

# A Comprehensive Comparative Review Of Epidemiology, Aetiology, And Depression Among Patients With Primary Liver Cancer In North America And South-East Asia.

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## ABSTRACT

**Introduction:** Primary liver carcinomas are of two main types - Hepatocellular carcinoma (HCC) and Intrahepatic cholangiocarcinoma (ICC). HCC originates from hepatocytes while ICC originates from bile ducts. HCC is the 5<sup>th</sup> most common carcinoma in the world and third most common death causing cancer but the most common cause of death in a patient with cirrhosis. In comparison to women, men are at risk to have HCC. HCC accounts for more than 80% of primary liver cancer cases worldwide (El-Serag & Rudolph, 2007). In USA five-year survival rate as per 2020 data on National Cancer Institute's SEER database is 19.6 percent which can be further reduced to 2.5 % depending upon the severity of the disease.

**Aspects:** The most common risk factors for the HCC are Hepatitis B, Hepatitis C, Non-alcoholic fatty liver disease, alcohol consumption, liver cirrhosis and exposure to dietary toxins such as aflatoxins and aristolochic acid. The prognosis of the liver cancer is made by Barcelona Clinic Liver Cancer (BCLC) Staging System. Hepatic cirrhosis remains the most common cause of HCC despite any etiology affecting the prognosis, staging of the tumor and the liver's function.

Depression and cancer go hand in hand, as per Lutgendorf and Anderson (2015) approximately 12% of cancer patients are suffering from depression. Now many studies are available online stating depression in HCC patients which is one of the most malignant tumors. A recent study by Chen, Huang, and Li in Taiwan (2019) states the worsening of psychological symptoms in different BCLC staging and treatment. It has been found through different studies that molecular changes in genes (gene2ensemble database), Hypocretin (Chunyun Pu et al), Glucocorticoids (Yawei Zhao et al) leads to depression in HCC patients.

**Methods and Techniques:** This study has been carried out by reviewing articles present on PUBMED, Medline, Google scholar, WHO website, and gene2ensemble database up to 2022. Keywords used are cancer, Hepatocellular Liver carcinoma, aetiology, epidemiology, WHO, India, Canada, and USA. The depression was self measured in the patients using HAMD (Hamilton depression rating scale).

**Results:** The highest number of cases of Hepatocellular carcinoma are seen in Asia and Africa and lowest in Europe and North America. The most common risk factor for liver cancer in the world is HBV and HCV, these infections lead to cirrhosis of the liver and are responsible for making liver cancer the most common cancer in South-East Asia. In USA, the most common cause of liver infections is hepatitis C virus contrary to hepatitis B virus in the developing world. Prevalence of depression in HCC is lowest in North America (16.44%) and highest in Southeast Asia (66.67%).

**Conclusion:** This has been concluded after going through all the articles present online that Hepatocellular liver carcinoma is one of the most common life-threatening cancers widely distributed all over the world with dominance in Southeast Asia as compared to North America and is closely related to depression.

