Risk Factors of Hepatocellular Carcinoma: An Updated Overview

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ABSTRACT

With around 500,000 new cases each year, HCC is the fifth most common cancer in the world and the third leading cause of cancer-related death. Nearly three-quarters of all hepatic malignancies are HCC. It has been listed as the fourth most frequent cancer in Africa. In Egypt, the incidence of HCC has grown. According to Egyptian studies, the rate of HCC cases has increased from 4% in 1993 to 7.3 percent in 2003.

It is one of the most lethal cancers, with recurrence and metastasis after surgical resection. HCC has a significant death rate, particularly in people detected late in the disease’s progression due to the lack of symptoms in the early stages. Because of the lack of screening techniques in impoverished nations, this problem is particularly pronounced. Hepatitis B and C infections are the most common causes of HCC, but persistent alcohol consumption, metabolic disorders (such as diabetes and obesity), and aging can all play a role in the development and progression of HCC. Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infections cause about 80% of HCC cases, especially in the setting of pre-existing cirrhosis or severe fibrosis.

People with HCV infection develop chronic hepatitis in 60–80% of cases, and 10–20% of those patients develop cirrhosis within 20–30 years. HCC can occur in 1–5% of patients with cirrhosis of the liver. Despite the fact that infection rates are reducing in industrialized countries, cirrhosis and hepatocellular carcinoma (HCC) mortality remains a big concern in Egypt. Patients infected with HCV have a 17-fold greater chance of developing HCC. Egypt has the world’s highest HCV prevalence rate, with 14.7 percent of the population infected.

Keywords: Hepatocellular; Carcinoma; HCC; Risk; Cirrhosis.
Epidemiology

Hepatocellular carcinoma (HCC) is the most prevalent type of primary liver cancer and the world’s sixth most frequent solid tumor. Its prevalence has risen dramatically in the previous 5-10 years, ranging between 3% and 9% annually among individuals with chronic liver disease, and it now accounts for around 692,000 fatalities per year. It’s the third most common reason for cancer-related death [1].

Every year, around 750,000 new instances of liver cancer are recorded worldwide. According to population-based studies, the incidence rate continues to approach the death rate, implying that the majority of patients who develop HCC die as a result of it [2].

The Middle East and Africa, notably Egypt, have the world’s highest HCV prevalence, with more than 90% of infections caused by HCV genotype 4 [3]. Gharbiah governorate has Egypt’s first population-based cancer registry, according to data from the National Cancer Institute [4]. After lung cancer, liver cancer is the second most common cancer among men. It accounts for a third of all cases. After breast cancer, non-lymphoma, Hodgkin’s and leukemia, it is the fourth most common malignancy in women. It accounts for 4.1 percent of the total number of cases.

HCC is frequent in the Nile Delta, and it is more prevalent in males, rural people, and farmers, particularly in HCV and HBV patients. Other risk factors in rural regions include aflatoxin (AF) exposure, occupational exposure to chemicals such as pesticides, and endemic illnesses such as Schistosomiasis [5,6].

Risk Factors of HCC

Hepatocellular carcinoma (HCC) is the dominant form of primary liver cancer and is histologically and etiologically distinct from other forms of primary liver cancer [7].
Primary liver cancer

Primary liver cancer is the fifth most prevalent cancer in men and the second leading cause of cancer-related death globally. Females, on the other hand, are less likely to develop liver cancer. The death to incidence ratio for liver cancer is 0.95, indicating an extremely dismal prognosis [8].

Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC), as well as other rare kinds of primary liver cancer, are examples. In most countries, HCC is the most common histologic type of liver cancer, accounting for around 80% of all occurrences. The second most prevalent histologic type is ICC, which accounts for about 15% of all cases [9].

Around 70%–90% of individuals with HCC have a history of chronic liver disease and cirrhosis, with main risk factors for cirrhosis including chronic hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, alcoholic liver disease, and nonalcoholic steatohepatitis (NASH) [10].

Aflatoxin-contaminated food, metabolic disorders such as diabetes and obesity, and certain inherited illnesses like as hemochromatosis are also risk factors for developing HCC [11].

1. Personal History

Gender

Men are more likely than women to get hepatocellular carcinoma. This disparity in the incidence rate could be explained by the fact that males are more prone to be infected with the hepatitis B and C viruses, to drink alcohol, to smoke cigarettes, and to have higher iron stores. Males may be at greater risk due to androgenic hormones and increased genetic predisposition. Female sex hormones may offer some protection [12].

Age

The age at which a person is diagnosed varies greatly depending on where they live. The median age at diagnosis in low-incidence areas is 65 years. Except in patients with cirrhosis, HCC is rarely detected before the age of 40. The age for diagnosis is significantly younger in high-incidence locations,
occurring in the fourth or fifth decades of life. The natural history of hepatitis B virus and hepatitis C virus-related HCC is assumed to reflect diagnosis at a younger age [13].

