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Hepatocellular carcinoma (HCC) in Egypt: Prevalence, risk factors, diagnosis and prevention: A Review

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Abstract:

Hepatocellular carcinoma (HCC) is the most often primary malignancy of the liver, accounting for about 90% of all primary liver malignancies, and is very prevalent in the majority of the world's most populous regions, Egypt was the country with the second-highest risk of liver cancer in 2018 after Mongolia, Over 90% of HCC cases occur in the setting of chronic liver disease. Cirrhosis from any etiology is the strongest risk factor for HCC**.** These risk factors that play an important role in the development of HCC are divided into four groups: 1. Hepatitis Viral infections, 2. the Environmental and chemical toxins risk factors, 3. Lifestyle risk factors, 4. genetic-related risk factors.

The diagnosis of HCC can be made by history, physical examination, and using noninvasive imaging methods such as ultrasound, MRI, and CT scan. In the screening and detection of HCC patients, the most used method is the combination of ultrasonography and serum levels of alpha-fetoprotein (AFP), There is a need for new biomarkers that are more disease-reflective and more sensitive for the identification of HCC patients.

HCC prevention is focused on early avoidance of HCC risk factors (primary prevention), early treatment of risk factors (secondary prevention), and avoiding or reducing HCC recurrence following successful curative therapy (tertiary prevention), In Egypt, HCC prevention by HBV vaccination program**,** and, more recently, the Egyptian government began the 100 Million Seha (100 Million Healthy Lives) campaign in late 2018, to eradicate HCV as a hazard to the public's health.

Keywords: HCC, HBV, HCV, AFP, Risk factors.

Introduction:

Liver diseases are a leading cause of mortality and morbidity globally, accounting for two million deaths annually worldwide (3.5% of all deaths); with 50% related to complications from cirrhosis and 50% related to Hepatocellular Carcinoma (HCC) and viral hepatitis infections (1). Hepatocellular carcinoma (HCC) is the most often primary malignancy of the liver, accounting for about 90% of all primary liver malignancies, and is very prevalent in the majority of the world's most populous regions (2,3). HCC ranks seventh among women and fifth among men globally, with over 700,000 new cases diagnosed and over 600,000 deaths annually. It accounts for 9.2% of all new cases of cancer worldwide and is the third leading cause of cancer-related death, exceeded only by cancers of the stomach and lungs (4). HCC distribution varies

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among the world's regions where rates are the highest in East Asia, Sub-Saharan Africa, and North and West Africa and the lowest in North, Central, and Eastern Europe and South-Central Asia (5).

Prevalence of HCC in Egypt:

In terms of individual countries, Egypt was the country with the second-highest risk of liver cancer in 2018 after Mongolia (Mongolia about four times that of men in China and the Republic of Korea) (6). In an underlying population, the worldwide age distribution of HCC cases is related to the prevalent type of viral hepatitis and the age at which it was obtained. In high-incidence areas, the most prevalent cause is HBV transmitted during labor. The diagnosis of HCC is about a decade earlier compared to areas where HCV is the most prevalent etiology obtained later in life (7).

However, research conducted in Egypt found that HCV infection was becoming more prevalent in the etiology of liver cancer, estimated to account for 40–50% of cases, and that HBV and HBV/HCV infection had a declining effect, accounting for 25% and 15% of cases, respectively (8).

HCC is the most common cancer in Egypt for males, the second most common for women, and the most common cancer overall for both sexes combined (9).

The incidence of HCC has increased to 19.7% of the total cancer cases (25,399 cases are HCC) in 2018. The 2018 incidence data were collected from Aswan, Damietta, and Minia Cancer Registries; HCC is the major cause of death from cancer in Egypt (32.35% of the total cancer deaths). Mortality data were available through the World Health Organization (WHO) (10).

