Epidemiology and aetiology of Hepatobiliary-Pancreatic tumors: Insight into the Indian context

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Hepatobiliary malignancies of interest

• Carcinoma gall bladder
• Hepatocellular carcinoma
• Carcinoma pancreas
• Cholangiocarcinoma
Estimated number of incident cases worldwide, both sexes, all ages
Estimated age-standardized incidence and mortality rates (World) in 2020, worldwide, both sexes, all ages

Data source: GLOBOCAN 2020
Carcinoma gall bladder

- Globally, the burden of gallbladder / other biliary tract cancers has risen over last 30 years
- Traditionally believed to be a disease of low socioeconomic groups
Risk Factors
Ca GB

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Susceptible host
- Age
- Female
- Parity
- Age at 1st pregnancy
- Tobacco
- Obesity
- OCP
- Genetic mutation-ABCB1/4
- Micronutrient deficiency

GBC

Vulnerable GB
- Cholelithiasis
- Porcelain GB
- Mirizzi's syndrome
- GB polyp
- APBDU
- CBD stone
- Xanthogranulomatous
- Cholecystitis
- GB stasis

Infection
- Salmonella carriers
- Helicobacter pylori
- Helicobacter bilis
- Irritants
- Mustard oil
- Red-chilli pepper

Heavy metals:
- Nickel, Cadmium
- Toxins
- DDT, organochlorines, benzene

Occupational exposure
- Rubber, coal, wood, paper, oil
- Greasing agents

Toxic environment
GB demographics

**Age**
- Incidence increases with age
- US data: median age 67 years

**Gender**
- Women are affected two to six times more often than men
- Association with high parity and number of pregnancies – possible relation with female sex hormones
- Increased co-expression of ER/PR in women with Ca GB: potential target for intervention

<table>
<thead>
<tr>
<th>Age</th>
<th>Incidence (AAR /100,000)</th>
<th>Mortality (AAR /100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-49 y</td>
<td>0.16</td>
<td>0.08</td>
</tr>
<tr>
<td>50-64 y</td>
<td>1.47</td>
<td>0.77</td>
</tr>
<tr>
<td>65-74 y</td>
<td>4.91</td>
<td>2.68</td>
</tr>
<tr>
<td>&gt;75 y</td>
<td>8.69</td>
<td>5.05</td>
</tr>
</tbody>
</table>
GB demographics

**Geography/ethnicity**

- Widely variable geographic pattern

- Incidence
  - High: Latin America and Asia >> Eastern and central Europe (Hungary, Germany, Poland)
  - Within Asia - northern Indian females, Pakistani females, Korean males
    - Korean men: Highest in Asia (AAR 8.1) – risk remains even in Koreans in US
  - Low incidence: United States, western Europe (UK, France, Norway), Mediterranean European countries
    - More common in White compared with Black people

- Mortality:
  - Native American Indians: mortality exceeds that from breast, cervix, pancreas, ovary
GB risk factors

1. Chronic GB inflammation
   Major factor in carcinogenesis
   - Gallstone disease
   - Porcelain gallbladder
   - Gallbladder polyps
   - Primary sclerosing cholangitis

   Inflammation—metaplasia — dysplasia — carcinoma sequence

   • Mucosal irritation & DNA damage
   • Repeated tissue proliferative attempts at restoration
   • Release of cytokines and growth factors
   • Local production & accumulation of carcinogens (e.g., secondary bile acids)
   • Higher predisposition to oncogenic transformation
GB risk factors

Gallstone disease

• ~85% patients with Ca GB have gallstones
• Only 0.5-3% pts with gallstones have Ca GB
• Compared to healthy individuals, patients with symptomatic GB disease (gallstones or self-reported cholecystitis) 34-fold more likely to develop Ca GB

• Gallstone characteristics influence risk
  • Stone size: 10-fold increase for stones >3 cm
  • Stone type - Cholesterol gallstones
  • Longer duration of stones (6-12 fold for >20y)

Cholecystectomy for gallstones: inverse correlated with Ca GB rates

• Poor socioeconomic status → limited access
• In the West, decline in incidence as well as mortality
GB risk factors

Porcelain gallbladder

• Calcium deposition in GB wall (<1%, women in 50s)
• ~25% risk of Ca GB
• Risk of malignancy: Stippled calcification > transmural calcification
→ Prophylactic removal of GB with partial calcification, stippled, or multiple punctate calcifications

Gallbladder polyps

• Most are non-malignant
• Risk of malignancy: large polyps (>10 mm – 25% are malignant), solitary or sessile mass, associated gallstones, Age >50 y, rapid growth
• EUS may help distinguish b/w benign and malignant polyp, follow up every 6-12m if not resected

