Short Communication

Etiology of Hepatocellular Carcinoma in Italian Patients with and without Cirrhosis

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Abstract

We performed a case-control study to assess the role of hepatitis B virus (HBV), hepatitis C virus (HCV), GB virus C/hepatitis G virus (HGV), TT virus, alcohol intake, and tobacco smoking as risk factors for hepatocellular carcinoma (HCC) in the presence or absence of cirrhosis. We prospectively recruited 174 patients with a first diagnosis of HCC admitted to the main hospitals in Brescia, North Italy. On the basis of histological, clinical, and radiological criteria, the presence of cirrhosis was established in 142 cases, excluded in 21 cases, and remained undefined in 11 cases. Among the HCC cases without cirrhosis, a histological picture of normal liver was found in a single patient, chronic viral hepatitis was found in 11 patients, alcoholic hepatitis was found in 5 patients, nonspecific reactive hepatitis was found in 3 patients, and hemochromatosis was found in 1 patient. As controls, we also included 610 subjects unaffected by hepatic diseases and admitted to the same hospitals as cases. The odds ratios for having HCC according to positivity for HCV RNA, HBsAg and/or HBV DNA, and alcohol intake > 80 g/day (95% confidence interval) were as follows, in the presence and absence of cirrhosis, respectively: (*a*) 33.5 (17.7–63.4) and 19.7 (6–64.8) for HCV RNA; (*b*) 17.6 (9.0–34.4) and 20.3 (5.7–72.6) for HBsAg; and (*c*) 5.5 (3.1–9.7) and 4.6 (1.5–13.8) for alcohol intake. No association was found with HGV or TT virus infections or tobacco. This study has shown that most HCC cases arising in the area are due to HBV, HCV, or alcohol intake, in both the presence and absence of cirrhosis.

Introduction

The development of HCC[2] is closely associated with cirrhosis because more than 80% of HCC cases are usually found in the cirrhotic liver (1). A different etiology of HCC when associated and not associated with cirrhosis has been hypothesized (2, 3). In effect, among the three main causes of HCC in Western countries (namely, HBV, HCV, and alcohol), only HBV seems to play a direct role in liver cell transformation (4). HCV has been found in some HCC cases without cirrhosis (5), but its carcinogenic role in the absence of cirrhosis is debated. Alcohol is believed to cause HCC mainly because it causes cirrhosis, whereas its association with HCC without cirrhosis is unresolved (6). A possible role for the recently discovered GB virus-C/HGV (7, 8) and TTV (9) and for tobacco smoking (6) in HCC development is debated.

Several case series comparing the prevalence of risk factors for HCC between cirrhotic and noncirrhotic cases have been published (2, 3, 10–12). However, these studies were not population based, so they may have been affected by selection bias. This investigation is part of a large case-control study carried out in a northern Italian area with a high incidence of primary liver cancer. The design of the study and the main results concerning the role of hepatitis viruses and alcohol intake, without considering the presence of cirrhosis in HCC cases, have been reported elsewhere (13–15). In this study, we aimed to investigate the etiology of HCC with respect to the presence or absence of cirrhosis in nontumor tissue.

Materials and Methods

Briefly, 174 subjects with an initial, histologically proven diagnosis of HCC (incident cases) admitted to the two main hospitals in Brescia from 1995–1997 were recruited prospectively. All of the subjects were born in Italy, lived in the province of Brescia, and were less than 75 years of age when diagnosed. Diagnosis of cirrhosis was based on morphological and clinical criteria, laparoscopy, ultrasound, computed tomography, or angiography, according to standard definitions (16). To define the presence or absence of cirrhosis, we used strict criteria based on the algorithm in Fig. 1. Of the 104 (60%) HCC cases with a biopsy of nontumor tissue, 77 had a histological picture of cirrhosis, and 6 had clinical or imaging evidence of cirrhosis, whereas 21 had no sign of cirrhosis. Of the 70 cases for which only tumor liver tissue was available, 59 had clinical or imaging evidence of cirrhosis, and no conclusion could be reached in the remaining 11 patients, who were excluded from further analysis. Overall, conclusive evidence of the presence or absence of cirrhosis was reached in 163 HCC cases: cirrhosis was present in 142 cases (87.1%) and absent in 21 cases (12.9%).

