Risk factors for developing hepatocellular carcinoma in Egypt

Ashraf Omar[1], Ghassan K. Abou-Alfa[2,3], Ahmed Khairy[1], Heba Omar[1]

[1]Endemic Medicine Department, Faculty of Medicine, Cairo University, Egypt; [2]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [3]Weill Medical College at Cornell University, New York, NY, USA

Corresponding to: Ashraf Omar. Endemic Medicine Department, Faculty of Medicine, Cairo University, Egypt. Email: abdelazizashraf@hotmail.com.

Abstract: Hepatocellular carcinoma (HCC) is a common disorder worldwide and ranks 2nd and 6th most common cancer among men and women in Egypt. HCC has a rising incidence in Egypt mostly due to high prevalence of viral hepatitis and its complications. Proper management requires the interaction of multidisciplinary HCC clinic to choose the most appropriate plan. The different modalities of treatment include resection (surgery or transplantation), local ablation, chemoembolization, radioembolization and molecular targeted therapies. This paper summarizes both the environmental and host related risk factors of HCC in Egypt including well-established risk factors such as hepatitis virus infection, aflatoxin, as well as possible risk factors.

Keywords: Hepatocellular carcinoma (HCC); Egypt; risk factors; epidemiology

Submitted Sep 14, 2013. Accepted for publication Oct 21, 2013.
doi: 10.3978/j.issn.2304-3865.2013.11.07
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Incidence

In Egypt, hepatocellular carcinoma (HCC) is the second most common cancer in men and the 6th most common cancers in women (*Figures 1,2*) (1). Hospital-based studies from Egypt have reported an overall increase in the relative frequency of all liver-related cancers in Egypt, from approximately 4% in 1993 to 7.3% in 2003 (2). This rising incidence (3) may be due to high prevalence of hepatitis C virus (HCV) and its complications (4) and the fact that people born 20 years ago or earlier in Egypt has not been vaccinated against hepatitis B virus (HBV) (5). Investigations in Egypt have shown the increasing importance of HCV infection in the etiology of liver cancer, estimated to account for 40-50% of cases, and the declining influence of HBV and HBV/HCV infection (25% and 15%, respectively) (2,6). The rising incidence of HCC in Egypt could be also explained through improvements in screening programs and diagnostic tools (7), as well as the increased survival rate among patients with cirrhosis allowing time for some of them to develop HCC. The higher HCC incidence among urban residents could represent better access to medical facilities, resulting in an underestimate of HCC in rural populations.

Environmental risk factors

Cirrhosis

It has been recognized that the most important clinical risk factor for the development of HCC is cirrhosis. Approximately 80% of HCCs develop in cirrhotic livers (8). The high rate of co-existing cirrhosis in HCC patients and the emergence of HCC in prospectively followed cirrhosis patients have led to the assumption that pre-existing cirrhosis is an important prerequisite for hepatocarcinogenesis, although some HCCs do arise in the absence of cirrhosis (9).

Viral hepatitis and HCC (Table 1)

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 (16). It was found that occult HBV infection and the HBV genotype B or D may influence the outcome of HBV infection leading to the development of HCC and may be strongly associated with HCV in liver carcinogenesis. A decrease in the immune status may

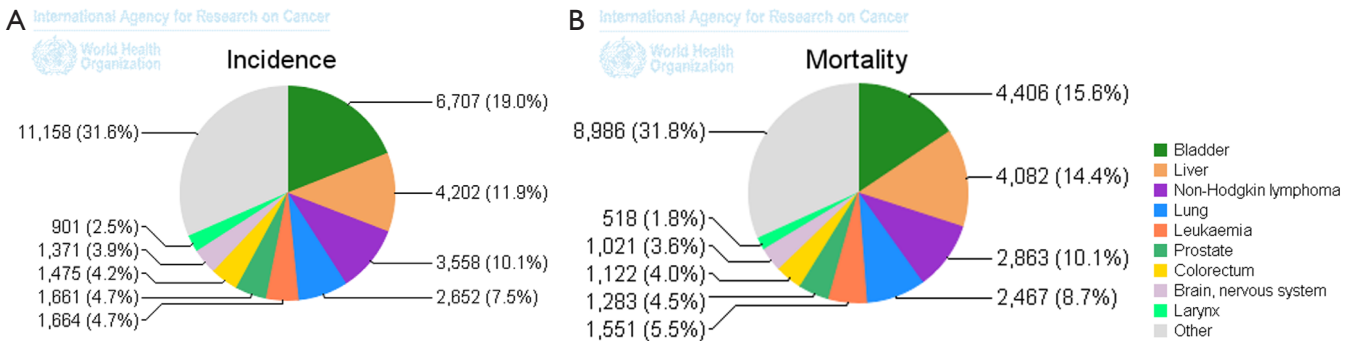

Figure 1 Incidence and mortality of HCC in Egyptian men (Globocan, 2008) (1).

