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RAPID COMMUNICATION

Differences in characteristics of patients with and without known risk factors for hepatocellular carcinoma in the United States

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Abstract

AIM: To examine the clinical characteristics of a subgroup of patients with hepatocellular carcinoma (HCC) and compare them to those with known risk factors.

METHODS: We used the HCC database of 306 patients seen at our institution from January 1, 1995 to December 31, 2001. Of the 306 patients, 63 (20%, group 1) had no known risk factors (hepatitis C virus, hepatitis B virus, alcohol, hemochromatosis or cirrhosis from any cause) and 243 (group 2) had one or more risk factors.

RESULTS: The median age was similar in both groups, but there were disproportionate numbers of younger (< 30 years old), older (> 80 years) patients, women (33% *vs* 18%), and Caucasians (81% *vs* 52%) in group 1 as compared to group 2. There were fewer Asians (2% *vs* 11%) and African Americans (13% *vs* 27%) in group 1. Abdominal pain (70% *vs* 37%) was more common while gastrointestinal bleeding (0% *vs* 11%) and ascites (4% *vs* 17%) were less common in group 1 compared to group 2. Group 1 had larger tumor burden (median size 9.4 cm *vs* 5.7 cm) at the time of presentation, but there were no differences in the site (right, left or bilateral lesions), or number of tumors between the two groups.

CONCLUSION: HCC patients without identifiable risk factors have different characteristics and clinical presentation compared to those with known risk factors. Absence of cirrhosis and larger tumor burden may explain the differences in the presenting symptoms.

Key words: Hepatocellular carcinoma; Patient characteristics; Risk factors

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a common cancer in the world with more than 500 000 new cases reported per year[1,2]. The disease is unevenly distributed worldwide with a higher incidence in South-East Asia and Sub-Saharan Africa than in other regions of the world[1,2]. Although it is less common in the United States and Western Europe, there are data to suggest that the incidence may be increasing secondary to hepatitis C virus (HCV)[1-5]. The common risk factors that predispose to HCC include hepatitis B virus (HBV), hepatitis C virus (HCV), aflatoxin, and cirrhosis in general[6-9]. In addition, hemochromatosis, alcoholism, and non-alcoholic fatty liver disease (NAFLD cirrhosis) increase the risk of developing HCC[10]. In the United States, alcoholism and hepatitis C are the leading predisposing causes of HCC[11]. However, a significant proportion of patients develop HCC despite the absence of any known risk factors including cirrhosis. There is only limited information on the differences in the characteristics and outcomes of patients with or without risk factors who develop liver cancer in the USA.

The purpose of this study was to define the clinical characteristics and presentation of patients without identifiable risk factors and compare them to those with known risk factors.

MATERIALS AND METHODS

For the purpose of this study, we studied patients who

Table 1 Patient characteristics *n* (%)

Category	Group 1 (*n* = 63)	Group 2 (*n* = 243)	*P*
Sex			
Male	42 (67)	198 (82)	< 0.05
Female	21 (33)	45 (18)	
Age (yr)			
Median (range)	66 (18–87)	61 (23–87)	
< 30	5 (8)	3 (1)	< 0.01
30-39.9	3 (5)	10 (4)	
40-49.9	6 (10)	35 (14)	
50-59.9	9 (14)	65 (27)	
60-69.9	10 (16)	76 (31)	
70-79.9	17 (27)	44 (18)	
> 80	8 (13)	7 (3)	
Unknown	5 (8)	3 (1)	
Race			
Asian	1 (2)	27 (11)	< 0.05
African American	8 (31)	66 (27)	
Caucasian	51 (81)	125 (51)	
Hispanic	1 (2)	8 (3)	
Other	1 (1)	12 (5)	
Unknown	1 (1)	5 (2)	
Country			
US born	58 (92)	201 (83)	
Immigrant	2 (3)	28 (11)	
Foreign visitor	3 (5)	14 (6)	

Table 2 Symptoms and signs at presentation *n* (%)