## INTRODUCTION

Primary liver carcinomas are of two main types - Hepatocellular carcinoma (HCC) and Intrahepatic cholangiocarcinoma (ICC) and less common cancers like angiosarcoma, hemangiosarcoma and hepatoblastoma. Most common primary liver carcinoma in adults is Hepatocellular Carcinoma <sup>(1)</sup> and is the most common cause of death in patients with cirrhosis <sup>(2)</sup>. Liver cirrhosis or hepatic cirrhosis and end stage liver disease are commonly known as cirrhosis. Cirrhosis is defined as the impaired liver function caused by the formation of scar tissue known as fibrosis due to damage caused by liver disease <sup>(3)</sup>. Hepatocellular carcinoma is 5<sup>th</sup> most common cancer in the world <sup>(4)</sup> and 3<sup>rd</sup> most common type of cancer related to mortality <sup>(5)</sup>. HCC originates from serotypes - hepatocytes the main parenchymal cells of the liver, while ICC originates from the bile ducts. In comparison to women, men are at higher risk to have HCC. HCC accounts for more than 80% of primary liver cancer cases worldwide. Globally men to women HCC ratio is 2.8:1 (El-Serag & Rudolph, 2007) <sup>(6)</sup>. Globally HCC is the 9<sup>th</sup> most common carcinoma in women with 4<sup>th</sup> most common carcinoma leading to mortality (Bray et al 2018) <sup>(7)</sup>. Secondary liver cancer occurs when a tumor from another part of the body metastasizes to the liver. Most common secondary liver carcinoma is from colorectal cancer. In USA five-year survival rate as per 2020 data on National Cancer Institute's SEER database <sup>(8)</sup> was 19.6 % (2012-2018) and 20.8 % according to 2022 data, which can be further reduced to 2.5 % depending upon the severity of the disease. As per Global Cancer Statistics (GLOBOCAN 2020) <sup>(9)</sup> the total number of cancer deaths by country are collected annually and are made available by the World Health Organization (WHO) <sup>(10)</sup>. Depression is a mental state of low mood and aversion to activity <sup>(11)</sup>. The experience of depression affects a person's thoughts, behavior, motivation, feelings, and sense of well being <sup>(12)</sup>. Physical symptoms of depression include fatigue, pain, or sleep disorder. Some patients may not show any symptoms of depression <sup>(13)</sup>. Among cancer patients, the morbidity of depression is approximately 12.5%, which is four times that of the general population <sup>(14)</sup>. Depression and anxiety are common in patients with HCC <sup>(15-16)</sup> and it is associated with poor prognosis and poor quality of life (QOL) <sup>(17)</sup> for the patient and family members.

## ASPECTS

The most common risk factors for the HCC are Hepatitis B, Hepatitis C, Non-alcoholic fatty liver disease (NAFLD), alcohol consumption, liver cirrhosis and exposure to dietary toxins such as aflatoxins and aristolochic acid. Chronic hepatitis B virus (HBV) infection was found to be responsible for 44% of all HCC cases worldwide, followed by hepatitis C virus (HCV) infection (21%) <sup>(18)</sup>. Hepatitis B virus (HBV) is a double-stranded, circular DNA molecule with eight genotypes (A to H). Genotypes B and C are more common in Asia <sup>(19)</sup>, 5% of the world's population is affected by HBV <sup>(20)</sup>. Hepatitis B virus is transmitted via contaminated blood transfusions, intravenous injections, and sexual contact. Vertical transmission from mother to fetus is the leading cause for HBV infection worldwide. Hepatitis C virus (HCV) is a small, single-

stranded RNA virus, which exhibits high genetic variability<sup>(21)</sup>. There are 6 types of different genotypes of HCV. Once infected with HCV, 80% of patients progress to chronic hepatitis, with ~20% developing cirrhosis<sup>(22)</sup>. Dual infection with HBV and HCV in a cirrhotic patient increases the risk of HCC with an odds ratio (OR) of 165 compared to 17 for hepatitis C and 23 for hepatitis B alone<sup>(23)</sup>. HCC rarely occurs in the absence of advanced hepatic fibrosis or cirrhosis<sup>(24)</sup>.

Alcohol consumption remains an important risk factor for the development of HCC<sup>(25)</sup>. The amount of alcohol intake is related to the severity of liver disease and HCC<sup>(26)</sup>. As per Turati et al (2014)<sup>(27)</sup> meta-analysis of 19 prospective studies showed that consumption of three or more drinks per day resulted in a 16% increased risk of liver cancer and consumption of six or more drinks per day resulted in a 22% increased risk. Fatty liver is described as non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD). As excessive fat deposits in hepatocytes are primarily a triglyceride, in both ALD and NAFLD it causes inflammation leading to fibrosis through different pathway and pathogenicity with absence of HBV and HCV. NASH (Non-Alcoholic Steatohepatitis) is considered primarily as a phenotype of NAFLD leading to fibrosis and chronic liver disease<sup>(28-29)</sup>.

