Hepatitis, Alcohol Consumption, Cigarette Smoking, and Hepatocellular Carcinoma in Los Angeles

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ABSTRACT

Seventy-eight black patients and white patients with primary hepatocellular carcinoma (PHC), 70 years or younger at diagnosis, and 78 age-, sex-, and race-matched neighborhood controls were interviewed. Information sought included usual dietary and drinking habits, cigarette smoking habits, prior medical conditions including a history of hepatitis, prior exposure to blood products, and occupational history. Cigarette smoking was a risk factor for PHC; the relative risk (RR) for current smokers of more than one pack/day compared to nonsmokers was 2.6. Alcohol consumption was also a significant risk factor for PHC; individuals who drank 80 g or more of ethanol per day had a RR of 4.2 compared to those drinking less than 10 g/day. In addition, a history of hepatitis (RR = 13.0) and a history of blood transfusions (RR = 7.0) were significant risk factors for PHC. Each of these factors remained significant after adjustment was made for the others.

INTRODUCTION

As part of a large multisite case-control study that we are conducting in Los Angeles County to investigate a wide range of risk factors, we have interviewed 78 PHC3 cases and matched controls. This paper reports our findings from this PHC questionnaire study.

MATERIALS AND METHODS

We interviewed 92 black patients and white patients with PHC, whom we identified from the files of the Los Angeles County Cancer Surveillance Program (3); Asian patients were excluded from this study. The patients were incident cases who were diagnosed in the 5 years from 1975 to 1979 and who were 70 years of age or younger at the time of diagnosis. There were 11 black patients, and 14 of the remaining 81 white patients had Spanish surnames. One of the authors, Dr. Robert L. Peters, reviewed pathology slides from 65 of these 92 PHC patients and judged them all compatible with a diagnosis of PHC.

For each of the 92 patients, we sought to interview a control who was matched to the patient on sex, birth date (within 5 years), race (black, Spanish-surnamed white, and other white), and neighborhood of residence at diagnosis. To search for the "neighborhood" control, we followed a procedure that defines a sequence of houses on specified neighborhood blocks. We attempted to identify the sex, age, and race of all inhabitants of each housing unit; not-at-home units were revisited to complete the census. Our goal was to interview the first resident in the sequence who met our matching criteria. We secured a control for 78 patients; 9 were blacks, 5 were Spanish-surnamed whites, and 64 were other whites.

All interviews were conducted by R. Hanisch. She interviewed 20 patients in person; the remaining 72 patients were dead when she first contacted the families. For the dead patients, she conducted the interview through a close family member; in 40 instances, she interviewed the spouse of the dead patient.

The questionnaire requested information on occupational history, usual dietary and drinking habits, cigarette smoking habits, prior medical conditions including a history of hepatitis, exposure to blood products, use of drugs, and family history of certain diseases.

Questionnaire data from the 78 patients and their matched controls were analyzed by standard matched-pair methods (2). Pairs in which either the case or the control failed to answer the relevant question were eliminated from the analysis. All statistical significance levels quoted (p values) are one-sided.

RESULTS

There were 50 male patients and 28 female patients. The mean age at diagnosis of the cases was 55.7 years. The mean age of the controls (at date of diagnosis of the index case) was 55.1 years. Cases and controls were similar with respect to religion, marital status, and education.

Our questions on cigarette smoking habits first asked whether the individual had ever smoked at least 100 cigarettes up to the date of diagnosis (for controls, date of diagnosis of the index case). For those who had smoked 100 or more cigarettes, we asked the age that they started smoking, the amount that they were smoking at the time of diagnosis and, for exsmokers, the year that they stopped smoking and the amount that they were smoking just before they stopped.

Table 1 presents the relative risks of PHC by various smoker categories. A nonsmoker was defined as one who either had never smoked 100 cigarettes or a smoker who stopped 10 or more years prior to diagnosis of PHC. We grouped exsmokers who stopped 10 or more years ago with nonsmokers to avoid bias that could arise from proxy respondents misclassifying such exsmokers as nonsmokers. All other smokers who stopped prior to diagnosis were classified as exsmokers. Cigarette smoking was positively associated with PHC [p (linear trend) = 0.03]. The RR for current heavy (>1 pack/day) smokers compared to nonsmokers was 2.6 (95% confidence limits = 1.0, 6.7).

Our questions on alcohol consumption referred to usual (recent past but before diagnosis with PHC) drinking habits. We asked the subject about intake frequency and amount for each of the 4 kinds of alcoholic beverages (beer, sweet wine, table wine, and hard liquor). We calculated the average daily ethanol intake for each subject by assuming that one fluid oz of beer, wine, and hard liquor contains 1.1, 2.9, and 9.4 g of ethanol, respectively (1). Alcohol consumption was positively associated with PHC (see Table 1). Individuals who drank 80 g or more of ethanol per day had a RR of 4.2 compared to those drinking less than 10 g/day. In addition, a history of hepatitis (RR = 13.0) and a history of blood transfusions (RR = 7.0) were significant risk factors for PHC. Each of these factors remained significant after adjustment was made for the others.
day had a RR of 4.2 compared to light (0 to 9 g/day) drinkers (95% confidence limits = 1.3, 13.8).

