RESEARCH ARTICLE

Why is Hepatocellular Carcinoma Less Attributable to Viral Hepatitis in Yemen?

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Abstract

The hepatitis B virus (HBV) and the hepatitis C virus (HCV) are still public health problems in Yemen, with older individuals having much higher prevalence than younger generations. However, research on the prevalence of viral hepatitis in association with hepatocellular cancer (HCC) has not yet been undertaken in Yemen. The aim of this study was to determine the prevalence of HBV and HCV infection among HCC patients and to estimate the risk of these infections being associated with the development of HCC. A cross-sectional study was conducted on patients attending oncology outpatient in Sana'a, Yemen, through the period 2008-mid 2010 with confirmed diagnosis of HCC. A total of 88 cases were studied thoroughly with different investigations such as CT-scan, ultrasound, tumour marker, alpha-feto-protein and histopathological biopsy. A structured questionnaire was also applied and physical examination done to assess the general condition of the patients. Statistical package (SPSS version 16) was used for analysis of the data. The mean age of the cases was 61.2 years (±12.6) with half over 60 years. There were fewer male patients (36%) compared to females and most (97%) only had basic /no formal education. Seventy nine (89%) were diagnosed as HCC cases with histopathological biopsy while the rest were diagnosed by ultrasound, CT scan, tumour marker, and alpha-feto-protein. Around one-third of the subjects were positive for HBsAg and HCV antibodies. Multivariate analysis showed infection with HCV and use of smoking was associated with HCC diagnosis. Although an association was observed between the occurrence of HCC and viral hepatitis (either HBV or HCV) and cigarette smoking, but the rate of viral infection was lower than what has been reported elsewhere.

Keywords: Hepatocellular carcinoma - hepatitis B virus - hepatitis C virus - Yemen.

Asian Pacific J Cancer Prev, **13**, 3663-3667

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver neoplasm and the fourth most frequently diagnosed cancer worldwide following lung, breast and bowel cancers with an increasing incidence, causing one million deaths per year (Cohen et al., 2011). In addition, it has very low annual survival rates (3 to 5%), and is considered to be the third most deadly cancer (Caron et al., 2008; WHO, 2008). According to Aden Cancer Registry report (2002-2006), HCC is the sixth commonest cancer in Yemen (Ba Saleem et al., 2010). However, GLOBOCAN estimation of 2008 ranks HCC as the most common cancer in Yemen for all newly diagnosed men with an incidence and mortality of 11.8% and 13.9%, respectively. The corresponding figures for females are 6.5% and 8.4% respectively making HCC as the fourth most common cancer in females in Yemen (IARC/WHO, 2008).

Epidemiological studies indicate that chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) are likely to be the most important oncogenetic agents for HCC development (Parkin, 2006; Oscar et al., 2007; De Mitri, 2008; Lehman, 2009). Over 80% of HCC worldwide is attributable to the combined effects of chronic hepatitis B and C infections (Amin et al., 2006). Chronic HBV infection, as detected by the presence of HBsAg, causes about 52% of the world's HCC, resulting in nearly 340,000 deaths per year; while 20% (124,000 deaths) in HCC patients are caused by HCV infection (Perz et al., 2006). Higher rates (around 60%) of chronic HCV infection leading to HCC were reported from Japan, Europe, and America, with 20% of HCC patients being attributed to chronic HBV infection (Befrits et al., 1995; Bosch et al., 2004). Similarly, co-infection with HCV and HBV has been found to increase the risk of HCC (Donato et al., 1998). Other risk factors like cigarette smoking, occupational exposure to chemicals such as pesticides, and schistosomiasis, may have a significant role in the aetiology or progression of HCC (Anwar et al., 2008; Di Bisceglie, 2009).

HBV and HCV infections are still a public health problem in Yemen, with older individuals having much

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higher prevalence than younger generations (Bawazir et al., 2010). However, the role of viral hepatitis in HCC has not yet been studied in Yemen. In addition, there are within country variations due to the variation in HBV and HCV infections as important risk factor for the development of HCC (Sallam et al., 2003). Therefore, we sought to study the association of viral hepatitis B and hepatitis C with HCC.

