Hepato Cellular Carcinoma

Corresponding Author:
Dr. Sreedhar Tirunagari,
Sr.Manager-Clinical Research, Makrocare Clinical Research Pvt Ltd, 3-1-230 Nimboliadda Kachiguda , 500027 - India

Submitting Author:
Dr. Sreedhar Tirunagari,
Sr.Manager-Clinical Research, Makrocare Clinical Research Pvt Ltd, 3-1-230 Nimboliadda Kachiguda , 500027 - India

Article ID: WMC004083
Article Type: Review articles
Submitted on: 02-Mar-2013, 10:59:36 AM GMT   Published on: 02-Mar-2013, 12:18:13 PM GMT
Article URL: http://www.webmedcentral.com/article_view/4083
Subject Categories: CLINICAL TRIALS
Keywords: HCC, Gastroenterology, Clinical trials, Epidemiology, Incidence
How to cite the article: Tirunagari S, Shaik D. Hepato Cellular Carcinoma. WebmedCentral CLINICAL TRIALS 2013;4(3):WMC004083
Copyright: This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC-BY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Source(s) of Funding:
Self

Competing Interests:
Clinical Trials on HCC
Hepato Cellular Carcinoma

Author(s): Tirunagari S, Shaik D

Introduction

Hepato Cellular Carcinoma (HCC) is primary malignant tumor of the Liver which begins in the main cells of the liver (hepatocytes) and most frequently occurs in those people who have chronic liver disease and scarring called cirrhosis. Cirrhosis is characterized by a decrease in hepatocyte proliferation, indicating an exhaustion of the regenerative capacity of the liver, and results in an increase in fibrous tissue and a destruction of liver cells, which may ultimately lead to the development of cancerous nodules. [4] Cirrhosis typically occurs in patients who have chronic infection with hepatitis B or C, or in patients who have a long history of alcohol abuse and is the third leading cause of Cancer related deaths in the World. Yearly the death rate of HCC is almost identical to the incidence throughout the world. [1]

Epidemiology

2.1 Incidence & Prevalence:

The HCC incidence differs between different geographical regions and between countries or geographic zones within the countries. The incidence of HCC ranges from <10 cases per 100,000 population to 50-150 cases per 100,000 population in North America and Western Europe as well as in Iran, Iraq and India in parts of Africa and Asia [3] as shown in figure:1[3]. HCC is a common cancer in the Asia-Pacific region and Africa with the age-standardized incidence of 14–36 per 100,000 men compared to 5–10 per 100,000 men in Europe, and 2–5 per 100,000 men in America, Australia and New Zealand. [7] HCC is the fifth most common cancer in men with the estimated of 523,000 cases, 7.9% of the total and the seventh in women estimated 226,000 cases, 6.5% of the total, and the burden is more in developing countries, where almost 85% of the cases occur, and particularly in men. The overall sex ratio male: female is 2.4. [2]

In the Year 2008 the deaths occurred due to liver cancer is estimated of 694,000 deaths (477,000 in men, 217,000 in women), and because of its high fatality (overall ratio of mortality to incidence of 0.93), liver cancer is the third most common cause of death worldwide. The geographical distribution of the mortality rates is similar to that observed for incidence. [2] The Incidence and Mortality rate among Male and female is shown in Figure2 [2]. However, a rise in the incidence of and mortality from HCC, most likely reflecting the increased prevalence of Hepatitis B virus (HBV) infections, further associated with hepatitis C virus (HCV) infection.[3][4] The variations in incidence rates Globally closely reflect the variation in risk factors for HCC; thus, countries with a high prevalence of HBV or HCV infections usually have a high incidence of HCC[5]. In most Asia-Pacific countries, chronic HBV infection accounts for 75-80% of cases; Japan, Singapore and Australia/New Zealand are exceptions because of higher prevalence of HCV infection. [6] The gender wise HCC incidence is shown in figure: 3[2] and figure:4[12].

Globally the median age for the HCC diagnosis is 55-62 years. In sub-Saharan Africa and Southeast Asia, an age of onset between late teens and 30s. This inconsistency is due to the different patterns of hepatitis B transmission in different populations-infection. [7] The age at which HCC develops in individuals infected with HBV or HCV is closely related to their age at acquisition of infection and the rate of active viral replication. [5]

The prevalence in Asians > whites > blacks > Hispanics > Native Americans.