	Group 1 (*n* = 46)	Group 2 (*n* = 217)	*P*
Symptoms			
Abdominal pain	32 (70)	81 (37)	< 0.001
Fatigue	7 (15)	39 (18)	
Anorexia	7 (15)	22 (10)	
Nausea and vomiting	7 (15)	23 (11)	
Change in bowel habits	3 (7)	15 (7)	
Gastrointestinal bleed	0 (0)	24 (11)	< 0.05
None	8 (17)	85 (39)	< 0.01
Signs			
Weight loss	12 (26)	38 (18)	
Abdominal mass	4 (9)	14 (7)	
Jaundice	3 (7)	26 (12)	
Fever	3 (7)	14 (7)	
Ascites	2 (4)	37 (17)	< 0.05
Encephalopathy	1 (2)	19 (9)	
None	25 (54)	113 (52)	

presented to the Johns Hopkins Hospital with HCC from January 1, 1995 to December 31, 2001. A retrospective database was created with the approval of the Institutional Review Board. Patients with HCC were identified for inclusion in the database by searching the medical records using an ICD-9 code for liver cancer (155.0) and the Database of Pathology Departments using the term "hepatocellular carcinoma". The information was collected on all patients using the hospital's electronic patient record.

To be included in the study, a patient was 18 years or older, visited Johns Hopkins Hospital during the designated period, and had a confirmatory diagnosis of HCC. HCC was diagnosed based on histological confirmation or an elevated alpha fetoprotein (AFP) > 400 IU/mL with a liver image showing characteristic features of HCC. In the absence of elevated AFP or histological confirmation, characteristic liver image along with a clinical history compatible with HCC was necessary[12]. A compatible clinical history included known cirrhosis, HBV or HCV infection, hemochromatosis or history of alcoholism.

The risk factors for HCC were defined as HBV, HCV, cirrhosis from any cause (based on imaging and/or liver histology), aflatoxin, alcoholism, hemochromatosis, pre-malignant liver tumors and rare metabolic syndromes that are known to predispose to HCC. Patients without any known identifiable risk factors were included in group 1 and compared to those patients with one or more risk factors (group 2).

Statistical analysis was performed with SPSS version 10.0. Statistical tests included chi-square and Student-*t* tests. $P < 0.05$ was considered statistically significant.

RESULTS

Three hundred and six patients were seen with HCC at our institution from January 1, 1995 to December 31, 2001. Of the 306 patients, 63 (20%, group 1) had no known risk factors (HCV, HBV, alcohol, hemochromatosis or cirrhosis from any cause) and 243 (group 2) had one or more risk factors.

Of the 243 patients (group 2) with a known risk factor for HCC, hepatitis B was documented in 49 (20%), hepatitis C was present in 110 (45%) and 115 (47%) acknowledged moderate or abusive alcohol use. Rare disorders such as Wilson's disease, porphyria cutaneous tarda, autoimmune hepatitis, schistosomiasis, and sclerosing cholangitis were noted in one patient each. Cirrhosis was documented by histology in 164 (67%).

Demographic data of both groups are shown in Table 1. There was a male predominance in both groups but there was a higher proportion of females in group 1 (2:1 *vs* 9:2) compared to group 2. The median age was greater in group 1 with a disproportionate distribution of patients at the extremes of age.

Presenting signs and symptoms are shown in Table 2, with complete data available in 263 of the 306 patients. The most common presenting symptom in each group was abdominal pain, but it was more common in group 1. Other statistically significant differences noted were the frequency of gastrointestinal bleeding and the presence of ascites. Weight loss was comparable in both groups. As expected , HCC was not diagnosed during routine screening or surveillance in any patient of group 1 but in 46 (21%) of group 2 ($P < 0.001$).

Diagnostic imaging data revealed differences between groups 1 and 2 (Table 3). We excluded studies that were not done at our institution since films were not available for confirmation. Imaging studies showed a larger tumor diameter (median 9.3 cm, range 4-25 cm *vs* 5.7 cm, range 0.7-20 cm) in group 1 than 2. Approximately half of the patients (52% and 48%) in both groups had a solitary tumor, and the majority of tumors were located in the right liver (67% and 60%). A higher proportion of patients in group 2 had bilateral tumors (7% *vs* 24%, P = NS). Portal vein involvement was similar in both groups.

