ABSTRACT

A case-control study was undertaken to evaluate the roles of the hepatitis B virus (HBV), cigarette smoking, and alcohol use in the etiology of hepatocellular carcinoma (HCC). A major purpose of the study was to evaluate the effect of cigarette smoking on HCC among hepatitis B surface antigen (HBsAg)-negative persons, since it had been suggested that the relative effect of cigarette smoking on HCC was higher among HBsAg-negative persons than among HBsAg-positive persons. Eighty-six cases and 161 hospital controls were included in the study.

This study confirmed the strong relationship between the HBV and HCC. Twenty-eight cases and none of 63 controls were chronically infected with HBV as evidenced by serum HBsAg. The study also found a moderately strong relationship between alcohol use and HCC.

The results of the present study do not support the hypothesis that cigarette smoking is a risk factor for HCC. Among all subjects, the relative rate of HCC for cigarette smokers compared with nonsmokers after adjustment for alcohol consumption was 1.0 with 95% confidence limits, 0.5 to 1.8. Among HBsAg-negative subjects, the relative rate was 1.1 with 95% confidence limits, 0.5 to 2.4. There was also no consistent dose-response relationship between quantity smoked and HCC in this study.

INTRODUCTION

Among persons negative for the HBsAg,5 cigarette smokers had an increased risk of HCC compared with nonsmokers in a case-control study by Trichopoulos et al. (1). There was little difference between the smoking habits of HBsAg-positive cases and controls in this study.

Few epidemiological studies have evaluated the association between HCC and cigarette smoking. The Surgeon General of the United States does not consider cigarette smoking a cause of HCC (2). The present study further evaluates the relationship between cigarette smoking and HCC according to the presence or absence of chronic infection with the HBV. Also included in this study is an evaluation of the role of the HBV and alcohol consumption in the etiology of HCC, since these agents are suspected causes of HCC.

MATERIALS AND METHODS

Cases. Eligible cases were persons aged 18 to 84 with HCC. The cases were interviewed at 12 hospitals affiliated with one of five participating study centers. A total of 86 cases is included in the study.

The cases were identified by review of the hospital admission reports, pathology reports, autopsy reports, and by contact with physicians. The diagnosis of HCC was made within the 6 mo before admission for 70 (81%) of the cases and within 12 mo for 77 (90%) of the cases.

Of the 86 cases, 80 were confirmed histologically. For the remaining six, the diagnosis of HCC was established clinically. The cases ranged in age from 18 to 80 yr with a median age of 63. Sixty of the cases were men, 66 were white, 19 were black, and 1 was oriental.

Controls. Two hospital controls were sought for each case. Since a major purpose of the study was to evaluate the relationship between cigarette smoking and HCC, patients admitted for the following tobacco-related diseases were ineligible as controls: cancers of the lung, oral cavity, esophagus, larynx, bladder, or pancreas; chronic bronchitis; and emphysema. A control could have a history of any of these diseases so long as his current admission was not for evaluation or treatment of this disease. Patients admitted for primary liver disease were also ineligible as controls.

The controls were matched to cases on gender, year of birth (plus or minus 5 yr), and race (white, black, oriental). In Miami, Cuban-born controls were selected for Cuban-born cases. The following procedure was used to select controls so that they would be comparable to cases according to their current residence: (a) if the case resided in the immediate catchment area of the hospital (typically the county or city), the controls for this case also must have resided in the catchment area; (b) if the case was referred to the hospital from outside the catchment area but within the state, then the controls also must have resided within the state but outside the catchment area; (c) if the case did not reside within the state, then the controls also must have been from outside the state. The purpose of this matching criterion was to minimize selection bias which might result from major differences in referral patterns between cases and controls. This matching criterion was successfully met for 76 of the matched sets.

Since most HCC cases had been diagnosed recently, controls were restricted to patients whose current hospital admission was for a condition diagnosed within 3 yr of the interview date. This restriction reduces the proportion of controls who may have recently modified their smoking and drinking habits as a result of a chronic disease. This criterion was successfully fulfilled for 98% of the 147 hospital controls.

