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Review Article

## An Overview of Hepatocellular Carcinoma -

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## INTRODUCTION

The frequency and mortality of liver cancer has become an increasingly urgent issue. Liver cancer is the second most common cause of cancer related death with an incidence rate that has more than tripled since 1980 [1-2]. Representing approximately 80% of liver tumors, Hepatocellular Carcinoma (HCC) is an aggressive type of liver cancer composed of malignant hepatocytes<sup>1</sup> which originate within the liver tissue itself [1,3]. HCC predominantly affects East and South Asia, the Middle East, and Middle and Western Africa, while lower rates are seen in North and South America as well as Northern and Eastern Europe [2,4-5]. Because HCC is often diagnosed after it metastasizes, the overall five-year survival rate for patients is between 14-18% [2-3].

## RISK FACTORS

Although there is no direct cause of HCC, there are many risk factors that are thought to contribute to its formation.

### Viral

Most commonly linked to the development of HCC is exposure to hepatitis B (HBV) or Hepatitis C (HCV) virus [3,6-11]. HBV is able to integrate its DNA into the host genome, altering both the chromosomal stability and endogenous functions of the cell by promoting proliferation and immortality [12-16]. In contrast, HCV is unable to integrate into the host genome, but instead induces the responses of the host cell through interactions with its own viral proteins, possibly contributing to the transformation of the host cell [17]. Other forms such as Hepatitis Delta (HDV) or Hepatitis G (HGV) virus have been hypothesized to lead to HCC as well [11].

### Carcinogenic

The two major substances associated with HCC are aflatoxin and alcohol [3,6,18-27]. Aflatoxins, a group of mycotoxins produced by mold, are consumed through corn, peanuts, milo, sorghum, copra, or rice, which are usually contaminated through improper growth, harvest, or storage [1,3,18-22,28]. Aflatoxins frequently mutate the third base at codon 249 of TP53, a tumor suppressor gene, ultimately resulting in loss of function [6,13,22,29]. Additionally, alcohol consumption causes cirrhosis of the liver, another leading mechanism for the development of HCC [3,6,22-27,30]. Estrogen-progestogen oral contraceptives, tobacco and caffeine have also been reported to potentially increase the chances of HCC [22,31-32].

### Physical

Demographic factors, such as age and sex, and health-related factors, such as weight and medical conditions, may play a key role in the development of HCC [3,6,10,22,33-35]. Elderly people and men are significantly more at risk for HCC than youth or women [1-4,5-6,36]. The disparity in age could be due to a longer duration of exposure to carcinogens, while the variation in sex could reflect a greater chance in alcohol abuse or a possible tumorigenic consequence of androgens [6]. Hereditary hemochromatosis, a condition resulting in abnormally high levels of iron stored throughout the body, has also been commonly observed as a factor for HCC, due to its likelihood of causing cirrhosis [3,6,22-23]. Additionally, both obesity and diabetes are widely thought to pose a risk for HCC [3,22].

## CLINICAL SIGNS & SYMPTOMS

In many cases, symptoms do not appear until HCC is advanced but, when present, are vague and not specific to HCC itself [3].

However, the most commonly presented signs and symptoms of HCC are: weakness and fatigue, upper right quadrant pain, a palpable liver mass, a nodular liver, loss of appetite and weight loss, hepatic bruits, ascites, pruritus, splenomegaly, jaundice, fever, peripheral edema, gastrointestinal bleeding, variceal bleeding, hepatic encephalopathy, nausea and vomiting, asthenia, cachexia, and early satiety [2,3,35,37-41].

## DIAGNOSIS

The diagnostic process first begins with the analysis of risk factors and a physical examination where the abdomen, with a focus on the liver, is palpated for abnormalities [3]. Laboratory tests may be performed to confirm risk factors and evaluate the functionality of the liver [3]. If abnormalities are indicated, imaging of the liver will be conducted [3,42-44]. Imaging of the liver is divided into three phases: the arterial phase, portal venous phase, and a late phase [44]. Ultrasound (US) is the most common imaging technique in the detection of HCC [43,44]. In addition to US, ultrasound contrast agents can be used, where gas bubbles stabilized by an outer shell allow for clear definition and visualization of the three phases [44,45]. Another method of imaging, Multidetector Row Helical Computed Tomography (MDCT), results in improved detection and characterization of tumors due to precise spatial and temporal resolution [42,44,46]. Further, Magnetic Resonance Imaging (MRI) uses pulse sequences to produce visual information about the liver and biliary tree as well as the patterns of tumor enhancement [42,44,47-49]. The last imaging technique, Positron Emission Tomography (PET), not only allows for cross-sectional imaging of the whole body, but also for small lesions to be detected through a high quality image [44,50]. If dynamic imaging is unable to confirm HCC, a liver biopsy may be performed [3,42,43]. A sample of tissue or fluid is extracted from the liver and examined, providing a conclusive diagnosis [3,42,43].

