سورة البقرة الآية: ٣٢

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a hypervascular malignancy arising from liver parenchyma and is the third leading cause of death worldwide ***(Bupathi et al., 2014).***Hepatocellular carcinoma (HCC), which account for 70% to 85% of the primary liver cancer cases, is rarely detected at its early stage, resulting in a short survival of few months ***(Sun et al., 2013).***An estimated 33,190 new cases of liver cancer (including intrahepatic bile duct cancers) are expected to occur in the US during 2014. Most (80%) of these cases are hepatocellular carcinoma (HCC) ***(American Cancer Society, 2014).***

Hepatocellular carcinoma (HCC) particularly has high prevalence in East and Southeast Asia and sub-Saharan Africa, whereas China alone accounts for more than 50% of all cases ***(Hu et al., 2012).***An estimated 28,720 new cases of liver cancer (including intrahepatic bile duct cancers) are expected to occur in the US during 2012. Liver cancer incidence rates were increased by 3.6% per year in men and by 3.0% per year in women from 2004 to 2008, trends that have persisted since 1992 ***(American Cancer Society, 2012).***

The behavior of HCC in Egypt is similar to Western countries with an overall frequency 2.3% among other types of cancer. In Egypt, the epidemiological situation differs from that of Western countries. Hepatitis C virus (HCV) prevalence was very high (estimated among adults at 10% and 20% in urban and rural areas respectively). The origin of the epidemic has been attributed to mass campaigns of parenteral anti-schistosomiasis treatment in

rural areas in the 1960s–70s. Since the virus has continued to spread, mainly through intravenous injections and other medical procedures ***(Sharaf El-din et al., 2008).***

Chronic hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infections resulting in chronic liver diseases are the major causative factors for HCC. Numerous studies have showed that HCC develops through aberrantly activation of various signaling pathways involved in cellular proliferation, differentiation, angiogenesis, and metastasis. But the precise molecular mechanisms underlying virus induced-HCC development and progression are still unclear ***(Fan &Tang, 2014).***

Furthermore, nearly 90% of HCC develops in the background of chronic liver diseases that are either caused by chronic inflammation related to various etiologies, including hepatitis B or C infection and alcohol intake, or other hepatic toxin exposure, and even non-alcoholic fatty disease. The complexity and heterogeneity of HCC tumorigenesis contributes to an intrinsic resistance of tumor cells to conventional chemotherapy and radiotherapy ***(Hung et al., 2014).***

Alpha- Fetoprotein (AFP) is one of the oncofetal proteins expressed during the fetal period and reexpressed in specific neoplastic cells. The protein is synthesized in the human fetal liver, yolk sac, and some gastrointestinal cells and is a characteristic marker of hepatocellular carcinoma (HCC), yolk sac tumor, and certain gastric carcinomas (GCs) ***(Ikeda et al., 2012).***

AFP is a tumor marker that is elevated in 60%-70% of patients with HCC. Normally, levels of AFP are below10 ng/ml, but

marginal elevations are common in patients with chronic hepatitis or cirrhosis. However, all patients with elevated AFP should be screened for HCC with imaging, especially if there has been an increasing trend from baseline level ***(Lau & Lai, 2008).***

Serum AFP is a marker that has low sensitivity and high specificity ***(Sun et al., 2008).*** Although AFP is a widely used biomarker for the diagnosis and follow-up of HCC, the AFP level is not increased in 40% of patients with HCC. Identification of additional novel biomarkers to improve the diagnosis and prognosis in HCC is needed ***(Hung et al., 2011).***

A secreted glycoprotein YKL-40 also named chitinase- 3- like-1 is normally expressed by multiple cell types such as macrophages, chondrocytes, and vascular smooth muscle cells. However, a prominently high level of YKL-40 was found in a wide spectrum of human diseases including cancers and chronic inflammatory diseases where it was strongly expressed by cancerous cells and infiltrating macrophages. In the chronic inflammatory diseases, YKL-40 is appreciated to mediate infiltration, differentiation, and maturation of macrophages, the primary leukocytes in response to inflammation ***(Shao, 2013).***

YKL-40 plays a role in inflammation, remodeling of extracellular matrix and regulation of cell proliferation. It has been suggested that YKL-40 may have an important effect on the proliferation and differentiation of cancer cells, on the prevention of cell apoptosis, and stimulate angiogenesis and fibroblasts surrounding the tumor***(Wang et al., 2012)***.

