

Hepatocellular Carcinoma in Cameroon: Epidemiology and Risk Factors

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Abstract

Background: Chronic hepatitis B and hepatitis C infections are major risk factors of Hepatocellular carcinoma (HCC), principally in Sub-Saharan Africa and Pacific Asia. In Cameroon, little is known about the role the various risk factors play in the pathogenesis of HCC. The aim of this study was to determine the contribution of the various risk factors to the pathogenesis of HCC and to analyze the related epidemiologic characteristics.

Methods: It was a prospective study from March 2012 to January 2013 of histologically proven HCC seen in 02 University Teaching Centers in Yaounde. Risk factors, demographic characteristics and the presence of cirrhosis were analyzed.

Results: We identified 79 cases of HCC. Eight of them (10.1%) were excluded given the fact that they were HIV-infected. Seventy one (89.9%) patients with histologically-proven HCC were included. The proportion with hepatitis B surface antigen (HBsAg) was 48%, that with anti-HCV was 36.6% and that with co-infection HBV/HCV was 5.6%. Alcohol abuse was found in 7% of patients and in 2.8% of patients, no evidence of either viral infection or alcohol abuse was found. Hepatitis B surface antigen patients were younger (mean age +/-SD, 38.5+/-12.3 years vs. 61.5+/-10.2 years, $p < 0.05$) than anti-HCV positive patients. A total of 44 (62%) patients had histologically proven cirrhosis, particularly those co-infected HBV/HCV (75%) and those anti-HCV positive (69.2%), rarely those hepatitis B surface antigen positive.

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Conclusion: Though the leading cause, HBV is closely followed by HCV in the development of HCC. Approximately 90% of cases of HCC in our environment are related to chronic HBV and HCV infection. The roles played by other risk factors are not as common.

Keywords: Viral hepatitis, hepatocellular carcinoma, cirrhosis, developing countries, Cameroon.

1 Introduction

Chronic hepatitis B and C viral infections, at the stage of cirrhosis, are responsible for the great majority of cases of hepatocellular carcinoma (HCC) worldwide [1-5]. Due to varying etiological factors, the incidence of HCC varies from one geographic region to another. In Pacific Asia and Sub-Saharan Africa, which are high risk regions, HBV is hyper endemic and appears to be the major cause of HCC. In Southern Europe and Japan, which are intermediate risk regions, HCV infection is the principal cause [2]. With the introduction of HBV vaccine since 2005 in the expanded immunization program, it is logical to believe that HCV infection will either equal or override HBV infection as major risk factor of HCC in Cameroon, as is the case in many other countries where HBV vaccine is effective [4,6]. Also, the lack of measures to secure blood transfusion before the 1980s, coupled to traditional rituals played a vital role in the initial viral transmission. However, the contribution of HCV in the occurrence of liver diseases in our country has not been established. Equally, it is not known whether alcohol abuse (>80g/day) is an enough risk factor of HCC in our environment.

The aim of our study was to determine the respective contribution of the various risk factors in the pathogenesis of HCC both in the presence and absence of cirrhosis.

2 Patients and Methods

Histologically proven cases of HCC were sampled both at the University Hospital Center, Yaounde and the Yaounde General Hospital, Cameroon between March 2012 and January 2013. Demographic data (age, gender), alcohol abuse (>80g/day), the presence or absence of cirrhosis were entered by a resident in internal medicine into a data entry form. Hepatitis B surface antigen (HBsAg) was tested using a 3rd generation ELISA test using the commercial kit DIA-HBV[®], DiaProph.Med, Ukraine, Russia. The test was considered positive when the optical density of the test-sample was greater than the threshold. It was considered negative when the optical density of the test-sample was lower than the threshold. Anti-HCV testing was done using a 3rd generation test using the commercial kit Fortress[®] diagnostics, Northern Ireland, United Kingdom. The diagnosis of HCC was established based on radiologic (ultrasonography and computed tomography) and histopathologic criteria. Cirrhosis was diagnosed based on radiologic criteria, carried out by a single radiologist and confirmed by histology. Exclusion criteria were HIV infection and patients with doubtful HCC and cirrhosis.

