# Lecture 12
# Cancers of The Liver and Pancreas


{ ومن لم يذق مرّ التعلُّمِ ساعةً.. تجرع ذلَّ الجهل طوال حياتهِ }

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Red: Important. Grey: Extra Notes Doctors Notes will be in text boxes

Objectives:

- Describe hepatocellular and cholangiocarcinoma.
- Understand the frequency of metastatic disease to the liver.
- Recognize the rarity of primary liver neoplasms in children.
- Recognize all aspects of pancreatic carcinoma.

References:

Lecture slides & Robbins.

## Malignant tumors of the liver:

- The liver and lungs are the visceral organs that are most often involved by metastatic tumors.
- Primary carcinomas of the liver are relatively uncommon.
- Most arise from hepatocytes and are termed *hepatocellular carcinoma* (HCC).
- Much less common are carcinomas of bile duct origin, *cholangiocarcinomas*.
- The rare forms of primary liver cancer are: hepatoblastomas and angiosarcomas.
- Common precursors are: Cellular changes and Nodular lesions.
    - Which are found in the setting of chronic liver disease, particularly chronic viral hepatitis, alcoholic liver disease, and metabolic diseases such as AAT deficiency and hereditary hemochromatosis.
    - Usually they are found in late-stage disease, when cirrhosis is already established.

- Most common metastasis: (2L=Lung, Liver) (2B=Brain , Bone)
- Hepatoblasoma common in children

## Hepatocellular Carcinomas:

- Male predominance.
- More than 85% of cases of HCC occur in countries with high rates of chronic HBV infection. In these regions, the HBV carrier state begins in infancy following vertical transmission of virus from infected mothers, conferring a 200-fold increased risk for HCC by adulthood.
- In the Western world where HBV is not prevalent, cirrhosis is present in 85% to 90% of cases of HCC, usually in the setting of other chronic liver diseases.

## Pathogenesis:

**The following have been implicated in human hepatocarcinogenesis (Risk Factors):**

| | |
|---|---|
| **Viral infection (HBV, HCV)** | Extensive studies link chronic HBV and chronic HCV infection with liver cancer. (The relation between virus B, C and carcinoma) |
| **Cirrhosis** | The development of cirrhosis appears to be an important, but not requisite, contributor to the emergence of HCC. |
| **Food contaminants** | Primarily aflatoxins from aspergillus -found in corn and beans-. High exposure to dietary aflatoxins derived from the fungus Aspergillus flavus. These highly carcinogenic toxins are found in "moldy" grains and peanuts. |
| **Other conditions** | **Chronic alcoholism, tyrosinemia** and **hereditary hemochromatosis.** |

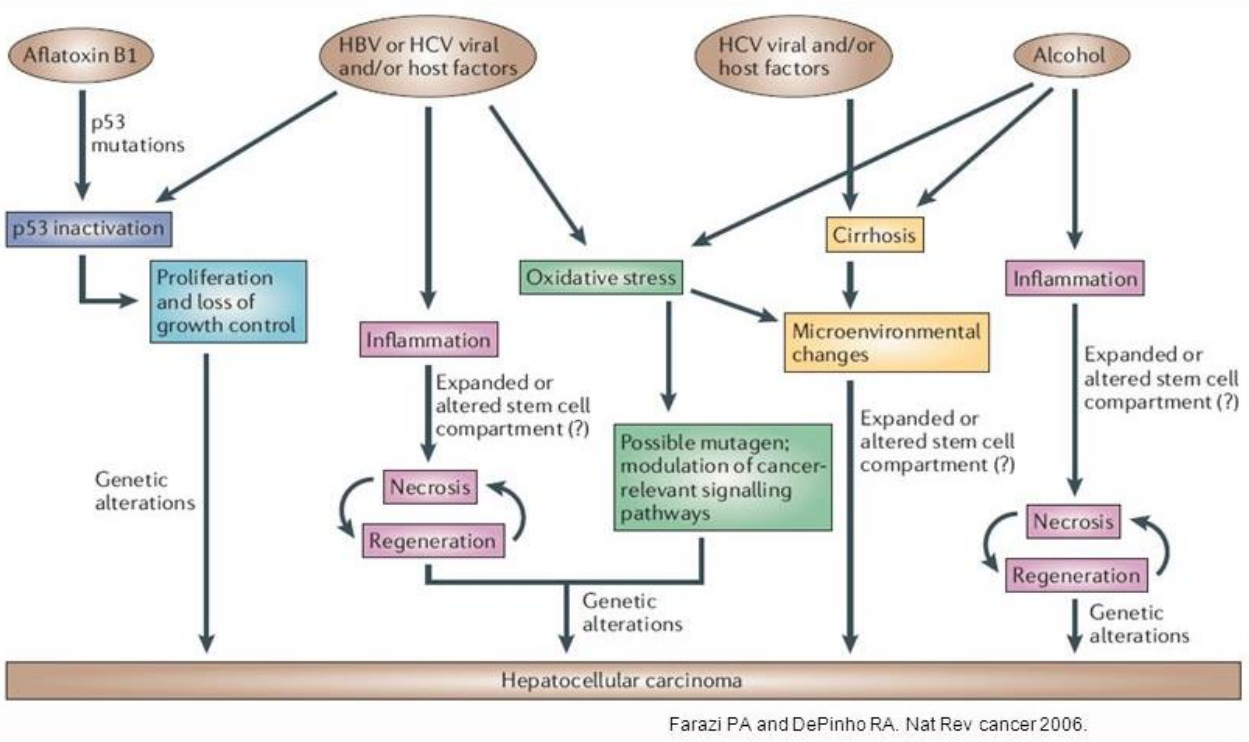
In the western world HCC is more related to alcohol and autoimmune diseases but here when the patient present with cirrhosis we directly think about HBV

**Several factors seem to be most important:**

- Inflammation and regeneration, seen in all forms of chronic hepatitis, are believed to be main contributors to acquired mutations in genomic DNA.
- Acquired mutations in specific oncogenes (such as *β-catenin*) and tumor suppressors (such as *TP53*) contribute to dysregulated growth and further increases in genomic instability.
- Acquired defects in DNA repair, particularly those in repair systems for double-stranded DNA breaks, also perpetuate DNA damage and may cause chromosomal defects.
- **HBV-X gene** may have some oncogenic potential.
- The tumorigenic capacity of viruses relates primarily to their capacity to cause chronic inflammation and increased cell turnover.