Table 1 also shows the relative risks of PHC by cigarette smoking and alcohol consumption simultaneously. Exsmokers were grouped together with nonsmokers due to their small numbers and their similarity in risk of PHC. Cigarette smoking and alcohol consumption were both significantly related to PHC after allowing for the effect of the other (2).

A history of hepatitis was a third significant risk factor for PHC (RR = 13.0; see Table 2). A history of blood transfusion (RR = 7.0; see Table 2) was also significantly associated with PHC. Only 3 patients reported both a history of hepatitis and blood transfusion. At least 21 of the 27 patients who had a history of hepatitis and/or blood transfusion had had the last episode more than 10 years before the diagnosis of PHC.

Multivariate analysis of the joint effect of cigarette smoking, alcohol consumption, and a history of hepatitis and/or blood transfusion showed that each risk factor remained significant after adjustment was made for the others. There were only 9 black patients and 9 black matched controls in our study. All risk factors reported above show an excess of black cases and white controls in their dietary habits, use of drugs, or family history of cancer.

**DISCUSSION**

Cigarette smoking as an independent risk factor for PHC was reported first in 1980 by Trichopoulos et al. (5) in a study conducted in Greece. They reported that, among individuals who were negative for HBsAg, current heavy (more than 1 pack/day) smokers had a 5.5-fold increased risk compared to non- plus exsmokers. Among HBsAg-positive individuals in the same study, the relative risk in current heavy smokers was 1.5. In an earlier publication, the relative risk of HBsAg positivity for this group of PHC patients had been reported to be 10.4 (6). These relative risks suggest that cigarette smoking and HBV infection may behave more like additive than multiplicative risk factors for PHC. Their results were later confirmed by a case-control study conducted among Hong Kong Chinese (4). The Hong Kong study reported an odds ratio of 3.3 in current smokers (at least 1 pack/day) compared to non- and exsmokers among HBsAg-negative individuals; the risk ratio was 1.2 among HBsAg-positive individuals. For this group of Chinese patients, the RR of PHC associated with HBsAg positivity was 21.3. These risk estimates are again suggestive of cigarette smoking and HBV infection acting as additive risk factors for PHC. Cigarette smoking could account for a large proportion of the non-HBV related cases in both studies. In the Greek study, 78% of HBsAg-negative patients were current smokers, one-half of whom smoked more than 1 pack/day; among control patients, 53% were current smokers with 25% of those smokers smoking more than 1 pack/day. In Hong Kong, 84% of HBsAg-negative patients were current smokers, and almost all of them smoked 1 pack or more/day; among HBsAg-negative controls, 65% were current smokers, and two-thirds of the smokers smoked 1 pack or more/day.

Our present findings on cigarette smoking are consistent with those of the 2 previous studies (4, 5). Our reported risks represent the overall effect of cigarette smoking in both HBsAg-positive and HBsAg-negative individuals. These estimated risks are very similar to those computed from the Greek data. Combining their HBsAg-negative PHC patients (50% of all cases) with their HBsAg-positive patients, we obtain RRs of 1.8 and 3.1 for current 1- to 20-cigarettes/day smokers and current 21+ cigarettes/day smokers, respectively. Yarrish et al. (7) recently reported that one-half of a group of PHC patients from the Philadelphia area (all but one were either black or white) were either HBsAg-positive or hepatitis B core antigen antibody-positive in the absence of hepatitis B surface antigen antibody so that, even though we did not test our patients for serological markers of HBV infection, there is some evidence that about the same proportion of PHC patients are HBV-related in the United States as in Greece.

Our data show excessive alcohol intake to be strongly associated with PHC independent either of dietary and cigarette smoking patterns or of a history of hepatitis and/or blood transfusion. In our group of current smokers of more than 1 pack/day, heavy (80 g of ethanol per day) drinkers had a 7.8-fold (14.0/1.8) risk of PHC compared to more moderate drinkers with similar smoking habits.

HBV infection is uncommon among blacks and whites in Los Angeles.
Angeles County, but our data suggest that it is still a very significant risk factor for PHC even in this low-risk population. If we consider a history of blood transfusions as a surrogate variable for possible transmission of hepatitis viruses via contaminated blood products, then 29% of our patients were infected by HBV compared to 7% of the matched controls.

Although population-attributable risks cannot be calculated without possibility of bias from matched case-control studies (2), some idea of the magnitude can still be thereby attained. From the data in Tables 1 and 2, we estimate that cigarette smoking, heavy alcohol consumption, and a history of hepatitis and/or blood transfusion can account for 20, 15, and 43%, respectively, of all PHC cases in blacks and whites occurring in Los Angeles.

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REFERENCES


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