Data was analyzed using the French version of Epi info 6.04 and Excel 2007. For quantitative variables, means, standard deviations and medians were calculated. For qualitative variables, proportions were calculated with their confidence intervals (CI). To examine the relationship between two discrete variables, we used Pearson's χ^2 test. Yates correction and Fischer's exact test were used for small sample sizes, with a p value set at 0.05. Kruskal Wallis test was used to compare the average ages of cirrhotic and non cirrhotic patients.

3 Results

Of the 79 cases of HCC identified, 08 (10.1%) were excluded given their co-infection with HIV. Seventy one (89.9%) met our inclusion criteria. The mean age was 50.01 ± 16.71 years (extremes 18 and 84 years), 53 (74.6%) patients were men (M/W ratio: 2.9). HBsAg was positive in 34 (48%) patients, anti-HCV was positive in 26 (36.6%) patients, while co-infection was found in 04 (5.6%) patients. Alcohol abuse was found in 05 (7.0%) patients and 02 (2.8%) patients were neither HCV/HBV infected nor consumed alcohol. Table 1.

Table 1: Risk factors of hepatocellular carcinoma in Cameroonian patients

Etiological factors	No. of cases	Percentage (%)	95%CI*
HBV	34	48	39-59
HCV	26	36.6	25.4-47.8
Co-infection HBV/HCV	04	5.6	0.6-10.6
Alcohol	05	7.0	2-12
Others	02	2.8	0-5.6
Total	71	100	-

*95% Confidence Interval, No: number of cases

HCC specific prevalence was established with respect of age, gender and cirrhosis. Table 2 shows two types of age-specific HCC prevalence, at 30-39 years (25.4%) and in those aged 60 years and above (32.4%). Cirrhosis was present in 44 (62.0%) patients against 27 (38.0%) who were cirrhosis-free ($p < 10^{-5}$).

Table 2: Prevalence of hepatocellular carcinoma according to age, gender and cirrhosis in 71 Cameroonian patients

Variables	Number of cases	Percentage (%)	95% Confidence Interval
Age (years)			
<30	6	8.5	3.5-17.5
30-39	18	25.4	15.8-37.1
40-49	10	14.1	7.0-24.4
50-59	14	19.7	11.2-30.9
≥ 60	23	32.4	21.8-44.5
Gender			
male	53	74.6	62.9-84.2
female	18	25.4	18.8-37.1
Cirrhosis			
yes	44	62.0	49.7-73.2
no	27	38.0	26.8-50.3

On comparing patients according to various causes of HCC as depicted by Table 3, patients with HBV-related HCC were younger than HCC due to other causes (mean age 38.5years,

$p=0.008$), men were more affected than women, but for cases of HCV-HBV co-infection where women were thrice more affected than men. Cirrhosis was significantly frequent in case of HCV-HBV co-infection (75%), anti-HCV positive patients (69.2%), and alcohol abuse (60%). On the contrary, the presence of cirrhosis was not significant in case of hepatitis B surface antigen positive patients (55.2% vs. 43.2% cirrhosis-free, $p=0.31$).

Table 3: Risk factors of hepatocellular carcinoma in 71 cameroonian patients with respect to age, gender and cirrhosis

Variables	HBV	HCV	Co-infection HBV/HCV	Alcohol	Others
Mean age (years)	38.5	61.5	62.3	52.8	65.5
Gender n (%)					
male	27(79.4)	18(69.2)	1(25)	5(100)	2(100)
female	7(20.6)	8(30.8)	3(75)	0	0
Male to female ratio	3.9:1	2.3:1	1:3	-	-
Cirrhosis n (%)					
yes	19(55.6)	18(69.2)	3(75)	3(60)	1(50)
no	15(43.2)	8(30.8)	1(25)	2(40)	1(50)

4 Discussion

Approximately 75% to 80% of cases of HCC in the world are related to chronic HBV and HCV infection [5, 7, and 8]. With the introduction of HBV vaccine in the expanded immunization since 2005, the respective contributions of both viral infections will be altered in the years to come. However, poor hygiene and sanitary measures before the 1980s have greatly influenced current trends. Our results show that 90.2% of HCC in our country are related to chronic HBV and HCV infection, followed by alcohol abuse (7.0%). In 2.8% of them, no evidence of either viral infection or alcohol abuse was found. Men are thrice more affected than women, but for cases of co-infection where the trend is inverted. Cirrhosis is principally found associated with co-infection HBV and HCV (75%), HCV alone (69.2%), and alcohol abuse (60%). On the contrary, it was not always found at the moment of the diagnosis of HCC when associated to HBV (55.6%).