**What do we see?**

- In most cases, HCC develops from **small-cell, high-grade dysplastic nodules** in cirrhotic livers.
- Tumors may arise from both **mature hepatocytes and progenitor cells** (known as ductular cells or oval cells)
- An important criterion for indication of malignancy is **nodule vascularization**, visualized by imaging.
- An almost universal feature of hepatocellular carcinoma is **the presence of structural and numeric chromosomal abnormalities** indicative of genomic instability.




Farazi PA and DePinho RA. Nat Rev cancer 2006.

- When we write the report, we depend on vascular invasion (tumor inside the blood vessels)
- HCC have high propensity for invasion of vascular channels.
- Carcinoma causes metastasis in the liver itself (multiple nodules around the main one)

## Morphology:

| | | | |
|---|---|---|---|
| **Grossly it may be:** | **1.** A **unifocal** mass | **2. Multifocal**, multiple nodules of variable size. | **3.** A **diffusely infiltrative** cancer. (the whole liver) |
| | All three patterns may cause liver enlargement (hepatomegaly). **All patterns of hepatocellular carcinomas have a strong propensity for invasion of vascular channels**. | | |
| **Microscopically** | Range from well-differentiated to highly anaplastic undifferentiated lesions. | | |
| | **Moderately & well-differentiated** | Cells that are recognizable as hepatocytic in origin. **Bile pigment** is usually present. The malignant cells may be **positive for alpha-fetoprotein** | |
| | **Poorly differentiated** | Tumor cells can take on a pleomorphic appearance with numerous anaplastic giant cells, can become small and completely undifferentiated cells. | |
| **What could we see?** | ▪ Extensive intrahepatic metastases may occur.<br>▪ Tumor may invade the portal vein (Snakelike masses) (with occlusion of the portal circulation) or inferior vena cava, extending even into the right side of the heart.<br>▪ Lymph node metastases to the perihilar, peripancreatic, and para-aortic nodes above and below the diaphragm can be present. | | |

## Fibrolamellar carcinoma:

- A distinctive variant of HCC is the fibrolamellar carcinoma. This tumor occurs in young male and female adults (20 to 40 years of age), more in males, has no association with HBV or cirrhosis, and often has a **better prognosis.**
- It usually presents as a **single large, hard "scirrhous[1]" tumor** with fibrous bands coursing through it.
- On microscopic examination, it is composed of **well-differentiated polygonal** cells growing in nests or cords and separated by parallel lamellae of **dense collagen bundles.**

## Clinical Features:

- Ill-defined upper abdominal pain, malaise, fatigue, weight loss, and feeling of abdominal fullness.
- In many cases, the enlarged liver can be felt on palpation. Jaundice and fever are uncommon.
- More often encountered in persons with **symptomatic cirrhosis of the liver**. In these persons, a **rapid ↑ in liver size**, sudden worsening of **ascites**, or the appearance of **bloody ascites**, **fever**, and **pain** call attention to the development of a tumor.

1 of, relating to, or being a hard slow-growing malignant tumor having a preponderance of fibrous tissue.

## Laboratory studies:

- **Elevated levels of serum *α*-fetoprotein** are found in 50% to 75% of patients with HCC (advanced tumors).
- False-positive results are obtained in yolk-sac tumors, and many non-neoplastic conditions such as cirrhosis, chronic hepatitis, normal pregnancy, and massive liver necrosis. Hence the test is neither specific nor sensitive.

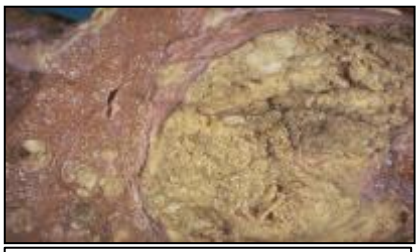
## Diagnosis:

Radiologic screening of patients with cirrhosis at 6-month intervals, looking for dysplastic nodules or early, small HCCs, is the current clinical frontier.

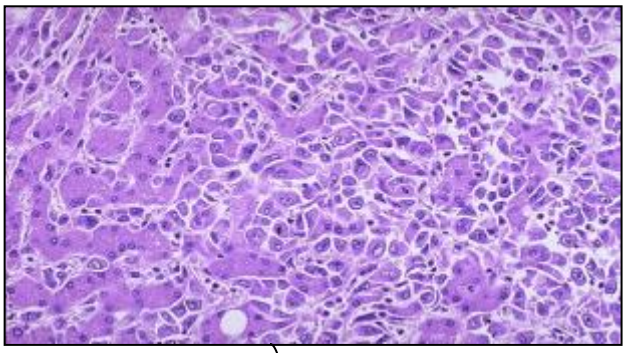
## Prognosis:

Grim, overall, death usually occurs from

(1) Cachexia: severe weight loss and weakness due to chronic disease.
(2) Gastrointestinal or esophageal variceal bleeding
(3) Liver failure with hepatic coma
(4) Rupture of the tumor with fatal hemorrhage. (intra-abdominal hemorrhage)



The satellite nodules of this hepatocellular carcinoma.



Malignant cells of HCC (seen mostly on right) are well differentiated and interdigitate with normal, larger hepatocytes (seen mostly at left).

Large nucleus, Prominent nucleolus, Mitosis, Polymorphism & Irregular nuclear couture

Such liver cancers arise in the setting of cirrhosis. Worldwide, viral hepatitis is the most common cause, but in the U.S., chronic alcoholism is the most common cause. The neoplasm is large and bulky and has a **greenish cast because it contains bile**. To the right of the main mass are small satellite nodules.

