Risk factors for hepatocellular carcinoma in Southern Iran

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ABSTRACT

Objective: Hepatocellular carcinoma (HCC) is one of the most common cancers in the world. Its etiology and incidence differ according to geographic area. In the present study, we sought to identify risk factors for HCC among a group of patients with HCC in Southern Iran.

Methods: During a 5-year period we retrospectively studied the characteristics of 71 HCC patients at Ahwaz Jundishapur University Hospital, Iran from February 1999 to August 2004. Blood samples and questionnaire data obtained from 71 (45 male and 26 female) incident cases of HCC, were pathologically diagnosed. Sera were tested for hepatitis B surface antigen and antibodies to hepatitis B core antigen, anti-hepatitis C virus and serum ferritin, iron and alfa fetoprotein (AFP), by enzyme immunoassays and cuper study.

Results: In 46.5% (33/71) of patients there was a history of chronic liver disease, and in 30 (42%) patients liver cirrhosis was documented. Of the 71 patients, 37 (52.1%) had hepatitis B, 6 (8.5%) had hepatitis C, and 2 (2.8%) had a history of excess alcohol intake. Of the 2 patients with a history of heavy alcohol intake, one had concomitant chronic viral hepatitis infection, and alcohol alone was the etiology of HCC in only one case (1.40%). No etiologic cause was identified in 23 cases (32.4%), there were 2 cases of diabetes mellitus. The value of AFP of >20 ng/ml was found in 29 cases(41%), varying from 24 ng/ml to 364 ng/ml (average 74.6 ng/ml).

Conclusions: In Southern Iran, the predominant etiology of HCC was hepatitis B, hepatitis C, but alcohol and metabolic diseases were only found in rare cases. Cryptogenic cases may be found in one fifth of patients hence, the contribution of virus infection, may have been underestimated in this area, which is based on serological testing only.

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Hepatocellular cancer (HCC) is the fifth most common cancer in the world, fifth among men and eighth among women.[1] Its etiology and incidence differ according to geographic area.[2,3] The identification of these differences suggest environmental agents to be significant as etiologic factors, of which hepatitis B and hepatitis C viruses (HCV) and aflatoxin exposure are the most relevant.[4] It is the epidemiological data that dictate preventive measures according to the impact of a particular etiologic agent. Estimates of the incidence of HCC cases in different geographical regions is best obtained through population-based cancer registries.[1-7] There are no cancer registries from Khuzestan in Southern Iran; therefore, no reliable figures on the epidemiological features of HCC in this area exist. Iran is a hepatitis B endemic country with a hepatitis B carrier rate of 3-5%.[8] The seropositivity rate for hepatitis C virus among blood donors is reported to be 0.5-1%.[8,9] Delta hepatitis is frequent in Khuzestan regions with a high HBV carrier rate.[10] It is to be expected that the etiology of

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HCC in Khuzestan will follow the epidemiology of hepatitis viruses in the country. When geographical proximity and hepatitis B carrier rates are taken into consideration, Khuzestan is likely to be in the group of intermediate-incidence areas for HCC according to age-adjusted incidence rates.[10] In the present study, we sought to identify risk factors for HCC among a group of patients with HCC referred to our gastroenterology clinics in Southern Iran.

Methods. During a 5-year period, we retrospectively studied the characteristics of 71 HCC patients at Ahwaz Jundishapur University Hospital (AJSUH), Iran from February 1999 to August 2004. Blood samples and questionnaire data obtained from 71 (45 male and 26 female) incident cases of HCC were reviewed. Cases diagnosis were based on histological or cytological characteristics, or on positive imaging studies (ultrasound, CT, and high alpha fetoprotein [AFP] levels). Information on gender, age at presentation, etiology of HCC, accompanying liver disease if present, and method of HCC diagnosis was collected. With regard to etiology of HCC, each patient was asked on the history of alcohol intake, drug history (with special emphasis on oral contraceptives and androgen steroids), and on whether the patient had one of the rather rare etiologies of chronic liver disease such as hemochromatosis, Wilson's disease, autoimmune liver disease, or primary biliary cirrhosis. Sera were tested for hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B core antigen (anti-HBc) anti-HCV and serum ferritin, AFP, by enzyme immunoassays and cuper study. Diagnosis of hepatitis B was based on positive HBsAg testing by enzyme immunoassay (EIA) (Abbott Laboratories) and that of hepatitis C on positive anti-HCV testing by second generation EIA assay (Abbott Laboratories). Diagnosis of alcoholic liver disease was based on a history of heavy alcohol intake according to classic criteria. Regarding to the accompanying liver disease, the questionnaire included questions on histology of nontumorous liver tissue, history of chronic enzyme elevations, physical examination findings (presence of hepatomegaly, splenomegaly, ascites, and so forth), Child-Pugh assessment, and presence of esophageal varices if endoscopy was performed.

Statistical analysis. This study is a descriptive case series study with its results depicted as frequency tables and distribution histogram. The unpaired Student's t test and x^2 tests that used where appropriate. A p=0.05 was considered significant.

