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Correlation of hepatocellular carcinoma with Hepatitis virus C, HBsAg and alcohol.

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Abstract

Alcohol intake has been definitely recognized as a cause of chronic liver diseases, including hepatocellular carcinoma (HCC) (1, 2). Alcohol could be involved in the development of HCC through both direct (genotoxic) and indirect mechanisms. An indirect mechanism includes the development of cirrhosis, which is probably the most common pathway to liver carcinogenesis in developed countries (3). We found that 87 percent of the cases of HCC developed in a cirrhotic liver, including most of those attributable to alcohol intake (4). No evidence exists on the dose-effect relation between alcohol intake and risk of HCC. Some authors argue that the risk of developing liver disease does not increase over a threshold alcohol intake of about 75 g per day (5). Liver damage due to alcohol has been suspected on the basis of metabolic differences (6). Other aspects of the relation between alcohol drinking and HCC are still unresolved, namely, the effects of type of alcoholic beverage usually consumed, duration of drinking, age at start, and time since quitting. Synergisms between alcohol and hepatitis B virus infection and between alcohol and hepatitis C virus infection in increasing the risk of HCC have been suggested by epidemiologic and pathologic studies (10, 11). However, we know of no data available on the pattern of this interaction for various levels of alcohol intake.

Keywords: Carcinoma, Liver, HBsAg, virus c.

Introduction

Alcohol intake has been definitely recognized as a cause of chronic liver diseases, including hepatocellular carcinoma (HCC). Alcohol could be involved in the development of HCC through both direct (genotoxic) and indirect mechanisms. An indirect mechanism includes the development of cirrhosis, which is probably the most common pathway to liver carcinogenesis in developed countries. We found that 87 percent of the cases of HCC occurring in Brescia, northern Italy, developed in a cirrhotic liver, including most of those attributable to alcohol intake.

No agreement exists on the dose-effect relation between alcohol intake and risk of HCC. Some authors argue that the risk of developing liver disease does not increase over a threshold alcohol intake of about 75 g per day. The relation between alcohol and HCC also could differ for men and women; for women, a higher susceptibility to liver damage due to alcohol has been suspected on the basis of metabolic differences. To date, some epidemiologic studies have evaluated women's risk of cirrhosis for various levels of alcohol intake, but no known research has yet been conducted to investigate the dose-effect

relation between alcohol intake and HCC in men and women separately.

Other aspects of the relation between alcohol drinking and HCC are still unresolved, namely, the effects of type of alcoholic beverage usually consumed, duration of drinking, age at start, and time since quitting. Synergisms between alcohol and hepatitis B virus infection and between alcohol and hepatitis C virus infection in increasing the risk of HCC have been suggested by epidemiologic and pathologic studies. However, we know of no data available on the pattern of this interaction for various levels of alcohol intake.

We investigated the relation between alcohol habits and HCC in men and women separately, also taking account of hepatitis B and hepatitis C virus infections. To this end, the decision to perform the study in the Brescia area seemed particularly appropriate because of the high incidence of liver cancer in the area (12) and because alcohol intake is a major cause of HCC and of cirrhosis as well as hepatitis B and hepatitis C virus infections in Italy.

Materials and Methods

The study design and preliminary results for a subset of cases and controls have been reported previously (13). Briefly, this hospital-based case-control study was carried out on the patients attending out and inpatient types. We recruited as cases 121 patients (93.5 percent of those eligible) with a first diagnosis of HCC who were admitted to the GGS Medical College & Hospital, Faridkot. We enrolled as controls 135 subjects (96.1 percent of those selected) who were admitted to the departments of ophthalmology, dermatology, urology, surgery, cardiology, and internal medicine of the same hospitals and were unaffected by liver disease or malignant neoplasm. Subjects hospitalized for injuries were also excluded because of the relation between such conditions and alcohol abuse. Among HCC cases, 84.7 percent were diagnosed by histology or cytology or had alpha-fetoprotein serum levels of >500 ng/ml; the remaining cases were diagnosed on the basis of sonography. At the hospital, a standardized questionnaire was used to interview cases and controls about their history of alcohol drinking (1). Given the evidence of a latency period of at least 5 years for alcohol-related onset of cirrhosis (8) and of the same interval between onset of cirrhosis and HCC development (11), computed average intake of alcohol during the period of regular consumption. Sera were collected and were tested for hepatitis B surface antigen (HBsAg) and anti–hepatitis C virus antibodies by using commercial immunoassays.

