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Smoking as a co-factor for development of hepato cellular carcinoma in Egyptian patients with chronic hepatitis

Abstract

Background: Hepato cellular carcinoma (HCC) represents a challenging malignancy of worldwide importance; it is the sixth most common cancer and the third most common cause of cancer-related death globally. Alcohol, tobacco, obesity, diabetes and viral etiology interact to increase the risk of HCC in patients with chronic liver diseases. Smoking is a well documented risk factor for many cancers and can play role in cancer development in patients with liver diseases. Egypt has a significant prevalence of HBV, HCV, bilharzial infections and smoking which may allow us to identify a high-risk group for HCC among patients with chronic liver diseases and cirrhosis.

Aim: The aim of this study is to evaluate the impact of smoking as a co-factor for HCC development in Egyptian patients with chronic hepatitis B and/or C with or without Schistosomal infestation.

Patients and method: A case control study was conducted on 320 Egyptian patients with chronic liver disease (CLD): 160 patients with HCC (Group I) and 160 patients without focal lesion (Group II) as a control group. All patients were assigned to full history taking with emphasis on special habits especially smoking, family history; clinical examination, laboratory investigations, abdominal ultrasound, rectal snip for bilharzial infestation and liver biopsy was conducted in some cases when imaging was inconclusive.

Results: There was no statistical significant difference between HCC cases and control group as regards age, gender nor residence. Out of 320 patients enrolled in this study, only 95(29.69%) patients were non smokers, most patients were smokers 225(70.31%). Among the smokers, males were more than females and most of them were heavy smokers. The HCC patients were found more with heavy smoking than control patients. All smokers were liable for developing HCC 1.8times more than non smokers (OR: 1.8, CI: 0.89-3.32) while heavy smokers were 3.15times more liable than non smokers (OR: 3.15, CI: 1.45-7). Smoking men with were liable to develop HCC 2.63times more than non smokers (OR: 2.63, CI: 1.06-5.83) and heavy smokers 2.55times more than non smokers (OR: 2.55, CI: 0.96-6.35), urban smokers were liable to develop HCC 3.57times more than non smokers (OR: 3.57, CI: 1.15-11.58) and heavy smokers 3.48times more than non smokers (OR: 3.48, CI: 0.86-13.9); Smokers with chronic HCV infection were liable to develop HCC 1.51times more than non smokers (OR: 1.51, CI: 0.60-2.94) and heavy smokers 2.6times more than non smokers (OR: 2.6, CI: 0.95-5.96). Smokers with cirrhosis were liable to develop HCC 2.17 times more than non smokers (OR: 2.17, CI: 0.93-5.07) and heavy smokers 4times more than non smokers (OR: 4, CI: 1.95-13.10).

Conclusion: The study revealed that smoking for long duration in CLD (chronic HBV, HCV infections and liver cirrhosis) is a highly risk factor for development of HCC among Egyptians.

Recommendations: Many efforts are needed to help and promote complete cessation of smoking generally and specially in patients with chronic liver diseases. Follow up of all patients with CLD especially smokers is needed to detect early focal lesion.

Keywords: bilharzial infections, schistosomal infestation, cytochrome p53, liver cirrhosis, smokers, alcohol, tobacco

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Abbreviations: HCC, hepato cellular carcinoma; CLD, chronic liver disease; IARC, international agency for research on cancer; HBV, hepatitis b virus; HCV, hepatitis c virus; SI, smoking index; ESR, erythrocyte sedimentation rate

Introduction

Hepato cellular carcinoma (HCC) is one of the most common cancers worldwide and a public health concern in many developing

countries.[1] The annual incidence is estimated to be 1,000,000 cases.[2] Primary liver cancer has a variable incidence over the world.[3] Alcohol, tobacco, obesity, diabetes and viral etiology interact together to increase the risk of HCC in patients with chronic liver diseases or cirrhosis.[4]