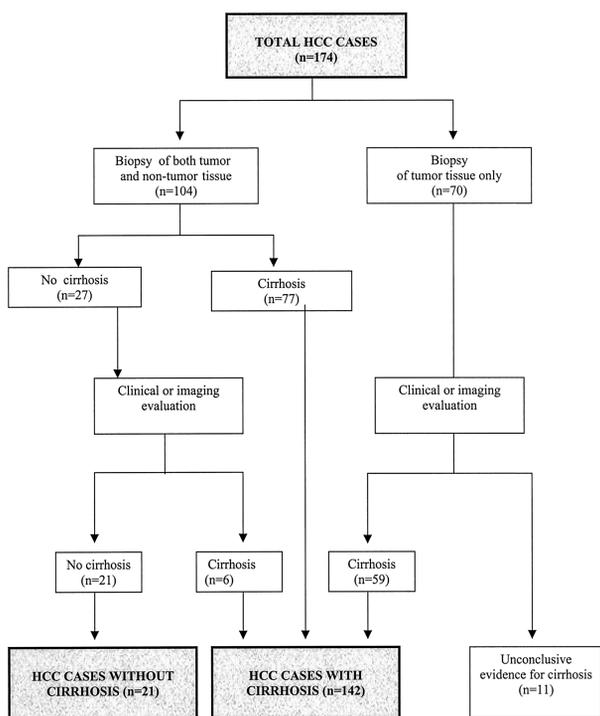In the HCC cases without cirrhosis, chronic viral hepatitis

Fig. 1. Algorithm followed for classification of total HCC cases in subjects with and without cirrhosis.

was classified by grading and staging according to Knodell's histological activity index and described as minimal, mild, moderate, or severe chronic hepatitis as suggested by Desmet *et al.* (17). Nonspecific reactive hepatitis was defined as an independent chronic liver lesion according to Liaw *et al.* (18).

The subjects were interviewed on their lifetime alcohol consumption using the validated standard questionnaire proposed by Corrao *et al.* (19). Alcohol intake of >80 g of ethanol/day for at least 5 years before development of the liver disease was regarded as "heavy." Subjects were also asked about their smoking habits. The presence of hemochromatosis was defined on the basis of serum ferritin concentration, the percentage of transferrin saturation, and liver iron stores at biopsy (20). Histological grading for iron overload was carried out according to Scheuer *et al.* (21) on Pearls'-stained sections.

In all of the HCC cases, we investigated the presence of HBsAg and anti-HCV in serum using commercial ELISAs (Abbott Laboratories, North Chicago, IL) and ORTHO HCV 3.0 ELISA (Ortho Diagnostic Systems, Raritan, NJ), and we investigated the presence of HBV DNA, HCV RNA, HGV RNA, and TTV DNA using the PCR technique, as described previously (13–15). HBV DNA was also investigated in HBsAg-negative cases, and we considered subjects positive for HBsAg and/or HBV DNA to be infected with HBV (22).

For comparison, 610 subjects unaffected by overt liver disease who were simultaneously admitted to the same hospitals in which the HCC cases were diagnosed were recruited as controls. The criteria for inclusion, characteristics of controls, and distribution of risk factors for HCC among them have been described previously (13–15).

Common statistical tests were performed for comparison between HCC cases with and without cirrhosis, using nonparametric tests when necessary. We also computed the ORs and the

attributable risks for each risk factor and their 95% CIs by comparing HCC cases with and without cirrhosis with the controls separately, using logistic regression analysis. All of the analyses were performed using the BMDP program (BMDP Statistical Software, Los Angeles, CA) and the LogXact-Turbo program (Log-Xact Turbo; CYTEL Software Corp., Cambridge, MA).

Results

The HCC cases with and without cirrhosis were similar with regard to distribution of sex (males, 81.7% and 90.5%, respectively), age (mean age, 63.5 and 64.4 years, respectively), area of residence (town of Brescia and surrounding municipalities, 43% and 61.9%, respectively), and education (<6 years of schooling, 64% and 52.4%, respectively; $P > 0.1$ for each variable). The proportions of HCC cases positive for the main risk factors investigated among patients with and without cirrhosis, respectively, were as follows: (*a*) 41.5% and 33.3% for HCV RNA; (*b*) 25.3% and 33.3% for HBsAg and/or HBV DNA; and (*c*) 57% and 57.1% for heavy alcohol intake. Hemochromatosis was the cause of the underlying chronic liver disease in three HCC cases with cirrhosis and one HCC case without cirrhosis. TTV DNA was found in 14.8% of the cases with cirrhosis and 14.3% of those without cirrhosis, and HGV RNA was found in 4.2% of the cases with cirrhosis and 9.5% of those without cirrhosis. No HCC patients had α_1-antitrypsin deficiency, autoimmune disease, or Wilson's disease. Among HCV RNA-positive HCC cases, genotype 1b was found in 64.4% of the cases with cirrhosis and in 57.1% of those without cirrhosis; the remaining HCC cases with cirrhosis had genotype 1a ($n = 2$) or 2 ($n = 19$), whereas all of the other cases without cirrhosis had genotype 2 ($n = 3$). The prevalence of each factor, alone or in combination with another, among HCC cases with and without cirrhosis is shown in Fig. 2. Overall, only 7.2% of HCC cases with cirrhosis and 4.8% of HCC cases without cirrhosis were negative for each factor.