Aflatoxins are a family of carcinogens produced by fungal species such as *Aspergillus flavus*, *Aspergillus parasiticus*, and *Aspergillus nomius* in warm, humid environments<sup>(30)</sup>. In Asia, these mycotoxins contaminate foods such as corn, peanuts and soybeans and cause liver damage<sup>(31)</sup>. There are more than 20 known aflatoxins, but the four important ones are aflatoxin B1, B2, G1 and G2, with aflatoxin B1 (AFB1) being the most potent hepatocarcinogen (Kumar, Mahato, Kamle, Mohanta, & Kang, 2016)<sup>(32)</sup>. Aristolochic acids (AAs) are natural compounds that are widely present in genera of *Aristolochia*, *Bragantia* and *Asarum*, are considered as a potent carcinogen due to their nephrotoxicity. They are commonly used in herbal medicine and traditional Chinese medicine.

Aristolochic acid I (AAI) react with DNA to form covalent aristolactam (AL)-DNA adducts, leading to subsequent A to T transversion mutation, commonly referred as AA mutational signature. Due to its well-defined nephrotoxicity, herbal remedies containing plant species of the genus *Aristolochia* were listed as Group 1 carcinogen by the International Agency for Research on Cancer. Due to their genetic toxicity, the use of AAs-containing drugs should be taken with more caution, especially in the underage group and patients with liver malfunction<sup>(33)</sup>.

Now many studies are available online stating depression along with other psychological and mental changes in HCC patients which is one of the most malignant tumors. A recent study by Chen, Huang, and Li in Taiwan (2019)<sup>(34)</sup> Chen states the worsening of psychological symptoms in different Barcelona Clinic Liver Cancer (BCLC) staging and treatment. In this Taiwanese study 128 HCC patients were studied and found psychological changes in the patients related to BCLC staging and Radiofrequency and surgical treatment. Lately, changes in pathophysiology of cancer and neurological changes in depression have shown associations between depression and cancer progression. It has been found through different studies that molecular changes in genes (gene2ensemble database)<sup>(35)</sup>, Hypocretin<sup>(36)</sup> (Chunyun Pu et al), Glucocorticoids<sup>(37)</sup> (Yawei Zhao et al) leads to depression in HCC patients. Genes associated with HCC and depression were identified on Pubmed2ensemble<sup>(35)</sup> database and those in common between the two subjected to GO and KEGG pathway analyses. Study done by Chunyun Pu et al suggest through the hypothalamic-pituitary-adrenal (HPA) axis that Hypocretin (HCRT, Orexin) are involved in stress regulation of depression. Hypocretin (HCRT, also known as Orexin)<sup>(38)</sup> is an excitatory neuropeptide which is secreted from hypothalamus by neurons on the lateral side and around the fornix<sup>(39)</sup> and acts via two G protein-coupled receptors, hypocretin-receptor-1 and -2<sup>(40)</sup>. The hypothalamic-pituitary-adrenal (HPA) axis is closely associated with Prefrontal cortex,

hippocampus, ventral tegmentum area and almond nucleus<sup>(41-43)</sup> which are the areas of HCRT and its receptors, which controls the response to stress. This study was done on 34 Sprague Dawley (SD) male rats to establish an animal model of cancer with depression by administrating n-nitrosodiethylamine (DEN) and chronic unpredictable mild stress (CUMS). Likewise, in study by Yawei Zhao, Glucocorticoids which are primary stress hormones originated from renal cortex and released into the blood from HPA in context to psychological and environmental stress<sup>(44)</sup>. Glucocorticoids suppress cell-mediated lytic activities as well as cytokine production by many immune cells like natural killer (NK) cells<sup>(45)</sup>, T cells, monocyte, and macrophage. NK cells perform a role in host defence against tumor cells and other pathogens due to their cytokine production and natural cytotoxicity<sup>(46)</sup>. The suppression of NK cells will lead to rapid tumor progression and viral replication.