Results. A total of 71 patients with HCC were analyzed. In 30 of these patients (42%), clinically or histologically diagnosed cirrhosis was present. In an additional 46.5% (33/71) of the patients there was a history of chronic liver disease. Of the 71 patients, 37 (52.1%) had hepatitis B, 6 (8.5%) had hepatitis C, and 2 (2.8%) had a history of excess alcohol intake. All 6 patients with HCV had liver cirrhosis and HCC. Of the 2 patients with a history of heavy alcohol intake, one had concomitant chronic viral hepatitis infection (HBV), and alcohol alone was the etiology of HCC in only one case (1.40%). No etiologic cause was identified in 23 cases (32.4%), diabetes mellitus was noted in 2 cases (2.81%). The value of AFP >20 ng/ml was found in 29 cases (41%) varying from 24 ng/ml - 364 ng/ml (average 74.60 ng/ml). There was no history of prolonged oral contraceptive or androgen steroid intake in any patient and history or physical or biochemical findings of Wilson's disease, autoimmune liver disease, primary biliary cirrhosis, and other etiologies of chronic liver disease. Anti-HDV was positive in 21 of the 37 patients with hepatitis B (56%). Child-Pugh classification was as follows: Child A: 4 patients; Child B: 4 patients; Child C: 22 patients. Median age at presentation in HCC cases in our series was 54 years (range 30-69). A progressive increase in the numbers of HCC was observed as age increased, with a significantly higher incidence beyond 50 years of age (55 cases of 71 [77.4%]). The main clinical features are summarized in **Table 1**.

Discussion. This study shows that hepatitis B infection is the number one etiologic factor in the development of HCC in Khuzestan. Hepatitis B was responsible for HCC in 37 cases (52.1%), anti-delta testing was positive in 21 of the 37 patients with hepatitis B (56%) while hepatitis B alone was responsible in 16 (44%) cases. Hepatitis C was the etiology of HCC in 8.5% of cases (n=6). This etiologic pattern is close to the etiology of HCC in Turkey[11] and Greece[12] but is strikingly different from that of European Mediterranean countries, where hepatitis C is the main cause of HCC.[13-14] Furthermore, our study also shows that anti-delta positivity was more frequent among HCC cases in

Table 1 - Main clinical features observed in studied patients.

Signs and symptoms	n	(%)
Abdominal pain	65	(91.5)
Weight loss	56	(78.9)
Jaundice	15	(21.1)
Hepatomegaly	25	(35.2)
Ascites	28	(39.4)

these regions which is similar to delta-positive HCC cases in various regions; however, it is too small to warrant further discussion.

The importance of hepatitis C for HCC development is likely to increase in Khuzestan according to the contribution of hepatitis B and hepatitis C in chronic hepatitis in the recent years which may be due to increased high risk behaviors. The contribution of hepatitis B to chronic hepatitis may also have dropped in recent years due to vaccination and immunization programs. In our study, all 6 patients with HCV had liver cirrhosis and hepatocellular carcinoma, but no genotype study was carried out. In Iran, most of patients with HCV had genotype 1a.[15] Patients with hepatitis B and HCC were younger than patients with hepatitis C and HCC, supporting previous observations.[16,17] As expected, most patients with HCC were male. Male preponderance was more evident in patients with hepatitis B and HCC when compared to other patients with hepatitis. An expected finding in this study was the impact of alcohol drinking in the development of HCC in our region which is less common than other causes. Two cases (4.6%) had a history of excess alcohol intake which is due to Islamic educations. In 23 (32.4%) cases of HCC, no etiologic factor could be identified. Hemochromatosis is very rare in Khuzestan. Cholestatic liver disease and Wilson's disease are rarely associated with HCC. Although the association of autoimmune liver disease and HCC may be higher than previously thought,[18] in a series of 823 patients, autoimmune liver disease was found to be responsible for chronic liver disease in approximately 1.5% of Turkish patients with chronic hepatitis.[19] In our study, autoimmune liver disease was not found in any case. An important factor for cryptogenic cases may be one of the major drawback of this study, namely, that only conventional serological methodology were used. Some of those cases could have been found to be actually secondary to hepatitis B infection if polymerase chain reaction methodology had been used for HBV DNA detection in serum or liver tissue.[20] The HBV DNA may also be detected in HCC cases without any hepatitis B virus markers.[21] Similarly, hepatitis C diagnosis based only on serology may underestimate the contribution of this infection to HCC. In anti-HCV-negative patients, HCV RNA was detected in serum (7%) and liver tissue 7(25%) on patients with HCC.[22]

In conclusion, this study indicates that hepatitis B virus infection is the leading cause of HCC in Khuzestan in Southern Iran, followed by hepatitis C infection. However, alcohol and metabolic diseases were only found in rare cases. Cryptogenic cases may be found in one third of patients; hence, the contribution of virus infection, may have been underestimated in this area, which is based on serological testing only.

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