Materials and Methods

Participants

The cases diagnosed with HCC at the oncology outpatient in Sana'a, Yemen throughout the period 2008-mid 2010 were consecutively enrolled in the study. All participants were provided with standardised information about the study. Written informed consent was obtained from all enrolled participants. The study protocol was approved by the Research Ethics Committee of the Ministry of Public Health and Population in Yemen. Currently no local study is available on the rates of HBV or HCV in association with HCC, so prevalence rates of HBV and HCV were obtained from studies undertaken elsewhere in the region. Based on the parameters obtained from these studies the sample size was estimated to be 86 HCC cases. However, to account for non-response and/or refusal to participate and to increase the power of study, we included 88 cases giving us confidence intervals of 95% with a precision of ±10%.

Demographic and Clinical information

Demographic and clinical parameters were recorded for each participant such as: age, gender, education level, employment status, smoking and drinking habits.

Laboratory Investigations

All the relevant investigations were undertaken that included complete blood count (using automated blood counter); serum chemistry including urea, creatinine, albumin, AST, ALT, alkaline phosphatase and bilirubin.

HBV and HCV Status

5 ml blood sample was obtained from each participant. Serum samples were tested by ELISA for HBsAg (HBV) using Monalisa Ag HBS PLUS ELISA kit (Bio-Rad 3, Boulevard Raymond Poincare 93430 Marnes- La coquette- France) and Bio-Rad ELISA kit (Monalisa Anti-HCV Plus Version 2. 3, Boulevard Raymond Poincare 93430 Marnes- La coquette- France) to detect antibodies against HCV.

Hepatocellular Carcinoma Diagnosis

The diagnosis of HCC cases was done by: Focal lesion in the liver on abdominal sonography; enhancement of focal lesion on abdominal triphasic computed tomography, magnetic resonance imaging (MRI), and typical histopathological findings on liver biopsy. Tumour marker - mainly alpha-feto protein - was used in some patients and measured by enzyme immunoassay (EIA) using human AFP EIA kit. Normal range was standardized to 9.3 kU/L for subjects <40 years to 12.6 in those >40 years. HCC diagnosis was made based on one or more combined diagnostic tests supplemented by the clinical findings (Lamerz et al., 2006).

Results

The mean age of the cases was 61.2 years (±12.6) and ranged from 10 years to 88 years and half of the participants were over 60 years. Thirty two patients (36%) were males. Most of the participants (98%) only had basic/ no formal education and 38 (42%) were employed.

The proportion of HBsAg infection, HCV infection and HCC was found to steadily increase with age. However, these differences were not statistically significant.

Around 65% of the participants (57) were diagnosed as HCC cases by histopathological examination and the rest (35.2%) were diagnosed by other reliable methods such as combination of ultrasound and α feto-protein and CT scan. Around one-third of participants were positive for HBsAg (30%) and HCV antibodies (28.4%). Only 13 (15%) HCC patients were previously diagnosed with cirrhosis. History of jaundice was mentioned by 47 (53%) patients. On examination, splenomegaly was present in 3 patients (3.4%). Serum bilirubin, serum GOT; serum GPT and α feto-protein level were very high in 17%, 18%, 10% and 13.6% of cases.

With regard to the lifestyle risk behaviours, 4.5%, 58% and 66% of HCC cases drank alcohol; smoked cigarettes and chew khat respectively.

Relationship between HBV and HCV infections was explored with socio-demographic and clinical characteristics of the HCC patients and, as shown in Tables 1, no association was found between HBV and HCV infections and age, gender, history of jaundice or dental extraction. The univariate logistic regression analysis showed an inverse association between patient with HBV infection and cirrhosis (protective OR: 0.291; 95%CI 0.087-0.974, $p<0.05$). However, we found higher risk of developing cirrhosis in patients with underlining HCV infection (OR: 5.628; 95%CI 1.211-26.147, $p<0.05$). Only three HCV cases were found among HCC-cirrhotic patients. Also, three HCC patients were found with dual infection of HBV and HCV. Factors like history of blood transfusion or blood groups showed no association with HBV ($p>0.05$). Of all socio-demographic and clinical characteristics of HCC patient with HCV infection, only underlying HBV infection had significant association (OR: 5.628; 95%CI 1.211-26.147, $p<0.05$).