Clinical studies of patients with different types of solid tumors (ovarian cancer, and with endometrial cancer, small cell lung cancer, glioma, colorectal cancer, gastric cancer, and breast cancer) have indicated that YKL-40 values are remarkably elevated in cancer patients compared to healthy one ***(Qin et al., 2007).***

GP73, also called Golgi phosphoprotein 2 (GOLPH2), is a resident Golgi trans-membrane glycoprotein with 400 amino acids and the 73kDa molecular weight was found up-regulated in expression in virus-infected hepatocyte. Several recent studies indicate that GP73 is one of the most promising serum markers for HCC. Although there are studies reporting that the sensitivity of GP73 was higher than that of AFP in the diagnosis of early HCC, the potential clinical value of GP73 as a better serum biomarker than AFP remains controversial ***(Hu et al., 2013).***

In addition to hepatocytes, GP73 was consistently expressed by normal biliary epithelial cells as well as hepatic stellate cells in injured livers. Further studies demonstrated constitutive expression in cells of the epithelial lineage, especially in the prostate, gut, breast, and thyroid, and within the central nervous system ***(Willyard, 2007).***

Review of Literature

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is among the most common human cancers ***(Jiang et al., 2012).***Liver cancer in men/women is the fifth/seventh most frequently diagnosed cancer worldwide but the second/ sixth most frequent cause of cancer death ***(Jemal et al., 2011).***An estimated 20,550 liver cancer deaths (6,570 women, 13,980 men) are expected in 2012. From 2004 to 2008, death rates for liver cancer increased by 2.2% per year in men and were stable in women. Incidence and mortality rates are more than twice as high in men as in women ***(American Cancer Society, 2012),*** **Fig. (1)**.

Being one of the most frequently diagnosed cancers worldwide, liver cancer is the second leading cause of cancer death in men and the sixth leading cause of cancer-related death in women ***(Jemal et al., 2011).*** About 90% of HCC cases arise from cirrhosis, which can be attributed to a wide range of factors including chronic viral hepatitis B or C (HBV or HCV) infections, alcohol abuse, nonalcoholic steatohepatitis (NASH), autoimmune hepatitis, primary biliary cirrhosis (PBC), and carcinogens exposure. On siderable progresses on unraveling molecular mechanisms of HCC have been achieved recently, paving the way to the early detection and treatment of HCC ***(Sun et al., 2013).***

Carcinogenesis of HCC is a multifactor, multistep, complex process, which is associated with a background of chronic liver diseases or persistent infection of hepatitis B virus (HBV) or

hepatitis C virus (HCV), along with alcohol and aflatoxin B1 intake which are widely recognized etiological agents in HCC ***(Ni et al., 2013 and Wei et al., 2013).***