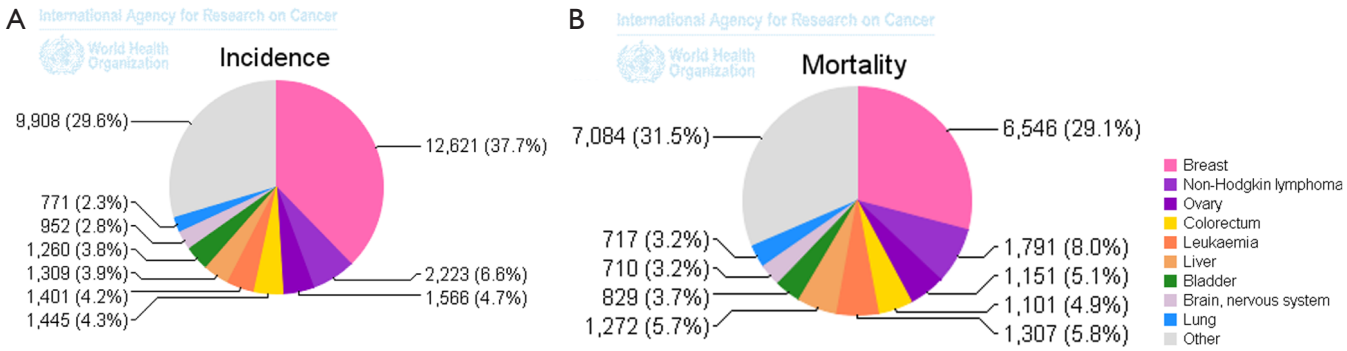

Figure 2 Incidence and mortality of HCC in Egyptian women (Globocan, 2008) (1).

Table 1 Frequencies of HBV and HCV in HCC Egyptian patients

First Author, year (ref.)	Study period	Patient source	Patient N	HBsAg	HCV Ab	HCV/HBV co-infection
Shaker *et al.* 2013 (10)		Tropical Medicine Department, Ain Shams University, Cairo, Egypt. 75% rural	1,313	2.51%	91.32%	
Schiefelbein *et al.* 2012 (11)		Tanta Cancer Center and the Gharbiah Cancer Society in the Nile delta region. Mainly rural	148		89.2%	
El Azm *et al.* 2013 (12)	March 2009 to February 2012	Tanta University Hospitals. Mainly rural	281	26 (9.25%)	186 (66.19%)	29 (10.32%)
Montaser *et al.* 2007 (13)		HCC clinic of the National Liver Institute, Menofeya University	32	15	22	12
Abd El-Moneim *et al.* (14)		National Liver Institute, Menoufiya University	60	19	31	
Hassan *et al.* 2001 (6)		National Cancer Institute, Cairo University	33	15.2%	75.8%	
Darwish *et al.* 1993 (15)		National Cancer Institute, Cairo University	70	43	48	28
Yates *et al.* 1999 (5)		National Cancer Institute, Cairo University	131	95/129 (74%)	99/131 (76%)	

Abbreviations: HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus.

result in HBV reactivation in anti-HBs positive patients undergoing chemotherapy (17).

Egypt has possibly the highest HCV prevalence worldwide (18), estimated among the general population to be around 14% (19). Studies of the HCV genome confirmed a uniquely high proportion of genotype 4 (over 90%) in Egypt (20,21). Yet, much of the HCV prevalence data are limited by variability in and selectivity of the populations studied, inconsistent HCV testing methods, and a lack of data regarding mode of transmission. A strong correlation between HCV infection and intravenous treatment for schistosomiasis was frequently reported (22). Schistosomiasis, trematode blood flukes, is endemic in tropical areas of Africa, South America, Asia and the Caribbean. Only S. japonicum which is not present in Egypt has been classified as possibly carcinogenic in humans (23). Since chronic HCV does not typically lead to carcinogenesis for 10-30 years following infection, the rates of liver cancer can be expected to continue increasing until the cohort of intravenous antischistosomal treatment related infected individuals has worked its way through (2,24). This suggests that the true burden of liver cancer in Egypt has yet to be realized.