HCC is among the top three causes of cancer death in the Asia Pacific region as of the high prevalence of its main etiological agents, chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. The Major risk factor is with Older age; the incidence increasing sharply after age 40 years. The prevalence is more in Male to female ratio of 3:1, except in elderly Japanese with equal sex incidence or female majority.[6]

In West Africa, HBV infection is generally acquired between the ages of 1 and 5 years, and viral replication declines rapidly after adolescence. In this region, the incidence of HCC stabilizes after age 45 years. In Low and Middle-Income countries the HBV is not endemic; HBV and HCV infections are usually acquired in middle age. In these countries, HCC rarely develops before the age of 50 years and the highest age-specific incidence rates are observed in people...
over age 75 years. [5]

2.2 SOUTH EAST ASIA Prevalence:

China: The overall HCC prevalence in China is 26–32 per 100 000 persons. In the east coastal areas of China the prevalence rate is as high as to 70–80 per 100 000. And prevalence is lower in western regions of China <10 per 100 000 population. The HCC incidence of increases with age, males have a higher incidence compared to females. 58 per 100 000 persons for men and 22 per 100 000 persons for women. The incidence of HCC is relatively low for women below the age of 40 years (<3 per 100 000 population), it is already at 21 per 100 000 persons for men between the ages of 35 and 40 years. The incidence increases with age for both sexes from the age of 40, reaching > 160 per 100,000 males and 94 per 100,000 females. The main risk factor for HCC in China is clearly chronic HBV infection, followed by HCV infection. [7]

Hong Kong: In Hong Kong the HCC is the third most common cancer in men. The age-standardized rates for men and women are 30 and 8.3 per 100 000 persons. The HCC patient ratio male to female is 3:1. There is increase in incidence after the age of 40. The median age for development of HCC for men and women is 63 and 71 years, respectively. The age-standardized mortality rates for men and women are 25 and 7.2 per 100 000 persons. [7]

India: The HCC incidence rates in India for men and women are 0.9–3.4 and 0.2–1.8 per 100 000 persons. The patients with cirrhosis, the incidence rate increases to 1.6 per 100 000 persons. The patients with chronic HBV infection accounts for 71% and chronic HCV infection for 16%. Considering different areas in India, the incidence is estimated that 36–74% of patients with HCC are positive for HBsAg and 0–33% is positive for anti-HCV. The highest HBV prevalence has been found in Chennai. The incidence of HCC is 2.4 for Chronic Hepatitis B (CHB) patients, 2.4 for chronic hepatitis C (CHC) and 3.4 for patients with HBV/HCV co-infection. [7]

Japan: In Japan the HCC positions the fourth most common cancer for both men and women. Incidence rates are approximately 8 and 6 per 100 000 persons. Similar to China and Hong Kong the mortality incidence rates to increase from the age of 40 years. 79% of patients with HCC had chronic HCV infection and only 11% had chronic HBV infection. 63% of patients with HCC were older than 65 years. [7]

Korea: In Korea the HCC is the third most common cancer leading cause of cancer death. The age-standardized incidence rate and mortality rate are, respectively, 45 and 34 per 100 000 persons for men and 12 and 8.8 per 100 000 persons for women. The incidence increases with age, particularly after the age of 40 years. It reaches a maximum of nearly 160 per 100 000 men at the age of 55 years, 72% of patients with HCC have CHB, 20% have CHC and less than 8% have other causes, including alcohol. [7]

Malaysia: In Malaysia HCC is the 8th most common cancer in Malaysian males. The patients in Malaysia with HCC are 59% Chinese, 29% Malays and 5% Indians. The ratio of male and female is 2.4 to the age standardized incidence rate is 3.6 per 100 000 persons for men and 1.6 per 100 000 persons for women. The HCC increases for both male and female after the age of 50. The mean age of development of HCC is 60 years. The ratio of HCC male to female is 3:1. [7]

Philippines: The fourth most common cancer with an age-standardized rate of 6.7 per 100 000 persons. The incidence rates are 14 per 100 000 persons for males and 4.8 per 100 000 persons for females. For male and female age-standardized mortality rates are 11 and 3.2 per 100 000 persons. According to the 2008 statistics, 55% of patients with HCC have CHB; 4.4% have CHC; 9.2% have chronic alcoholism and 24.9% have cryptogenic cause. The mean age of development of HCC is 60 years. The ratio of HCC male to female is 3:1. [7]