We tested lifestyle factors by univariate analysis for their association with HBV or HCV infections in HCC patients as shown in Table 1. Only smoking was found associated with HBV infection (OR=3.3, 95%CI 1.1-9.4, $p<0.05$) whilst no association was observed with HCV infection.

We performed multivariate logistic regression analysis using mean age, blood transfusion, smoking, and infection with HCV or being diagnosed with cirrhosis (Table 2). Only two factors: smoking and HCV infection were found associated with HCC in patients with positive HbsAg i.e., being carrier of HBV (AOR 3.47, 95%CI 1.19-10.11 and AOR 4.42, 95%CI 1.15-16.88, respectively and $p<0.05$).

Table 1. Association with Socio-Demographic and Clinical Characteristics of HCC Patients

		Yes		No		p-value	OR	95% CI
Association of HBV Infection (presence of HBsAg) with socio-demographic and clinical characteristics of HCC patients								
Age (years) mean (±SD)		61.7	(12.6)	59.6	(14.3)	0.63	2.1	-17.043
Gender:	Female	19	(33.9)	37	(66.1)	0.24	0.545	0.200-1.488
	Male	7	(21.9)	25	(78.1)	**	**	**
History of Jaundice:	Yes	10	(32.3)	21	(67.7)	0.7	0.829	0.317-2.168
	No	15	(28.3)	38	(71.7)	**	**	**
Dental extraction:	Yes	10	(32.3)	21	(67.7)	0.68	0.82	0.317-2.117
	No	16	(28.1)	41	(71.9)	**	**	**
HCC		22	(27.8)	57	(72.2)	0.6	0.648	0.127-3.292
Cirrhosis		7	(53.8)	6	(46.2)	0.04*	0.291	0.087-0.974
History of blood transfusion		6	(30)	14	(70)	0.73	0.824	0.275-2.467
Blood group A		3	(27.3)	8	(72.7)	0.6	**	**
Blood group B		2	(50)	2	(50)	0.42	0.375	0.035-3.999
Blood group O		7	(25)	21	(75)	0.88	1.125	0.232-5.455
HCV co-infection		3	(8.3)	22	(91.7)	0.03*	5.628	1.211-26.147
Association of HCV Infection (presence of HCV antibodies) with socio-demographic and clinical characteristics of HCC patients								
Age (years) mean (±SD)		60.7	(10.4)	61.9	(13.7)	0.69	1.007	0.972-1.044
Gender:	Female	16	(28.6)	40	(71.4)	0.96	0.978	0.373-2.566
	Male	9	(28.1)	23	(71.9)	**	**	**
History of Jaundice:	Yes	11	(35.5)	20	(64.5)	0.29	0.591	0.225-1.552
	No	13	(245)	40	(75.5)	**	**	**
Dental extraction:	Yes	9	(29)	22	(71)	0.92	0.954	0.363-2.509
	No	16	(28.1)	41	(71.9)	**	**	**
HCC		23	(29.1)	56	(70.9)	0.23	0.271	0.032-2.259
Cirrhosis		3	(23.1)	10	(76.9)	0.73	1.273	0.319-5.083
History of blood transfusion		3 (15)	17	(85)	0.18	2.479	0.656-9.376	
Blood group A		4	(36.4)	7	(63.6)	0.54	**	**
Blood group B		2	(50)	2	(50)	0.64	0.571	0.057-5.775
Blood group O		7	(25)	21	(75)	0.48	1.714	0.384-7.659
HBsAg (HBV co-infection)		2	(8.3)	22	(91.7)	0.03*	5.628	1.211-26.147
Association of lifestyle characteristics with HBV and HCV infections in HCC patients								
HBV; Drinking alcohol:	yes	1	(25)	3	(75)	0.839	1.271	0.126-12.819
	no	25	(29.8)	59	(70.2)	**	**	**
Smoking:	yes	20	(39.2)	30	(60.8)	0.023 *	3.333	1.179-9.424
	no	6	(16.2)	31	(83.8)	**	**	**
Chewing khat:	yes	18	(31)	40	(69)	0.671	1.237	0.464-3.304
	no	8	(26.7)	22	(73.3)	**	**	**
HCV; Drinking alcohol:	yes	0	(0)	4	(100)	0.999	0	0.000-0.000
	no	25	(29.8)	59	(70.2)	**	**	**
Smoking:	yes	14	(27.5)	37	(72.5)	0.815	0.894	0.351-2.279
	no	11	(29.7)	26	(70.3)	**	**	**
Chewing khat:	yes	16	(27.6)	42	(72.4)	0.812	0.889	0.337-2.345
	no	9	(30)	21	(70)	**	**	**

