Liver Cancer

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Liver cancer occurrence has been steadily increasing since the early 1980s in the U.S. In 2023, The American Cancer Society estimates that 42,210 new cases of liver and intrahepatic bile duct cancer and 29,380 deaths will occur in the U.S. Liver cancer is the fifth major cause of cancer-related deaths in the U.S.[1]

Liver cancer currently carries a poor prognosis since most of the cases are not detected at early stages.

This cancer is the seventh most common cancer for women and the fifth for men. Europe, Australia and the United States have the most occurrences of liver cancer.[2]

Below is a list of the information found within this section:

- Anatomy of the Liver
- Types of Liver Cancer
- Risk Factors
- Symptoms and Detection
- Pathology Report and Staging
- Liver Cancer Tumor Biology
- Treatment
- Liver Cancer Resources
- Section Summary

Anatomy Of The Liver

The liver forms part of the gastrointestinal system, which is responsible for breaking down food into smaller parts that can be used by cells. The liver is located in the abdomen, below the ribcage. It is a large organ with many different functions, including:[3]

- Production and secretion of bile and bile salts to help digestion and absorption.
- Production of insulin-like growth factor (IGF-I).
- Production of clotting factors.
- Release of glucose into the blood to provide energy for cells.
- Production of urea, a waste product.
- Cholesterol production.

Behind the liver, there's a small organ called the gallbladder, which function's to store bile produced by the liver and empty it into the small intestine to aid digestion and absorption.[4]

The large number of different cell types in the liver makes it vulnerable to the formation of more than one type of cancer. As with tumors that form in any other location, these can be either invasive (malignant) or contained (benign).[5]

The image above is in the public domain and can be found here.

Types Of

Hepatocellular carcinoma (HCC)
The most common type of liver cancer is hepatocellular carcinoma. HCC starts with an abnormal growth of a cell called hepatocytes ('hepat' and 'hepato' are derived from the Greek word for liver). This is a liver-specific cell that is the start of the tumor. Most patients with this type of cancer are over 50 and it is more common in males than in females. Hepatocellular carcinoma can metastasize, and when it does, it frequently goes to nearby lymph nodes and to the lungs.[6]

Cholangiocarcinoma

This kind of carcinoma, also known as bile duct cancer, comes from the tissues of the tubes that connect the liver to the gallbladder and the gallbladder to the small intestine (hepatic bile ducts). Cholangiocarcinoma can also come from the ducts located inside the liver (intrahepatic ducts). Review the anatomy of these organs here.

Most cholangiocarcinomas are **adeno**carcinomas (they form in glandular tissue) but they frequently grow slowly and don't metastasize for long periods of time. Because the cancer has few specific symptoms and can be confused with other liver conditions (hepatitis or cirrhosis), it is difficult to detect early and is usually in advanced form when discovered. The average age of patients at diagnosis with cholangiocarcinoma is 65.7

Hepatoblastoma
Hepatoblastoma characteristically develops in children; it is most frequently diagnosed in infants between 14 and 24 months and almost all patients are diagnosed by the age of 5. 8Older children and adults can develop this carcinoma, but it is very rare. This type of cancer is the result of an uncontrolled proliferation (meaning that the cells that won't stop dividing) of undeveloped liver cells (hepatocytes). Hepatoblastoma is usually found in only one place (unifocal), it's uncommon for it to metastasize.9

Risk Factors

Hepatitis C Virus (HCV):
For Western countries including the U.S., infection with hepatitis C is the leading cause of both hepatocellular carcinoma (HCC) and chronic liver disease. It is of special importance because unlike the hepatitis B virus, there is no vaccine available for the hepatitis C virus.10

Excessive alcohol intake:
Alcohol liver disease is the second most common risk factor for HCC in the U.S., after infection with hepatitis C virus.11http://www.ncbi.nlm.nih.gov/pubmed/11088082?dopt=Abstract&holding=npg] [PUBMED]

Geography:
More than 80% of HCC cases appear in Eastern Asia or sub-Saharan Africa. North and South America, Northern Europe and Oceania have much lower incidence rates.12

Ethnicity:
In the United States, HCC incidence rate of Asians is twice as high as that of African Americans and four times that of whites.12

Sex:
Males have a higher liver cancer rate than females. The difference in the male:female ratio is greatest among Europeans. The difference between the rates is likely caused by different exposure to risk factors including alcohol consumption, cigarettes, and infection with hepatitis B virus (HBV) or hepatitis C virus (HCV). More on HBV and HCV here.12

Age:
In developed countries (including Canada and the United States) and most Asian populations, HCC is most likely to occur in people 75 years old and older. On the other hand, the peak age of African men with HCC is 60 and 65 years old and the number of individuals with HCC then decreases. The peak age for African women occurs between 65 and 70 years old and then decreases.12

Hepatitis B Virus (HBV):
Those who carry HBV have a 5 to 15 fold increased risk of developing HCC over the general population. Between 70 and 90% of HCCs related to the presence of HBV are diagnosed in patients that suffer from cirrhosis. Cirrhosis is advanced scarring on the liver caused by liver diseases (including hepatitis) and other conditions.

In places with high HCC incidence rates, HBV is usually transmitted from mother to child (vertical transmission), whereas in areas with low HCC incidence rates patients usually get infected with HBV through sexual and parenteral ways (horizontal transmission).12

Obesity:
A 16-year period study in the United States showed a 5 fold increase in cancer mortality in people with great body mass index in contrast to those who had a normal body mass index. Liver cancer is frequently found in patients with metabolic disarrangements.12

Diabetes Mellitus:
Many studies around the world have found a significant relationship between diabetes and the development of HCC. Between 10 and 20% of cirrhosis patients have overt diabetes and a higher percentage present impaired glucose tolerance.12

Tobacco:
The association between smoking and HCC still is not yet clear. Studies have produced conflicting results, showing

both negative and positive relationships. However, two studies focused on women both reported a positive association, so smoking may be a higher risk factor for women than men.12

Exposure to aflotoxins:
Aflatoxins are a type of mycotoxin, toxic chemicals made by some types of fungi. Aflatoxin is produced by *Aspergillus* fungi when the fungus grows on improperly stored food products. Aflatoxins are capable of causing DNA mutations, including the tumor suppressor, *TP53* (p53). Aflatoxins may be found in peanuts, tree nuts, corn, wheat and other grains, and oil seeds.13, 10

Symptoms & Detection

Liver cancer generally does not have symptoms. Nonspecific symptoms that can be associated with HCC may include:
· Yellowish color of the skin (Jaundice)
· Inability to eat (Anorexia)
· Weight Loss
· Abdominal pain and/or swelling
A surveillance ultrasound is recommended every six months for individuals with a high risk of developing HHC. In patients with liver cirrhosis, if the ultrasound reveals a suspicious liver lesion, a CT or MRI can be used to determine if the abnormality (lesion) is HCC. If the patient has no underlying cirrhosis or if imaging results prove inconclusive a biopsy can be used.

Staging & Pathology Report

If there is suspicion that a patient may have liver cancer, a sample of tissue (biopsy) may be taken for examination. After a biopsy is taken, the physician who performed the biopsy sends the specimen to a pathologist. The pathologist examines the specimen at both the macroscopic (visible with the naked eye) and microscopic (requiring magnification) levels and then sends a pathology report to the physician. The report contains information about the tissue's appearance, cellular make up, and state of disease or normalcy. For more information about pathology reports, refer to the Diagnosis & Detection section.

A variety of staging systems have been used for liver cancer. T/N/M and the Barcelona Clinic Liver Cancer staging system (BCLC) are the most common.14

The BCLC uses a four-stage system:
A. Includes patients with asymptomatic early tumors (meaning that they do not show symptoms)
B. Patients with asymptomatic multinodular HCC (still no symptoms, but now there's a handful of grapes versus only one grape like in stage A)
C. Patients with symptomatic tumors and/or invasive tumor pattern
D. End stage disease. Should only receive symptomatic treatment

The T/N/M system assigns a degree of severity based on size, location, and spread of the cancer in the body. Learn more about T/N/M staging.

Tumor Biology

TP53:
p53 is a tumor suppressor gene in charge of regulating cell division and apoptosis. About half of all human tumors have a mutation in the *TP53* tumor suppressor gene. Several studies have reported that mutations in p53 have a critical role in the development of HCC.15

pRb:
pRb is a tumor suppressor gene. Together with TP53 it regulates cell division. the disruption of the pRb pathway in HCC is similar to that of other cancers. 15

Ras:
The human ras protein family is a family of proteins that drive cell division.
A recent study reported that some of the Ras family inhibitors are inactivated in human HCC, demonstrating the role of Ras pathway signals in liver cancer. 15

NOTCH 2:
The NOTCH family is involved in several cell functions, such as proliferation, differentiation and cell death (apoptosis).16Hepatoblastoma can be the result of more than one type of translocation in the long arm (q) of chromosome 1. The NOTCH 2 protein has been found to delay the maturation of hepatoblasts during liver

development; its expression is associated to the differentiation of the hepatoblasts into hepatocytes and biliary cells. It is thought that NOTCH 2 contributes to hepatoblastoma by keeping a population of hepatoblasts from differentiating.17

Treatment

Treatment options for HCC depend on how well the liver is functioning, the tumor stage, and the physical status of the patient.
As our focus is on the biology of the cancers and their treatments, we do not give detailed treatment guidelines. Instead, we link to organizations in the U.S. that generate the treatment guidelines.

Learn about treatment guidelines for HCC from the National Comprehensive Cancer Network (NCCN).

A study from 2011 suggests that liver cancer may arise from a type of cancer stem cell that is resistant to chemotherapy and has the ability to metastasize to the rest of the body. These capabilities make it possible for liver cancer to recur after it is surgically removed.18

For more information about how these and other cancer treatments work, refer to the Cancer Treatments section.

Information about clinical trials:
. General clinical trial information from CancerQuest
Click here for information about clinical trials from the National Cancer Institute.
·Click here for information about clinical trials from Georgia Clinical Trials Online.

Liver Cancer Resources

Risks for Liver Cancer

Liver Cancer Risks (ACS)

CTCA Liver Cancer Risk Factors

Detection and Diagnosis of Liver Cancer

Winship Cancer Insitute: Liver Cancer Diagnosis and Staging Make an Appointment

Liver Cancer (ACS)

Liver Cancer Network

MayoClinic: Liver Cancer

What You Need To Know About: Liver Cancer

Liver Cancer Treatments

Adult Liver Cancer Treatment (NCI)

Child Liver Cancer Treatment (NCI)

Treating Liver Cancer (ACS)

Liver Cancer Survivorship

Liver Cancer Support (CTCA)

Liver Cancer: Survivorship

National Coalition for Cancer Survivorship (NCCS)

Long Term Risks for Liver Cancer Survivors

Liver Cancer Treatment Effects

Side Effects of Chemotherapy for Liver Cancer

International Liver Cancer Resources

About Liver Cancer (Cancer Research UK)

British Liver Trust (UK)

NHS Choices: Liver Cancer (UK)

Liver Cancer Prevention & Treatment (India)

Liver Cancer Treatment in India

Cancer Council: Liver Cancer (Australia)

Australian Cancer Research Foundation: Liver Cancer

Canadian Liver Foundation

Canadian Cancer Society: Liver Cancer

Section Summary

Introduction

· Liver cancer is the fifth major cause of cancer-related deaths in the U.S.

· In the U.S., this cancer is the fifth most common cancer in men and seventh in women.

Types of Liver Cancer

· Hepatocellular carcinoma (HCC) is the most common form, patients are usually over 50.

· Cholangiocarcinoma arises from the connective tissues of the bile ducts.

· Hepatoblastoma characteristically develops in children.

Risk Factors

· Infection with hepatitis C is the leading cause of HCC in Western countries.

· Alcohol-related liver disease is the second most common risk factor for HCC in the U.S

· More than 80% of HCC cases appear in Eastern Asia or sub-Saharan Africa

· Males have a higher liver cancer rate than females, presumably due to different exposure to risk factors.

· Liver cancer risk increases with age.

· Those who are infected with the Hepatitis B virus (HBV) have a 5 to 15 fold increased risk of developing HCC over the general population.

· Liver cancer is frequently found in patients with metabolic disorders.

  o A significant relationship has been found between diabetes and HCC.

Symptoms and Detection

· Liver cancer rarely presents with specific symptoms.