## METHODS AND TECHNIQUES

This study has been carried out by reviewing articles present on PUBMED, Medline, Google scholar, WHO website, and gene2ensemble database up to 2022. Keywords used are cancer, Hepatocellular Liver carcinoma, aetiology, epidemiology, WHO, India, Canada, and USA. The depression was self measured in the patients using HAMD (Hamilton depression rating scale).

## RESULTS

The highest number of cases of Hepatocellular carcinoma are seen in Asia and Africa and lowest in Europe and North America (GLOBOCAN 2020). In the United States, HCC accounts for 65% of all cases of liver cancers as per US surveillance, epidemiology, and end results (SEER) database program<sup>(47)</sup>. As per the WHO fact sheet of July 2018, approximately 257 million people are infected with chronic HBV across the globe<sup>(48)</sup>. The most common risk factor for liver cancer in the world is HBV and HCV, these infections lead to cirrhosis of the liver and are responsible for making primary liver cancer the most common cancer in South-East Asia. In USA, the most common cause of liver infections is hepatitis C virus<sup>(49)</sup> contrary to hepatitis B virus in the developing world. In contrast to HBV, In HCV infection the cirrhosis and fibrosis is always present in HCC cases<sup>(50)</sup>. Overall, metastatic disease is known to be responsible for greater than 90 % of solid tumor related mortalities<sup>(51)</sup>. As per gene2ensemble database<sup>(35)</sup> 382 depression and 2586 HCC associated genes were identified, 199 genes were found to common both in HCC and depression.

## DISCUSSION

In last few years, Hepatocellular carcinoma (HCC) incidence has increased in many countries. Primary liver cancer (HCC) is the main liver cancer leading to cancer deaths<sup>(52)</sup>. Many patients do not respond to existing treatment of depression<sup>(53)</sup>. Chronic or early life stress is one of the key risk factors for depression. Epidemiological investigation found that the prevalence of depression in cancer patients is higher than that in the general population<sup>(54)</sup>. In North America, HCV is the leading cause of HCC associated with other causes leading to cirrhosis as alcohol abuse, non-alcoholic steatohepatitis (NASH), alpha-1 antitrypsin deficiency and hemochromatosis<sup>(55)</sup>. In Southeast Asia HBV related cirrhosis is the leading cause of HCC<sup>(56)</sup>. Depression and cancer go hand in hand, as per Lutgendorf and Anderson (2015)<sup>(57)</sup> approximately 12% of cancer patients are suffering from depression, this is approximately four times higher than the general population. As per Darren Juan et al prevalence of depression in HCC is lowest in North America (16.44%) and highest in Southeast Asia (66.67%). Most of the studies on NAFLD epidemiology, has been from the USA and North America stating prevalence rate of NAFLD 21– 24.7% and it is on a rise in Southeast Asia<sup>(58)</sup>. In the United States, studies showed that the risk of liver cancer is increased two to four-fold among persons drinking more than 60 g/d of ethanol<sup>(59)</sup>. The etiology of HCC in Asia is undergoing a transition from viral factors to non-viral factors, including NAFLD. As per

GHE2015 data, NAFLD and other causes account for 10.5% of all liver cancer deaths in mainland China <sup>(60)</sup>. In Asia long term slow exposure to aflatoxins is a risk factor for HCC <sup>(61)</sup>. In the United States, liver metastasis is more common than primary liver tumors <sup>(62)</sup>.

## CONCLUSION

This has been concluded after going through all the articles present online that Hepatocellular liver carcinoma is one of the most common life-threatening cancers widely distributed all over the world with dominance in Southeast Asia as compared to North America and is closely related to depression.

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