## MOLECULAR GENETICS

### Disruption to signaling pathways in HCC can lead to many consequences

1. Disturbances to the regulation of the cell cycle, commonly a result of a p53 point mutation or loss of heterozygosity
2. Increased angiogenesis due to the secretion of Vascular Endothelial Growth Factor (VEGF) or Platelet-Derived Growth Factor (PDGF)
3. Avoidance of apoptosis, resulting from deregulation of apoptotic pathways
4. Immortality through the reactivation of Telomerase Reverse Transcriptase (TERT) [14,51-54].

The two most common mutational events which contribute to HCC are point mutations or small deletions which activate  $\beta$ -catenin and inactivate p53 [1,13,14,55-59]. As summarized before, HBV and HCV are thought to directly interact with the signaling cascades of the host cell, promoting hyperproliferation through inflammation and hepatocellular death and therefore contributing to either oncogenic effects or the risk of cell transformation [51].

### Wnt/ $\beta$ -Catenin Signaling

In the liver, this pathway regulates hepatocyte proliferation, liver tumorigenesis, and is responsible for the accumulation of  $\beta$ -catenin in the cytoplasm as well as its translocation into the nucleus [51,55,60].  $\beta$ -catenin is a protein involved in the regulation of cell



adhesion and gene transcription [51,55,60]. When Wnt binds to Frizzled (Fz), its cell-surface receptor, the complex formed ultimately leads to the inactivation of Glycogen Synthetase Kinase 3 $\beta$  (GSK3 $\beta$ ) which prevents  $\beta$ -catenin from being phosphorylated and therefore degraded [51,55,60]. Once accumulated,  $\beta$ -catenin travels to the nucleus and suppresses the expression of certain genes to promote cell proliferation, survival, and angiogenesis [51]. HCC with  $\beta$ -catenin mutations are more likely to be associated with HCV as its protein acts as a Wnt ligand [51,55,61,64,67].

### p53 Signaling

p53 is a crucial protein which regulates the cell cycle and functions as a tumor suppressor [14,51,68,69]. Murine Double Minute 2 (MDM2) regulates p53 activity and, if increased without regulation, may lead to greater ubiquitylation and degradation of p53 [51,70]. A consequence of aflatoxin, loss of p53 activity can be localized to a hot-spot at codon 249, which substitutes a serine for arginine (R249S) [51]. In contrast, another mutation in p53 could be due to HBV X protein (HBVX), which may inactivate certain activities such as p53-mediated transcription and apoptosis, regulation of the cell cycle checkpoints, and DNA repair [13,14,51,71,72]. As such, HCC with p53 mutations are more likely to be associated with aflatoxin and HBV [51,71,73,74].

## TISSUE CHANGES AND METASTASIS

**Cells and tissue within the liver change significantly as HCC progresses. Cancerous hepatocytes are characterized by**

1. Clear, fatty, or eosinophilic cytoplasm
2. High levels of accumulated copper or iron
3. A lack of connective fibrous septa
4. A fibrous, peripheral encapsulation
5. Anaplasia
6. Expansive nodules which compress the adjacent liver
7. Well-developed but unpaired arteries
8. A significant decrease or loss of the reticulin framework
9. Thickened and possibly multilayer trabeculae
10. High nuclear to cytoplasmic ratio
11. Irregular nuclei with prominent nucleoli
12. A loss in cell to cell contact
13. Fibroblastic phenotypes [51,75-79].

HCC metastasis can be divided into two categories: intrahepatic and extrahepatic. Intrahepatic metastasis is characterized by a significant frequency of tumor thrombi within the portal vein, hepatic vein, and inferior vena cava [78,80]. Extrahepatic metastasis is characterized by cancerous hepatocytes most commonly translocating to the lungs, bones, adrenal gland, brain, and lymph nodes [78,80-84]. Also, rarely reported is translocation to the esophagus, stomach, small intestine, colon, spleen, peritoneum, kidneys, uterus, ovaries, breasts, thyroid gland, parotid gland, testes, heart, Central Nervous System (CNS), and skin [78,80,85-88].

## TREATMENT

Treatment for HCC can be guided by many staging systems, yet

the Barcelona Clinic Liver Cancer (BCLC) Staging System is the most widely accepted and results in better prognoses [42,89-92]. The BCLC classifies HCC, and therefore treatment, into five stages depending on liver function, tumor progression, physical status, and cancer-related symptoms [42,91-93].