Race

Japan and Africa have high rates of infection. Hepatitis B infections in childhood are the most common cause of HCC among Asians. The incidence of HCC among Asians is predicted to reduce after the adoption of childhood hepatitis B immunization programs in many Asian nations [14].

2. Family History

The high incidence of chronic HBV infection has been linked to a familial susceptibility to liver cancer. In Asians, vertical HBV transmission is also a prominent source of viral transmission. The found link between a family history of liver cancer and HCC could be explained by HBV infection clustering among family members. Furthermore, HCC development is believed to be linked to first-degree family history of liver cancer in American and European populations, regardless of chronic HBV and HCV infection [15].

3. Liver cirrhosis

The main risk factor for HCC is liver cirrhosis, which is caused mostly by HBV and HCV infection. Indeed, there is evidence that HBV infection is linked to 50% of all HCC cases worldwide, and HCV infection is linked to 25% [16].

Cirrhosis is defined by a decline in hepatocyte proliferation, showing exhaustion of the liver’s regenerative ability, and develops after extended durations of chronic liver illness [17]. This is linked to an increase in fibrous tissue and liver cell death, which provides fertile ground for the growth of malignant nodules [18].

Chronic hepatitis B virus infection

HBV infection causes acute and chronic liver damage, and chronic carriers have been demonstrated to have a 100-fold increased chance of developing
liver cancer [19]. Chronic HBV infection is the leading cause of HCC in the
globe, accounting for 50 to 55 percent of all cases [20]. Despite the fact that
HBV infection is a key risk factor for liver cirrhosis and HCC around the
world, the prevalence of HBV infection in Egypt has been decreasing for the
past two decades [21]. It was discovered that occult HBV infection and HBV
genotypes B or D may have an impact on the outcome of HBV infection and
the development of HCC, and may be significantly linked to HBV in liver
carcinogenesis. In anti-HBs positive patients receiving chemotherapy, a
reduction in immunological state may result in HBV reactivation [22].

HBV-induced malignant transformation has a complicated etiology. HBV-
mediated hepatocarcinogenesis has been linked to at least three distinct
pathways. HBV viral DNA can integrate into the host genome and cause
chromosomal instability, according to research [23]. Second, insertional
mutations caused by HBV integration at certain places in the genome can
activate endogenous genes including the retinoic acid-receptor, cycin A, and
the TRAP1 gene. HBV integration caused changes in 15 genes in tumors,
implying that viral integration near genes governing cell proliferation,
viability, and differentiation is a common mechanism in HBV
hepatocarcinogenesis [24].

HBV modulates cell proliferation by the production of viral proteins,
particularly the X protein, which is the third way by which it contributes to
carcinogenesis (HBx). The 154-amino-acid protein is known as the X protein
since its major function is unknown. Much of the study on HBV
hepatocarcinogenesis has centered on the HBx gene, which appears to have a
role in the malignant transformation process according to numerous lines of
evidence. Despite the fact that HBx does not directly bind to DNA,
investigations have shown that it co-activates the transcription of a number of
critical viral and cellular genes, as well as coordinating the balance between
cell proliferation and death [25].

Co-infection of HBV and hepatitis D virus

In comparison to infection with HBV alone, both superinfection and
coinfection with HDV cause more severe consequences. In acute infections,
these problems include a higher risk of liver failure and a faster development to liver cirrhosis, as well as a higher risk of liver cancer in chronic infections. Hepatitis D has the greatest mortality rate of all hepatitis infections, accounting for 20% of all deaths when combined with the hepatitis B virus [26].

**Chronic hepatitis C virus infection**

Infection with the hepatitis C virus is the leading cause of HCC in the United States, Europe, and Japan, accounting for 48 percent, 56 percent, and 75 percent of cases, respectively [27].

El-Zayadi et al., [28] investigated the prevalence of HCC in Egypt, which accounts for roughly 4.7 percent of CLD patients. HCV antibodies and hepatitis B surface antigen (HBsAg) were discovered in 86.9% of HCC patients, according to the researchers.