Results

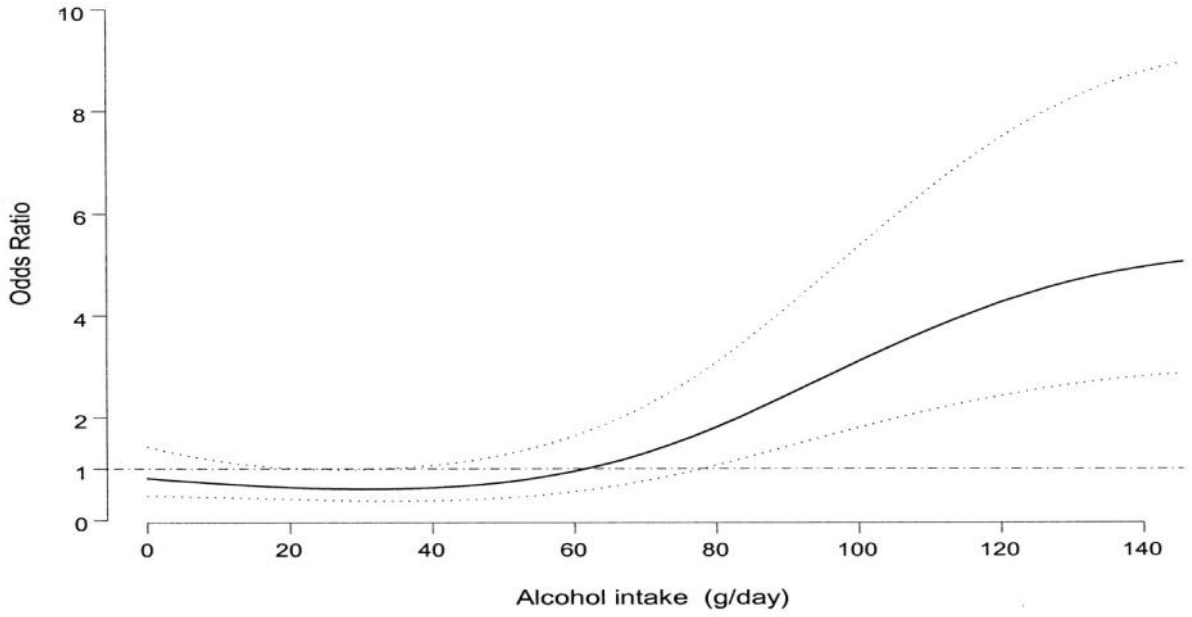
A total of 121 HCC cases and 135 controls were enrolled. The distribution of cases and controls by sex, age, and residence were considered. Mean age was 64.2 years (standard deviation, 7.6) for cases and 63.8 years (standard deviation, 18.4) for controls. The distribution of subjects according to alcohol drinking and to hepatitis C and hepatitis B virus infection markers, and the corresponding odds ratios and 95 percent confidence intervals, are set out in. Alcohol consumption was common among men, since only 2.1 percent of cases and 6.1 percent of controls had never drunk alcohol (abstainers).Controls were affected by a variety of acute and chronic diseases, such as those involving the eye, skin, and urogenital tract, and other disorders treated in medicine and surgery departments of general hospitals. The proportion of drinkers of >60 g/day of ethanol did not vary among controls according to groups of diseases ($p = 0.15$) (data not shown). Both hepatitis C virus and HBsAg positivity were found in a much higher proportion of cases than controls. Among drinkers, all but five cases and nine controls drank wine regularly, with or without beer or spirits. Therefore, we could not compare drinkers of wine with drinkers of other beverages. The interaction between alcohol intake and hepatitis B and hepatitis C virus infection was investigated after excluding 14 cases and one control that had both infections. A monotonic trend of increasing odds-ratio logarithm with increasing alcohol intake was observed for subjects with and without hepatitis B or hepatitis C virus infection (figure 1). For each level of intake, the dose-effect curves showed the highest odds-ratio values for subjects with hepatitis C virus ratio for subjects drinking >60

g/day of ethanol; (3) for former drinkers, the risk was highest for those who had stopped drinking less than 10 years previously; and 4) a synergism between alcohol intake and hepatitis virus infections was evident, with a more than additive but less than multiplicative increase in risk of infection, followed by those with hepatitis B virus infection and finally by those without hepatitis virus infection. The interaction was not significant when the likelihood ratio test was used ($p > 0.1$), suggesting parallelism of the curves.