### Treatment for BCLC stages 0 and A

Treatment for early-stage HCC usually consists of curative therapies such as surgical resection, liver transplantation, or ablation [42,93]. Surgical resection is the most common treatment and, depending on tumor stage and liver function, five-year Overall Survival (OS) rate post-treatment ranges between 40-70% [42,93-102]. Indicated for patients with feasible tumor location and sufficient liver reserve and remnant, resection obstructs the tumor-feeding portal vein and attempts to enlarge the remaining portion of the liver [93,103]. Liver transplantation is limited by the scarcity of donors but, when available, eliminates cirrhosis and boasts a five-year OS of about 70% [42,94,104]. Liver transplant is usually indicated for patients with moderate to severe cirrhosis [93]. Ablation of the tumor is indicated only when resection and transplant are not advisable and access to the tumor is percutaneous or minimally invasive [42]. Five-year OS rate is around 59% [42].

### Treatment for BCLC stages B and C

Treatment for intermediate- and advanced-stage HCC usually consists of palliative therapies such as Transcatheter Arterial Chemoembolization (TACE), targeted therapy, or radiation therapy [42,93,104,105]. TACE involves the administration of chemotherapy or vaso-occlusive particles through cannulation or use of drug-eluting beads for targeting selected hepatic arteries [42,91,93,106,107]. Targeted therapies such as Sorafenib are indicated for patients with relatively well functioning livers [42,93]. Sorafenib is a multiple kinase inhibitor which reduces angiogenic and proliferative effects by suppressing the activity of Raf kinases as well as many growth factors [42,91,92,108,109]. Chemotherapy, or radiation therapy, is considered an atypical form of treatment as HCC is chemotherapy-refractory and often not tolerated well in patients with significantly poor liver function [42,93,110]. However, advancements in technology have allowed direct and precise radiation to the liver, resulting in a more tolerated form of focal HCC treatment [42,111].

### Treatment for BCLC stage D

Treatment for end-stage HCC usually consists of supportive care and possibly palliative therapies [42].

## PREVENTION

**Approaches to the prevention of HCC are divided into two categories**

1. Primary
2. Secondary

Primary prevention involves the prevention of exposure to risk factors while secondary prevention involves the prevention of HCC development in patients with risk factors [112].

**Primary Prevention:** In cases of HCC related to viral hepatitis, the infant vaccination for HBV has shown to be successful in preventing HBV transmission from the infected mother to her newborn during birth [112]. In cases of HCC unrelated to viral hepatitis, elimination of food at risk for contamination by aflatoxin may reduce the frequency

of HCC [112,113]. Additionally, certain carcinogenic and physical risk factors may be eliminated through education and medical care [112,114].

**Secondary Prevention:** In cases of HCC related to viral hepatitis, alpha interferon as well as nucleoside and nucleotide analogs suppress viral replication and therefore reduce the chances of HCC [112,115-126]. Additionally, it is thought that the reduction or suppression of hepatic inflammation could reduce the risk of HCC development [112]. In cases of HCC related to aflatoxin, chlorophyllin, a water-soluble salt of chlorophyll, acts as an interceptor molecule and reduces carcinogenic effects of aflatoxin, as well as acting as an antioxidant [112,127,128]. Furthermore, Oltipraz, a dithiolethione originally intended as an antischistosomal drug, may promote enzymes that detoxify aflatoxin [112].

## DISCUSSION

In recent history, vast improvements in the understanding of HCC have been made. Through copious research regarding HCC, significant risk factors have been determined, many clinical signs and symptoms have been identified, diagnostic techniques have been improved, insight into the molecular genetics of the cancer has been enhanced, patterns in tissue changes and metastasis have been observed, advances in successful treatment have been made, and knowledge regarding prevention has been developed. However, despite the progression science and technology has seen in terms of HCC, there are still great lengths to be covered before the disease is cured.

As with all research, there are certain limitations and impossibilities. Nonetheless, continued improvements and, eventually, a cure will not be discovered in the absence of creativity. Many studies show that cancer cells can be targeted through the blockage of overactive oncogenes [13]. However, what if it were possible to target cancer cells through the promotion of previously lost tumor suppressor genes? Additional studies have shown that reactivation of p53, however brief, can result in complete tumor regression [51,129].

Should DNA damage be detected within a cell, protein kinases are activated. One protein kinase, ATM serine/threonine kinase, phosphorylates p53 and therefore increases the level of p53 within the cell. While the level of MDM2 increases as p53 does, MDM2 cannot ubiquitinate or degrade p53 while p53 is phosphorylated. Additionally, p14ARF, an alternate reading frame protein, regulates MDM2 by binding to it. Therefore, a drug that expressed both constitutively active ATM serine/threonine kinase and p14ARF could inhibit or possibly, regress HCC development in patients. If combined with known therapies, scientists may find an effective treatment strategy for patients with HCC.

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