Liver diseases associated with chronic hepatitis B virus infection including HCC account for more than one million deaths annually worldwide.[5] In endemic areas, the risk of developing HCC among individuals chronically infected with HBV is up to 100times more than that of non-HBV carriers.[6] HCV is now recognized to be a major risk factor for HCC. This is evidenced by finding both antibody to HCV and HCV-RNA in serum of a substantial proportion of patients with HCC and by the progression of liver disease in HCV patients to cirrhosis and HCC.[7] Current estimates indicate that about one-third of all adults smoke. Teenagers of both sexes seem to be smoking more. The liver is an important organ that has many tasks. Among other things, the liver is responsible for processing drugs, alcohol, and other toxins to remove them from the body. There is evidence that smoking alters the ability of the liver to handle such substances. In some cases, this may influence the dose of medication necessary to treat an illness. Some research also suggests that smoking can aggravate the course of liver disease.[8]

Multivariate logistic regression showed that smoking is a significant risk factor for acquiring HCV infection.[9] This might be so because smoking is highly associated with an increased use of outpatient physician and hospital services. Cigarette smoke contains many chemicals, polycyclic aromatic hydrocarbons and nitrosamines which are primarily metabolized in the liver. Polycyclic aromatic hydrocarbons leads to specific genetic mutations in cytochrome P53 tumour suppressor gene in addition to increased levels of DNA methyl transferase enzyme, resulting in increased risk of initiation and promotion of cancer.[10] El-Zayadi AR et al.[11] have reported an association between heavy smoking and liver cell injury in the form of necro inflammation, apoptosis and excess iron deposition in the liver.[11] Both hepatitis B and C virus infections cause liver cell necrosis, hepatocyte re-growth and eventual malignant transformation induced by mutational genetic error. Cigarette smoking promotes this process, because the liver is the target organ for chemicals in tobacco. The sustained hepato cellular proliferation may render chronic HBV carriers more susceptible to the effects of environmental carcinogens.[9] Smoking promotes transition to high risk state in hepato-carcinogenesis,[12] from liver cirrhosis to liver cancer,[13] and from HCV related chronic liver disease to liver cancer.[14] In Egypt, Darwish MA et al.[19] found that 21.4% of patients with HCC were positive for HBsAg alone, 30% were positive for anti-HCV, 40% were positive for both markers while 8.6% were negative for both. Wahab MFA et al.[16] found that 54% of HCC patients were sero-positive for anti-HCV. Many reports concluded that HBV, HCV and smoking are of high prevalence in patients with HCC.[17–19] El-Zayadi A et al.[20] reported that smokers suffering from chronic hepatitis C tend to have a lower response rate to interferon therapy and so, recommended that chronic hepatitis C patients should be advised to avert smoking before embarking on interferon therapy.[20]

Aim

This study was done to evaluate smoking as risk factor for hepato cellular carcinoma in Egyptian patients with chronic hepatitis B, C or both, with or without schistosomal infestation.

Patients and methods

This is case controlled study conducted on 320 Egyptian patients from Tropical Medicine Departments, Al-Azhar, Beni-Suef and Tanta University hospitals, in the period from July 2007 to August 2009. The patients were divided into two groups:

Group I: One hundred and sixty patients had chronic liver disease and hepato cellular carcinoma (HCC). Group II: One hundred and sixty patients (matched for sex, age+3years) with chronic liver diseases without HCC (control group).

All HCC patients and controls were subjected to history taking with special emphasis on special habits as smoking (cigarette or tobacco) and classified according to smoking index (SI) into light smokers (less than 200 SI), moderate smokers (200-400 SI) and heavy smokers (more than 400 SI) where smoking index (SI) is the number of cigarettes smoked per day multiplied by the number of smoking years (SI=No. of Cig./day×No. of years). History included data of risk factors for HCC, blood transfusion, surgical procedure and family history of malignancy. Clinical examination, abdominal ultrasound and routine laboratory tests were done to all patients included: complete blood picture, erythrocyte sedimentation rate (ESR), liver function tests (ALT, AST, ALP, GGT, S albumin and bilirubin), pro-thrombin time and concentration, hepatitis markers for hepatitis B and C viruses, renal function tests. Serum levels of alpha fetoprotein (AFP) and tri-phasic abdominal spiral CT were done to HCC group. Liver biopsy from hepatic mass was taken when imaging was un-conclusive. Rectal snip was done for detection of bilharzial ova. The data were analyzed statistically to predict smoking as a risk factor of HCC in chronic liver disease using SPSS for Windows, version 11.5(SPSS).