Singapore: HCC is the fourth most common cancer in males. The age-standardized incidence of HCC is 58%, 17 to 7.1 per 100 000 persons, in men and 47%, 2.8 to 1.5 per 100 000 persons in women. The overall prevalence of chronic HBV infection in Singapore is 9–10%. 35% have CHB; 13% have CHC. [7]

Taiwan: The age-standardized incidence rates are 53 per 100 000 persons for men and 21 per 100 000 persons for women. 67% of male HCC are related to chronic HBV infection, but 55% of female HCC are related to chronic HCV infection. The mean age of patients with HBV-related HCC is 53 and for those with HCV-related HCC is 65 years. Male-to-female ratio is 6.4 for HBV related HCC, while it is 1.7 for HCV-related HCC. The percentage of HBV-related HCC progressively decreases from 82 to 66% in men, and from 67 to 41% in women. This is not due to a decrease in prevalence of chronic HBV infection. Instead, it is caused by an increase in HCV-related HCC. [7]
Thailand: HCC is an endemic cancer in Thailand. It ranks as the number one among all cancers in men, with the incidence rate of 33 per 100 000 persons per year, and ranks as the third most common cancer in women, with an incidence of 13 per 100 000 per year. The incidence rate starts to rise at age of 35 years; it peaks around age of 60–65 years, with an incidence rate of ~180 per 100 000 persons. The majority (80%) of HCC cases are related to chronic HBV infection, followed by CHC (15%) and others, such as alcoholic, metabolic liver disease. [7]

### Risk factors

#### Chronic liver disease and cirrhosis:

The Major risk factors for HCC are chronic liver disease and cirrhosis, the cirrhosis is developed by chronic infection with hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholic liver disease, and nonalcoholic steatohepatitis (NASH). Additional risk factors for developing HCC include intake of aflatoxin-contaminated food, diabetes, obesity, certain hereditary conditions such as hemochromatosis, and some metabolic disorders.

Indeed, there is evidence to show that 50% of all cases of HCC worldwide are associated with HBV infection, with a further 25% associated with HCV. [4]

### Etiology

There are multiple factors involved in the etiology of HCC, all of which have a direct impact on patient characteristics and disease course, and although a causative agent can often be identified, the well-known factors are elevated body mass index, especially in men as well as diabetes mellitus. Hepatitis B virus infection, hepatitis C virus. Other risk factors for developing HCC include alcoholic liver disease, nonalcoholic steatohepatitis, intake of aflatoxin-contaminated food, diabetes, and obesity.[4]

Etiology of virus varies by region with high HBV incidence in non-Japanese Asians and accounting for approximately 70-80% of cases. In Japan, Europe, and in the United States, HCV is more common than HBV among viral etiologies. However, in the United States, 67% of HCC cases are sero negative for both viruses. Compared to Japan and Western nations there is increased incidence of HBV-HCC in Eastern Asia. Survival differences have been observed according to geographic region and viral etiology, though the reasons for these observations remain unclear. [10]

### Diagnosis

Imaging plays an important role in the diagnosis of HCC. The various diagnostic imaging techniques used such as Ultrasound, CT scan, Magnetic resonance imaging (MRI) with contrast enhancement or angiography with lipiodol injection and follow up CT may increase the accuracy of detection of other liver lesions [12] and PET scan [11]. Biopsy is rarely required for diagnosis. [12]

### Treatment

The treatment options include Surgical resection, Liver transplantation, Radiofrequency ablation, Percutaneous ethanol or acetic acid ablation, Transarterial chemoembolization, Cryoablation and Radiation therapy, which includes: Stereotactic radiotherapy, Radioembolization Systemic therapy, Molecularly targeted therapy: sorafenib, Cytoxic chemotherapy. [13]. The only proven potentially curative therapy for HCC remains surgical, either hepatic resection or liver transplantation. Liver transplantation should be considered in any patient with cirrhosis and small. Patients with replicating HBV had a worse outlook due to HBV recurrence and was previously not considered candidates for transplantation. Hepatic resection should be considered as primary therapy in any patient with HCC and a non-cirrhotic liver (including fibrolamellar variant).