: **The Effect of Lifetime Intake and Hepatitis Virus Infections**

TABLE 1.

Alcohol intake (g/day)	Men			Women		
	Cases/controls (no.)	**OR†,‡**	**95% CI†**	**Cases/controls (no.)**	**OR‡**	**95% CI**
0	8/42	Reference		24/54	Reference	
1–20	24/56	2.3	0.7, 7.2	22/49	0.6	0.2, 1.7
21–40	27/101	0.9	0.3, 2.7	15/19	1.4	0.4, 5.4
41–60	44/130	1.6	0.5, 4.6	11/10	1.9	0.4, 8.1
61–80	33/89	2.4	0.8, 7.1	4/3	3.1	0.3, 29.7
81–100	62/112	4.2	1.5, 11.7	8/3§	16.55	3.0, 90.1
101–120	47/50	7.7	2.7, 22.7			
121–140	48/38	9.8	3.3, 29.1			
>140	87/68	11.0	3.9, 31.0			
Total	380/686			84/138		



Alcohol and Hepatocellular Carcinoma: The Effect of Lifetime Intake and Hepatitis Virus Infections .

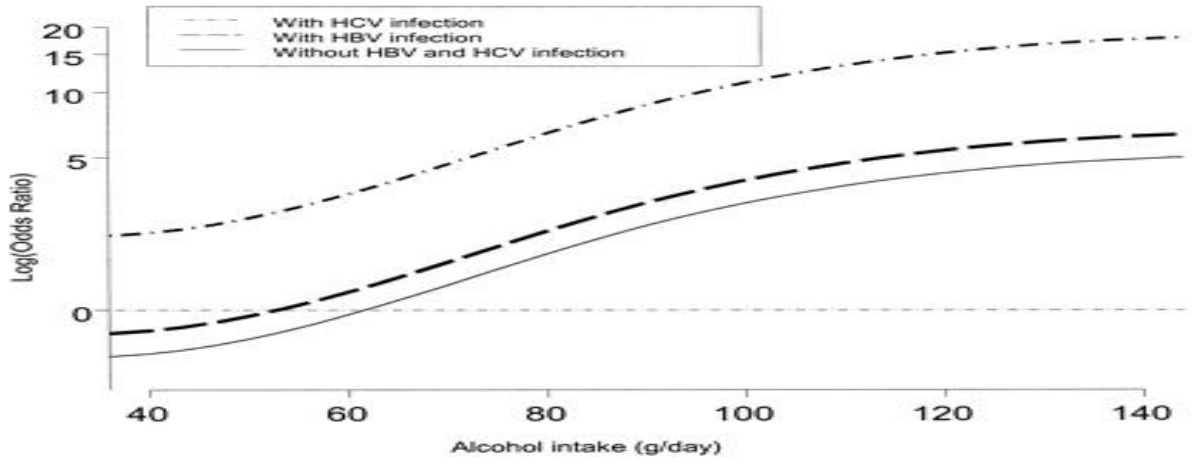


Figure 2

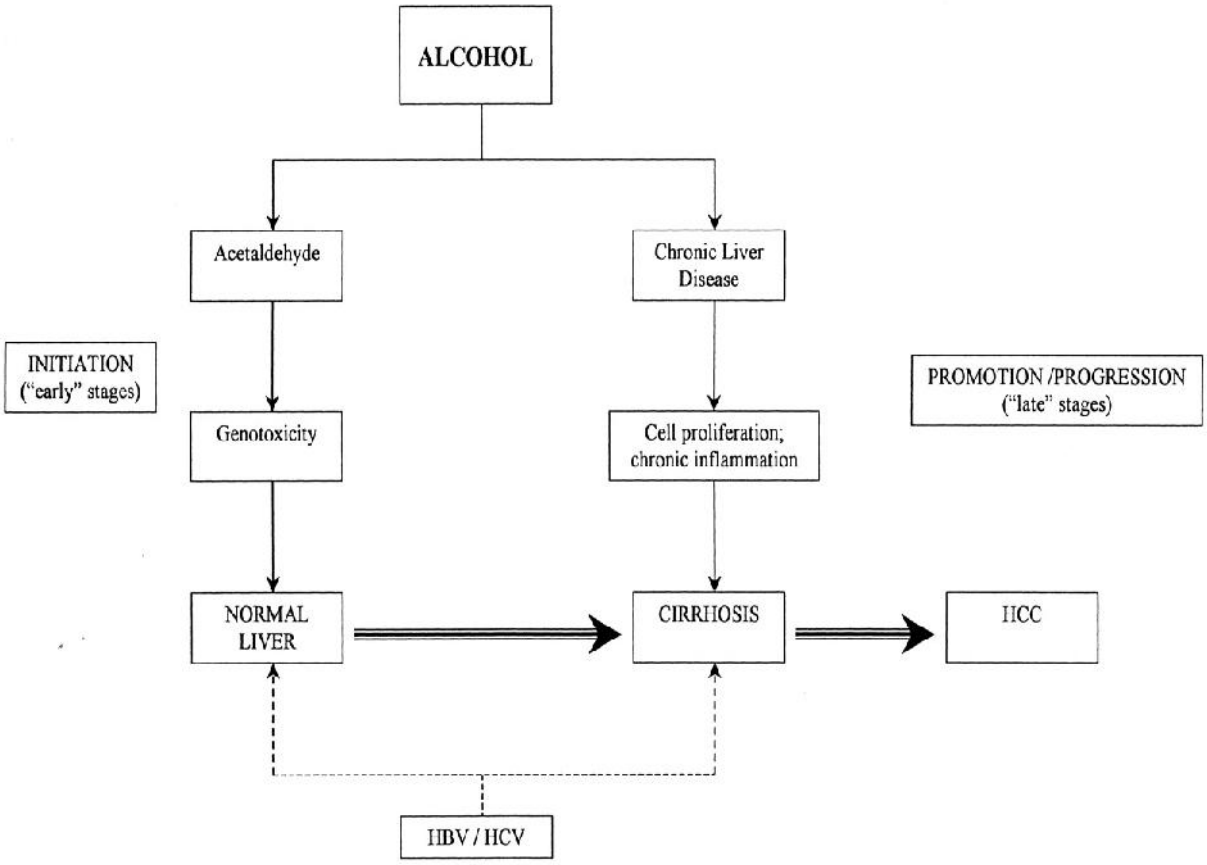
Odds ratios for hepatocellular carcinoma, according to alcohol intake and the presence of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.

Similar results were found when alcohol intake was considered as a dichotomous variable (0–60, >60 g/day); drinkers of 0–60 g/day (abstainers and "light" drinkers) who were negative for both infections were taken as the reference, and subjects with both hepatitis B and hepatitis C virus infection were excluded., the odds ratio for drinking >60 g/day of ethanol was 7.0 for subjects negative for both infections, whereas the odds ratios for drinking 0–60 and >60 g/day were, respectively, 55 and 109 for subjects positive for hepatitis C virus RNA and 22.8 and 48.6 for subjects positive for HBsAg. The synergy indexes for the interaction between drinking >60 g/day and the presence of hepatitis virus infection were 1.8 for hepatitis C and 1.7 for hepatitis B virus infection.