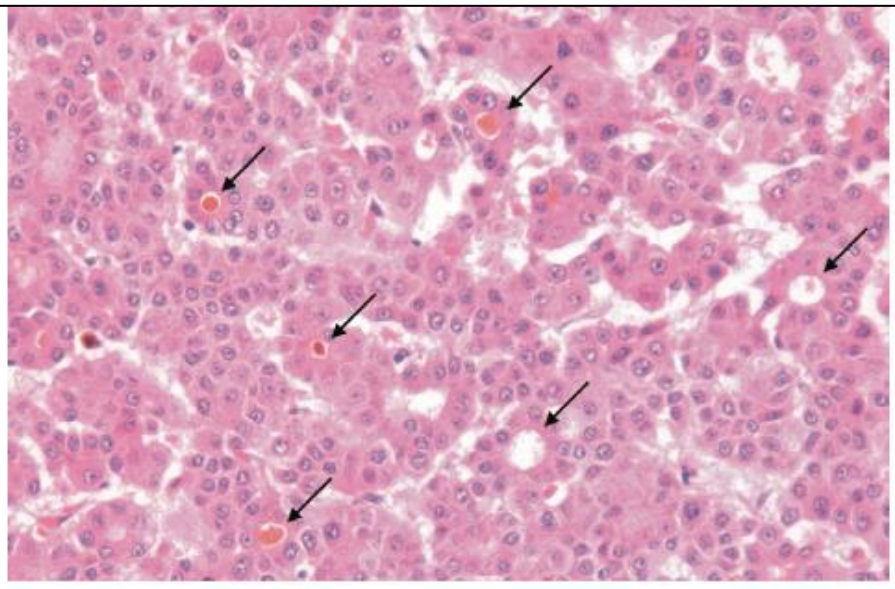


**Figure 15–34** Well-differentiated hepatocellular carcinoma has distortions of normal structures: Liver cell plates are markedly widened, and frequent "pseudoacinar" structures (*arrows*)—abnormal bile canaliculi—often contain bile.

## Cholangiocarcinoma: (adenocarcinoma) Cell origin: Bile duct

A malignancy of the biliary tree, arising from bile ducts within and outside of the liver. Occur mostly in persons of 50 to 70 years of age.

- Extrahepatic cholangiocarcinomas constitute approximately 2/3 of these tumors and may develop at the hilum (known as Klatskin tumors) or more distally in the biliary tree.
- Several consistent genetic changes have been noted in these tumors, including activating mutations in the *KRAS* and *BRAF* oncogenes and loss-of-function mutations in the *TP53* tumor suppressor gene.

### Risk factors:

- Primary sclerosing cholangitis.
- Previous exposure to Thorotrast[2].
- Congenital fibropolycystic diseases of the biliary system (particularly Caroli[3] disease and choledochal[4] cysts).
- In the Orient, the incidence rates are higher, and it is due to chronic infection of the biliary tract by the liver fluke Opisthorchis sinensis (*Clonorchis sinensis* or *Opisthorchis viverrini*)[5].

All risk factors for cholangiocarcinomas cause **chronic cholestasis and inflammation**, which presumably promote the occurrence of somatic mutations in cholangiocytes.

### Morphology:

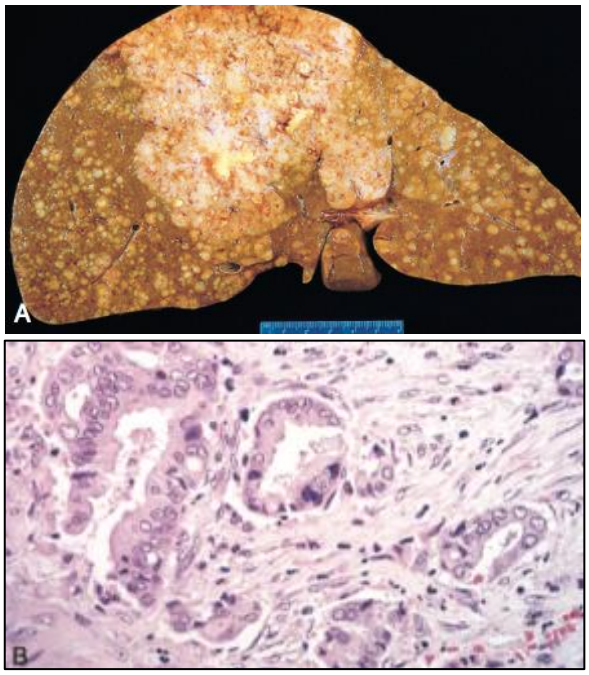
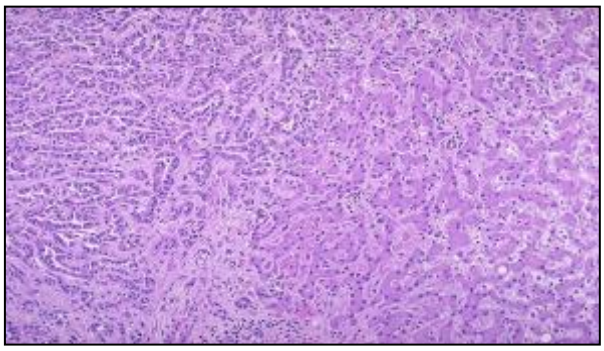



**Figure 15–38** Cholangiocarcinoma. **A,** Massive neoplasm in the right lobe and widespread intrahepatic metastases. **B,** Tumor cells forming glandular structures surrounded by dense sclerotic stroma.



The carcinoma at the left has a glandular appearance. Do not make bile, but the cells do make mucin, and they can be almost impossible to distinguish from metastatic adenocarcinoma on biopsy or fine needle aspirate

It's adenocarcinoma but we can't tell if its primary or metastasis

2 A suspension containing particles of the radioactive compound thorium dioxide, $ThO_2$, that was used as a radiocontrast agent in medical radiography (for the biliary tract) in the 1930s and 1940s.
3 A nonobstructive dilatation of the intrahepatic bile ducts, congenital disorder.
4 Congenital bile duct anomalies
5 A species common throughout Asia, acquired by humans who eat poorly cooked fish that contains the larval forms. *O. sinensis* is a relatively uncommon cause of biliary obstruction in Western nations

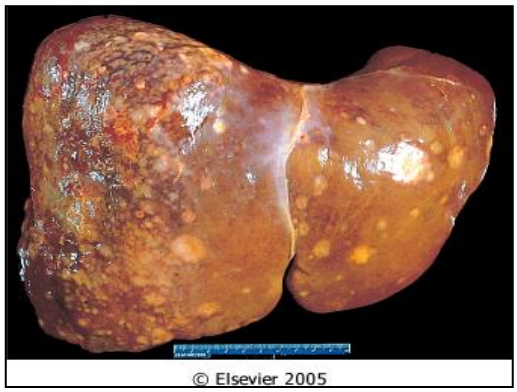
| | |
|---|---|
| Microscopically | ▪ Resemble adenocarcinomas arising in other parts of the body. Most are well to moderately differentiated. Rarely bile stained, because differentiated bile duct epithelium does not synthesize bile.<br>▪ Mixed variants occur, in which elements of both hepatocellular carcinoma and cholangiocarcinoma are present.<br>▪ Hematogenous metastases to the lungs, bones (mainly vertebrae), adrenals, brain. Lymph node metastases to the regional lymph nodes are also found |
| Intrahepatic | ▪ Occur in the **non-cirrhotic** liver and may track along the intrahepatic portal tract system to create **a treelike tumorous mass** within the liver or a massive tumor nodule.<br>▪ Lymphatic and vascular invasion are **common**.<br>▪ Cause symptoms only when much of the liver is replaced by tumor. |
| Extrahepatic | ▪ Because partial or complete obstruction of bile ducts rapidly leads to jaundice, extrahepatic biliary tumors tend to be relatively small at the time of diagnosis.<br>▪ Cholangiocarcinomas may spread to extrahepatic sites such as regional lymph nodes, lungs, bones, and adrenal glands. Invasion along peribiliary nerves is another route of spread to the abdomen.<br>▪ Cholangiocarcinoma has a greater propensity for extrahepatic spread than does hepatocellular carcinoma. |

## Clinical Features:

- Because both intra- and extrahepatic cholangiocarcinomas generally are asymptomatic until they reach an advanced stage, the prognosis is poor.
- **Intrahepatic cholangiocarcinoma** is usually **detected late** in its course, either as the result of obstruction to bile flow through the hilum of the liver or as a symptomatic liver mass. And nonspecific signs and symptoms such as weight loss, pain, anorexia, and ascites.
- Symptoms and signs arising from **extrahepatic cholangiocarcinomas** (jaundice, alcholic stools, nausea and vomiting, and weight loss) result from biliary obstruction.
- **Poor prognosis.** The median time from diagnosis to death is **6 months**. Aggressive surgery remains the only treatment offering hope for long-term survival.
- Alpha-fetoprorein is **not elevated.**
- Elevated serum levels of **alkaline phosphatase and aminotransferases**

## Metastatic Tumors:

- Metastatic involvement of the liver is far **more common** than primary neoplasia.
- Although the most common primaries producing hepatic metastases are those of the breast, lung, and colon, **any cancer in any site** of the body may spread to the liver, including leukemias and lymphomas. (Lung to liver, not the other way around)
- Typically, multiple nodular metastases are found that often cause striking **hepatomegaly** and may replace over 80% of existent hepatic parenchyma. The liver weight can exceed several kilograms (Very large liver).




Numerous mass lesions of variable size. Some of the larger ones demonstrate central necrosis. The masses are metastases to the liver.

**Angiosarcoma: (Origin: endothelial cells)**

- Consists of pleomorphic **endothelial cells** with large hyperchromatic nuclei, giant cells in frequent mitosis and **irregular anastomosing vascular channels.**
- Cells may appear spindle shaped and cirrhosis is present in 20% to 40% of the cases. These have also been linked to vinyl chloride and thorostrast exposure.

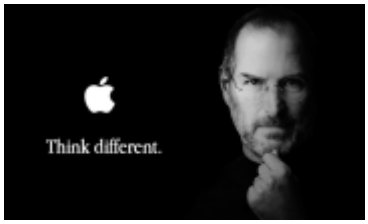
**Pancreatic Carcinoma:**

- Pancreatic cancer has one of the highest mortality rates of any cancer.
- It is carcinoma of the exocrine pancreas. It arises from ductal epithelial cells.
- It occurs in the 6th to 8th decade, blacks more than whites, males more than females, diabetics more than non-diabetics.

**Risk Factors:**

- The strongest environmental influence is **smoking**, which doubles the risk.
- **Chronic pancreatitis.**
- **Diabetes mellitus:** can also occur as a consequence of pancreatic cancer, and in fact, new-onset diabetes in an elderly patient may be the first sign of this malignancy.
- **Inherited genetic defects**. E.g., germline mutations of the familial breast/ovarian cancer gene BRCA2 are seen in 10% of cases arising in Ashkenazi Jews

- Tumor in children less common than adult
- Steve jobs died of pancreatic carcinoma
- Appears with jaundice




**Clinical Features:**

- Remain **silent** until their **extension** impinges on some other structure.
- **Pain** is the first symptom, but by that point these cancers are often beyond cure.
- **Obstructive jaundice**, associated with carcinoma in the head of the pancreas.
- Weight loss, anorexia, generalized malaise and weakness are manifestations of **advanced** disease.
- **Migratory thrombophlebitis** (*Trousseau syndrome*) (vein inflammation) occurs in about 10% of patients and is attributable to the elaboration of platelet-aggregating factors and pro-coagulants from the tumor or its necrotic products.

## Morphology:

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| **Info** | Usually hard, stellate, gray-white, poorly defined masses. Arises in:<br>▪ 60% of cancers of the pancreas arise in the head of the gland<br>▪ 15% in the body and 5% in the tail<br>▪ 20% of the neoplasm diffusely involves the entire gland. |

| | | |
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| **Ductal adenocarcinomas (majority)** | Two features are characteristic: | 1. It is **highly invasive.**<br>2. It elicits an intense non-neoplastic host reaction called a **"desmoplastic response".** (non-neoplastic itself only a response to a neoplastic gland) |

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| **Involvement** | Peripancreatic, gastric, mesenteric, omental, and portahepatic lymph nodes are frequently involved. Distant metastases occur, principally to the lungs and bones. |

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| **Less common variants** | ▪ Acinar cell carcinomas<br>▪ Adenosquamous carcinomas with focal squamous differentiation in addition to glandular differentiation<br>▪ Undifferentiated carcinomas with osteoclast-like giant cells of monocytic lineage intermixed within the neoplasm. |

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| **Carcinomas** | Head | **Most obstruct the distal common bile duct** as it courses through the head of the pancreas. In 50% of such cases, there is marked distention of the biliary tree, and patients typically exhibit jaundice. |
| | Body & tail | In marked contrast, **those do not impinge on the biliary tract and hence remain silent for some time. They may be quite large and widely disseminated by the time they are discovered.** |

| | |
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| **Microscopically** | ▪ Usually is a moderately to poorly differentiated adenocarcinoma forming abortive tubular structures or cell clusters and exhibiting an aggressive, deeply infiltrative growth pattern<br>▪ Dense stromal fibrosis accompanies tumor invasion, and there is a proclivity for perineural invasion within and beyond the organ.<br>▪ Lymphatic invasion also is commonly seen. |

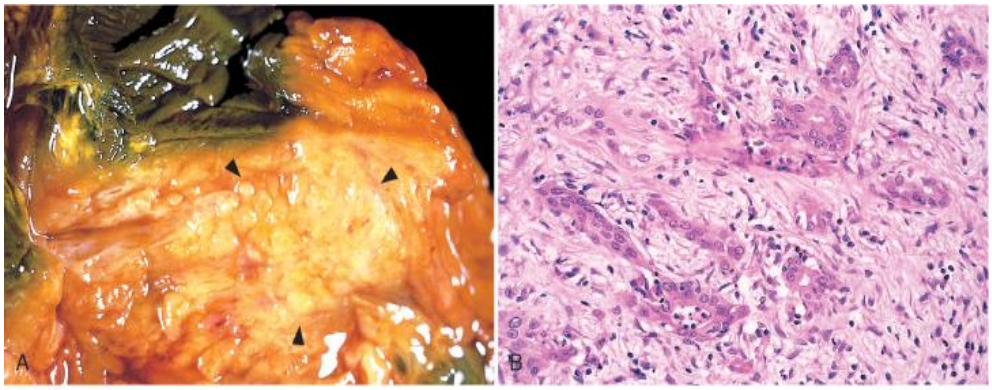



**Figure 16–9** Carcinoma of the pancreas. **A,** A cross-section through the head of the pancreas and adjacent common bile duct showing both an ill-defined mass in the pancreatic substance (*arrowheads*) and the green discoloration of the duct resulting from total obstruction of bile flow. **B,** Poorly formed glands are present in a densely fibrotic (desmoplastic) stroma within the pancreatic substance.

## Pathogenesis:

There is a progressive accumulation of genetic changes in pancreatic epithelium as it proceeds from non-neoplastic, to noninvasive precursor lesions, to invasive carcinoma.

- Both intraductal papillary mucinous neoplasms and mucinous cystic neoplasms can progress to invasive adenocarcinoma and are thus considered bona fide precursors of cancer.
- The most common antecedent lesions of pancreatic cancer arise in small ducts and ductules, and are called **pancreatic intraepithelial neoplasias (PanINs).**
- Four genes are **most commonly** affected by somatic mutations in this neoplasm: **KRAS, CDKNA2A/p16, SMAD4, and TP53.**

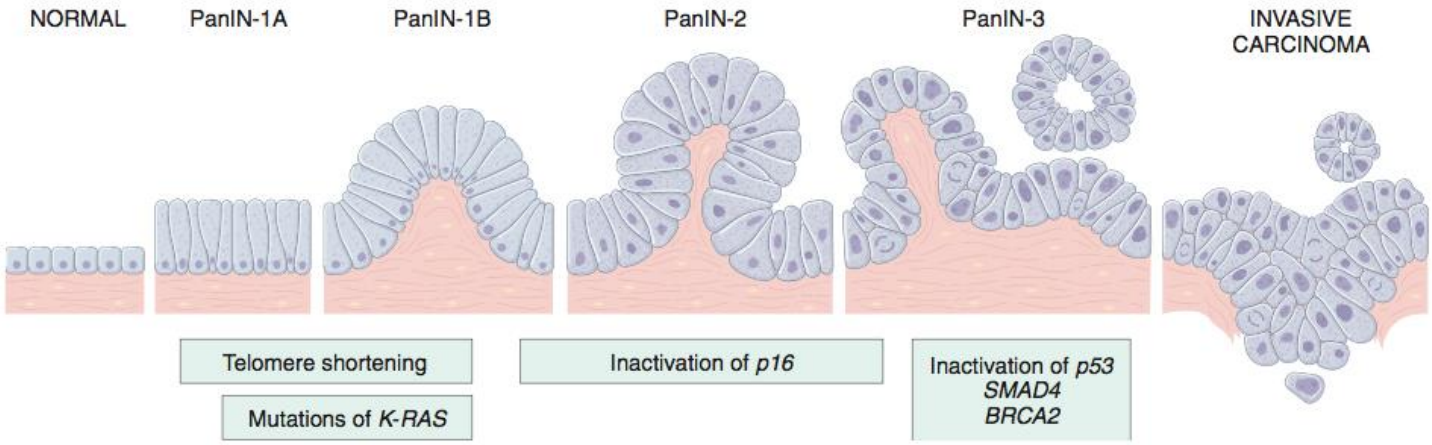



**Figure 16–8** Progression model for the development of pancreatic cancer. It is postulated that telomere shortening and mutations of the oncogene *K-RAS* occur at early stages, inactivation of the *p16* tumor suppressor gene occurs at intermediate stages, and the inactivation of the *TP53*, *SMAD4*, and *BRCA2* tumor suppressor genes occurs at late stages. Note that while there is a general temporal sequence of changes, the accumulation of multiple mutations is more important than their occurrence in a specific order. PanIN, pancreatic intraepithelial neoplasm. The numbers following the labels on the top refer to stages in the development of PanINs.
*(Modified from Maitra A, Hruban RH: Pancreatic cancer. Annu Rev Pathol Mech Dis 3:157, 2008.)*

## Further Reading:

Further explanation regarding the genes in pancreatic cancer:

- ***KRAS*** is the most frequently altered oncogene in pancreatic cancer. These mutations impair the intrinsic GTPase activity of the Kras protein so that it is constitutively active. In turn, Kras activates a number of intracellular signaling pathways ("Kras effectors") that promote carcinogenesis.

- **The *p16 (CDKN2A)* gene** is the most frequently inactivated tumor suppressor gene in pancreatic cancer. The p16 protein has a critical role in cell cycle control; inactivation removes an important checkpoint.

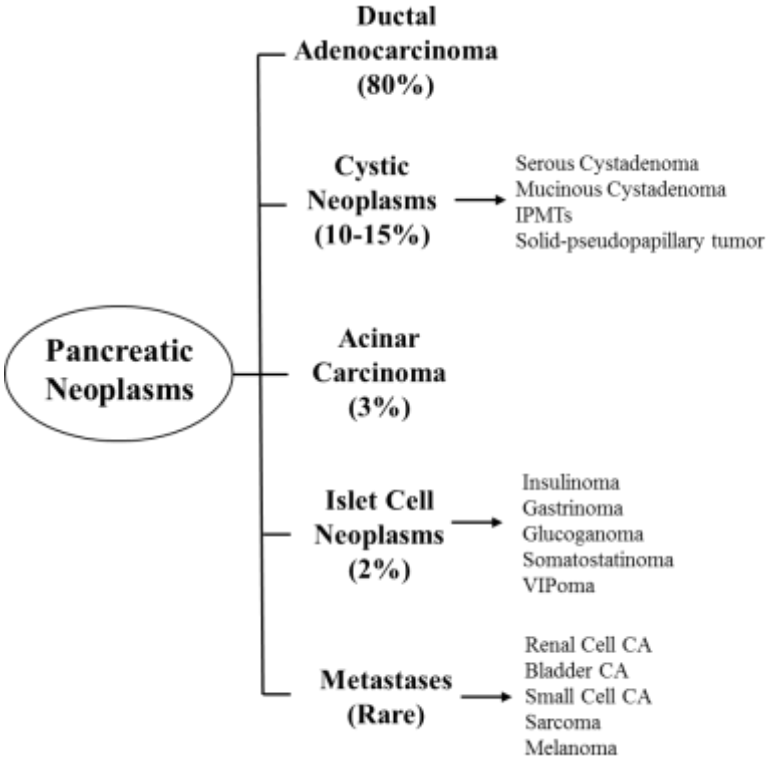
- ***SMAD4* tumor suppressor gene** is inactivated in 55% of pancreatic cancers; it codes for a protein that plays an important role in signal transduction downstream of the transforming growth factor-β receptor.

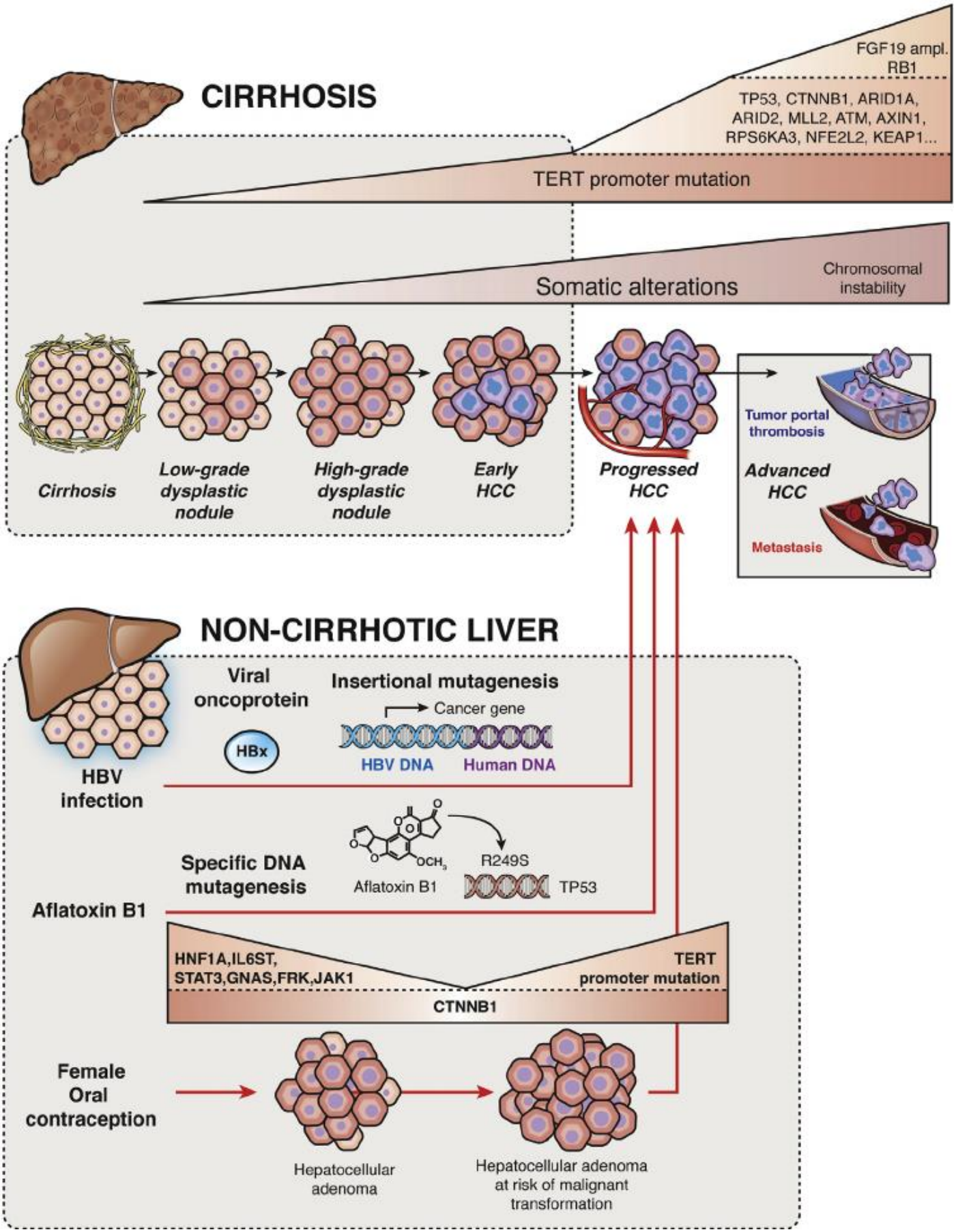
## Liver Tumors Summary:

- The most common malignant tumors of the liver are metastatic carcinomas, most often from colon, lung, and breast.
- The main primary malignancy is hepatocellular carcinoma.
- The main etiologic agents for hepatocellular carcinoma are hepatitis B and C, alcoholic cirrhosis, hemochromatosis, and, more rarely, tyrosinemia and $\alpha$1-antitrypsin (AAT) deficiency.
- In the Western population, about 90% of hepatocellular carcinomas develop in cirrhotic livers; in Asia, almost 50% of cases develop in noncirrhotic livers.
- The chronic inflammation and cellular regeneration associated with viral hepatitis may be predisposing factors for the development of carcinomas
- Hepatocellular carcinomas may be unifocal or multifocal, tend to invade blood vessels, and recapitulate normal liver architecture to varying degrees.