The University of Alabama in Birmingham (37 cases); Duke University (24 cases); University of Miami (9 cases); University of Pennsylvania (8 cases); and the Harvard School of Public Health, Boston (8 cases).
It became evident after data collection had begun that too few patients in the Boston center were identified who met the eligibility criteria for controls. Therefore, population-based controls were obtained in Boston. These controls were matched to cases on age, gender, race, and city or town of residence.

A total of 161 controls was interviewed. There were 75 matched triplets and 11 matched pairs. The controls ranged in age from 19 to 81 yr with a median age of 62. One-hundred-ten controls were men, 126 were white, 33 were black, and 2 were oriental.

**Interviews.** Subjects were questioned about their history of tobacco and alcohol use. The interviews were usually conducted in the hospital. The population controls were interviewed at their homes. The interview was done by telephone for 11 cases, while for 4 cases and for 3 controls, the interview was started in-person and completed by telephone. Nine cases were either too sick or had died before an interview could be arranged. Interviews were obtained from spouses or other close relatives of these cases.

**Blood Specimens.** Blood specimens were obtained from 49 cases and from 59 controls. Sera were tested for evidence of HBV infection by the Hepatitis Laboratories Division, Centers for Disease Control. The samples were tested by radioimmunoassay for the HBsAg (Austria II; Abbott Laboratories), anti-HBc (Corab; Abbott Laboratories), and anti-HBs (Ausab; Abbott Laboratories). The presence of HBsAg in an asymptomatic person indicates a chronic HBV carrier state.

**Statistical Procedures.** The matching was accommodated in the analysis through logistic regression models using conditional likelihood procedures to obtain maximum likelihood estimates of parameters (3, 4). The antilogarithm of parameter estimates is interpreted as the RR of HCC among those exposed compared with those not exposed. Conditional logistic regression models also allow for control of confounding by factors not matched by design. Dose-response relationships were evaluated by including in the model a single ordinal exposure variable, usually with three or four equally spaced levels including the unexposed. The statistical significance of the parameter obtained from this model was used as a trend test. This procedure is analogous to Mantel's trend test for unmatched data (5), but the dose-response relationship is evaluated conditionally upon the matched sets. All reported P values are two tailed unless stated otherwise.

**RESULTS**

**Hepatitis B Virus.** Eight of the 49 cases and none of the 59 controls whom we tested for HBV were HBsAg positive (exact one-tailed P value, 0.01). HBsAg status was available in the medical record for 21 of these subjects. The 2 sources of data were in agreement for 20 of these subjects (1 subject was reported positive in the medical record, but was not confirmed by serum testing). In total, 12 of 67 (18%) and 0 of 63 controls for whom HBsAg status was ascertainable by use of either source were HBsAg positive. The exact one-tailed P value obtained for these results is 0.0002 with an exact one-sided lower 95% confidence limit for the RR of 3.8.

All HBsAg-positive cases were men. The prevalence of HBsAg among the 45 male cases tested for HBsAg was 27%. None of the 22 female cases tested for HBsAg was positive. This large difference between the prevalence of HBsAg among male and female cases is statistically significant (P = 0.01). Among the 45 male cases, 5 of 30 (17%) whites and 7 of 15 (47%) nonwhites were HBsAg positive (P = 0.08). The mean age of the 12 HBsAg-positive male cases was 48 yr, while for the 33 HBsAg-negative male cases, the mean age was 64 (P < 0.01).

One HBsAg-negative case and one HBsAg-negative control had low levels of anti-HBc but were negative for anti-HBs. Although the presence of anti-HBc without anti-HBs may indicate a "low level carrier state" (6), these two subjects were not considered chronic HBV carriers because of their low levels of anti-HBc. Among the remaining 98 HBsAg-negative subjects, 7 of 40 cases (18%) and 5 of 58 (9%) controls had evidence of a resolved HBV infection indicated by the presence of anti-HBs with or without anti-HBc.