Discussion

The main results of this study follow: 1) the risk of HCC increased with increasing level of alcohol intake, irrespective of duration of consumption and age at start; 2) curves for HCC risk by alcohol intake were fairly similar for case control study. Most epidemiologic studies conducted on the relation between alcohol and HCC have not had enough power to investigate more than two or three categories of intake. Only one study found a linear trend of increasing risk with increasing intake (5), whereas the others found an elevated risk for arbitrarily chosen "high" levels of consumption (7). Using both a traditional, category-based modeling approach and spline regression as alternative models based on continuous variables, we found a linear increase in HCC risk with increasing alcohol intake for both sexes, from a level of about 60. The shape of the alcohol intake curve was undefined for >140 g/day because of the small number of controls claiming to have drunk so much. It is reasonable to assume that very few or no subjects who have drunk >100–140 g/day are still free from liver disease at the average age of 64 years. No influence of duration of intake or age at start was found on HCC risk when intake was taken into account, in agreement with recent studies on alcohol and cancer of the upper digestive tract (4-6) and on alcohol and liver cirrhosis (14). These findings suggest that a low intake for a long time is likely to cause less damage than a similar cumulative level of consumption distributed over a shorter period. These findings are in agreement with those from studies on alcohol and cancer of the upper digestive tract, which show a higher risk for former than for current drinkers (12), a peak in risk immediately after stopping (4), and no clear decline in risk up to 10 years after stopping (12). Taken together, these results are compatible with the role of alcohol as a cause of HCC at both the initial and final stages of the process, as occurs with other alcohol-related cancers. This study confirmed drinking has a "pure" effect in increasing the risk of HCC and that its effect

can be modified by hepatitis B or hepatitis C virus infection. Note that, among HCC cases, the proportion of those with hepatitis B or hepatitis C virus infection declined progressively with increasing alcohol intake, from 91 percent among abstainers to 40 percent among drinkers of >140 g/day, but it did not decline among controls. This finding suggests that HCC rarely, if ever, develops in the absence of either alcohol intake or hepatitis virus infection.. As an additional explanation, people with chronic viral hepatitis may reduce their alcohol intake to prevent liver damage, which would inflate the categories of nondrinkers and light drinkers for those who subsequently develop HCC. As regards the interaction between alcohol consumption and viral hepatitis, we found that the odds ratios for hepatitis C and for hepatitis B virus infection approximately doubled when intake level increased from 0–60 to >60 g/day. Accordingly, the synergy index between an intake of >60 g/day and each hepatitis virus infection was 1.8 for hepatitis C and 1.7 for hepatitis B virus infection. This finding confirms our previous analyses based on lower numbers of cases and controls (4), and it suggests a more than additive but less than multiplicative effect between heavy alcohol intake and each hepatitis virus infection. On the other hand, heavy drinkers in one study did not have a higher risk of cirrhosis if they were positive for hepatitis B virus serologic markers (9); in another study, hepatitis B virus infection did not increase the influence of alcohol drinking in producing cirrhosis (11). The most likely explanations for these contrasting results are the different levels of alcohol intake in different populations and the low power of these studies because of the small numbers of subjects with both hepatitis B virus infection and “heavy” alcohol intake. In contrast, strong evidence supports the hypothesis of a synergism between hepatitis C virus infection and alcohol in causing liver disease. Among people with hepatitis C virus-related disease, those with cirrhosis or HCC had a higher alcohol intake than those with less advanced disease (44). Reciprocally, studies among alcoholics showed a greater severity of liver disease and a higher risk of HCC in the presence of hepatitis C virus infection (4).



Proposed model of liver carcinogenesis by alcohol intake: the effects of early and late intake and interaction with hepatitis virus infection. HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus. Choosing hospital controls to estimate the prevalence of exposure in the study base is another matter of concern. However, population-based case-control studies may also be affected by selection bias if participants are asked to provide blood samples. To prevent selection bias, we excluded from the control series people hospitalized for liver disease, cancer, and other possibly alcohol-related conditions such as injuries. Controls were affected by a wide range of acute and chronic diseases, and we verified that the prevalence of drinkers of >60 g/day of ethanol did not vary according to group of diseases. However, the drinking habits of the male controls recruited for our study were similar to those found in case-control studies performed in Italy on alcohol drinking and other neoplasms (9,10,7): very few subjects were abstainers, about 30 percent claimed to drink at least 80 g/day of alcohol, and almost all drinkers drank wine, with or without beer or spirits. Finally, the seroprevalence of HBsAg and anti–hepatitis C virus/hepatitis C virus RNA positivity among controls is in agreement with that found in Italian case-control studies on the etiology of cirrhosis (9, 10).

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