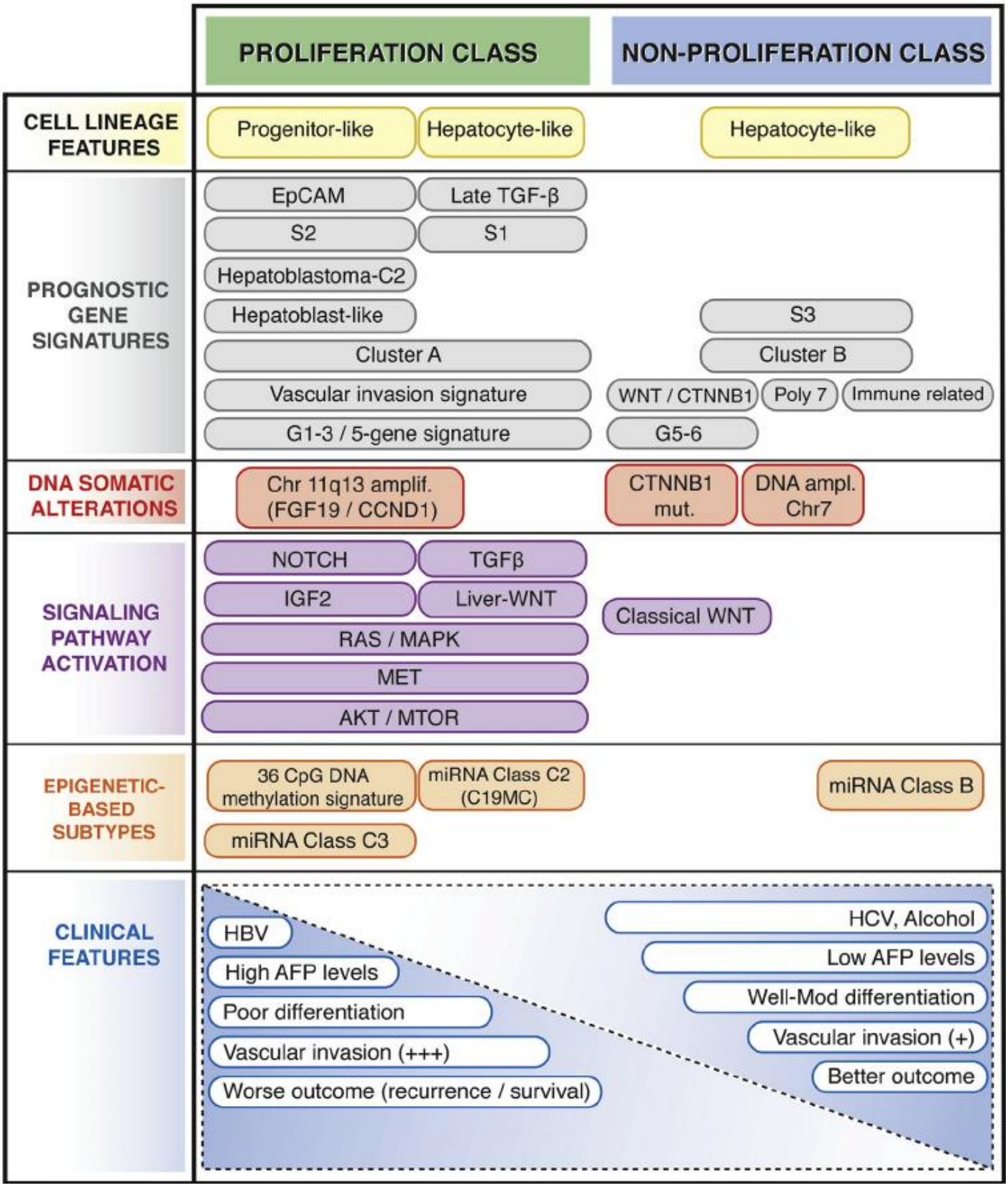
## Pancreatic Neoplasms Summary:

- Pancreatic cancer probably arises from noninvasive pre- cursor lesions (most commonly, PanINs), developing by progressive accumulation of characteristic mutations of oncogenes (e.g., KRAS) and tumor suppressor genes (e.g., CDKN2A/p16, TP53, and SMAD4).
- Typically, these neoplasms are ductal adenocarcinomas that produce an intense desmoplastic response.
- Most pancreatic cancers are diagnosed at an advanced stage, accounting for the high mortality rate.
- Obstructive jaundice is a feature of carcinoma of the head of the pancreas; many patients also experience debilitating pain.

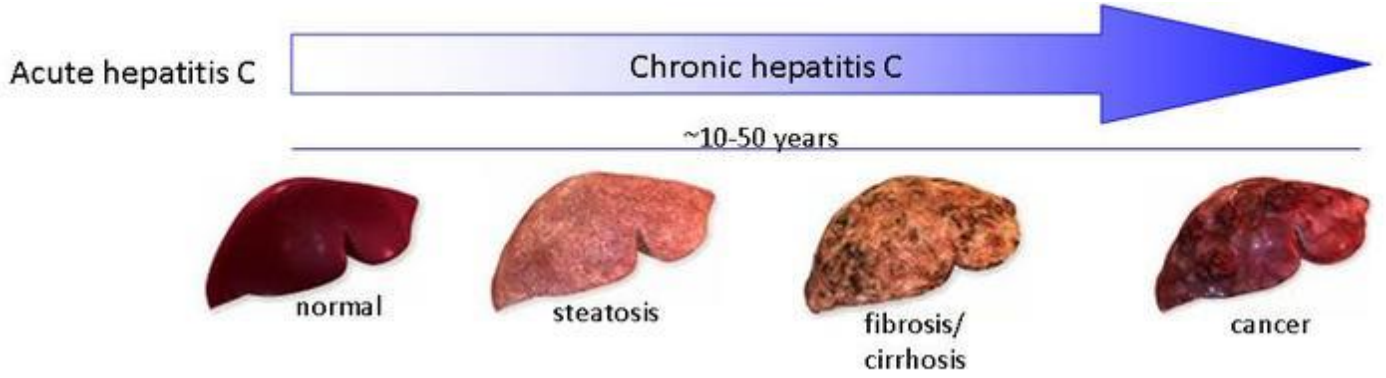



CIRRHOSIS
FGF19 ampl.
RB1
TP53, CTNNB1, ARID1A,
ARID2, MLL2, ATM, AXIN1,
RPS6KA3, NFE2L2, KEAP1...
TERT promoter mutation
Somatic alterations
Chromosomal instability
Cirrhosis
Low-grade dysplastic nodule
High-grade dysplastic nodule
Early HCC
Progressed HCC
Tumor portal thrombosis
Advanced HCC
Metastasis
NON-CIRRHOTIC LIVER
HBV infection
Viral oncoprotein
HBx
Insertional mutagenesis
Cancer gene
HBV DNA
Human DNA
Aflatoxin B1
Specific DNA mutagenesis
Aflatoxin B1
R249S
TP53
HNF1A,IL6ST,
STAT3,GNAS,FRK,JAK1
TERT promoter mutation
CTNNB1
Female Oral contraception
Hepatocellular adenoma
Hepatocellular adenoma at risk of malignant transformation