**Alcohol Consumption.** Subjects were questioned about their use of beer, wine, and liquor. A subject was considered to have used any of these items if he had consumed at least 100 servings of that item in his entire lifetime. The matched RRs for any consumption versus no consumption and their 95% confidence limits are: beer, 2.0 (1.0, 3.8); wine, 1.2 (0.7, 2.2); and liquor, 1.6 (0.8, 3.0).

The subjects had been asked to classify their beer, wine, and liquor consumption into one of four ordinal categories: 1, no use; 2, infrequent use; 3, occasional use (at least one serving per week, but not daily); and 4, regular use (at least one serving per day). Subjects were classified according to their highest ordinal level of beer, wine, or liquor consumption. The results are displayed in Table 1. There is approximately a 3-fold increase in HCC risk among regular drinkers compared with nondrinkers. There is also a dose-response relationship between HCC risk and this ordinal classification (one-tailed P value for trend test, 0.01).

Subjects were also classified according to a measure of their cumulative alcohol consumption. This measure was obtained by multiplying the number of servings of each type of beverage by the number of years it was consumed and then by adding the results for beer, wine, and liquor. In this analysis, 12 oz of beer, 4 oz of wine, and 1.25 oz of liquor were considered equivalent. Infrequent users of any item were combined with nonusers. The frequency distribution of this cumulative measure was examined among the controls and divided into three approximately equal groups. The cases were then classified into these categories. The results are displayed in Table 2. There is also evidence of a

| Table 1 | Distribution of cases and controls and the relative rates according to an ordinal classification of their beer, wine, and liquor habits |
|-------------|-----------------|-----------------|-----------------|
| Alcohol category | Cases | Controls | RR* |
| Nondrinker | 19 | 51 | 1.0 |
| Infrequent drinkers | 14 | 33 | 1.4 |
| Occasional drinkers | 25 | 37 | 2.3 |
| Regular drinkers | 27 | 38 | 2.6 |
| Total | 85 | 159 | |

* The conditional RRs obtained from the matched sets.

| Table 2 | Distribution of cases and controls and the relative rates according to a cumulative measure of consumption of beer, wine, and liquor |
|-----------------|-----------------|-----------------|-----------------|
| Cumulative alcohol consumptiona | Cases | Controls | RRb |
| Nondrinkers | 32 | 81 | 1.0 |
| Low | 12 | 23 | 1.4 |
| Medium | 13 | 17 | 2.5 |
| High | 18 | 17 | 3.3 |
| Total | 75 | 138 | |

a Low is greater than 0 but less than 18 "drink-years." Medium is between 18 and 56 drink-years. High is greater than 56 drink-years.

b The conditional RRs obtained from the matched sets.
dose-response relationship between HCC risk and alcohol consumption in this analysis. The one-tailed \( P \) value for a trend test is 0.005.

Thirty-one of the cases were diagnosed with cirrhosis. Eight of these were classified as macronodular, 5 micronodular, 3 were described as postnecrotic, 2 were described as Laennec’s cirrhosis, 2 were described as mixed micronodular, and 11 were not histologically classified. This prevalence of 36% for cirrhosis is probably an underestimate, since pathologists may have failed to note that an HCC patient had underlying cirrhosis, or the tissue specimen may have been inadequate to establish a diagnosis of cirrhosis.

Cigarette Smoking. A smoker was defined as a person who had smoked at least one cigarette a day for at least 1 yr. The matched RR for persons who had ever smoked cigarettes compared to lifetime nonsmokers is 1.3. However, after adjustment of this RR for the four ordinal levels of alcohol consumption displayed in Table 1, the RR is reduced to 1.0 with 95% confidence limits, 0.5 to 1.8. This adjustment was made by use of the ordinal classification of alcohol habit because there were fewer missing data for this variable than for the cumulative measure. However, adjustment for the cumulative measure of alcohol consumption yielded similar results.