Inclusion criteria

Adult patients (more than 18years old) with chronic with chronic hepatitis B, C or both with HCC (group I) and chronic liver disease patients without HCC (group II). A written consent was taken from each patient to participate in this study.

Exclusion criteria

Other chronic liver disease (as auto-immune hepatitis…etc) Patients with deteriorated general condition including encephalopathy, hematemesis or melena.

Results

A case control study conducted on 160 HCC patients, 132 males and 28 females (4.7:1) plus 160 chronic liver disease patients as hospital controls, 130 males and 30 females (4.3:1). The age for HCC cases ranged from 42-76years (mean=56.97±8.6) compared to 40-75years (mean=54.63) for controls. The age in HCC patients were below 50years in 18(11.25%) compared to 37(23.12%) controls, between 50-69years in 136(85.0%) HCC patients compared to 120(75.0%) controls, over 70years in 6(3.75%) HCC patients compared to 3(1.88%) controls (Table 1). HCC cases were found as: 62(38.84%) in urban areas compared to 60(37.33%) controls while 98(61.16%) HCC cases and 100(62.67%) controls from rural area. There was no statistical differences between HCC cases and control groups as regard gender, age and residence (P>0.05). Smokers were significantly higher among HCC group, (Table 2).

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Table 1 Age distribution of studied groups

Range of age(years)	HCC		Control	
	No.	%	No.	%
<50	18	11.25	37	23.12
50-69	136	85	120	75
≥70	6	3.75	3	1.88
Total	160	100	160	100
P	X^2=4.73 P>0.05			
Range	42-76		40-75	
Mean ±SD	56.97±8.56		54.63 ± 8.32	

There was no statistical differences between HCC cases and controls as regard to biochemical analyses, symptoms and most signs except liver tenderness in HCC patients where P value was very highly significant (P<0.0001), Table 2. Also there was no statistical difference between HCC cases and controls regarding bilharzial infection by rectal snip, where it was positive in 34(21.25%) of HCC patients versus 36(22.5%) in controls (Table 2).

In HCC cases 18(13.6%) male were non-smokers compared to 38(29.2%) male controls while 114(86.4%) HCC cases and 92(70.8%) controls were smokers (Table 3A).

There is statistical difference between male HCC cases and control group as regards smoking habit where (P<0.05) in both none and light smokers but not in moderate and heavy smokers (Table 3A). In HCC cases 21(75.0%) female were non smokers compared to 18(60.0%) female in control group while 7(25%) female HCC cases and 12(40%) female control group were smokers. No statistical differences between female cases and control groups in smoking habit (P<0.05) (Table 3B).

Table 2 Baseline characteristics of studied groups

Characteristics	HCC(160)		Control(160)		X^2	P
	No.	%	No.	%		
Sex						
Males	132	82.5	130	81.3	0.08	>0.05NS
Females	28	17.5	30	18.7		
Residence						
Urban	62	38.84	60	37.33	0.05	>0.05NS
Rural	98	61.16	100	62.67		
Smoking status						
Non smokers	39	24.37	56	35	4.33	<0.05 S
Smokers	121	75.63	104	65		
Liver examination and abdominal ultrasound characteristics						
Not enlarged	32	20	40	25	0.92	>0.05
Enlarged with sharp border	128	80	120	75.3		
Enlarged and hard consistency	80	50	24	15		
Irregular surface	52	32.5	32	20	3.1	>0.05
Tenderness	120	75	54	33.75	25.18	>0.0001
Cirrhosis	92	57.5	91	56.88		
Viral sero markers and bilharzial infection						
HBsAg*	49	30.6	34	21	1.93	>0.05
HCV Ab*	120	75	139	86.8	3.83	<0.05
Mixed HBV and HCV infections	9	5.6	13	8.1		
Bilharzial infection	34	21.3	36	22.5		

Table 3A Distribution of HCC cases and control group in relation to smoking habit among males, SI=smoking index