Chronic HCV infection mostly leads to hepatic cirrhosis before developing HCC (25). HCV is a RNA virus and hence cannot integrate into the host genome. The carcinogenesis of HCV-associated HCC is proposed to be a multistep process involving upregulation of inflammatory cytokines and induction of oxidative stress from chronic hepatitis, fibrosis, liver regeneration, and, ultimately, the development of cirrhosis (26). Moreover, HCV may play a direct role in hepatic carcinogenesis through involvement of viral gene products in inducing liver cell proliferation (27).

Aflatoxins and HCC

There is suggestive evidence for an additional etiologic role of aflatoxin in hepatocarcinogenesis in Egypt. Aflatoxins are toxic and carcinogenic metabolites of moulds, mainly Aspergillus flavus and parasiticum that contaminate a variety of agricultural commodities, particularly peanuts, maize and cottonseed, in countries with hot and humid climates. Aflatoxin B1 (AFB1) is the major metabolite produced by these moulds. Aflatoxins are classified as human carcinogens based on sufficient evidence of carcinogenicity (28).

Dilber *et al.* detected a significant higher percent of aflatoxins in the serum of Egyptian patients with HCC compared to their controls; with a two-fold increased risk (29). Also, Rahman El-Zayadi *et al.* examined 200 HCC cases and 120 healthy controls and detected AFB1 in 17% of the HCC cases compared to 9.4% of the healthy controls (risk ratio =2) (30). The level of AFB1 was significantly higher in patients having multiple lesions and also in patients presenting with tumor size more than 5 cm. This may be related to the effect of AFB1 as predisposing factor affecting all the liver homogenously (31). El-Kafrawy *et al.* documented the presence of *p53* codon 249 mutations associated with aflatoxin exposure in a sample of HCC tumor tissues analyzed by gene chip analysis in Egypt (32). Generally, in human cancer, in more than 50% of tumors, *p53* is mutated and these mutations occur at the third position of codon 249 with the GC-TA transversion (33,34). Both aflatoxin exposure and HCV were strongly correlated with liver disease progression to stage G3S3, that was indicative of HCC (35).

Role of pesticides in the etiology of HCC

Occupational exposure pesticides may have a contributory role in the etiology or progression of HCC. A major segment of the Egyptian population (i.e., around 26%) is employed in agriculture (36) and uses pesticides routinely to control insects, weeds, rodents, and fungal infections of crops and livestock. Studies suggested that exposures to organophophorus and carbamate pesticides, as a result of increasing discharge of untreated industrial wastes and agricultural irrigation waste water, are additive risk factors to current HCV and HBV infection among rural males (37,38). Future investigation should address the possible hepatocarcinogenicity of pesticides using biomarkers of exposure and other techniques to better estimate dose-response relationships (35).

Alcohol, coffee, smoking, OCs

Alcohol consumption increases the risk of HCC primarily through the development of cirrhosis. It has been suggested that heavy alcohol consumption of >80 g/d ethanol for at least five years increases the risk of HCC by nearly 5-fold (39). Epidemiological studies suggested a strong synergistic effect of alcohol on both HBV and HCV infections in developing HCC (40). Egyptian surveys have found a gradual increase in the consumption of alcohol, leading to the prediction that this will be the most common form of substance misuse in the coming years (41).

Coffee consumption may have a potentially favorable

effect on the prevention of liver diseases, including liver cirrhosis and HCC (42,43). Some components in coffee, including diterpenes, cafestol, and kahweol, may act as blocking agents via modulation of multiple enzymes involved in carcinogenic detoxification as demonstrated in animal models and cell culture systems (44-46). Moreover, coffee constituents modify the xenotoxic metabolism thorough induction of glutathione-S-transferase and inhibition of N-acetyltransferase (47,48).