*p-value <0.05; **reference category

Table 2. Multivariate Logistic Regression for Adjusted Factors Associated with HBV and HCC

	P-value	AOR	95% CI
Smoking	0.022	3.477	1.195-10.117
HCV infection	0.03	4.422	1.158-16.883

* p-value <0.05; **reference. AOR=Adjusted Odds Ratio.

However, none of these factors were associated with HCV and HCC.

Discussion

To the best of our knowledge, our study represents the first comprehensive attempt to outline multiple diagnostic parameters and tumour indicators for HCC in Yemen. There are little published data concerning HCC and its relationship to HBV and HCV infections and other risk factors in Yemen. Although this is a descriptive study of patients with HCC, several interesting observations were recorded. The rate of HBV infection (HBsAg) and HCV infection was positive in 30% and 28% of patients diagnosed with HCC, respectively. However, comparing to the previous community researches in Yemen, our findings are considered to be high. A study in Aden city, Yemen among participants from the community and employees in the main hospital has shown rates of 4.6% and 5.5% for HBV carrier (HBsAg), respectively (Al-Jarba, 2003; Bawazir et al., 2010). Also other studies among pregnant mothers and blood donors in Sana'a City (Yemen) have shown a carrier prevalence of 13% and 15%, respectively (Al-Shamahy et al., 2003; Sallam et al., 2003). However, this reported rate of HBV carriers in our study is lower than

what was found in other studies among HCC patients. For instance, in Africa and East Asia, the largest attributable fraction in HCC is due to hepatitis B (60%), whereas in the Western world, approximately 20% of HCC cases can be attributed to HBV infection (Colina et al., 2004; Di Bisceglie, 2009). Many studies in the region and elsewhere in the world showed an association between HCC and the infection with either HBV or HCV. Ayoola et al, reported a high risk of HCC in the presence of HBsAg (OR: 34.3; 95%CI: 14.8-79.1; p<0.001) and with presence of HCV (OR:12.2; 95% CI: 3.2-47.3; p<0.001) and only 24.6% of HCC patients were found with absence of any infection (Ayoola Gadour, 2004).

Similarly for HCV infection, we found a higher seroprevalence rate in patients with HCC in this study compared to studies conducted in non-HCC patients in Yemen with rates varying from <1% to 9% (Scott et al., 1992; Haidar, 2002; Al-Jarba, 2003; Sallam et al., 2003). Recently, a meta-analysis conducted by Franceschi and Riza (2009) showed an increasing trend of HCV infection among HCC cases in Europe, the United States, Japan, Pakistan, Mongolia and Egypt (Franceschi, 2009; Jahan et al., 2012). Rates of HBV, HCV and HCC showed steady increase with age. The older generations showed higher rate of infection and of cancer. Similar trend was found in the community-based study in Aden City where higher rates of HBV carriers and positive HCV were found in those in older age groups (Bawazir et al., 2011). This is probably due to the cumulative effect where the rates of disease increase with a long period of exposure to the risk factor (HBV infection) due to increasing age. In addition, the lower rate among the younger generations is probably also due to the low rate of transmission of infection mainly due to the implementation of safety measures in the country during the last 20 years in blood transfusion procedures or the use of disposable syringes and needles.