Smoking habits	Males				X^2	P
	HCC(n132)		Control(n130)			
	No.	%	No.	%		
Non smokers	18	13.6	38	29.2	5	<0.05
Smokers	114	86.4	92	70.8		
Light < 200 SI	22	19.3	6	6.5	6.57	<0.01
Moderate 200- 400 SI	25	21.9	25	27.2	0.99	>0.05
Heavy >400 SI	67	58.8	61	66.3	1.06	>0.05

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Table 3B Distribution of HCC cases and control groups in relation to smoking habit among females, SI=smoking index

Smoking habits	Females				X^2	P
	HCC(n28)		Control(n30)			
	No.	%	No.	%		
Non smokers	21	75	18	60	0.42	>0.05
Smokers	7	25	12	40		
Light < 200 SI	5	72	6	50	0.11	>0.05
Moderate 200- 400 SI	1	14	3	25	0.82	>0.05
Heavy > 400 SI	1	14	3	25	0	

Table 4A shows the prevalence of smoking and odds ratio (95% CI) of developing HCC in patients and matched control group as regard gender where all smokers are liable for HCC 1.8times more than non smokers (OR: 1.8, CI 0.89-3.32) and heavy smokers 3.15times more than non smokers (OR: 3.15, CI 1.45-7). Smoker men are liable to develop HCC 2.63times more than non smokers (OR: 2.63, CI 1.06-5.83) and heavy smokers 2.55times more than non smokers (OR: 2.55, CI 0.96-6.35), but females are not at risk to develop HCC due to smoking.

Table 4A Prevalence of smoking & odds ratio of developing HCC in patients & matched controls as regard gender

	No.	Non-smokers	Smokers			OR(95%CI)	
			Light <200SI	Moderate 200-400	Heavy >400SI	smoking	Heavy smokers
Groups							
HCC	160	39	27	26	68	1.8	3.15
Control	160	56	12	28	64	0.89-3.32	1.45-7
Men							
HCC	132	18	22	25	67	2.63	2.55
Control	130	38	6	25	61	1.06-5.83	0.96-6.35
Women							
HCC	28	21	5	1	1	0.72	0
Control	30	18	6	3	3	0.18-3.38	

Table 4B shows the prevalence of smoking and odds ratio (95% CI) of developing HCC in all patients as regard residence where all urban smokers are liable to develop HCC 3.57times more than non smokers (OR: 3.57, CI: 1.15-11.58) and heavy smokers 3.48times more than non smokers (OR: 3.48, CI: 0.86-13.9) but rural cases are not at risk to develop HCC due to smoking.

Table 4B Prevalence of smoking & odds ratio of developing HCC in patients & matched control cases as regard residence

	No.	Non-smokers	Smokers			OR(95% CI)	
			Light <200SI	Moderate 200-400	Heavy >400SI	smoking	Heavy smokers
Urban							
HCC	62	14	3	23	22	3.57	3.48
Control	60	31	11	4	14	1.15-11.58	0.86-13.9
Rural							
HCC	98	25	24	3	46	0.63	0.64
Control	100	25	1	24	50	0.27-1.45	0.25-1.78

Smoker cases with chronic HBV infection are liable to develop HCC 1.83times more than non smokers (OR: 1.83, CI: 0.47-8.61) and heavy smokers 2.63times more than non smokers (OR: 2.63, CI: 0.40-14.2). Smoker cases with chronic HCV infection are liable to develop HCC 1.51times more than non smokers (OR: 1.51, CI: 0.60-2.94) and heavy smokers 2.6times more than non smokers (OR: 2.6, CI 0.96-5.96). Smoker cases with cirrhosis are liable to develop HCC 2.17times more than non smokers (OR: 2.17, CI 0.93-5.07) and heavy smokers 4times more than non smokers (OR: 4, CI: 1.95-13.10).

There was no statistical difference between HCC cases and controls as regards HBV infection (P>0.05) while HCV infection was significantly higher in HCC cases than controls (P<0.05).