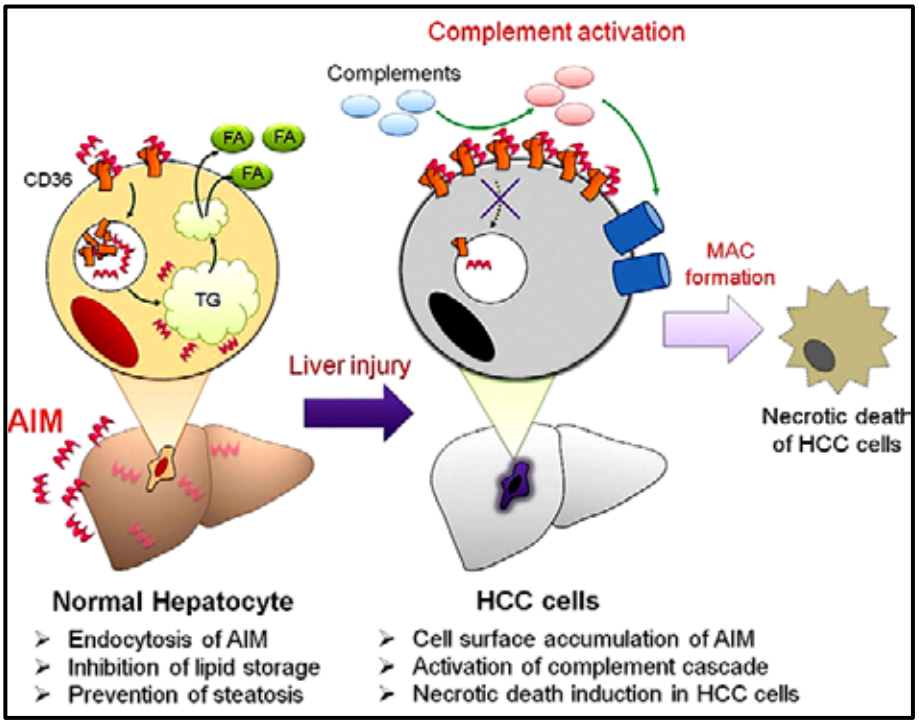


Figure (1): The stages of liver damage ***(Maehara et al., 2014).***

Epidemiology of HCC

Geographical Variation

This disease is predominant in Asia and Africa, but its incidence is steadily increasing throughout the rest of the world ***(Jemal et al., 2011).***Asian countries account for 75–80% of the roughly 650,000 HCC cases reported globally each year. Of particular note is the fact that China alone accounts for 55% of HCC cases worldwide ***(Jemal et al., 2011).***

From 2006 to 2010, rates increased by 3.7% per year in men and by 2.9% per year in women. An estimated 23,000 liver cancer deaths (7,130 women, 15,870 men) are expected in 2014. From 2006 to 2010, death rates for liver cancer increased by 2.3% per year in men and 1.4% per year in women ***(American Cancer Society, 2014)*.**

HCC ranks the second in China among all malignancies and its mortality is almost equal to its morbidity. The incidence of HCC is increasing in China, and HCC is the second most common cancer in urban areas and first most common in rural areas***(Tanaka et al., 2011).***The number of incidence cases and liver cancer deaths are similar because most HCCs are detected at an advanced stage in patients with underlying liver dysfunction, making this a highly lethal cancer ***(Yang & Roberts, 2010)***.

In Middle Eastern countries, liver cancer is a major concern among men, especially in certain countries such as Egypt and Saudi Arabia, and to a lesser extent in other countries of this region as shown in ***(Poustchi et al., 2010),*** **Table (1)**.

The prevalence of HCC is high in the Nile Delta area. Hepatocellular carcinoma is more common in males, rural residents and farmers which it is believed that pollution due to insecticides might be one of the risk factors ***(Abdel-Wahab et al., 2007)***.

Table (1): Population based Cancer Registry Data for Middle Eastern Countries ***(Poustchi et al., 2010)***.

Country	Annual incidence of liver cancer per 100,000	
	Males	**Females**
Egypt	21.9	4.5
Kuwait	8.1	3.6
Oman	7.4	3.2
Saudi-Arabia	5.9	2.2
Bahrain	5.3	3.1
Lebanon	3.5	2.2
Qatar	3.4	1.8
Palestine	2.6	0.7
Tunisia	2.2	0.7
Jordan	1.9	1.3
Iran	1.4	1.9

Age and Sex Distribution

Liver cancer incidence rates are about three times higher in men than in women. Liver cancer is the second leading cause of cancer death in men and the sixth leading cause of cancer-related death in women ***(Jemal et al., 2011).***In Japan, HCC ranks as the third leading cause of cancer-related deaths in males and the fifth leading cause of cancer-related deaths in females. More than 30,000 patients die of HCC every year ***(Chung et al., 2010).***

In China, HCC ranks as the second leading cause of cancer-related deaths in males and the third leading cause of cancer-related deaths in females. Indeed, according to the GLOBOCAN estimates for 2002.The overall male: female incidence ratio was 2.4, and this ratio was even higher in areas

of greater HCC risk **(*Venook et al., 2010)*.** The gender- specific age- adjusted incidence rate (AAIR) ratio ranges from 1.3 to 3.6 worldwide ***(Poustchi et al., 2010),*** **Table (2)**.

In Egypt, HCC is third among cancers in men with > 8000 new cases predicted by 2012 ***(Goldman et al., 2007)*.** Moreover, there has been an alarming increase in incidence of liver cancer in Egypt, which is now three times higher than that in the USA ***(Lehman et al., 2008)*.**

The HCC epidemic in Egypt is associated with hepatitis C viral (HCV) infection; Egypt has the highest prevalence of HCV in the world with about 13.8% of the population infected and 7 million with chronic HCV liver disease. Up to 90 % of HCC cases in the Egyptian population were attributed to HCV ***(Goldman et al., 2007)***. Several reports showed seropositivity for HCV ranging from 12.7 % in seashore governorate to 36.3% in the Nile delta regions of Egypt ***(Anwar et al., 2008 and Lehman & Wilson, 2009)***.