The variable geographic distribution of the various risk factors of HCC is known. In Pacific Asia and Sub-Saharan Africa, where HBV is hyper endemic, HBV accounts for close to 70% to 80% of HCC amongst adults and close to 100% amongst children, while HCV accounts for close to 24% of HCC in adults [6, 9, and 10]. These trends were not verified in our study. Though the leading cause, HBV (48%) was closely followed by HCV (36.6%). This result can be accounted for by the fact that before the 1980s preventive measures of HCV transmission namely parenteral exposition (through blood and blood products) were lacking, and also traditional rituals (scarifications, tattooing and piercing). The role of co-infection is divergent in two studies [11, 12]. Co-infection was more frequent in aged women with a past history of parenteral exposition. Despite a known synergistic role with HCV [13], the role of alcohol abuse is minute compared to that of viral infections, as reported by Zidan et al in Iran [4]. Alcohol abuse is rare in our

setting, especially among women. Non infectious and non alcohol induced HCC were fewer than that reported in western countries [3].

Men are preferentially more concerned with the development of HCC, with a men-women ratio of 3:1 in literature [2, 3, and 10], a value close to that found in our study (2, 9:1). Due to reasons still unknown to us and other authors [7, 10], the proportion of men affected by HBV-related HCC is greater than that of HCV-related HCC. The ratio men-women was greater in HBV-related HCC than HCV-related HCC (3.9:1 and 2.3:1 respectively), except in situations of co-infection, where the ratio was inverted (1:3) in favor of women. The three cases of women with co-infection had a parenteral exposition. In a study in Japan, there was a female predominance among aged patients [10].

The mean age of Cameroonian patients with HCC is slow (50.01 years), compared to findings in most studies where the incidence gradually increases with age after 40 years (mean age 65 years) [3, 10]. This is accounted for by both the vertical transmission and early horizontal contamination of HBV in our setting. Patients are generally younger in Pacific Asia and Sub-Saharan Africa [14, 15]. Also, patients with HBV were 20 years younger than those infected with HCV or co-infected. The two types of age-specific HCC prevalence at 30-39 years and at 60 years and above coincide with the predominance of both infections, HBV in patients less than 40 years (mean age 38.5 years) and HCV in those aged 60 years and above (mean age 61.5 years). Both vertical transmission and early horizontal contamination of HBV, coupled to parenteral exposition in the 1980s for HCV explain our findings. Cirrhosis, irrespective of its cause was found in 62% of patients with HCC in our study. This finding is different from that reported in western studies where 90% of HCC are associated with cirrhosis [2, 7, 16, and 17]. Cirrhosis could be vital for the expression of the oncogenic properties of certain risk factors like HCV and alcohol. Our results could be explained by the fact that HBV has a direct oncogenic effect, not needing the presence of cirrhosis on one hand, and by the low life span of patients with cirrhosis as a result of inadequate management in our environment on the other hand. Moreover, among all the major causes of HCC, HBV infection is the least associated with cirrhosis. The timing of the initial viral infection could influence the pathogenesis of HCC in cirrhosis-free subjects.

5 Conclusion

HCC is associated to both chronic HBV and HCV infections in Cameroon. Alcohol abuse and viral co-infection are not so common. Cirrhosis is not always found at the moment of diagnosis of HCC when associated with HBV. With the introduction into the expanded immunization program of the vaccine against HBV, chronic HCV infection will turn out to be the main risk factors for the occurrence of HCC in the years to come, highlighting the need to prevent the initial HCV infection and controlling all infections with antiviral therapy.