Table 4C Prevalence of smoking & odds ratio of developing HCC according to HBV, HCV and cirrhosis

	No.	Non-smokers	Smokers			OR(95% CI)	
			Light <200SI	Moderate 200-400	Heavy >400SI	smoking	Heavy smokers
HBV patients							
HCC	49	3	5	20	21	1.83	2.63
Control	34	9	8	6	11	0.47-8.61	0.40-14.2
HCV patients							
HCC	120	25	17	27	51	1.51	2.6
Control	139	34	32	42	31	0.60-2.94	0.95-5.96
Cirrhosis							
HCC	92	17	11	29	35	2.17	4
Control	91	20	20	36	15	0.93-5.07	1.95-13.10

Discussion

Hepato-cellular carcinoma (HCC) is the most frequent primary cancer of liver worldwide. HCC is the seventh most common tumor in males and ninth in females. The annual incidence is estimated to be 1,000,000 newly diagnosed cases.[2] The Middle East, including Egypt, is considered an area of intermediate incidence rate.[9] HCC incidence in Egypt was between 5-7per 100000 populations per year.[21]HCC is one of the few human cancers for which an etiological factor can be identified in many cases.[9] Hepatic viruses, particularly hepatitis B virus (HBV) and hepatitis C virus (HCV) are major causes of HCC worldwide.[22] Cigarette smoking is a major source of 4-aminobiphenyl, a hepatic carcinogen which has been implicated as a causal risk factor for HCC.[23] Smoking and alcohol drinking were possible risk factors for liver cancer, since many case control studies[24,25] and a few cohort studies[26,27] have indicated a relation between these life style factors and the risk of liver cancer. The International Agency for Research on Cancer (IARC) classified liver cancer as a tobacco related malignancy.[28] Hirayama T[29] found that cigarette smoking involved in the development of liver cancer due to liver cirrhosis. Skolnick AA[30] found that smoking appears to increase the risk of liver cancer and Kuper H et al.[31] found that there was an interactive effect of heavy smoking and heavy drinking in the development of HCC. Also, Evans AA et al.[32] found that there was an association of smoking with HCC in females but not in males. In this study, the smoking habit of the HCC studied men was 114(86.40%) smokers and 18(13.6%) non smokers. In women 7(25%) were smokers and 21(75%) were non smokers. This may be due to cultural and traditional attitudes. Kew, 1985(33) found that smoking habit among HCC men was: 120(59.2%) were smokers out of 203 and 83(40.8%) non smokers, but in women, 4(10.8%) out of 37cases were smokers and 33(89.2%) were non smokers. This finding revealed that smoking habit is experienced by men more than women and may be a risk factor for HCC.

The dose-response relationship between cigarette smoking and HCC has been unclear in most epidemiological studies.[34–36] In this study there was significant association between light smoking and HCC. Hara M et al.[37] reported that comparison of HCC cases with CLD patients, no dose response relationship was evident for peak-year during lifetime, and yet more recent cigarette consumption such as pack-years during the last 5 years was significantly associated with HCC risk in a dose dependant manner. HCV is proved as a risk factor for HCC and in this study, it was found that there was positive correlation between heavy smoking and HCC development in chronic HCV patients, similar findings were reported by El-Zayadi A et al.[20] Mori M et al.[38] Hirayama T[29] and Chen CJ et al.[41] they found a significant association between the daily use of cigarette smoking and the primary liver cancer in chronic HCV infected males. In addition, a substantial numbers of case control studies or hospital based prospective studies, have also a positive relation between cigarette use and the risk of HCC in chronic hepatitis C.[25,35] HBV is documented as a risk factor for HCC and in this study; we found a positive association between HBV infection and smoking as an increasing risk for HCC, previous case control study by Chen CJ et al.[39] had presented an evidence of increased risk for the concurrent positivity of HBV infection and cigarette smoking. Mori M et al.[38] in a prospective study found that chronic hepatitis B and C infections were significantly associated with HCC risk, although a history of cigarette smoking was not significantly related to risk. As these infections are at least partly responsible for the pathogenesis of HCC, it may be reasonable to suppose that hepatitis B or C virus infection causes continuous liver cell necrosis, hepatocyte re-growth and eventual malignant transformation induced by mutational genetic error.[25] Cigarette smoking may promote these processes, because the liver is a target organ for chemicals in tobacco. However, the detailed biologic mechanism of the effect of viral infection combined with life style habits on HCC development remains to be explained.[38] Kuper H et al.[31] found that tobacco smoking has an important role in the etiology of HCC, but the association of tobacco smoking with HCC risk appear to be more evident among individuals without chronic infection with HBV or HCV. This observation is compatible with an additive role of chronic viral infection and tobacco smoking in the etiology of HCC, since the effect of tobacco smoking in those cases with HBsAg and/or HCV Ab is concealed by the extremely strong carcinogenic effect of HBV and HCV. An effect of smoking on development of HCC as biologically plausible, given the carcinogenic potential of several compounds in tobacco smoke and the role that the liver plays in their metabolism.[42] Mohamed NH et al.[43] reported that 49.6% of HCC cases had history of smoking[43] and El-Zayadi A et al.[20] reported also that smoking yields chemicals with oncogenic potential that increase the risk of HCC.[23] Elfert A et al.[44] concluded that cigarette smoking may aggravate liver disease in patients with HCV infection due to the possible hepato-toxicity of cigarette smoking. In a study done by Ohishi W et al.[45] on 224 HCC patients, smoking was marginally significantly associated with increased risk for HCC even after adjusting for liver fibrosis.