This rising incidence of HCC may be due to the increased frequency of HCV and its complications, advances in screening programs and diagnostic techniques, together with the rising survival rate of individuals with cirrhosis, enabling some patients to develop HCC. The increased incidence of HCC among urban inhabitants could be a consequence of improved access to medical services, leading to an underestimation of HCC in rural communities (11).

Risk factors

Over 90% of HCC cases occur in the setting of chronic liver disease. Cirrhosis from any etiology is the strongest risk factor for HCC (12). These risk factors that play an important role in the development of HCC are divided into four groups: 1. Hepatitis Viral infections, 2. the Environmental and chemical toxins risk factors, 3. Lifestyle risk factors, 4.
genetic-related risk factors.

1. Hepatitis Viral infection risk factors

(a) HBV infection

HBV is a double-stranded DNA-containing virus that can integrate its DNA into the hepatic cells, act as a mutagenic agent, and cause secondary chromosomal rearrangement and increasing genomic instability. This is the reason why the risk of HCC development is 100-fold higher for patients who are infected with HBV in comparison with those who are not infected (13).

Almost 50% of all cases of HCC are associated with HBV infection and 25% are associated with HCV, the lifetime risk of HCC development among HBV carriers being from 10% to 25% (14).

The countrywide vaccination program has significantly reduced the prevalence of HBV infection (15), in Egypt, the prevalence of HBV infection has decreased over the last 20 years due to a successful nationwide vaccination approach (16).

(b) HCV infection

HCV does not integrate into the DNA of the host. Cirrhosis is an important phase in the viral carcinogenesis of HCC. Chronic inflammation caused by chronic hepatitis C virus infection, followed by fibrosis, necrosis, and regeneration, leads to the development of HCC. Viral structural and non-structural proteins (NS3, NS4A, NS4B, NS5A, and NS5B) have been identified as molecular biomarkers in liver carcinogenesis. HCV-associated HCC is more common in individuals with cirrhosis or severe fibrosis (17,18).

HCV protein expression induces mutation and malignant transformation in infected hepatic cells, leading to the development of HCC (19). The major cause of malignant transformation is thought to be repeated inflammation, damage, and regeneration (20).

There are six distinct genotypes of HCV isolated, according to phylogeny and sequencing studies of HCV genomes. In Egypt, genotype 4 is the most common, accounting for up to 92.5% of infected patients, followed by genotype 1 (3.6%) (21,22). The prevalence of HCV infection decreased from 14.7% in 2008 to 10% in 2015. This was linked to the age of the antischistosomal therapy group (23).

2. Environmental and chemical toxins risk factors

(A) Chemical compounds

The liver is the primary organ involved in chemical agent metabolism; it has a distinct blood supply and is involved in several metabolic and excretory activities. This causes liver damage such as fatty liver, hepatocellular injury, cirrhosis, and HCC (24). Because about 26% of Egyptians are employed in agriculture (11) , there is a high risk that they will come into contact with pesticides. According to a study by Abou El Azm et al. (2014), pesticides, superphosphate, and ammonium sulfate fertilizers accounted for the majority of risk factors other than HBV or HCV, accounting for 13.87 percent of all HCC cases in Egypt (94.87%, $P < 0.001$), with significant exposure occurring in farming, industry, and residential settings. According to Abou El Azm AR et al. (2014), the HCC in these patients met certain characteristics, including being solitary, smaller in size, and having lower alpha-fetoprotein (AFP) titers **(25)**.

(b) Aflatoxins

It is well-recognized that aflatoxins played a significant part in the development of HCC in Egypt. These are recognized carcinogenic byproducts of molds, mainly *Aspergillus flavus*, and parasites that contaminate a wide range of agricultural products, including cottonseed, peanuts, and maize (26). High serum levels of aflatoxin were detected in Egyptians with HCC in a study that was carried out by **Dilber *et al., 1999***. (27) AFB1 is the main metabolite produced and is the most carcinogenic, teratogenic, and mutagenic metabolite **(28)**. It was present at high levels in those presenting with multiple hepatic focal lesions over 5 cm in diameter **(29)**. Anwar *et al* found that the presence of Aflatoxins and HCV is connected to hepatic disease progression to G3S3 which indicates HCC (30). In a study done by Sharaf-Eldin et al reported that Aflatoxin levels were shown to be considerably higher in HCC patients than in cirrhotic persons and controls (31).

(c) oral contraceptives

The link between oral contraceptive COC usage and liver cancer risk assessments has provided conflicting results. A meta-analysis of 12 case-control studies including over 700 women found mixed findings for malignancies such as HCC (32). Six studies in one review found a 2- to 20-fold increase in risk (32). Simultaneously, a larger study found that COC consumption was not associated with an increased incidence of hepatic neoplasms (33).

(d) Autoimmune hepatitis (AIH)

Autoimmune hepatitis (AIH) is an inflammatory disease of the liver caused by the immune system. In rare cases, HCC can develop as a result of chronic autoimmune hepatitis (AIH)-dependent liver cirrhosis. HCC is substantially less common than other causes of liver cirrhosis, such as chronic viral hepatitis, alcohol, or hemochromatosis (34).

3. Lifestyle and metabolic factors

(a) Smoking

Smoking is another risk factor for HCC related to tobacco (2). A Korean study found a link between smoking and primary liver cancer, with the risk increasing by up to 50% when compared to nonsmokers (35). According to Bakir and Ali-Eldin, 64% of Egyptian patients with HCC smoke (36). Heavy smoking is one of the primary risk factors for non-B non-C HCC in Egypt, according to Abou El Azm et al (25). Another study identified smoking as a major cause of HCC in Egypt (37). Another Egyptian study found that patients who smoked 20 cigarettes per day for more than 29 years had an elevated chance of developing HCC (38).

(b) Obesity

Globally, about 1.9 billion individuals are overweight, with 600 million obese (39). Obesity is associated with the development of various metabolic disorders, including diabetes mellitus and hypertension, as well as an elevated risk of HCC development. Premorbid obesity is linked to a twofold increase in the risk of HCC-related mortality (39). According to Wang Y et al. (2012), every 5-unit rise in BMI body mass is associated with a 39% higher risk of HCC (40).

A survey of primary school pupils in Egypt revealed that the overall prevalence of obesity and overweight was 13.9% and 16.2%, respectively (41). It is estimated that 61%70% of persons aged 20 and over have it, with a frequency of 18%22% in males and 39%48% in women (42).

(c) Diet

Although a case-control study in Greece found no effect of diet (particular food category or specific nutrients) on the etiology of HCC (43), other investigations did. Case-control research in Italy (44) discovered an inverse relationship between HCC risk and a diet high in both linoleic acid and β-carotene. Another Italian case-control research (45) found that patients at high risk for HCC benefitted from a high diet of particular foods. Research studies that investigate the relationship between diet and HCC risk in Egypt are lacking.

(d) Diabetes

Many genome-wide association studies (GWAS) have identified many loci that affect the risk of type 2 diabetes (46). There are many hypotheses (47) that explain the link between diabetes and the increased risk of HCC. Diabetes is one of the components of metabolic syndrome that may lead to non-alcoholic steatohepatitis (NASH) and consequently HCC. Also, persistent increase in insulin levels in type 2 diabetic patients leads to both insulin resistance (IR) and an increase in the level of insulin-like growth factor-1 (IGF-1) in most tissues including the liver which may accelerate carcinogenesis. In addition, chronic hyperglycemia may cause both oxidative stress and damage to hepatocytes (48,49).

Many research have documented the prevalence of diabetes in HCC Egyptian patients (50), and one study verified that type 2 diabetes raises the risk of HCC by 2-3-fold (37).