The effect of tobacco in the development of HCC is biologically plausible, due to the carcinogenic potential of several of the ingredients in tobacco that are metabolized in the liver (49). A Korean study has found a 50% increase in the risk of primary liver cancer for current male smokers compared to never smokers (50). However, a population based case-control study from the United States did not observe a significantly increased risk of primary liver cancer among current male smokers (51). A prospective study of 12,008 men observed that smoking significantly increased the risk of HCC only in anti-HCV-positive patients but not in those who were anti-HCV-negative when compared to anti-HCV-negative nonsmoking individuals (52). In Egypt, a preliminary case-control study showed significantly higher percentage of HCC patients used to smoke for more than 20 years, more than 20 cigarettes/day and heavier than those in the controls (53). Bakir *et al.* reported that smoking was found in 64% of Egyptian patients with HCC compared to 38% in patients with liver cirrhosis and 39% in controls (54). Another study revealed that tobacco smoking was a common risk factor of HCC among both cirrhotic and noncirrhotic patients (55). According to WHO statistics 2009, an estimated 40% of Egyptian males above the age of 15 years are smokers.

Oral contraceptives (OCs) appear to be associated with the development of benign liver tumors such as hepatic hemangioma, hepatocellular adenoma or focal nodular hyperplasia (56). Malignant transformation can occur within the context of hepatic adenomas after 11 years mean duration of OCs use (57). The frequency of HCC among hepatic adenomas appears to vary from 5% to 18% (58,59). In Egypt, 10.8% of married women aged 15-49 years were relying on OCs (60).

Host-related risk factors

Obesity

The prevalence of obesity has increased to epidemic proportions over the last three decades. According to WHO statistics 2008, an estimated 46.3% of females in this age group are said to be obese, in comparison with approximately 22.5% of Egyptian males. Excess body mass is classified as overweight if the body mass index (BMI) is >25 and <30 kg/m^2, or obese if the BMI is ≥30 kg/m^2. Both are associated with a higher risk of developing all cancers, including liver cancer (61). Those patients who were overweight had a 17% increase in risk of developing HCC, whereas obese patients had an 89% increase in risk (62). Thus, surveillance is important for diagnosis of asymptomatic HCC among this population.

Diabetes mellitus (DM)

A positive correlation between the history of diabetes mellitus and HCC was observed (63). Some possible mechanisms explained this association. Most non-insulin dependent diabetics show hyperinsulinemia. Thus, insulin or its precursors may interact with liver cells to stimulate mitogenesis or carcinogenesis (64,65). Another possible pathway is that a *p53* mutation (an apoptotic factor) was noted frequently in HCC patients with diabetes rather than non-diabetics, this might provide an evidence for a molecular mechanism involving this common association (66).

According to WHO statistics 2008, an estimated 7.4% of Egyptian females and 7% of Egyptian males above the age of 25 years are said to have elevated blood glucose. An Egyptian study revealed high prevalence of DM in liver cirrhosis and HCC but no statistically significant difference in prevalence of DM between HCC and liver cirrhosis patients (54).

Nonalcoholic fatty liver disease (NAFLD)

NAFLD is being diagnosed with increasing frequency as a manifestation of the metabolic syndrome, obesity and diabetes mellitus type 2. The key process in NAFLD that predisposes patients to HCC is the development of NASH. The diagnosis of NASH relies on a biopsy with a histopathology showing features of steatosis, hepatocellular injury (ballooning, Mallory bodies), and fibrosis (67). The presence of NASH places patients at risk for progressive fibrosis and subsequent cirrhosis. The pathophysiology of hepatic carcinogenesis in patients with NAFLD-NASH has not been completely elucidated (68). But initial research suggests that excess fatty acid supply and hepatocellular steatosis elicit increased fatty acid oxidation with subsequent enhanced reactive oxidative stress (69). This process further promotes the release of proinflammatory cytokines, prooncogenic signals and

epigenetic changes. Importantly, these cascades of events may take place in the absence of cirrhosis. In fact, case reports have been published where HCC arose in patients with NASH in the absence of cirrhosis (70).

Most population-based cohort and case-control studies support the link between NAFLD and HCC by showing that patients who are obese and have diabetes mellitus type 2 are twice as likely to develop HCC compared to non-obese and nondiabetic patients (71-74). An Egyptian epidemiological study over last 15 years including 1,759 HCC patients found that 5.3% of patients had suffered from NASH (75).