The distribution of cases and controls according to their current cigarette habit is displayed in Table 3. The matched RR for all current smokers compared with nonsmokers is 1.5; however, this RR is reduced to 1.1 after adjustment for alcohol consumption.

Among current cigarette smokers, there is a slight inverse trend between amount smoked and HCC risk as seen in Table 3. The dose-response relationship between cigarette smoking and HCC was also evaluated by pack-years of smoking. Pack-years were obtained by multiplying the usual daily number of packs of cigarettes smoked by current or former smokers by the total number of years of smoking. There was no consistent dose-response relationship between pack-years of smoking and HCC.

Cigarette Smoking, Alcohol Consumption, and the HBV. It was anticipated that the relative effect of cigarette smoking on HCC risk would be larger among HBsAg-negative subjects than among HBsAg-positive subjects, because of the findings of the study by Trichopoulos et al. (1). The relationship between HCC and cigarette smoking was therefore evaluated among the known HBsAg-negative cases and their controls.

The distribution of these cases and their controls according to three ordinal categories of alcohol habit and cigarette smoking is displayed in Table 4. The matched RRs displayed in the body of Table 4 are based on small numbers and are therefore unstable. Although the RRs for HCC among current smokers who at least occasionally use alcohol compared with nonusers of both alcohol and cigarettes are elevated, no consistent pattern between alcohol use and cigarette smoking on HCC risk is evident in the data. A test for interaction between alcohol and cigarette use on HCC risk is not statistically significant (\( P = 0.50 \)).

The matched RR for those who had ever smoked cigarettes compared with lifetime nonsmokers after adjustment for alcohol habit is 1.1 with 95% confidence limits, 0.5 to 2.4. The matched RR for current cigarette smokers compared with lifetime non-smokers after adjustment for alcohol habit is 1.6 (95% confidence limits, 0.7 to 3.7). However, among current smokers smoking a pack or less per day and among those smoking more than a pack per day, the matched RRs are 1.7 and 1.2, respectively.

The distribution of the HBsAg-negative cases and their controls according to pack-years of cigarette smoking is displayed in Table 5. There is no consistent positive relationship between HCC and pack-years of smoking.

Other Forms of Tobacco. Each of the RRs presented below was adjusted for alcohol habit because alcohol use was a risk factor for HCC in this study. The matched RR and 95% confidence limits for those who had ever smoked cigars compared with those who had not are 0.8 (0.3, 1.9). Fourteen cases and 14 controls had ever smoked pipes (RR = 2.5; 0.9, 6.9). However among pipe users, the controls had smoked more bowlfuls per week and had smoked pipes for more years than had the cases.

The RR for persons who had used chewing tobacco compared with those who had not is 2.0 (0.7, 5.6), while the RR for snuff users compared with nonusers is 1.1 (0.3, 4.2). There is no consistent or statistically significant dose-response relationship for either intensity or duration of use for either chewing tobacco or snuff.

**DISCUSSION**

The present results support the hypothesis that chronic infection with the HBV is a cause of HCC. There is considerable scientific evidence implicating the HBV as a cause of HCC. This evidence includes the observation of a strong positive correlation between the prevalence of chronic HBV infection and the incidence rate of HCC throughout the world (7); the results of numerous other case-control studies (8-13); the results of prospective follow-up studies (14, 15); and the finding of integrated HBV-DNA sequences in chromosomes of human liver cancer cells (16-18).

Among the cases in the present study, the prevalence of HBsAg was higher among nonwhites than it was among whites. Also, the average age of HBsAg-positive cases was less than that of the HBsAg-negative cases. Such findings have been reported by others (19-22). A notable finding from the present study is a higher prevalence of HBsAg among male cases than among female cases. This has been reported in two other studies, one from the United States and the other from Great Britain (11, 19). These findings suggest that the proportion of HCC cases attributable to the HBV is higher among men than it is among women in the United States.