Although these findings point towards a relationship between HBV and HCV infections and the occurrences of HCC, the question remains on the likely factors that lead to the occurrence of HCC in the Yemeni population. Most likely there are other stronger risk factors in Yemen that lead to HCC. Further investigation with other design and larger sample are needed to answer this question.

Infection with HCV and smoking were the only two factors that were statistically significantly associated with HCC in patients already infected with HBV. Moreover, smoking as behavioural risk factor was also associated with HBV infection in HCC patients (AOR 3.47, 95%CI 1.19-10.11, p<0.05). Many studies conducted elsewhere support our findings on the relation of HBV and HCC (Purdy et al., 1993; Badawi, 1999; Seeff, 2006; Steven, 2007; Tsai et al., 2007; Lehman, 2009). However, a study in Egypt showed that viral infection mainly with HCV (89%) was the most important risk factor for HCC (OR 13.80, 95%CI 5.57, 34.21) (Di Bisceglie et al., 1993). Other factors being investigated in ours study such as the history of blood transfusion, dental extraction or history of jaundice were not significantly associated with HCC, HBV or to HCV (p>0.05). Al-Shamahy et al., (2003) reported an association between HBV infection and blood transfusion (Al-Shamahy et al., 2003). This risk factor is dependent on the application of safety control measures of blood transfusion from one country to another. In industrialized countries, this factor is now of low concern (Niederhauser et al., 2008) but still is of great importance in poor economic countries like Yemen, where goal of safe blood transfusion is still not achieved (El-Hazmi, 2004; Imarengiaye et al., 2006).

Cigarette smoking releases chemical components, which have been found to be hepatic carcinogens in animal models(Zein, 2000). This causal relationship between cigarette smoking and HCC was also established in a population-based case–control study among American whites (Yuan et al., 2004; Pocha, 2010). Likewise, smokers among patients with chronic liver disease were found to have about two-fold risk of developing HCC in a prospective study in Japan (Hayashi, 2006). Findings from our study support the relation between HCC and cigarette smoking particularly among those infected with either HBV or HCV. However, one of the limitations in our study was the absence of information on the duration of smoking, quantity of cigarette or alternative types of tobacco use.

Also, we only used HBsAg as indicator for HBV infection where other measures of the infection such as antibodies to hepatitis B core antigen (HBcAb) for past infection or hepatitis e antigen (HBeAg) were not investigated due to financial constraints. Similarly, we only performed single test to detect HCV infection due to the same reasons. Risk factors like occupational exposure to chemicals such as pesticides, and endemic infections in the community, such as schistosomiasis, may have additional roles in the aetiology or progression of HCC (Anwar et al., 2008). For example, a preliminary study carried out in Japan, found that 19.1% (173/907) of patients with chronic liver disease and 51% (35/68) of HCC cases were infected with schistosomiasis (Iida et al., 1999). Although schistosomiasis is prevalent in some areas of Yemen, this factor was not investigated in this study. Similarly, exposure to aflatoxins is also considered one of the common risk factors in sub-Saharan Africa and some parts of south-east Asia as it is in Yemen, and is believed to be the cause of up to 80% of liver cancer cases that occur in these regions (Chuang et al., 2009). In Yemen and mainly in Al-Hodeida region, where people plant the nuts and store them in inadequate conditions, we can assume this to be among the factors leading to HCC and thus needs to be investigated further in such conditions.

In conclusion, our findings underline the importance of HBV and HCV infection in the development of HCC, but the rate is quite low for a country with significant endemicity of HBV and HCV infections. However, other risk factors are of paramount importance to be studied in Yemen. To our knowledge, this is the first study investigating the relationship between HCC and HBV or HCV infections.

Acknowledgements

The authors would like to thank Prof. dr. Karel Geboes,

Prof. dr. Wim Ceelen, Sowath Ly and Dr. Kathleen Lambein for their help in editing this manuscript. They declare that there is no conflict of interest with this work.

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