# Extra
# Molecular Classification of HCC



# Extra
# Example of how HCV leads to HCC




5-20% with steatosis or fibrosis will develop hepatic cirrhosis

**Acute hepatitis C infection**

- short-term
- 15-25% will clear HCV without treatment
-75-85% will develop chronic HCV

**Chronic hepatitis C infection**

- long-term
- 60-70% of those with chronic HCV will develop chronic liver disease

**Hepatic Steatosis**

- "fatty liver"
- a "chronic liver disease"

**Hepatic Fibrosis**

- mild "scarring of the liver"
- a "chronic liver disease"
- reversible, if HCV is cleared

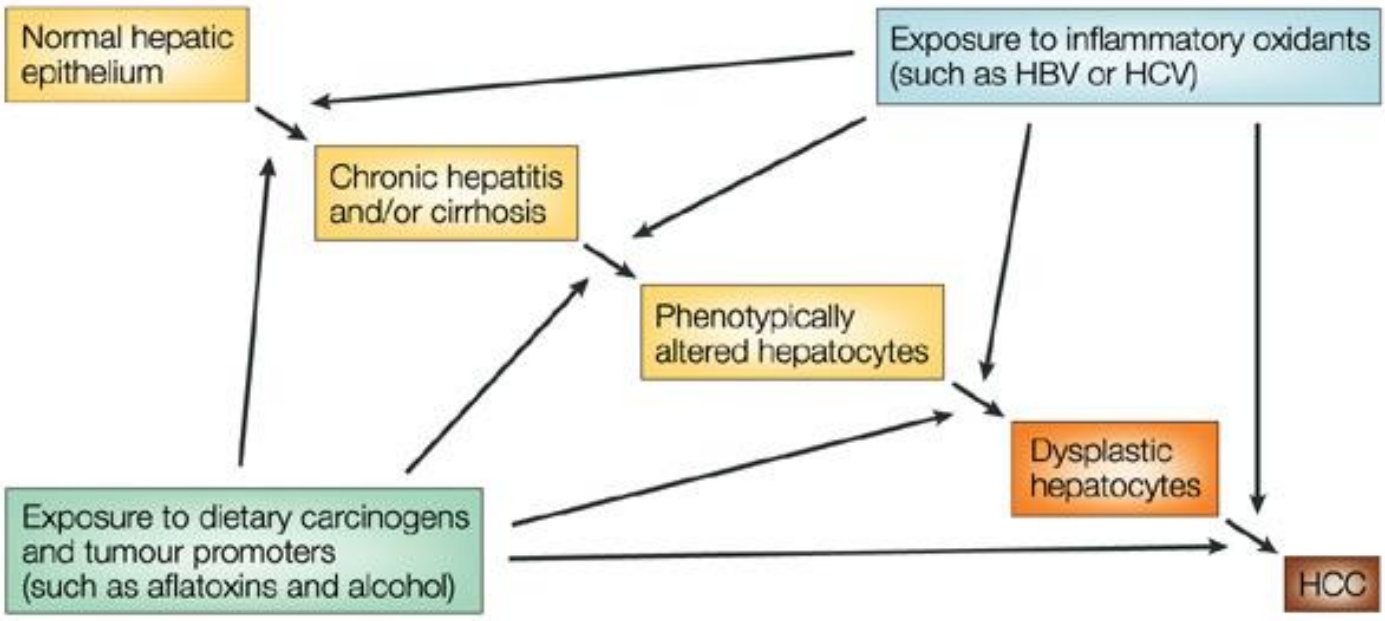
**Hepatic Cirrhosis**

- severe hepatic fibrosis or "scarring of the liver"
- irreversible
-1-5% with hepatic cirrhosis will develop hepatocellular carcinoma

**Hepatocellular Carcinoma**

- formation of a malignant tumor arising from hepatocytes

# Pathogenesis of HCC (another diagram)




Nature Reviews | Cancer

# Check Your Understanding

**MCQs:**

1. **A 51-year- old man presents with jaundice, alcoholic stools, nausea and vomiting, and weight loss the enlarged liver can be felt on palpation. The patient elevated serum levels of alkaline phosphatase. What's the most likely diagnosis?**
   A. fibrolamellar carcinoma
   B. Hepatic Adenoma
   C. extrahepatic cholangiocarcinomas
2. **A 51-year- old man with history of Caroli disease is now complaining of weight loss, pain, anorexia, and ascites. The enlarged liver can be felt on palpation. What's the most likely diagnosis?**
   A. fibrolamellar carcinoma
   B. Pancreatic Carcinoma
   C. Intrahepatic cholangiocarcinomas
3. **Which of the following is a laboratory finding in cholangiocarcinomas?**
   A. Alpha-fetoprorein is not elevated
   B. Alpha-fetoprorein is elevated
   C. Alpha-fetoprorein is decreased
4. **The most common carcinomas of the liver will arise from**
   A. Bile ducts
   B. Hepatocytes
   C. Blood vessels
5. **The rapidly increasing incidence of hepatocellular carcinoma in western countries is owed to**
   A. Hepatitis B
   B. Aflatoxin exposure
   C. Hepatitis C
6. **Common precursor lesions of hepatocellular carcinoma include**
   A. Cirrhosis
   B. Cellular Changes
   C. Nodular Lesions
   D. B & C
7. **Primary hepatic malignancies are almost all _____:**
   A. Hepatoblastoma
   B. Angiosarcoma
   C. Hepatocellular Carcinoma

1: C 2:C 3:A 4:B 5:C 6:D 7:C

8. **Which of the following is the most common risk factors of primary liver cancer?**
   A. HCV and HBV
   B. Smoking
   C. Alcoholic cirrhosis
   D. A and C

9. **The most common Malignant tumor of the liver?**
   A. Cholangiocarcinoma
   B. Hepatocellular Carcinoma
   C. Metastatic

10. **Hepatocellular Carcinomas have a strong tendency to?**
   A. Necrotize the surrounding structures
   B. Invade vascular channels
   C. None of the above

11. **A male patient complained of upper abdominal pain, fatigue and weight loss he was diagnosed with Hepatocellular carcinoma which one of the following may be positive?**
   A. Alpha fetoprotein
   B. Alpha 1 acid glycoprotein
   C. Beta-2 microglobulin

8:D 9:C 10:B 11:A

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**Team Members:**

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قال صلى الله عليه وسلم: {من سلك طريقًا يلتمس فيه علمًا سهَّل الله له بهِ طريقًا إلى الجنة}

دعواتنا لكم بالتوفيق

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