· Nonspecific symptoms that can be associated with HCC include jaundice (yellow coloring), anorexia, weight loss, and abdominal pain.

Staging and Pathology Report

· A sample of liver tissue is examined micro- and macroscopically in order to create a pathology report.

· The Barcelona Clinic Liver Cancer (BCLC) system has four-stages.

· The T/N/M system assigns a degree of severity based on size, location, and spread of the cancer in the body

Tumor Biology

· Mutations in p53 have a critical role in the development of HCC

· The disruption of the pRb pathway seen in HCC is similar to that of other cancers.

· NOTCH 2 contributes to hepatoblastoma by preventing a population of hepatoblasts from differentiating.

Treatment

· Treatment options for HCC depend on how well the liver is functioning, the tumor stage, and the physical status of the patient.

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1 American Cancer Society.Cancer Facts & Figures 2023. Atlanta: American Cancer Society. (2023). Retrieved from https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/2023-cancer-facts-figures.html
2 Liver Cancer Incidence and Mortality Worldwide in 2008 Summary [http://globocan.iarc.fr/factsheets/cancers/liver.asp]
3 Human Physiology: The Mechanisms of Body Function. AJ Vander, J Sherman, D Luciano, EP Widmaier, H Raff, H Strang; published by McGraw-Hill, New York (2004).
4 Starr C, McMillian B. "Human Biology" 2008 pp.493
5 Liver Cancer Overview [http://www.cancer.org/Cancer/LiverCancer/OverviewGuide/liver-cancer-overview-what-is-liver-cancer]
6 Hepatocellular carcinoma [http://www.nextbio.com/b/search/ov/Hepatocellular%20carcinoma?id=162995&type=disease&synonym=Liver%20carcinoma]
7 Cholangiocarcinoma [http://www.nextbio.com/b/search/ov/Cholangiocarcinoma%20of%20biliary%20tract?id=171632&type=disease&synonym=Cholangiocarcinoma%20of%20biliary%20tract]
8 Pre- and Postnatal Imaging of a Congenital Hepatoblastoma [http://content.karger.com/produktedb/produkte.asp?DOI=000327580&typ=pdf]
9 Hepatoblastoma [http://www.nextbio.com/b/search/ov/HEPATOBLASTOMA]
10 [ab] Hepatocellular Carcinoma: A global view. http://www.nature.com/nrgastro/journal/v7/n8/full/nrgastro.2010.100.html#B44 [http://www.nature.com/nrgastro/journal/v7/n8/full/nrgastro.2010.100.html#B44] [PUBMED]
11 Risk factors for the rising rates of primary liver cancer in the United States. http://www.ncbi.nlm.nih.gov/pubmed/11088082 [
12 [abcdefgh] Hepatocellular Carcinoma: Epidemiology and Molecular Carcinogenesis [http://www.sciencedirect.com/science/article/pii/S0016508507007998#sec1.1]
13 MedlinePlus: Aflatoxin http://www.nlm.nih.gov/medlineplus/ency/article/002429.htm [http://www.nlm.nih.gov/medlineplus/ency/article/002429.htm]
14 Prognosis of Hepatocellular Carcinoma: The BCLC Staging Classification https://www.thieme-connect.de/DOI/DOI?10.1055/s-2007-1007122 [https://www.thieme-connect.de/DOI/DOI?10.1055/s-2007-1007122] [PUBMED]
15 [abc] Molecular mechanisms of hepatocellular carcinoma. http://onlinelibrary.wiley.com/doi/10.1002/hep.22580/full [http://onlinelibrary.wiley.com/doi/10.1002/hep.22580/full] [PUBMED]
16 Effect of experimental varicocele on the expressions of notchnext term 1, previous term2,next term and 3 in rat testes: An immunohistochemical study [http://www.sciencedirect.com/science/article/pii/S0015028204026196#sec2.4]
17 Activated NOTCH2 is overexpressed in hepatoblastomas: an immunohistochemical study [http://www.pedpath.org/doi/abs/10.2350/10-09-0900-OA.1?prevSearch]
18 CD24+ Liver Tumor-Initiating Cells Drive Self-Renewal and Tumor Initiation through STAT3-Mediated NANOG Regulation [http://www.sciencedirect.com/science/article/pii/S1934590911002918]