Study of the Risk Factors for Hepatocellular Carcinoma: Effect of Their Synergism

Ibrahim Baghdady[1], Nabil EI-Kaffrawy[1], Ehab Abd EI-Atti[1], Nasser Abd EI-Bary[2] and Mohamed Fathi Saber[1]

[1]Internal Medicine and [2] Clinical Oncology departments, Faculty of Medicine - Menofiya University.
ehab_abdelatty@hotmail.com

Abstract: Background: Risk factors associated with HCC are well documented, but the synergism between these risk factors are not well examined. The aim of this study was to detect the effect of synergism of two or more risk factors on the development of HCC. **Patients & methods:** This is a retrospective study of the risk factors of HCC in 300 patients with HCC and 50 patients with chronic liver diseases without HCC as controls. All patients were interviewed about smoking, drinking and family history of HCC. They underwent laboratory investigations (HCVAb, HBsAg, Alpha-fetoprotein and HCV PCR), abdominal ultrasonography and Triphasic CT. **Results:** Prevalence rate of DM and smoking was significantly higher in HCC cases (59.3% and 69% respectively) than controls (38% and 50% respectively)(*P*=0.005 and 0.006 respectively). The prevalence of HBsAg and HCVAb was significantly higher in HCC cases (18% and 70% respectively) than controls (4% and 40% respectively)(*P* =0.02 and 0.0001 respectively). On multivariate analysis, the risk of HCC development in smokers with HBV or HCV was 4.90 and 8.47 respectively (OR) (*P* =0.0001). It was higher than in non-smokers with HBV or HCV (OR=2.48 and 4.44 respectively)(*P* =0.037 and 0.0001 respectively) and in smokers without HBV or HCV (OR=2.56 and 2.77 respectively) (*P* =0.01). The risk of HCC development in HBV or HCV positive patients with DM was 3.98 and 9.19 respectively (OR) **(***P* =0.001 and 0.0001 respectively). It was higher than for HBV or HCV positive patients without DM (OR=2.80 and 4.65 respectively)(*P* =0.031 and 0.0001 respectively) and that for HBV or HCV negative patients with DM (OR=2.56 and 2.23 respectively)(*P* =0.011and 0.0001 respectively).**Conclusion**, HCV and HBV infections, diabetes and smoking are the main determinants of HCC development in Egypt. There is a synergistic effect of many risk factors. An active surveillance and secondary prevention programs for patients with chronic hepatitis are the most important steps to reduce the risk of HCC.
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Key Words: HCC, HBV, HCV, DM, smoking

1.Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. It is rarely detected early. Hepatocellular carcinoma is one of the 130 major causes of morbidity and mortality in the world. It represents the third leading cause of cancer death in males and the fourth in females with more than 600000 deaths per year. (1) Geographical distribution of HCC varies throughout the world with an incidence rate ranging from 2.1 in Central America to 35.5 in Eastern Asia. The burden of HCC has been increasing in Egypt with a doubling in the incidence rate in the past 10 years. (2)

There is a geographic correlation between the incidence of HCC and the prevalence of chronic hepatitis B and C, suggesting that these two viral infections are the most important risk factors of HCC worldwide. (3) Co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) is associated with a higher risk for developing HCC than either infection alone. (3)

Several risk factors for the development of HCV-associated HCC have been reported such as aging, gender, alcohol intake. Recent studies have indicated that interferon (IFN) treatment can reduce the incidence of HCC. (4)

Nonalcoholic steatohepatitis (NASH) is a well-recognized cause of cirrhosis and has been increasingly associated with the development of HCC. Visceral fat accumulation has been reported to increases the risk of HCC development in patients with chronic liver disease. (5)

Risk factors associated with HCC are well documented, but the synergism between these risk factors is not well examined. The aim of this study was to detect the effect of synergism of two or more risk factors on the development of hepatocellular carcinoma.