### Clinical Trials

Globally about 1500 clinical trials is been conducted for HCC. The number of clinical trials geographical location wise is shown in figure 5[14].
References:

3. Blum,HE; Spangenberg,HC.; Hepatocellular Carcinoma
4. Sanyal AJ, Yoon SK, Lencionic R.; The Etiology of Hepatocellular Carcinoma and Consequences for Treatment; http://theoncologist.alphamedpress.org/cgi/content/full/15/suppl_4/14
5. Ju Dong Yang; Lewis R. Roberts; Hepatocellular carcinoma: a global view
10. Winnie Yeo, et.al; Eastern asian expert panel opinion: designing clinical trials of molecular targeted therapy for hepatocellular carcinoma.
11. Eldad S. Bialecki and Adrian M. Di Bisceglie; Diagnosis of hepatocellular carcinoma; http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2023919/.
13. Eddie K Abdalla, Keith E Stuart; Overview of treatment approaches for hepatocellular carcinoma.
14. Clinicaltrials.gov
Illustrations

Illustration 1

Figure 1: World wide Incidence of HCC

![World wide Incidence of HCC](image1)

Illustration 2

Figure 2: Liver cancer Incidence and Mortality world wide

![Liver cancer Incidence and Mortality world wide](image2)
Illustration 3

Figure 3: Estimated Liver cancer Incidence worldwide in Men and Women

Illustration 4

Figure 4: Global variation in liver cancer Incidence rates
Illustration 5

Figure 5: HCC Clinical trials conducted globally

Illustration 6

Table 1: Summary of Incidence rates for Male and Female in different countries of Asia Pacific region (per 10000 persons)

<table>
<thead>
<tr>
<th>Country</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>58</td>
<td>22</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>20.9</td>
<td>8.3</td>
</tr>
<tr>
<td>India</td>
<td>0.9-3</td>
<td>0.2-1.8</td>
</tr>
<tr>
<td>Japan</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Korea</td>
<td>45</td>
<td>33.5</td>
</tr>
<tr>
<td>Malaysia</td>
<td>3.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Philippines</td>
<td>13.4</td>
<td>4.8</td>
</tr>
<tr>
<td>Singapore</td>
<td>7.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Taiwan</td>
<td>53</td>
<td>21</td>
</tr>
<tr>
<td>Thailand</td>
<td>33.4</td>
<td>12.3</td>
</tr>
</tbody>
</table>
Illustration 7

Table 2: Common causes of liver cirrhosis that could develop HCC

<table>
<thead>
<tr>
<th>Most common causes of cirrhosis</th>
<th>Less common causes of cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol (60%–70%)</td>
<td>Autoimmune chronic hepatitis</td>
</tr>
<tr>
<td>Biliary obstruction (5%–10%)</td>
<td>Drugs and toxins</td>
</tr>
<tr>
<td>Primary/secondary biliary cirrhosis</td>
<td>Genetic metabolic diseases</td>
</tr>
<tr>
<td>Chronic hepatitis B or C virus (10%)</td>
<td>Infection</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Vascular abnormalities</td>
</tr>
<tr>
<td>Nonalcoholic fatty liver disease (10%)</td>
<td>Veno-occlusive disease</td>
</tr>
<tr>
<td></td>
<td>Idiopathic</td>
</tr>
</tbody>
</table>

Disclaimer

This article has been downloaded from WebmedCentral. With our unique author driven post publication peer review, contents posted on this web portal do not undergo any prepublication peer or editorial review. It is completely the responsibility of the authors to ensure not only scientific and ethical standards of the manuscript but also its grammatical accuracy. Authors must ensure that they obtain all the necessary permissions before submitting any information that requires obtaining a consent or approval from a third party. Authors should also ensure not to submit any information which they do not have the copyright of or of which they have transferred the copyrights to a third party.

Contents on WebmedCentral are purely for biomedical researchers and scientists. They are not meant to cater to the needs of an individual patient. The web portal or any content(s) therein is neither designed to support, nor replace, the relationship that exists between a patient/site visitor and his/her physician. Your use of the WebmedCentral site and its contents is entirely at your own risk. We do not take any responsibility for any harm that you may suffer or inflict on a third person by following the contents of this website.