The overall prevalence of the chronic HBV carrier state among HCC cases in the present study is 18%. Since the RR of HCC

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**Table 3**

<table>
<thead>
<tr>
<th>Cigarette habit</th>
<th>Cases</th>
<th>Controls</th>
<th>RR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smoked</td>
<td>27</td>
<td>58</td>
<td>1.0</td>
</tr>
<tr>
<td>Exsmoker</td>
<td>26</td>
<td>50</td>
<td>0.9</td>
</tr>
<tr>
<td>Current smoker</td>
<td>21</td>
<td>29</td>
<td>1.2</td>
</tr>
<tr>
<td>≤ Pack/day</td>
<td>9</td>
<td>18</td>
<td>0.8</td>
</tr>
<tr>
<td>&gt; Pack/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>83</td>
<td>155</td>
<td></td>
</tr>
</tbody>
</table>

*The RRs were obtained from a conditional logistic regression model with indicator variables for each smoking category and adjusted for the ordinal classification of alcohol habit.
consumers, Jensen observed a standardized mortality ratio for excess of HCC compared with light and nondrinkers. In a cohort study (1), moderate and heavy drinkers experienced about a 50% increase of exposure would tend to produce spuriously high RRs at the null value, unity, after adjustment for alcohol consumption. Even among HBsAg-negative subjects, the RR for those who had ever smoked cigarettes compared to those who had not is 1.1 after adjustment for alcohol. There was no consistent dose-response relationship between HCC risk and cigarette consumption as measured by pack-years of cigarette smoking. Furthermore, among current cigarette smokers, the RR was higher for those smoking a pack or less per day than it was for those smoking more than a pack.

The apparent absence of a positive relationship between cigarette smoking and HCC could be the result of bias. Included among the controls were 33 persons admitted to the hospital for cardiovascular diseases. Seventy-six% of these subjects had smoked cigarettes compared with 60% of the remaining controls. However, the exclusion of controls with cardiovascular diseases had very little effect on the RRs relating HCC and cigarette smoking. For example, among HBsAg-negative subjects, the matched RR for current smokers compared with lifetime nonsmokers after the exclusion of cardiovascular disease controls and after adjustment for alcohol habit is 1.5 (95% confidence limits, 0.6 to 3.8). Lack of association of cigarette smoking and HCC might also occur if the smoking histories were excessively error prone. However, we observed the anticipated positive correlation between smoking and drinking habits. Furthermore, the observation that a higher proportion of persons with cardiovascular disease had a history of smoking than did the other controls also supports the contention that the information obtained on smoking habits in the present study is reasonably valid.

The results of this study also suggest a strong association between alcohol consumption and HCC. Some studies have reported only a weak or moderate association between alcohol and HCC. For example, in the case-control study by Trichopoulos et al. (1), moderate and heavy drinkers experienced about a 50% excess of HCC compared with light and nondrinkers. In a cohort study of Danish brewery workers believed to be heavy beer consumers, Jensen observed a standardized mortality ratio for PLC of 1.5 (24). In another cohort study, Hakulinen found an standardized mortality ratio for PLC of 1.5 among persons who had violated state laws concerning alcohol usage (25). On the other hand, Yu et al. found that individuals who drank 80 g or more of ethanol per day experienced about a 4-fold increase in HCC risk compared with light or nondrinkers (26).

The results of the present study suggest that moderate alcohol consumption increases HCC risk. However, people may considerably underreport their alcohol use. This type of misclassification of exposure would tend to produce spuriously high RRs at the lower levels of alcohol consumption. Nonetheless, the evidence that alcohol abuse is a cause of HCC is persuasive, and moderate use may entail some increase in the risk of HCC.