Hepatitis B virus (HBV) was found at high rates, but after increase in HCV prevalence the rates of HBV declined ***(Soliman et al., 2010)***. Also, the environmental factors might contribute to the incidence of HCC in Egypt ***(Lehman et al., 2008)***. Hospital-based studies from Egypt have reported an overall increase in the relative frequency of all liver related cancers in Egypt (>95% as HCC), from approximately 4% in 1993 to 7.3% in 2003 ***(Lehman et al., 2008)***.

Table (2): Age- Standardization Incidence Rates for HCC ***(Yang & Roberts, 2010).***

Countries	Men	Women
Low resource		
Mongolia	116.6	74.8
Middle Africa	18.9	9.6
Eastern Africa	7.2	3.6
Intermediate resource		
China	37.4	13.7
Caribbean	6.3	4.4
South Africa	13.9	5.1
High resource		
Korea	38.4	10.6
Southern Europe	9.8	3.2
Western Europe	7.2	2.1

Etiology of HCC

Most HCC develop in patients with a history of chronic hepatitis or cirrhosis in which there is continuous inflammation and regeneration of hepatocytes. Unlike other solid malignancies, the coexistence of inflammation and cirrhosis makes the early diagnosis and prognostic assessment of HCC much more difficult ***(Zhu et al., 2013).***

The global variation in HCC incidence has led to the realization that largely geographic differences in the prevalence of different disease risk factors as indicated in ***(Motola-Kuba et al., 2006),*** **Table (3).** This disease has underlying causative risk factors including hepatitis B and C, aflatoxins, and alcoholic and nonalcoholic steatohepatitis***(Bupathi et al., 2014).***

About 90% of HCC cases arise from cirrhosis, which can be attributed to a wide range of factors including chronic viral hepatitis B or C (HBV or HCV) infections, alcohol abuse, nonalcoholic steatohepatitis (NASH), autoimmune hepatitis, primary biliary cirrhosis (PBC), and carcinogens exposure ***(Sun et al., 2013).***

Table(3): Risk factors for HCC development ***(Motola-Kuba et al., 2006).***

Major risk factors	Minor risk factors
v **Cirrhosis**	v **Primary biliary cirrhosis**
v **Male sex**	v **Thorotrast exposure**
v **Older age**	v **Tobacco**
v **HBV or HCV infection**	v **Vinylic exposure**
v **Hemochromatosis, Wilson's**	v **Estrogen use**
v **Alfatoxin exposure**	v **Androgen use**

Many risk factors seem to predispose HCC, which either present individually or collectively depending on the environmental situations. Most of intermediating steps of HCC pass through molecular and transcriptional events leading to hepatocyte malignant transformation. These steps are triggered by hepatitis B or C or coinfected together ***(Abdel- Hamid, 2009),*** **Fig. (2)**.