(e) Alcohol

Alcoholism is a well-known risk factor for the development of HCC (51). Excessive drinking is responsible for 60%-80% of liver-related mortality in the European Union (52), and alcohol-related chronic disease is the second most common indication for liver transplantation, accounting for approximately 40% of all primary liver transplants (53). This risk is low in Egypt Heavy alcohol use raises the risk of HCC by up to 16% (54). Heavy ethanol drinking for more than ten years increases the risk by a factor of five to sevenfold (55).

(f) Nonalcoholic fatty liver disease (NAFLD)

It is distinguished by an abnormal increase of hepatic triglycerides (> 5%) without extra alcohol intake (56). In general, nonalcoholic fatty liver disease (NAFLD) increases the risk of HCC through developing NASH. In NASH patients, HCC is an independent risk factor for mortality with a hazard ratio = 7.9 (57).

(g) Gender

HCC incidence varies by gender, with males having the fifth highest rate (7.5%) and women having the ninth highest rate (3.4%) (10). In Egypt, HCC ranks second and sixth in cancer in males and females, respectively (11). This gender difference can be explained by two factors: biological and environmental. The quantity of estrogen hormone explains the biological explanation for the variance in HCC incidence in women. It contributes to the suppression of interleukin (IL)-6-mediated inflammation, which lowers both compensatory proliferation and liver damage (58).

Whereas testosterone in men can increase androgen receptor signaling leading to promoting liver cell proliferation (59). This is in addition to variations in epigenetics and immune response. The difference in environmental HCC incidence is explained by men's greater rate of exposure to liver carcinogens such as occupational exposure to chemical compounds, alcohol, and smoking, as well as hepatitis virus infection (60).

4. Genetic risk factors

Some hereditary liver diseases with genetic mutations are thought to increase the risk of developing HCC. These diseases are Wilson disease, hemochromatosis, alpha-1 antitrypsin deficiency, tyrosinemia, glycogen storage diseases, and porphyrias. The same is true for polymorphisms with increased risk for HCC. Polymorphisms in *UGT1A7*, *MnSOD*, and *IL-1B* have been linked to increased risk (61). HCV and HBV infection have been linked to an increased risk of gene mutation, which can contribute to the development of HCC (62). In an Egyptian study, the TNF-α-308 G > A polymorphism was associated with increased HCC risk in an Egyptian population, but no significant difference was found for cytokines interleukin (IL)-1β and IL-10 (63,64). In another study on Egyptian patients, XRCC1 G28152A (rs25487) and XRCC7 G6721T (rs7003908) polymorphisms were found to have a role in susceptibility to HCC in the Egyptian population (65). Epidermal growth factor gene polymorphism 61*G was found to be positively associated with HCC risk in Egyptians. Increased concentration of EGF was associated with the G/G genotype (66). The prevalence of hereditary hemochromatosis in Egypt is reported to be 0.5% (26), this indicates that hereditary disorders are not a major cause of HCC.

HCC diagnosis and surveillance:

The diagnosis of HCC can be made by history, physical examination, and using noninvasive imaging methods such as ultrasound, MRI, and CT scan. In the screening and detection of HCC patients, the most used method is the combination of ultrasonography and serum levels of alpha-fetoprotein (AFP) (67).

European Association for the Study of the Liver (EASL) recommends semi-annual abdominal ultrasound, with or without alpha-fetoprotein (AFP), as the primary strategy for HCC surveillance **(EASL Guidelines 2018)** **(68)**.

Ultrasound is the most widely used imaging technique for regular screening for HCC. It has many advantages, being easy, readily available, non-invasive, and inexpensive. The sensitivity of ultrasound in detecting HCC is not more than 45% (69).

AFP is the most often utilized biomarker in HCC screening. Although it is widely available, inexpensive, and easy to use, its inclusion in the guidelines alongside ultrasonography was controversial (70,71).