Histological examination demonstrated fibrolamellar

Table 3 Tumor imaging characteristics

	Group 1	Group 2
Size	*n* = 24	*n* = 159
Median (cm)	9.3	5.7
Minimum (cm)	4	0.7
Maximum (cm)	25	20
	n (%)	*n* (%)
< 2 (cm)	0 (0)	15 (9)
2.01-5.0	2 (8)	59 (37)
5.01-10.0	13(54)	68 (43)
> 10.0	9 (38)	7 (11)
Focality	*n* = 25	*n* = 149
Unifocal	13 (52)	72 (48)
Multifocal	12 (48)	77 (52)
Hemiliver	*n* = 30	*n* = 162
Right	20 (67)	97 (60)
Left	5 (17)	27 (17)
Bilateral	5 (7)	38 (24)

Please note that size could not be determined in 6 patients in group 1 and 3 in group 2. Similarly 'focality' could not be determined in 5 patients in group 1 and 13 in group 2.

variant HCC in 6/63 patients of group 1 and 0/243 patients of group 2.

DISCUSSION

In this study, we described the characteristics of patients who presented to a tertiary care center in the United States without known risk factors for HCC and compared them to those with one or more identifiable risk factors. The patients in group 1 without identifiable risk factors had a relatively higher proportion of women and Caucasians. The age distribution of this group was asymmetrical, with a disproportionate number of patients less than 30 years old and older than 80 years. The increased frequency of younger HCC patients in this group could be explained by the fibrolamellar variant of HCC that is known to affect younger patients without risk factors. This tumor was exclusively seen in group 1, 4 out of the 6 patients less than 30 years old had fibrolamellar variant. While fibrolamellar variant could explain the disproportionate number of younger patients in group 1, another explanation must be found for the increased number of patients over the age of 80 years in this group. It is certainly possible that these patients may have had occult viral hepatitis or alcohol use, and examination of liver tissue or peripheral blood monocytes may have detected occult HBV and HCV infections in some of them. The retrospective nature of this study also did not permit us to determine whether these patients had adequate tests to rule out viral hepatitis. Another demographic difference between the two groups of patients was the ratio of males to females. Group 1 had a relatively higher proportion of female patients, and it is possible that some of these patients may have progressed from adenoma.

The clinical presentation was also different in both groups. Group 2 was more likely to present without any symptoms (40% *vs* 17%) and this could be partly explained by the fact that many of these patients (19%) were diagnosed with HCC during surveillance or screening. Abdominal pain was the most common symptom in both groups, but it was more common in group 1 and this could be explained by the larger tumor burden. Despite the smaller (40% smaller) tumor size in group 2, portal vein involvement and metastases were similar in both groups, suggesting that there may be differences in tumor biology.

Our study suggested that there were differences in patient characteristics, symptoms, and tumor size in patients who presented with and without known risk factors for HCC. Absence of cirrhosis and tumor size may explain the differences in symptoms, and there is a suggestion that tumor biology may be different in these groups. The higher proportions of women and older patients without risk factors remain poorly explained. It is important to note that our study had all the inherent weaknesses of a retrospective study. It is more than likely that a more detailed diagnostic work-up may have revealed more risk factors in both groups. In addition, we could not independently confirm the laboratory test results in many patients. The prospective and complete collection of data on risk factors and tumor characteristics of patients diagnosed with HCC will further distinguish the differences between patients who present with and without risk factors.

Most patients with HCC have known risk factors such as HCV, HBV, or cirrhosis. Genetic changes that lead to HCC are complex and poorly understood, and most studies have focused on the genetic changes in the 'high risk' population[13,14]. Genetic changes that lead to HCC take place over 30-50 years, and this may partly explain the difficulty to define the sequential molecular changes that lead to HCC. There is increasing circumstantial evidence that the development of HCC, like most other cancers, is a multi-step process including inactivation or loss of tumor suppressor genes, activation or over expression of multiple oncogenes and heterozygosity of multiple chromosomes[13-18]. There is experimental evidence that p53, Rb1 and Wnt pathways are important molecular pathways involved in the development of HCC. The early genetic changes may vary depending on the etiology of liver disease and geographic location. Even in the same patient, there may be considerable genetic heterogeneity among different tumor nodules, suggesting that we may not find a common unifying pathway in the pathogenesis of HCC. However, accumulating evidence indicates that hepatocytes with multiple genetic changes may expand in a clonal fashion leading to dysplastic nodules and liver cancer. The molecular mechanisms of liver cancer in patients without known risk factors are difficult to explain. It is possible that many of these patients have been exposed to known or unknown carcinogens. Prospective studies should be designed to identify hitherto unidentified factors including the role of obesity or non-alcoholic fatty liver disease, occult HBV or HCV infections and genetic predisposition.

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