2. Patients and methods:

For achieving the objective of the case-control retrospective study is adopted. Cases were already diagnosed patients of HCC attending or admitted to Clinical Oncology hospital and internal medicine department, faculty of Medicine, Menofiya University (totaled 300 cases). Control group included 50 patients with chronic liver diseases of different etiologies without HCC. The study was carried out during 2010.

All subjects (cases and controls) were asked to participate in the present study. An informed consent was signed by all contributors and the study was approved by the local Medical Research and Ethics committee. Patients with metastatic (secondary) liver cancer, other types of liver cancer (cholangiocarcinoma, hepatoblastoma, angiosarcoma and hemangiosarcoma), benign liver tumors (hepatocellular adenoma, focal nodular hyperplasia and hemangiomas) were excluded.

All of the patients were interviewed using a pre-designed questionnaire to yield basic demographic data and information about the history of liver disease, family history of HCC, history of smoking, drinking and treatment received. They also underwent comprehensive physical examination, laboratory investigations (HCVAb, HBsAg, Alpha-fetoprotein and HCV PCR quantitative). Also abdominal ultrasonography and Triphasic CT were done for all patients.

Statistical Analysis:

Results are presented as mean ± standard deviation (SD) unless otherwise stated. Comparison between groups was performed using student t test and non-parametric Mann-Whitney test. Fisher Exact analysis was also applied to compare proportions between groups. Multiple logistic regression analysis was used to detect the independent risk factors of HCC. 5% was chosen as a level of significance for the used statistical tests. All statistical analyses were performed using the Statistical Package for Social Science (SPSS) software version 10.

3. Results

The study included 239 male and 61 female patients with HCC and 50 patients with chronic liver diseases of different etiologies without HCC.

Table 1 shows a comparison between HCC cases and controls. There was no significant difference between HCC cases and controls as regards: age, gender, residence, marital status, occupation, social class, obesity, hyperlipidaemia, bilharziasis, alcohol intake and blood groups ($P > 0.05$).

Positive familial history was significantly higher in HCC cases (71.1%) than in controls (32%) (P=0.0001).

Prevalence rate of DM was significantly higher in HCC cases (59.3%) than controls (38%) (P=0.005). Smoking is significantly more prevalent in HCC cases (69%) than controls (50%) (P=0.006).

The prevalence of HBsAg and HCVAb was significantly higher in HCC cases (18% and 70%, respectively) than controls (4% and 40%, respectively) (P=0.01 and 0.0001 respectively).

Table 1. Comparison between HCC cases and controls:

	HCC cases n = 300	Control n = 50	*P* value
Age (years)			
10 – 30	1.3% (n = 4)	0% (n = 0)	0.62
30 – 50	12.3% (n = 37)	10% (n = 5)	
> 50	86.4% (n = 259)	90% (n = 45)	
Gender (Male %)	79.7% (n = 239)	78% (n = 39)	0.78
Residence			
Rural	86.7% (n = 260)	88% (n = 44)	0.79
Urban	13.3% (n = 40)	12% (n = 6)	
Marital status			
Single	3.7% (n = 11)	4% (n = 2)	1.0
Married	96.3% (n = 289)	96% (n = 48)	
Occupation			
Do not work	9.3% (n = 28)	12% (n = 6)	
House wife	13% (n = 39)	20% (n = 10)	
Farmer	24.3% (n = 73)	12% (n = 6)	0.33
Employee	34.3% (n = 103)	40% (n = 20)	
Butcher	1% (n = 3)	0% (n = 0)	
Administrative	18% (n = 54)	16% (n = 8)	
Social class			
Low	81.3% (n = 244)	68% (n = 34)	
Middle	17.3% (n = 52)	28% (n = 14)	0.07
High	1.3% (n = 4)	4% (n = 2)	
Family history (positive)	71.7% (n=215)	32% (n=16)	**0.0001***
DM (present)	59.3%(n=178)	38%(n=19)	**0.005***
Smoking	69.7%(n=209)	50%(n=25)	**0.006***
Alcoholism	1.3%(n=4)	2%(n=1)	0.54
Obesity	20.7%(n=62)	12%(n=6)	0.15
Hyperlipidaemia	27.7%(n=83)	20%(n=10)	0.25
Bilharziasis	53.3%(n=160)	58%(n=29)	0.54
HBsAg (Positive)	18%(n=54)	4%(n=2)	**0.02***
HCV antibody (Positive)	70%(n=211)	40%(n=20)	**0.0001***
HCV PCR	n = 211	n=20	
Low viremia	9%(n=19)	10%(n=2)	
Moderate viremia	34.6%(n=73)	35%(n=7)	0.98
High viremia	56.4%(n=119)	55%(n=11)	
Interferon therapy	29%(n=86)	20%(n=10)	0.52
Blood group			
A	25.3%(n=76)	20%(n=10)	
B	38.7%(n=116)	36%(n=18)	0.41
AB	16.3%(n=49)	14%(n=7)	
O	19.7%(n=59)	30%(n=15)	

Quantitative HCV PCR was done in 211 patients out of 300 HCC cases and in 20 patients out of 50 controls. There was no significant difference between HCC cases and controls as regards viral load (P=0.98). Eighty six cases of HCC received interferon therapy (29%) and 10 controls received interferon therapy (20%) without significant difference between both groups (p=0.4).

Table 2 shows multivariate regression analysis of the risk factors of HCC. We found that positive family history (OR=4.42 and P=0.002), HBsAg (OR=3.40 and P =0.02) and HCVAb (OR=3.29 and P =0.02) are independent risk factors of HCC. But there was no

association between DM (OR=1.76 and *P* =0.22) or smoking (OR=1.58 and *P* =0.35) and HCC.

Table 2. Multivariate regression analysis for risk factors of HCC:

Risk factors	*P* value	Odds Ratio	95% CI	
			Lower	Upper
Positive family history	**0.002***	**4.42**	**1.70**	**11.51**
DM	0.22	1.76	0.69	4.47
Smoking	0.35	1.58	0.60	4.13
HB s Ag	**0.02***	**3.40**	**1.21**	**9.55**
HCVAb	**0.02***	**3.29**	**1.20**	**9.02**

Table 3 shows the interaction between chronic HBV and HCV infections and both smoking and presence of DM as risk factors of HCC. There was a synergism between HBV infection and smoking as well as between HBV infection and DM. The risk of HCC development in smokers with HBV infection was 4.90 (OR) (*P* =0.0001). It was higher than that in non-smokers with HBV infection (OR=2.48 and *P* =0.037) and in smokers without HBV infection (OR=2.56 and *P* =0.01). The risk of HCC development in HBV positive patients with DM was 3.98 (OR) (*P* =0.001). It was higher than for HBV positive patients without DM (OR=2.80 and *P* =0.031) and that for HBV negative patients with DM (OR=2.56 and *P* =0.011).

There was a synergism between HCV infection and smoking as well as between HCV infection and DM. The risk of HCC development in smokers with HCV infection was 8.47 (OR) (*P* =0.0001). It was higher than that for non-smokers with HCV infection (OR= 4.44) (*P* =0.0001) and that for smokers without HCV infection (OR=2.77 and *P* =0.016). The risk of HCC development in HCV positive patients with DM was 9.19 (OR) (*P* =0.0001). It was higher than that for HCV positive patients without DM (OR= 4.65) (*P* =0.0001) and that for HCV negative patients with DM (OR=2.23) (*P* =0.0001).

Table 3. Interaction between HBV and HCV infections and both smoking and DM as risk factors of HCC.

		HCC Cases n = 300	Controls n = 50	P value	OR (95% CI)
HB sAg	**Smoking**				
Negative	Negative	25.7%(n=77)	50%(n=25)		
Positive	Negative	4.7%(n=14)	2%(n=1)	**0.037***	2.84 (1.04 – 7.76)
Negative	Positive	56.3%(n=169)	46 %(n=23)	**0.01***	2.56 (1.23 – 5.35)
Positive	Positive	13.3%(n=40)	2%(n=1)	**0.0001****	4.90 (2.0 – 11.99)
HB sAg	**DM**				
Negative	Negative	35.3%(n=106)	62%(n=31)		
Positive	Negative	5.3%(n=16)	2 %(n=1)	**0.031***	2.80 (1.07 – 7.32)
Negative	Positive	46.7%(n=140)	34%(n=17)	**0.011***	2.65 (1.22 – 5.74)
Positive	Positive	12.7%(n=38)	2%(n=1)	**0.0001****	3.98 (1.70 – 9.34)
HCV Ab	**Smoking**				
Negative	**Negative**	8.7%(n=26)	32%(n=16)		
Positive	**Negative**	21.7%(n=65)	18%(n=9)	**0.0001****	4.44 (1.75 – 11.32)
Negative	**Positive**	21%(n=63)	28%(n=14)	**0.016***	2.77 (1.18 – 6.48)
Positive	**Positive**	48.7%(n=146)	22 %(n=11)	**0.0001****	8.17 (3.41 – 19.57)
HCV Ab	**DM**				
Negative	**Negative**	10.3%(n=31)	38%(n=19)		
Positive	**Negative**	30.3%(n=91)	24%(n=12)	**0.0001****	4.65 (2.03 – 10.66)
Negative	**Positive**	19.3%(n=58)	22%(n=11)	**0.006***	3.23 (1.37 – 7.65)
Positive	**Positive**	40 %(n=120)	16%(n=8)	**0.0001****	9.19 (3.68 – 22.97)

OR = Odd ratio, CI = confidence interval

Table 4 shows the independent and joint effects of chronic HCV and HBV infections as risk factors of HCC. The risk of HCC development in patients positive for HBV infection only was 17.65% (OR) (*P* =0.01). The risk of HCC development in patients positive for HCV infection only was 24.33% (OR) (*P* =0.0001). The risk of HCC development in patients positive for both HBV and HCV infections was 19.86% (OR) (*P* =0.0001).

Table 5 shows the interaction between DM and smoking as risk factors for HCC. There was a synergism between DM and smoking as risk factors of HCC. The risk of HCC development in diabetic smokers was 5.69 (OR) (*P* =0.0001). It was higher than that for non-smoker diabetics (OR 2.98 and *P* =0.017) and that for non-diabetic smokers (OR 2.76 and *P* =0.011).

Table 4. Interaction between HBV and HCV infections as risk factors of HCC.

		HCC Cases n= 300	Controls n = 50	P value	OR (95% CI)
HB sAg	**HCV Ab**				
Negative	Negative	25.7%(n=77)	64%(n=32)		
Positive	Negative	4%(n=12)	2%(n=1)	**0.01****	17.65 (6.41 – 48.56)
Negative	Positive	56.3%(n=169)	32%(n=16)	**0.0001****	24.33 (9.57 – 61.85)
Positive	Positive	14%(n=42)	2%(n=1)	**0.0001****	19.86 (6.66 – 59.24)

OR = Odd ratio, CI = confidence interval

Table 5. Interaction between DM and Smoking as risk factors of HCC.

		HCC Cases n = 300	Controls n = 50	P value	OR (95% CI)
DM	**Smoking**				
Negative	Negative	11.3%(n=34)	32.0%(n=16)		
Positive	Negative	19.0%(n=57)	18.0%(n=9)	**0.017***	2.98 (1.19 – 7.48)
Negative	Positive	29.3%(n=88)	28.0%(n=14)	**0.011***	2.76 (1.23 – 6.19)
Positive	Positive	40.3%(n=121)	22.0%(n=11)	**0.0001****	5.69 (2.37 – 13.69)

OR = Odd ratio, CI = confidence interval

4. Discussion

Worldwide, HCC is one of the most common malignancies among chronic liver disease patients ranging from 4.0% to 7.2% over a decade. This rising proportion may be explained by the increasing risk factors such as the emergence of HCV over the same period of time, the contribution of HBV infection, improvement of the screening programs and diagnostic tools of HCC, as well as the increased survival rate among patients with cirrhosis to allow time for some of them to develop HCC. [6]

In a study in USA by **Hassan and co-workers** [1], a history of liver cancer in first degree relatives was significantly associated with HCC development independently of HBV and HCV. In the present study, there was a predominance of those with positive family history 71.7% and after adjustment, it was highly significant. Moreover, in addition to HCV and HBV infections, DM appears to be associated with HCC. [7] In the present study, DM increased the risk of HCC development independent of chronic HCV hepatitis and chronic HBV hepatitis as previously described. [8]

Possible biological mechanisms of the association between diabetes mellitus and HCC have been elucidated, and it has been suggested that patients having non–insulin-dependent diabetes mellitus experience hyperinsulinemia and an elevated level of insulin-like growth factor I, which may stimulate liver-cell proliferation and increase susceptibility to cancer development. [7] DM was frequently associated with cirrhosis in HCC patients and likely plays an indirect role in HCC pathogenesis through predisposing the liver parenchyma to Non-Alcoholic Fatty Liver Disease (NAFLD). [9] Recent studies performed in the Middle-East or North-Africa indicates that DM, early obesity, metabolic syndrome and NAFLD represent serious public health problems. [9-11] However, the role of DM or NAFLD is still not clear in the development of HCC. Some authors reported DM as a risk factor of HCC in some cases from Saudi Arabia and Egypt; this association is not confirmed by studies conducted in Lebanon. [12, 13] DM has been frequently associated with other risk factors for HCC by promoting cirrhosis. [14] Moreover, an increased blood glucose level may stimulate glycosylation of proteins, including hemoglobin, leading to an increase in the release of iron from hemoglobin and further production of free radicals causing oxidative stress. [15] The fact that iron is a powerful pro-oxidant and that oxidative stress is increased in impaired glucose tolerance states suggests a possible role for oxidative stress in pathogenesis of diabetes mellitus and its complications, such as cirrhosis. [16]

A prominent role of tobacco smoking in the etiology of HCC can be observed. Such a relationship is due to several chemicals in tobacco smoke metabolized and then activated to be carcinogenic in the liver. [17] In the present study, smoking increased the risk of HCC development independent of HCV and HBV infections.

Epidemiologic data indicate that chronic hepatitis B and C are independent risk factors for development of HCC. The mechanisms of carcinogenesis in HBV and HCV infection differ. HBV is known to play a direct role in liver cell transformation through direct interactions between viral and cellular proteins or by integration of HBV genome into the host genome. [18, 19] HCV, in contrast, is thought to promote a fibrotic process progressing to cirrhosis and ultimately to HCC. [19, 20] Moreover, it has been recently suggested that several aspects of the HCV life cycle are important in the mechanism of carcinogenesis. Furthermore, animal models confirm the oncogenic potential of HBV and HCV in the liver. [21] Several lines of evidence indicate a strong causal association between HCV and HCC, as

shown by the raised prevalence of anti-HCV and/or HCV-RNA in patients with HCC. [22]

In the present study, chronic HBV infection increases the risk of HCC irrespective of smoking, DM and HCV infection. Persistent HBV infection causes chronic phasic necroinflammation and regenerative proliferation in the liver. The sustained hepatocellular proliferation may render chronic HBV carriers susceptible to the effects of environmental carcinogens. [23]

Alcohol is an independent and a synergistic risk factor for HCC. **[24-26].** This is not proved in the current study and this is attributed to the fact that the number of alcoholics in Egypt, especially in rural areas is too limited and even negligible.

Extensive collaborative research was carried out during the last decade to explore independent and combined effects of HBV and HCV and other factors in the etiology of HCC. Although HBV is considered worldwide as a major risk factor for liver cirrhosis and HCC, the prevalence of HBV infection in Egypt has been declining over the last two decades, while HCV has increased. Egypt has possibly the highest HCV prevalence worldwide around 14%. [27] In the present study, HCV positive patients are 211 representing 70% of the total number of HCC cases, while HBV positive cases are only 54 representing 18%. There is a higher OR for HCV +ve cases compared with those of HBV representing 24.33 and 17.65 respectively. The rising trend of HCC has been associated with increased prevalence of HCV infection. Serum HCV RNA level does not determine the degree of hepatic injury precisely and liver biopsy is necessary to determine the extent of liver damage. [28] In the present study, there was no relation between HCC development and level of viremia.

Previous studies suggest that HCV, HBV and DM play an independent role and synergistic effect in liver tumorigenesis [29, 30]. A study in Taiwan by **Wang and co-workers [31]** showed that anti-HCV positive patients with diabetes had a higher risk of HCC than those without diabetes. Seronegative individuals with diabetes also had a higher risk of HCC than those without diabetes. The same finding was revealed in the study. There was a synergism between HCV and DM as risk factors for HCC. The highest OR is observed in HCV positive patients with DM than patients with HCV positive alone or DM alone (OR= 9.19, 4.65 and 3.23 respectively).

In southern Taiwan, a small community with a total population of about 40,000 residents, a study was done by **Chang and co-workers** [32] have reported a synergistic effect between HBV infection and DM as risk factors for HCC. A similar result was observed in the study. There was a synergism between HBV and DM. The highest OR is observed in HBV positive patients with DM than HBV positive alone or DM alone (3.98, 2.80 and 2.65 respectively).

In the present study, there was a synergism between HBV and smoking as risk factors for HCC. Smokers with HBV +ve have an OR significantly higher than HBV +ve alone or smoking alone. (OR= 4.90, 2.84 and 2.56 respectively). Similar results were observed in Italy by **Franceschi and co-workers** [33]**.** They had demonstrated that tobacco smoking was related to HCC risk and seemed to enhance HCC risk among viral hepatitis patients.

A case-control study of HCC in China by **Zhang and co-workers** [34] have provided evidence that chronic HBV infection is strongly associated with the development of HCC among this population and that HCV and HBV infection are independent and probably additive risk factors for HCC. Anti-HBc–positive is a marker of high risk for HCC among patients with HCV-related cirrhosis. Interferon therapy might be less effective in preventing HCC among patients with chronic hepatitis C who are anti-HBc–positive than in those with chronic hepatitis C who are anti-HBc–negative. [35] On the other hand, interferon therapy significantly reduces the risk for hepatocellular carcinoma, especially among virological or biochemical responders [36]. In the current study there was no relation between IFN therapy and risk of HCC. Most of patients enrolled in the present study are non-responders to interferon therapy. This can explain the difference between the current study and the formerly mentioned results.

A debate can be observed in considering obesity as an independent risk factor for HCC. Obesity is not an independent risk factor for HCC in patients with chronic viral hepatitis B or C. [37] Obesity per se could not be considered a risk factor for HCC in the current study. On the other hand, excess weight is involved in the transition from healthy HBV carrier state to HCC and liver-related death among men. The association of higher body mass index (BMI) with increased risk of HCC or death resulting from liver disease is independent of diabetes. [38] Moreover, increased BMI is associated with increased risk for early HCC development in HCV-infected patients. [39] Recent studies have proved that visceral fat accumulation is an independent risk factor of HCC recurrence after curative treatment in patients with suspected NASH. [40]

CONCLUSION: HCV and HBV infections, diabetes and smoking are the main determinants of HCC development in Egypt. There is a synergistic effect of many risk factors. An active surveillance and secondary prevention programs for patients with chronic hepatitis are the most important steps to reduce the risk of HCC.

Corresponding author
Ehab Abdel-Atti
Internal Medicine Department, Faculty of Medicine, Menofiya University, Shabin Elkom, Egypt.
E-mail:ehab_abdelatty@hotmail.com

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