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In this study smoking was associated with HCC in urban patients but not in rural ones. Urban patients may be exposed more to pollutions. HCC development is a multistage process and is influenced by environmental and genetic factors.[46] Eldin MS et al.[47] found that 45% of HCC cases had history of smoking, half of them were heavy smokers[47] and similar results was reported by Mohamed NH et al.[43] In this study, 92 patients of group I (57.5%) had a confident sonographic evidence of liver cirrhosis, 70 patients (73.7%) had it as a solo finding while only 34 patients (21.25%) had sonographic evidence of an additional background schistosomal periportal fibrosis. This high association between cirrhosis and HCC is agreed upon by Rosen CB et al.[48] who stated that more than three quarters of the patients with HCC have underlying cirrhosis. Abdelaziz A et al.[49] stated that smoking may play an important role in pathogenesis of HCC in cirrhosis. Furthermore, a study by Mabrouk GM[50] on 34 Egyptian patients with HCC revealed that all of them (100%) had liver cirrhosis and 77% of them had schistosomiasis antibodies in their sera which present a much higher incidence than our study and this may be due to the difference in sample size. Tabor E,[51] reported that serologic evidences of HBV infection is detected in about 70% of HCC patients in Africa, which is a figure much higher than that documented in our study. The difference was yet more pronounced in a study by Yates SC et al.[52] on 131 Egyptian patients with proven HCC, where chronic HBV infection was detected in 102 patients (78%). HBsAg was positive in 28 patients (29.4%) which is strikingly lower than reported by Darwish MA et al.[19] who found it to be positive in 61.4% of HCC cases. As expected, the strongest risk factors for HCC in Ezzat S et al.[53] study were HCV RNA (OR=16–17) and current HBV infection (OR=27–28). Soliman AS et al.[54] concluded that occupational exposure may play an important role in the development of HCC in Egypt. Farming, industrial exposures and cigarette smoking may increase the risk of HCC among HCV-seropositive individuals. Worldwide there is a strong association between HCV infection and HCC.[18,52] Mabrouk GM[50] reported that 84% of 34 Egyptian patients with HCC were HCV Ab positive and similar results obtained by Khella AK et al.[55](83.6%) and Darwish MA et al.[19](70%). Our results recorded 75.0% HCV Ab positivity in patients with HCC and this will triggers an alarm, that high percentage of patients with chronic HCV infection will develop HCC if left unscreened and untreated and also support the need for a more effective therapy at an earlier stage.

Conclusion

This study revealed that smoking for long duration in CLD (chronic HBV and/or HCV infections and liver cirrhosis) is highly risk factor for development of HCC among Egyptians. Smoker males, urban and heavy smoking is more liable to development of HCC than non smoker females, non smoker urban and light smokers respectively. Recommendation: Screening for HCC in chronic liver diseases is highly recommended specially in patients with high risk factors as HCV, HBV infection and cirrhosis especially with smoking. These figures arouse the necessity for strict national programs to stop smoking generally and especially in patients with liver diseases.

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Conflict of interest

Author declares that there is no conflict of interest.

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