Unlike HBV, practically all HCV-related HCC is associated with cirrhosis or severe fibrosis. The typical duration from the commencement of HCV infection to the development of HCC is around 28 years, and the risk of HCC increases rapidly once cirrhosis develops [26]. Male sex, older age, HBV or HIV co-infection, heavy alcohol consumption, diabetes, and HCV infection acquired through blood transfusion or organ donation are all factors that predispose people to HCC [29]. The pathways of tumor growth in chronic HCV patients are unknown. Chronic hepatitis' inflammatory effects and fibrogenesis are frequently blamed. Because the HCV RNA virus lacks reverse transcription ability, its viral genome, unlike that of HBV, is unable to integrate into the genome of the infected cell. As a result, HCV causes HCC indirectly by inducing persistent inflammation, cell death, proliferation, and cirrhosis, but this appears implausible considering the increased risk relative to other chronic liver diseases. As a result, the virus is likely to play a part in the process. The fact that cirrhotic patients who fail to clear HCV with antiviral medication have a 2.5-fold higher risk of HCC than those who successfully clear the infection supports this theory [30, 31].
Co-infection with HIV

HIV infection shortens the survival of patients with HCV-related cirrhosis\cite{32}. In addition, hepatocarcinogenesis could be a more rapid and aggressive process in HIV/HCV coinfected patients\cite{33}.

4. Nonalcoholic fatty liver disease (NAFLD)

The development of NASH is a crucial step in NAFLD that predisposes people to HCC. Patients with NASH are at risk of developing progressive fibrosis and cirrhosis. However, preliminary evidence suggests that increased fatty acid oxidation is induced by excess fatty acid supply and hepatic steatosis, with higher reactive oxidative stress as a result\cite{34}. Proinflammatory cytokines, prooncogenic signals, and epigenetic alterations are all aided by this mechanism. Importantly, these events can happen even if you don't have cirrhosis. The majority of population-based cohort and case-control studies support the association between NAFLD and HCC, revealing that obese and diabetic patients are twice as likely to develop HCC as non-obese and non-diabetic patients\cite{35}. In a 15-year Egyptian epidemiological research of 1,759 HCC patients, it was discovered that 5.3 percent of the patients had NASH\cite{36}. Given the world’s soaring prevalence of obesity and diabetes, NAFLD-NASH is an emerging risk factor for HCC that has the potential to contribute to and eventually overtake HCV as the primary risk factor for HCC\cite{37}.

5. Inherited liver diseases

Hereditary hemochromatosis and iron overload syndromes

Hemochromatosis is characterized by an excess of bodily iron, the majority of which is deposited in parenchymal organs including the liver and pancreas. Excessive iron appears to be directly harmful to host tissues, causing fatal injury or propensity to HCC through interactions of reactive oxygen species and iron itself with DNA. In hemochromatosis, HCC accounts for roughly 3% of all iron-related deaths\cite{38}. According to an Egyptian study, the rates of the HD and DD genotypes of the H63D mutation were considerably higher in HCC patients compared to the control and cirrhotic groups\cite{39}. In fact,
patients with increased total body iron due to etiologies other than genetic hemochromatosis, such as thalassemia or iron overload, have been demonstrated to have a greater risk of HCC in the absence of genetic hemochromatosis \[^{[40, 41]}\].

**Alpha-1-antitrypsin deficiency**

Epidemiological 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 \[^{[42]}\].

**Hereditary Tyrosinemia**

Hereditary Tyrosinemia is an autosomal recessive inborn error of tyrosine metabolism caused by a deficiency of fumaryl acetoacetate hydrolase (FAH) enzyme. 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 \[^{[43]}\]. Tyrosinemia might be complicated by the development of HCC \[^{[44]}\]. Thus, dietary or pharmacological management of hereditary tyrosinemia might offer a strategy for prevention of HCC in these cases \[^{[45]}\].

6. Environmental risk factors

**Alcohol intake**

The mechanism by which alcohol consumption increases the risk of HCC is primarily through the development of cirrhosis. It has been suggested that heavy alcohol consumption of > 80 g/day for at least 5 years increases the risk of HCC by nearly fivefold \[^{[46]}\].

**Coffee**

Patients who drank coffee on a daily basis had a decreased risk of HCC than those who drank it rarely \[^{[47, 48]}\]. Patients at risk of NAFLD or viral-related hepatic fibrosis appear to benefit from moderate consumption of brewed
regular coffee [49]. As established in animal models and cell culture systems, several components in coffee, such as diterpenes, cafestol, and kahweol, may act as blocking agents by modulating various enzymes involved in carcinogenic detoxification [50]. In addition, coffee components alter xenotoxic metabolism by inducing glutathione-S-transferase and inhibiting N-acetyl transferase [51, 52].

**Smoking**

When compared to anti-HCV antibody negative nonsmoking individuals, a prospective research of 12,008 men found that smoking increased the incidence of HCC only in anti-HCV antibody positive patients, but not in those who were anti-HCV antibody negative [53]. A preliminary case-control research in Egypt found that a much greater percentage of HCC patients smoked more than 20 cigarettes per day for more than 20 years and were significantly heavier than the controls [54]. According to the study, smoking was discovered in 64% of Egyptian patients with HCC, compared to 38% of patients with liver cirrhosis and 39% of controls [55]. Another study found that both cirrhotic and noncirrhotic patients were at risk for HCC when they smoked [56].