Primary sclerosing cholangitis

6% may have GB masses, of which half may be Ca GB
Annual screening USG is recommended; Cholecystectomy if lesions >0.8 cm)
GB risk factors

2. Chronic Infections

- Chronic bacterial cholangitis
  - *Salmonella* (eg, *S. typhi* and *S. paratyphi*) and *Helicobacter* (eg, *H. bilis*)
  - Ca GB risk increases 12-fold in typhoid carriers

Degradation of bile constituents (ie, bacterial hydrolysis of primary bile acids forming carcinogens and/or the action of β-glucuronides) --> malignant transformation

Contributors: chronic inflammation, alterations of tumor suppressor genes (*p53*) or proto-oncogenes (*K-ras*)

- Chronic parasitic infestations
  - Clonorchis and Opisthorchis
  - Contributors: chronic inflammation, increased biliary stone formation
GB risk factors

3. Anatomic changes

- **Congenital biliary cysts** (intra- or extrahepatic)
  - more often linked to cholangiocarcinomas (risk increases with age)
  - more often in patients with an anomalous pancreaticobiliary duct junction

- **Anomalous pancreaticobiliary duct junction**
  - Congenital anomaly (picked on ERCP/MRCP/EUS)
  - More common in Asians (Japanese), young women
  - 10% of GB cancer
  - Lesser risk of invasion and metastases
  - Higher reflux of pancreatic juice into the biliary tree → increased amylase levels in bile, intraductal activation of proteolytic enzymes, alterations in bile composition → inflammatory and malignant change
  - Prophylactic cholecystectomy is recommended
GB risk factors

4. Genetics
• Family history (25% risk)
• Interaction between innate genetic predisposition and exposure to environmental risk factors
• Multistep sequence involving cumulative genetic and epigenetic alterations

5. Obesity
• Higher risk with BMI > 30 kg/m^2 (OR 1.8-2.1)
• RR increased by 1.59 for women and 1.09 for men for each 5-point increase in BMI
• Diabetes – increases risk of GSD, higher risk of Ca GB even without gallstones
GB risk factors

6. Exposures

• Heavy metals, like nickel and cadmium, have been implicated
• Workers in the oil, paper, chemical, shoe, textile, and cellulose acetate fiber manufacturing industries
• Miners exposed to radon (inhaled)
• Tobacco consumption
• Drugs: methyldopa, isoniazid, ?OCP/HRT
• Exposure to aflatoxin, a mycotoxin that commonly contaminates corn, soybeans, and peanuts
Estimated age-standardized incidence and mortality rates (World) in 2020, gallbladder, all ages (excl. NMSC)
Estimated age-standardized incidence rates (World) in 2020, gallbladder, both sexes, all ages

Geographic variability – correlates with prevalence of cholelithiasis/salmonella

High rates in
South America - Chile, Bolivia, Ecuador
East Asia (Korea, Japan), South East Asia (north India, Pakistan), Poland
Southwestern Native Americans and in Mexican Americans

Low rates in
North America
Estimated age-standardized incidence rates (World) in 2020, gallbladder, both sexes, all ages

**ASR (per 100,000) in India**
- **Overall**: 1.4
- **Males**: 0.96
- **Females**: 1.9

GLOBOCAN 2020
Highest mortality in Chile (3.5 per 100,000)

**ASR (per 100,000) in India**
- Overall: 1.1
- Males: 0.73
- Females: 1.5

GLOBOCAN 2020
Gall bladder disease in India

• North > South
• Most prevalent in northern and northeastern states of UP, Bihar, Orissa, West Bengal and Assam
• Leading GI cancer in women in northern Indian cities
• Detailed geographic tracking of GBC patients attending TMH Mumbai (1990-95): majority of patients from UP (41.9%) and Bihar (35.8%)
Ca GB: Comparison of AAR of 28 PBCRs

<table>
<thead>
<tr>
<th>Districts with highest AAR</th>
<th>Males (AAR)</th>
<th>Females (AAR)</th>
<th>Annual percent change</th>
<th>Crude rate 1988</th>
<th>Crude rate 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kamrup urban</td>
<td>7.9</td>
<td>16.2</td>
<td></td>
<td>1.4</td>
<td>8.4</td>
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<tr>
<td>Cachar</td>
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<td>Delhi</td>
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<tr>
<td>Papumpare</td>
<td>10.7</td>
<td></td>
<td></td>
<td>2.4</td>
<td>9.5</td>
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<tr>
<td>Dibrugarh</td>
<td></td>
<td></td>
<td></td>
<td>1.7</td>
<td>23.1</td>
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</tbody>
</table>
Gallbladder Abnormalities in Northern Gangetic Area (GANGA survey)