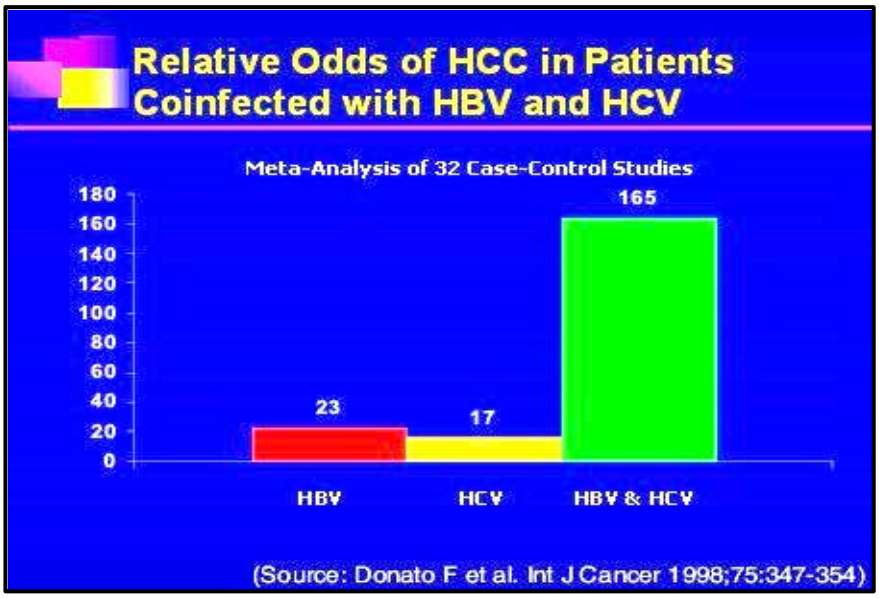
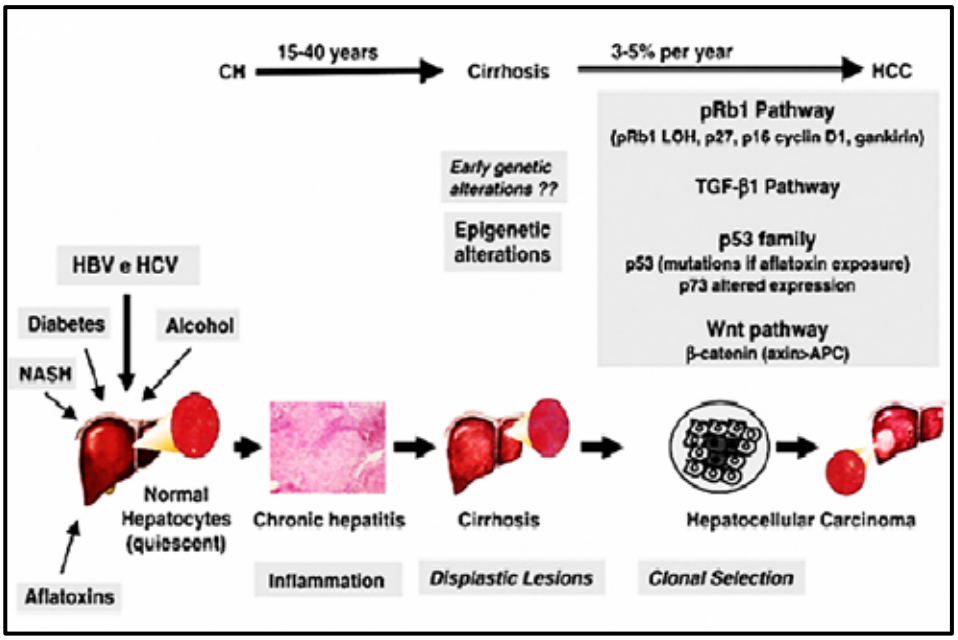


Figure (**2)**: Hepatitis B coinfection in patients with hepatitis C seems to contribute heavily to HCC development ***(De Giorgi et al., 2009).***

Other environmental and genetic risk factors (e.g. excessive alcohol consumption, aflatoxin intake, microcystin, anabolic steroids); parasitic infections (schistosomiasis and liver flukes) are known to increasing the prevalence of HCC***(Yang & Roberts, 2010)***. Hereditary diseases as (hemochromatosis, alpha-1- antitrypsin deficiency and Wilson's disease), steatosis, and non-alcoholic fatty liver diseases (NAFLD) as diabetes, obesity play a role in minor number of cases ***(Gomaa et al., 2008 and Abdel- Hamid, 2009)*** as shown in **Fig. (3).**



Figure(3): Risk factors for HCC and different pathways of pathogenesis. NASH = non-alcoholic steatohepatitis, CH = chronic hepatitis ***(Levrero, 2006).***

I- Hepatitis Virus Infection

Hepatitis is an inflammation of the liver. It can have a number of different causes, including infection (viruses, bacteria, fungi and parasites), drugs and chemicals. Viruses are the most common causes of hepatitis due to infection. There are a number of different viruses that cause hepatitis (hepatitis A, B, C, D, E, F, G, and H), but only the hepatitis B, C and D viruses can cause chronic hepatitis infections.

A-Hepatitis B Virus

Hepatitis B virus (HBV) infection constitutes a significant health challenge worldwide and is considered as one of the most prevalent chronic viral infections in human. Chronic hepatitis can lead to a variety of liver disorders such as cirrhosis and