NAFLD-NASH is an emerging risk factor for HCC with the potential to contribute and eventually overtake HCV as the main risk factor for HCC given the galloping rates of obesity and diabetes in the world (76). Efforts should continue to better understand the link of NAFLD-NASH with HCC.

Iron overload

Hereditary hemochromatosis, a rare autosomal recessive genetic disorder characterized by excess iron absorption, is caused by mutations in the *HFE* gene and/or other mutations in the iron metabolism machinery (77). The estimated prevalence of Hereditary hemochromatosis in Egypt is around 0.5% (78). The altered iron metabolism seen in hereditary hemochromatosis leads to excess iron storage in the liver and the subsequent development of liver cell damage. Several studies have shown that the diagnosis of hereditary hemochromatosis confers a consistent and markedly elevated risk for the development of HCC (79-81). An Egyptian study revealed that the frequencies of *HD* and *DD* genotype of *H63D* mutation were significantly increased among HCC patients compared to control group and to cirrhosis group (82).

In fact, patients with excess total body iron secondary to other etiologies such as β thalassemia or iron overload in people of African descent have been shown to have a higher risk of HCC in the absence of genetic hemochromatosis (83,84). Regardless of etiology, surveillance for HCC should be undertaken in case of iron overload (85).

Autoimmune hepatitis (AIH)

AIH is a disease of unknown etiology affecting females mainly (86). It is an inflammation of the liver that occurs when immune cells mistake the liver's normal cells for harmful invaders and attack them. The risk of HCC among AIH patients with cirrhosis is 1.9% per year. This is comparable to HCC risk among patients with cirrhosis secondary to HBV, HCV or alcohol-related liver disease (87). In Egypt, an epidemiological study over last 15 years including 1,759 HCC patients found that 0.5% of patients had suffered from AIH (75). HCC incidence of about 1% has been reported from different geographic areas among chronic AIH dependent liver cirrhosis (88-90).

Others

Epidemiology studies revealed that severe alpha1 antitrypsin deficiency (A1ATD) is a significant risk factor for cirrhosis and HCC unrelated to HBV or HCV infections. However, predisposition to HCC in moderate A1ATD is rare, and probably occurs in combination with HBV and/or HCV infections or other unknown risk factors (91). It is proposed that accumulation of polymers of A1ATD variants in endoplasmic reticulum of hepatocytes leads to damage of hepatocytes by gain-of-function mechanism (92). The increased frequency of mutant A1AT deficiency alleles together with the existance of *HFE* mutant alleles among HCV liver cirrhosis Egyptian patients may warrant us to do further studies assessing their relevance for risk stratification for disease progression (93).

Hereditary Tyrosinemia is an autosomal recessive inborn error of tyrosine metabolism caused by a deficiency of fumarylacetoacete hydrolase (FAH). Hepatomegaly with focal hepatic lesions is the commonest presentation. It is increasingly recognized among Egyptian children; this may be explained by the high rate of consanguinity among Egyptians (94). Tyrosinemia might be complicated by the development of HCC (95). Thus, dietary or pharmacological management of hereditary tyrosinemia might offer a strategy for prevention of HCC in these cases (96).

Conclusions

As in many developing countries, Egypt is undergoing an epidemiologic transition. With increasing urbanization, smoking rates, environmental exposures, aging and life style changes, in addition to the heavy burden of HCV, it is likely that HCC will continue to rise in the next few years. However, with wider use of Hepatitis B vaccination, the importance of HBV will decrease in the future. As HCV related HCCs are on the increase in many geographical areas, a safe and effective vaccine that prevents and treats

HCV infection is urgently required. Other possible risk factors of HCC such as DM and obesity deserve more concern for their rapid increasing worldwide. Such review should help define the complex aetiology of HCC, enabling policy makers to create targeted and more efficient prevention and screening programs. Our review produced important preliminary insights that can be used to develop more refined, prospective analyses of HCC magnitude and risk in Egypt.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Omar A, Abou-Alfa GK, Khairy A, Omar H. Risk factors for developing hepatocellular carcinoma in Egypt. Chin Clin Oncol 2013;2(4):43. doi: 10.3978/j.issn.2304-3865.2013.11.07