Our findings do not support the hypothesis that cigarette smoking is a cause of HCC. The overall RR for current smokers compared with nonsmokers is 1.3, and this RR is reduced to the null value, unity, after adjustment for alcohol consumption. Even among HBsAg-negative subjects, the RR for those who had ever smoked cigarettes compared to those who had not is 1.1 after adjustment for alcohol. There was no consistent dose-response relationship between HCC risk and cigarette consumption as measured by pack-years of cigarette smoking. Furthermore, among current cigarette smokers, the RR was higher for those who smoked a pack or less per day than it was for those smoking more than a pack.

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Trichopoulos et al. reported a RR for current smokers compared with nonsmokers of 3.0 (95% confidence limits, 1.4, 6.5, estimated from published data) among HBsAg-negative subjects. Although the lower limit of this RR is consistent with a small treatment effect, the wide confidence interval about the RR. Also, among 87 HBsAg-positive cases and 19 HBsAg-positive controls, the RR for cigarette smokers compared with non-smokers after the exclusion of cardiovascular disease controls and after adjustment for alcohol habit is 1.5 (95% confidence limits, 0.6 to 3.8). Lack of association of cigarette smoking and HCC might also occur if the smoking histories were excessively error prone. However, we observed the anticipated positive correlation between smoking and drinking habits. Furthermore, the observation that a higher proportion of persons with cardiovascular disease had a history of smoking than did the other controls also supports the contention that the information obtained on smoking habits in the present study is reasonably valid.

In a case-control study from Hong Kong, Lam et al. (27) found a RR of HCC among HBsAg-negative subjects for cigarette smokers compared to nonsmokers of 2.9 (95% confidence limits, 0.8 to 10, estimated from published data). This study supports the findings of Trichopoulos et al. However, the study was small, as evidenced by the wide confidence interval about the RR. Also, among 87 HBsAg-positive cases and 19 HBsAg-positive controls, the RR for cigarette smokers compared with non-smokers was 0.3. The overall RR of HCC for cigarette smokers compared with non-smokers in this study is 1.1 with 95% confidence limits, 0.4, 2.6 (estimated from published data). These RRs are not adjusted for alcohol consumption.

In a case-control study from Los Angeles, Yu et al. reported that the matched RR of HCC for persons currently smoking more than a pack of cigarettes per day compared with nonsmokers was 2.6 (26). However, this RR was not adjusted for alcohol habit. It is possible to estimate from their published data the
corresponding unmatched RR of 2.4, suggesting that the matching cannot be ignored in this study without introducing appreciable bias. After adjustment for the two alcohol categories displayed in their Table 1 (less or more than 80 g of ethanol per day), this RR of 2.4 is reduced to 1.5. This observation suggests that the matched RR would also be diminished after adjustment for alcohol. The unmatched RR for all current smokers compared with nonsmokers, after adjustment for alcohol, is 1.3 with 95% confidence limits, 0.7 to 2.7.

Information derived from other studies is less specific than the results described above. None of these other studies distinguished between HBsAg-negative and -positive persons, and they pertained to all PLC, not specifically to HCC. In one case-control study, there was a positive trend, which was not statistically significant, between cigarette smoking and PLC (28), while two other case-control studies found either no or a slightly negative association between cigarette smoking and PLC (29, 30). On the other hand, follow-up studies have generally found about a 2-fold increase in the rate of PLC among smokers compared with nonsmokers (31–33).

In summary, two studies have found a relatively strong effect of cigarette smoking on HCC among HBsAg-negative persons but found little or no effect among HBsAg-positive persons. The present study found neither an overall positive relationship between cigarette smoking and HCC, nor did it find a strong positive effect among HBsAg-negative persons. The relationship between cigarette smoking and HCC was confounded by alcohol habit in the present study and in other studies. Overall, the evidence to date indicates a weakly or moderately positive relationship between cigarette smoking and HCC. However, the causality of this association and its relation to the HBV is uncertain.

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A Case-Control Study of Hepatocellular Carcinoma and the Hepatitis B Virus, Cigarette Smoking, and Alcohol Consumption

Harland Austin, Elizabeth Delzell, Seymour Grufferman, et al.


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