Advanced HCC is characterized by elevated serum AFP levels. This has no relationship with tumor size or vascular invasion. With a cut-off of 10.9 ng/mL (typical value between 10 and 20 ng/mL), serum AFP has a sensitivity of around 66% and a specificity of 80% (72).

HCC development and progression are caused by the accumulation of genetic changes that result in tumor-related gene expressions: oncogenes, tumor suppressor genes, genes involved in many regulatory pathways, such as cell cycle control, apoptosis, and angiogenesis, expression of thousands of mRNAs can be measured at the same time due to advanced technology, this provides a thorough data for both diagnosis and therapy of HCC (73). There is a need for new biomarkers that are more disease-reflective and more sensitive for the identification of HCC patients, so many studies have been conducted to evaluate many biomarkers such as miRNA-122 (74), TNF-α (75), Osteopontin Protein (76), Cartilage Oligomeric Matrix Protein (77).

Prevention of HCC:

A clear evaluation of HCC risk variables is extremely beneficial for well-designed HCC preventive methods. In general, HCC prevention is focused on early avoidance of HCC risk factors (primary prevention), early treatment of risk factors (secondary prevention), and avoiding or reducing HCC recurrence following successful curative therapy (tertiary prevention) (78).

There are many ways to primary HCC prevention. WHO recommends routine HBV vaccination of all newborns (within 24 hours) and high-risk populations (79). This widespread vaccination, as well as other behavioral modifications that reduce the risk of infection, are critical components of primary prevention, coupled with the implementation of surveillance programs. Furthermore, antiviral therapy for chronic HBV and HCV patients is employed for secondary prevention of HCC (80)

In Egypt, there are two methodologies for HCC primary and secondary prevention; the HBV vaccination program (16), and, more recently, HCV eradication through a national campaign (81). On the other hand, the World Gastroenterology Organization's worldwide guidelines rank HCC prevention through education as the number one recommendation (82). As a pilot research, an education intervention study was done and yielded promising outcomes (83).

By 2030, the WHO signatories planned to eliminate viral hepatitis no longer a danger to public health. In comparison to the baseline year of 2015, WHO defined elimination as a 65% decrease in mortality and a 90% decrease in incidence **(WHO. Global Health Sector Strategy on Viral Hepatitis, 2016–2021).** The report concentrates on hepatitis B and C since they account for 96% of all hepatitis-related deaths (84)

Despite a widespread immunization campaign across the world, hepatitis B virus (HBV) infection is still a serious health issue, because of its role in the pathogenesis of Hepatocellular carcinoma (HCC), cirrhosis, and chronic liver disease. Acute hepatitis B is a self-limiting condition that affects around one-third of the world's population and disappears after the virus is eradicated (85)

Direct-acting antivirals (DAA) have made it possible to successfully treat HCV in the vast majority of instances, even though there is no vaccination for the disease. As a result, there are currently significant global initiatives to eradicate HCV **(WHO Global Health Sector Strategy 2016) (86-88).**

With a population of 100 million and a lower middle-income status, Egypt has one of the highest rates of HCV infections worldwide (89).

In 2008, 1 in 10 Egyptians between the ages of 15 and 59 had chronic HCV infection, and 15% of the population tested positive for HCV antibodies (seropositive) (90).

The Egyptian government began the 100 Million Seha (100 Million Healthy Lives) campaign in late 2018, to eradicate HCV as a public health issue by 2021**(91).** When the campaign of 100 Million Health Lives concluded, the Egyptian Ministry of Health and Population MOHP said that of the planned 62 million people, almost 50 million Egyptians, and 36,000 foreign citizens had HCV screenings as of the campaign's conclusion (92) 2.2 million of them had seropositive results, a sign of HCV exposure or chronic infection, and were recommended for follow-up testing. 1.6 million of those referred individuals had chronic HCV infection verified **(91).**

It is on track to become the world's first country to eradicate HCV within its borders. The lessons learned from this experience can help other low- and middle-income nations with high HCV burdens develop eradication strategies (92).

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