References

- [1] Sinclair M, Roberts S, Kemp W, Knight V, Dev A, Gow P, Philpott H, Kronborg I, Arachchi N, Bell S, Lim L, Gorelik A, Nicoll A; Melbourne collaboration for the study of Hepatocellular carcinoma. Epidemiology of Hepatitis B-associated Hepatocellular Carcinoma in Victoria. *Intern Med J.* 2012 Dec 24. doi: 10.1111/imj.12068.
- [2] Michielsen P, Ho E. Viral hepatitis B and hepatocellular carcinoma. *Acta Gastroenterol Belg.* 2011 Mar; **74**(1):4-8.
- [3] El-Serag HB. Epidemiology of hepatocellular carcinoma in USA. *Hepatol Res.* 2007 Sep; **37** Suppl 2:S88-94.
- [4] Zidan A, Scheuerlein H, Schüle S, Settmacher U, Rauchfuss F. Epidemiological pattern of hepatitis B and hepatitis C as etiological agents for hepatocellular carcinoma in Iran and worldwide. *Heat Mon.* 2012 Oct; **12**(10 HCC):e6894. doi: 10.5812/hepatmon.6894.
- [5] Lok AS. Does antiviral therapy for hepatitis B and C prevent hepatocellular carcinoma? *J Gastroenterol Hepatol.* 2011 Feb; **26**(2):221-7. Doi: 10.1111/j.1440-1746.2010.06576.x.
- [6] Chang MH. Cancer prevention by vaccination against hepatitis B. *Recent Results Cancer Res.* 2009; **181**:85-94.
- [7] David Yiu-Kuen But, Ching-Lung Lai, and Man-Fung Yuen Natural history of hepatitis-related hepatocellular carcinoma *World J Gastroenterol.* 2008 March 21; **14**(11): 1652–1656. Doi: 10.3748/wjg.14.1652.
- [8] McGlynn KA, London WT. Epidemiology and natural history of hepatocellular carcinoma. *Best Pract Res Clin Gastroenterol.* 2005; **19**:3–23.
- [9] Wild CP, Hall AJ. Primary prevention of hepatocellular carcinoma in developing countries. *Mutat Res.* 2000 Apr; **462**(2-3):381-93.
- [10] Yuen MF, Hou JL, Chutaputti A; Asia Pacific Working Party on Prevention of Hepatocellular Carcinoma. Hepatocellular carcinoma in the Asia pacific region. *J Gastroenterol Hepatol.* 2009 Mar; **24**(3):346-53. doi: 10.1111/j.1440-1746.2009.05784.x.
- [11] Shi J, Zhu L, Liu S, Xie WF. A meta-analysis of case-control studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma in China. *Br J Cancer.* 2005 Feb 14; **92**(3):607-12.
- [12] Cho LY, Yang JJ, Ko KP, Park B, Shin A, Lim MK, Oh JK, Park S, Kim YJ, Shin HR, Yoo KY, Park SK. Coinfection of hepatitis B and C viruses and risk of hepatocellular carcinoma: systematic review and meta-analysis. *Int J Cancer.* 2011 Jan 1; **128**(1):176-84. Doi: 10.1002/ijc.25321.
- [13] Kumar M, Kumar R, Hissar SS, Saraswat MK, Sharma BC, Sakhuja P, Sarin SK. Risk factors analysis for hepatocellular carcinoma in patients with and without cirrhosis: a case-control study of 213 hepatocellular carcinoma patients from India. *J Gastroenterol Hepatol.* 2007 Jul; **22**(7):1104-11.
- [14] Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology.* 2004 Nov; **127**(5 Suppl 1):S35-50.
- [15] Wan DW, Tzimas D, Smith JA, Kim S, Araujo J, David R, Lobach I, Sarpel U. Risk factors for early-onset and late-onset hepatocellular carcinoma in Asian immigrants with hepatitis B in the United States. *Am J Gastroenterol.* 2011 Nov; **106**(11):1994-2000. Doi: 10.1038/ajg.2011.302.

- [16] Stroffolini T. Etiological factor of hepatocellular carcinoma in Italy. *Minerva Gastroenterol Dietol.* 2005 Mar; **51**(1):1-5.
- [17] Lodato F, Mazzella G, Festi D, Azzaroli F, Colecchia A, Roda E. Hepatocellular carcinoma prevention: a worldwide emergence between the opulence of developed countries and the economic constraints of developing nations. *World J Gastroenterol.* 2006 Dec 7; **12**(45):7239-49.