Logistic regression analysis showed a higher OR for anti-HCV and HCV RNA positivity in the presence of cirrhosis (OR = 33.5; 95% CI, 17.7–63.4) than in the absence of cirrhosis (OR = 19.7; 95% CI, 6.0–64.8; data not shown). Similar ORs were found in the presence or absence of cirrhosis for HBsAg and/or HBV DNA positivity (OR = 17.6 and 95% CI = 9.0–34.4 and OR = 20.3 and 95% CI = 5.7–72.6, respectively) and for heavy alcohol intake (OR = 5.5 and 95% CI = 3.1–9.7 and OR = 4.6 and 95% CI = 1.5–13.8, respectively). HGV RNA, TTV DNA, and tobacco smoking were not associated with HCC. The attributable risks for HBV and HCV infection and heavy alcohol intake together were 86.7% (95% CI, 80.2–89.6) in the presence and 91.5% (95% CI, 63.2–94.6) in the absence of cirrhosis.

Multinodular cancer was more common in HCC patients with cirrhosis (45.1%) than in those without cirrhosis (28.5%; $P = 0.09$). Among subjects with a solitary nodule, the mean diameter of the tumor was smaller among HCC cases with cirrhosis (mean, 3.5 cm) than among HCC cases without cirrhosis (mean, 5.3 cm; $P = 0.07$ using the Mann-Whitney test). The median value of α-fetoprotein was lower among HCC cases with cirrhosis (17.5 ng/ml) than among cases without cirrhosis (41 ng/ml; $P > 0.1$).

The classification of chronic liver disease in the HCC cases without cirrhosis according to their putative etiology is shown in Table 1. All but one of these cases occurred in a histological background of chronic liver disease: (*a*) 11 cases had chronic viral hepatitis; (*b*) 5 cases had alcoholic hepatitis; (*c*) 3 cases had nonspecific reactive hepatitis; and (*d*) 1 case had hemochromatosis with grade 3 iron storage. Two cases with a history of heavy
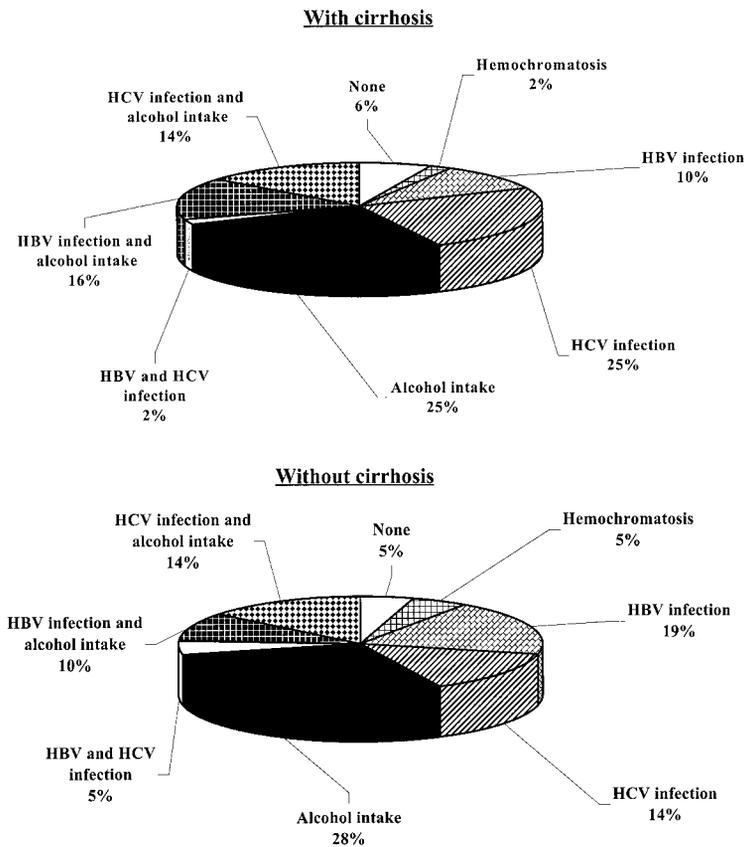
Fig. 2. Prevalence of HBV infection (HbsAg and/or HBV DNA positivity), HCV infection (HCV RNA positivity), heavy alcohol intake, and hemochromatosis in HCC cases with and without cirrhosis.

alcohol intake and one case with a history of HCV infections also showed grade 3 iron storage at histology in the absence of clinical signs of hemochromatosis. The patient with hemochromatosis had mild to moderate fibrosis and no regeneration.