**Oral contraceptive pills**

Oral contraceptives (OCs) appear to be associated with the development of benign liver tumors such as hepatic hemangioma, hepatocellular adenoma and focal nodular hyperplasia [57]. Malignant transformation can occur within the context of hepatic adenomas after 11 years mean duration of OCs use [58]. The frequency of HCC among hepatic adenomas appears to vary from 5% to 18% [59, 60]. In Egypt, 10.8% of married women aged 15-49 years were relying on OCs [61].

**Aflatoxin exposure**

In many parts of the world, especially Sub-Saharan Africa and Asia, where fungal contamination of grain is frequent, hepatocellular carcinoma is linked to dietary exposure to aflatoxin. This risk appears to be limited to people with
persistent HBV infection, as HBsAg-positive patients with detectable aflatoxin-albumin adducts in the urine have a higher risk of HCC than those who do not have this signature. This is due to the fact that persistent HBV infection and aflatoxin B1 (AFB1) exposure work together to generate HCC. The increased activation of AFB1 in chronically HBV-infected patients is one possible reason for this interaction [62]. AFB1 was found in 17 percent of HCC cases compared to 9.4 percent of healthy controls (risk ratio =2) in a study of 200 HCC cases and 120 healthy controls [63]. AFB1 levels were considerably greater in patients with numerous lesions as well as those with tumors larger than 5 cm in diameter. This could be related to the effect of AFB1 as a predisposing factor that affects the entire liver in a uniform manner [64].

7. Medical Risk Factors

_Obesity_

Overweight and obesity are associated with a higher risk of developing all cancers including liver cancer [65]. Those patients who were overweight had a 17% increase in risk of developing HCC whereas obese patients had an 89% increase in risk [66]. Thus, surveillance is important for the diagnosis of asymptomatic HCC among this population [67].

_Diabetes mellitus (DM)_

Hyperinsulinemia is seen in the majority of non-insulin-dependent diabetics. Insulin or its precursors may thereby trigger mitogenesis or carcinogenesis in liver cells [68, 69]. Another probable possibility is that a p53 mutation (an apoptotic factor) was found more frequently in diabetic HCC patients than in non-diabetics, suggesting a biological mechanism involving this common relationship [70].

According to an Egyptian study, DM is common in individuals with liver cirrhosis and HCC, although there is no statistically significant difference in DM frequency between HCC and liver cirrhosis patients [55].
8. Autoimmune hepatitis (AIH)

AIH is a disorder of unclear cause affecting females mostly [71]. It is an inflammation of the liver that arises 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 percent every year. This is equivalent to HCC risk in patients with cirrhosis secondary to HBV, HCV or alcohol-related liver disease [67]. In Egypt, an epidemiological investigation over the last 15 years encompassing 1,759 HCC patients revealed 0.5 percent of patients have suffered from AIH [36]. Moreover HCC incidence of about 1 percent has been recorded, from diverse geographic areas, among chronic AIH dependent liver cirrhosis [72].

9. Schistosomiasis

Schistosomiasis is a major public health issue in Egypt, and Schistosoma mansoni infection is a leading cause of liver illness. Until control the schistosomiasis infestation, the Egyptian Ministry of Health (MOH) ran a community-wide therapeutic effort employing parenteral tarter emetic from the 1950s to the 1980s. Unfortunately, this resulted in a huge reservoir of HCV infection in the country due to needle re-use throughout therapy [73]. Several investigations have demonstrated that co-infection with schistosomes may alter the course of hepatitis C genotype and contribute to more serious consequences, including as portal hypertension at an earlier stage and rapid progression to hepatitis C-associated fibrosis. This causes HCC to proceed more quickly than in those who do not have a parasite burden [28].

10. Precancerous lesions predisposing to HCC

Adenomatous hyperplasia (AH)

The liver adenomatous hyperplasia, commonly known as the macro-regenerative nodule (MRN), is a regenerative overgrowth with restricted growth capacity [74]. AH is characterized as type I MRN (or regular AH) or type II MRN (or atypical AH) based on cytological and architectural atypia (or atypical AH). Cirrhosis of the liver is generally linked with the lesions. As a result, AH is regarded to be a precursor to hepatocarcinogenesis,
particularly when it is unusual. While distinguishing between malignancy and AH is crucial in clinical practice, it is still difficult [75].

Liver cell dysplasia

The nuclear pleomorphism and multinucleation of dysplastic liver cells are microscopically delineated. There are two types of dysplastic cells: large and small dysplastic cells. The tiny dysplastic cell, which was characterized by a disrupted nucleocytoplasmic ratio, was morphologically considered to be the more important candidate for the precancerous cell in the liver [76].

References:


