the following factors: HBV infection; ingestion of foods that might be contaminated with aflatoxins; cigarette smoking; and alcohol consumption.

## MATERIALS AND METHODS

From March 1977 to September 1980, 149 Chinese patients with PHC were admitted to the University Department of Medicine, Queen Mary Hospital, in Hong Kong. One hundred seven (72%) of these patients were interviewed. For each case patient, a sex- and age ( $\pm 5$  years)-matched control patient who was admitted to the orthopedic ward of the same hospital with a diagnosis of trauma was interviewed. All control interviews took place within 1 month of the index case interview.

All subjects were interviewed in person by one interviewer. The questionnaire requested information on socioeconomic status; birth-

place; prior exposure to HBV; smoking habits; coffee, tea, and alcohol consumption; and current dietary habits as well as those of 20 years ago. A blood specimen was drawn from each participant to test for HBsAg by radioimmunoassay (AUSRIA II; Abbot Laboratories, North Chicago, Ill.).

There was a sex mismatch when all interviews had been completed. In the statistical analysis, the matching on sex and age was taken into account by stratification; the conditional maximum likelihood estimate of the common odds ratio was used as a point estimate of RR (14). We excluded individuals who did not answer the relevant question from the corresponding analysis.

## RESULTS

Of the 107 cases of PHC, 106 were histologically confirmed. The remaining case had arteriographic features of PHC and a positive  $\alpha$ -fetoprotein reaction. There were 95 (89%) male cases of PHC with a mean age of 52.3 years; the 12 (11%) female cases had a mean age of 47.7 years. Ninety-four control patients were males with a mean age of 52.5 years; the 13 female control patients had a mean age of 48.7 years. Social class (as determined by education, monthly income, and living space per resident) was similar between the case and the control groups. Ninety % of the case fathers and 89% of the case mothers were born in Kwangtung province, compared to 85% of the control fathers and 85% of the control mothers, respectively.

Eighty-eight (82%) of the PHC cases were HBsAg+ compared to 19 (18%) of the controls. The RR of PHC associated with HBsAg positivity was 21.3 (95% CL, 10.1 and 45.9). There was no difference in sex distribution between the HBsAg+ and HBsAg- groups of PHC patients. There were 10 (11%) females among the 88 HBsAg+ cases and 2 (11%) females among the 19 HBsAg- cases. However, the HBsAg+ PHC patients were younger compared to the group of HBsAg- PHC patients (see Table 1). Thirty-nine (44%) of the HBsAg+ cases were under age 50 compared to 4 (21%) in the HBsAg- group.

Each participant was asked about his or her current frequency of consumption of a number of food items that are either common in Chinese diet or are suspected of aflatoxin contamination. In addition, each individual was asked whether his reported frequency for each food item was different from that of 20 years ago. Over 95% of the participants reported no change in habits for most of the food items asked. Thus, only current dietary frequencies are shown in Table 2. Shank *et al.* (10) carried out a market survey of commonly consumed food items in Hong Kong from 1967 to 1969 to determine the extent of aflatoxin contamination. Their results indicated that corn was the most frequently contaminated food item among those sampled, followed by beans (see Table 2). Peanuts were not an important source of aflatoxin contamination in Hong Kong.

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<sup>3</sup> The abbreviations used are: HBV, hepatitis B virus; PHC, primary hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; RR, relative risk; HBsAg+, hepatitis B surface antigen positive; CL, confidence limits; HBsAg-, hepatitis B surface antigen negative.

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Our dietary data did not show an increase in risk for PHC associated with ingestion of aflatoxin-contaminated foods except "other grains," but the increase was not significant. The results were similar when we adjusted for HBsAg status.

Fourteen cases reported a history of jaundice compared to 6 controls (RR, 2.6; 95% CL, 0.9 and 8.6), and 11 cases reported a history of jaundice more than 5 years ago compared to 4 controls (RR, 3.0; 95% CL, 0.8 and 13.5). The strong association was independent of HBsAg status. There were 4 HBsAg- cases who reported a prior episode of jaundice more than 5 years ago; the mean interval between diagnoses of jaundice and PHC was 17.5 years. These 4 cases were the youngest among the 19 HBsAg- PHC patients; they were all diagnosed under age 50. Prior history of liver disease in the family was associated with an increased risk for PHC (RR, 7.1),

but all 7 positive cases either were HBsAg+ or had a history of jaundice.

We found a significant association with cigarette smoking among the cases of PHC who were negative for HBsAg. Table 3 shows the smoking habits of PHC patients and of controls by age (<50, 50+) and HBsAg status. All 13 female controls were nonsmokers as were the 6 female cases under age 50. Two of the 6 female cases age 50+ were heavy smokers (20+ cigarettes/day); they were both HBsAg-. There were more heavy smokers among HBsAg+ controls compared to HBsAg- controls, but the excess was not statistically significant (one-sided *p*, 0.14). Therefore, all 107 controls were used to test for an association between cigarette smoking and HBsAg- PHC. The RR of HBsAg- PHC for heavy smokers was 3.3 (95% CL, 1.0 and 13.4) compared to non- or light smokers. The mean duration of smoking for the 14 HBsAg- cases who were heavy smokers was 28.0 years, compared to 26.5 years for the 47 controls who smoked the same amount. Eleven of the 14 heavy smokers did not drink Chinese wine; only one was a heavy ( $\geq 1$  glass/day) drinker. The strong association between cigarette smoking and HBsAg- PHC was restricted to cases age 50+. The RR for heavy smokers in this older age group was 8.2 (95% CL, 1.5 and 91.9). The 4 HBsAg- cases under age 50 (all of whom had a history of jaundice more than 5 years ago) had smoking habits similar to those of the 35 male controls in the same age group.

There was no significant positive association between PHC and alcohol consumption, history of blood transfusion, history of daily injection for over 1 month, and consumption of Cantonese salted fish.

DISCUSSION

The strong association between HBsAg positivity (as indicative of active HBV infection) and PHC has been demonstrated in case-control studies conducted among European (16), Black African (13), Malay (5), and Chinese (3) populations. The estimated RRs from these studies range from 1.1 (5) to 21 (13). Our study further confirms this association among Hong Kong Chinese.

Aflatoxins are toxic to many animal species including monkeys, with the liver being the organ usually affected. The histological changes range from acute hepatic necrosis to liver cell dysplasia to the development of liver neoplasia (1, 4, 6). Aflatoxins can be found in many food items including peanuts, groundnuts, corn, wheat, beans, etc., when stored under conditions favorable for the growth of fungi. Three studies carried out in Africa consistently demonstrated a significant correlation between the level of dietary aflatoxin intake and incidence of primary liver cancer in the population (7, 8, 17). Dietary surveys

Table 1  
PHC cases and controls by age and HBsAg status

Age	Cases		Controls	
	HBsAg+	HBsAg-	HBsAg+	HBsAg-
<30	6 (7) <sup>a</sup>	0 (0)	1 (5)	4 (5)
30-39	4 (5)	2 (11)	0 (0)	8 (9)
40-49	29 (33)	2 (11)	7 (37)	20 (23)
50-59	29 (33)	7 (37)	7 (37)	30 (34)
60-69	17 (19)	5 (26)	4 (21)	21 (24)
70+	3 (3)	3 (15)	0 (0)	5 (5)
Total	88 (100)	19 (100)	19 (100)	88 (100)

<sup>a</sup> Numbers in parentheses, column percentage.

Table 2  
Dietary frequencies of PHC patients and of hospital controls

Food items	No. of cases			RR <sup>a</sup>
	Daily	Weekly	Less than weekly	
Corn (25) <sup>b</sup>	5 (4) <sup>c</sup>	4 (5)	96 (97)	1.0
Beans (13)	0 (0)	50 (53)	55 (53)	0.9
Mung beans (8)	0 (0)	43 (43)	62 (63)	1.0
Other grains <sup>d</sup> (5)	3 (2)	13 (6)	89 (98)	2.2
Fermented bean curd (1)	0 (1)	11 (20)	94 (85)	0.5
Peanuts (0)	0 (0)	10 (7)	95 (99)	1.5
Peanut oil (1)	96 (94)	0 (0)	8 (10)	1.3 <sup>e</sup>
Peanut butter (1)	1 (2)	3 (5)	100 (99)	0.6
Yellow vegetable	0 (0)	78 (88)	27 (18)	0.6
Green vegetable	94 (95)	11 (11)	0 (0)	1.0 <sup>e</sup>
Salted fish	11 (11)	27 (26)	67 (69)	1.1
Pork	45 (58)	56 (47)	4 (1)	0.6 <sup>e</sup>
Fruits	33 (38)	54 (54)	18 (14)	0.8 <sup>e</sup>
Rice	105 (106)	0 (0)	0 (0)	

<sup>a</sup> Based on at least weekly (versus less frequent) consumption of food item.  
<sup>b</sup> Numbers in parentheses (Column 1), estimate of percentage of samples containing detectable concentrations of aflatoxins based on a market survey (12).  
<sup>c</sup> Numbers in parentheses (Columns 2 to 4), number of controls.  
<sup>d</sup> Wheat, barley, and oats.  
<sup>e</sup> Based on daily (versus less frequent) consumption of food item.

Table 3  
Smoking habits of PHC patients and of controls by age and HBsAg status

Smoking habits	Age, <50				Age, 50+				Total	
	HBsAg+		HBsAg-		HBsAg+		HBsAg-		Cases	Controls
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls		
Nonsmoker	17	1	1	11	7	1	2	20	27	33
1-19 cigarettes/day	6	4	2	10	15	2	0	11	23	27
20+ cigarettes/day	15	3	1	11	27	8	13	25	56	47
Total	38	8	4	32	49	11	15	56	106	107

in Thailand, which is a high-risk area for primary liver cancer, showed a high level of aflatoxin ingestion (10–12). A recent case-control study in the Philippines reported a RR of 17.0 for primary liver cancer associated with a heavy (7+  $\mu\text{g}$ ) dietary aflatoxin load per day (2). Thus, available epidemiological evidence seems to suggest that ingestion of aflatoxins is an important cause of primary liver cancer in Africa and southeast Asia. However, the frequency of aflatoxin contamination in Hong Kong foods is low. Shank *et al.* (12) reported that, among 878 market foods sampled, only 22 contained aflatoxins. Our dietary results confirm that aflatoxin exposure is not a major risk factor for PHC in Hong Kong. We found no association between dietary intake of corn and beans, chief sources of aflatoxins in Hong Kong, and the occurrence of PHC.

Data from a case-control study in Senegal showed that past history of hepatitis and/or jaundice was more frequent among primary liver cancer patients than among hospital controls (9). The authors stated, "This history was unrelated to serologic evidence of HB [hepatitis B] exposure," but no other information relating to the history of jaundice was given in the report. Our findings were consistent with that of the Senegal study. Prior history of jaundice more than 5 years ago was significantly related to an increased risk for PHC, independent of HBsAg status. The 4 HBsAg– PHC patients with a history of jaundice more than 5 years ago were all under age 50. The history of jaundice preceded the PHC by at least 12 years. Only one of these 4 was a moderately heavy smoker (20+ cigarettes/day for 16 years compared to a mean of 28 years for all heavy smokers among HBsAg– PHC patients). The above findings suggest that some other type(s) of chronic liver condition, not related to HBV infection or cigarette smoking but associated with a prior history of jaundice, was the cause of PHC in these young HBsAg– cases. An alternative explanation for this finding is that the 4 cases represent chronic HBV carriers that were missed by the HBsAg test. It is widely believed that the presence of antibody to the core antigen in the absence of antibody to HBsAg is indicative of chronic HBV infection. Two of the 4 cases were tested also for antibody to HBsAg; both tests were positive.

Trichopoulos *et al.* (15) reported a significant association between cigarette smoking and PHC patients who were negative for HBsAg. The Greek study reported that the association of PHC (HBsAg–) with smoking was stronger among persons 60 or more years old (mean age of their patients was 63 years). Our data support their findings. Fourteen (74%) of our 19 HBsAg–PHC patients were heavy smokers (20+ cigarettes/day). Moreover, the strong association between cigarette smoking and HBsAg– PHC is confined to our older cases (age 50+) whose disease status was not related to a prior history of

jaundice. Among heavy smokers in this older age group, the RR for PHC is 8.2 compared to light smokers and nonsmokers. We would like to point out that our observed RR of 1.2 for heavy smokers among HBsAg+ cases compared to light smokers and nonsmokers is compatible with cigarette smoking and HBV infection as additive risk factors for PHC.

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