Discussion

The main strengths of this study are the population basis of recruitment of HCC cases, the use of strict criteria for exclusion of cirrhosis, and the accurate investigation of the main risk factors for HCC. To verify the population basis assumption, we compared the HCC cases included in our study with the hospital discharge data for 1 year. Among the total cases arising in the area, 86% were actually admitted to the two hospitals from which we recruited the cases. Among the HCC cases admitted to these hospitals, we recruited 83% of those eligible, on the basis of the inclusion criteria of our case-control study (age up to 75 years, residence in the province of Brescia, and availability for interview). Therefore, because we recruited the majority of all of the incident cases arising in the area, no relevant bias due to selection of patients for surgery, transplantation, or medical treatment probably occurred.

The low proportion of cases without cirrhosis found in our study (12.9%) is in line with figures from autoptic series in Italy and Japan (23) and from large HCC case series in Europe (10, 11). The etiology of HCC in the absence of liver cirrhosis is debated. Recent data suggest that the development of HCC is a process that is independent of but often parallel to cirrhosis (24) and that the premalignant lesion is a clonal expansion of hepatocytes, which could start before the development of cirrhosis (25). However, the regenerative process associated with chronic liver disease could influence the clonal expansion of degenerative hepatocytes and hence promote HCC development. In effect, we found that all but one of the HCC cases without cirrhosis had evidence of chronic liver disease. The only patient with HCC and normal liver was first diagnosed as having the disease at an early age (27 years), was negative for each risk factor, and had an unusual type of cancer, which was classified as an "intermediate (hepatocyte-bile duct cell) phenotype" according to Robrechts *et al.* (26). These findings, in agreement with those of others (12), suggest that HCC development usually occurs in histologically abnormal liver and that chronic liver diseases place patients at risk for the development of HCC.

HBV and HCV infection and heavy alcohol intake seem to be the main determinants of HCC in this area because 86.7% and 91.5% of the HCC cases are attributable to these factors in the presence or absence of cirrhosis, respectively. Tobacco smoking and HGV and TTV infection were not associated with HCC. A direct role of HCV infection in HCC development in the absence of cirrhosis has been suspected when HCV RNA was detected in cases without cirrhosis and with no other risk factors (5). We found a higher OR for HCV infection in the presence of cirrhosis (OR = 33.5) than in the absence of cirrhosis (OR = 19.7). This is in agreement with a prospective study among HCV-infected people showing a higher HCC incidence rate among subjects with cirrhosis than among those with chronic hepatitis (27). In our study, all of the HCC cases without cirrhosis with HCV infection had a histological picture of chronic hepatitis, suggesting that, in the absence of cirrhosis, HCV infection can cause HCC via a chronic inflammatory process. Accordingly, we found that all of the HCC

Definition of the grading and staging of chronic hepatitis is based on the components of the Histologic Activity Index according to Desmet *et al.* (17). Nonspecific reactive chronic hepatitis was defined according to Liaw *et al.* (18).

Liver disease	Total	HBsAg and/or HBV DNA positivity	HCV RNA positivity	Alcohol intake > 80 g/day	High liver iron stores
		Risk factor			
Chronic viral hepatitis	11	5[a]	7[a]	5	1
Grading					
Minimal chronic hepatitis	1		1	1	
Mild or moderate chronic hepatitis	10	5	6	4	1
Staging					
Mild fibrosis	5	3	2	3	
Severe fibrosis (bridging fibrosis)	6	2	5	2	
Alcoholic hepatitis	5			5	2
Nonspecific reactive hepatitis	3	2[b]		1	
Hemochromatosis	1				1
Normal tissue	1				

[a] One patient was HBsAg positive, HBV DNA negative, and HCV RNA positive; one patient was positive for both HBsAg and HBV DNA, two patients were HBsAg positive and HBV DNA negative; and one patient was HBsAg negative and HBV DNA positive.
[b] One patient was HBsAg positive and HBV DNA negative, and one patient was HBsAg negative and HBV DNA positive.

cases without cirrhosis with HBV infection had histological evidence of chronic hepatitis.

We found that a history of heavy alcohol intake was equally common among HCC cases with and without cirrhosis. This finding was unexpected because alcohol is thought to determine HCC because it is causally involved in the development of cirrhosis. However, 63% of the HCC cases without cirrhosis had a history of heavy alcohol intake in a French series (12), and liver fibrosis without cirrhosis was found in patients with HCC associated with pure alcoholic liver disease in a Japanese study (28). In our research, one of the five HCC cases with alcoholic hepatitis had a history of alcohol-related liver disease, whereas the remaining subjects had only a history of heavy alcohol intake without other known risk factors for the disease. Therefore, we cannot draw any firm conclusion regarding the issue of whether alcohol or rather another unknown agent can determine HCC development in subjects with heavy alcohol intake as the only known risk factor for liver disease.

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