• Population survey of environmental risk factors for GB disease
• 60 villages of Uttar Pradesh and Bihar, persons aged >30y
• GB diseases surveyed - acute & chronic cholecystitis, solitary & multiple GSD, GB polyps and Ca GB

<table>
<thead>
<tr>
<th>Gall bladder disease</th>
<th>Gallstones</th>
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<tbody>
<tr>
<td>Prevalence</td>
<td></td>
</tr>
<tr>
<td>6.2%</td>
<td>4.15%</td>
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<tr>
<td>7.12% with symptoms</td>
<td>F 5.59%</td>
</tr>
<tr>
<td>2.99% without symptoms</td>
<td>M 1.99% (P &lt; 0.05)</td>
</tr>
</tbody>
</table>

Significant risk factors for GBD | Odd’s ratio |
Females >50 years | 1.703 |
Multiparity | 1.862 |
Genetic history | 1.564 |
Males with diabetes | 4.271 |
Chickpea consumption | 2.546 |
Drinking unsafe water | 2.835 |

Cluster analysis: positive correlation of nickel, cadmium and chromium in water with a high prevalence of GBD in adjacent villages in Vaishali district, Bihar.

3-y prospective study for Ca GB (KGMU Lucknow)

- Peak incidence: 31-50 y
- Male: Female = 1: 4.83
- On average, females were 5 years younger than males at diagnosis
- 68% patients: low socioeconomic strata - Kuppuswamy classes IV, V (lower class)
- 84% consumed mustard oil (home made/loose packed) as predominant cooking medium
- Age of menarche <14y (83%), Age at FCB <20y (56%), Parity >2 (57%)—higher incidence
- >70% were postmenopausal
- 80% had gallstones
- 32% had incidental GBC diagnosis, 52% presented with distant mets

**Contribution of lifestyle, cultural, dietary factors**

**Balanced diet, prevention of malnutrition/adulteration, tobacco prevention and early intervention for cholelithiasis may help decrease incidence**

Case control study at TMH Mumbai

• Role of cooking with mustard oil and other dietary factors in relation to Ca GB in high- and low-incidence regions of India

• Increased risk of Ca GB
  • High consumption of mustard oil in both high-risk (OR 1.33) and low-risk regions (OR = 3.01)
  • Deep frying of fresh fish in mustard oil (OR = 1.57)

• Protective association
  • Consumption of leafy vegetables, fruits, onion and garlic

• No association
  • Consumption of meat, spicy food, turmeric, pulses
  • Any other oil as cooking medium

NCRP HBCR data – GI cancers

• 58 HBCRs
• GB cancers constitute 10% of GI cancers in males (rank 4) and 23.8% in females (rank 2)
• 80% GB malignancies were adenocarcinomas
• Younger age (45-49 years) in women compared to other cancers
• ~70% have locally advanced or metastatic disease
• For the period 1982-2016, annual percentage change in AAR was
  • 1.76% for Delhi
  • 2.31% for Mumbai

Hepatocellular carcinoma

• HCC and Intrahepatic cholangio - 6\textsuperscript{th} most common cancer
• HCC – 3\textsuperscript{rd} most common cause of mortality, second most lethal tumor (5y S 18%)
• Increasing incidence and mortality: North America, Latin America, and central Europe (recent decline or plateau in deaths due to increased detection of localised HCC)
Hepatocellular carcinoma – Risk factors

- Cirrhosis due to any cause
- Non-alcoholic fatty liver disease

Susceptible host
- Gender: M > F
- Diabetes mellitus
- Obesity
- Genetic susceptibility:
  - Hereditary hemochromatosis
  - Alpha-1 antitrypsin deficiency
  - Acute intermittent porphyria
  - Porphyria cutanea tarda

Pancreatic cancer

Local factors

Environment / lifestyle
- Infections – HBV, HCV, HDV
- Lifestyle factors – Alcohol, tobacco
- Tobacco
- Toxins — synergistic effect
  - Aflatoxin B1 - parts of Africa & Asia
  - Betel nut chewing
  - Iron overload - non-dietary sources (e.g., chronic transfusion of RBCs for hereditary anemia)
  - Contaminated drinking water (China - algal toxin Microcystin)
Hepatocellular carcinoma – Risk factors

Cirrhosis

• Cirrhosis from any etiology increases HCC risk
• Nearly 1/3 cirrhotic patients develop HCC during their lifetime (annual incidence rate 1-8%)
• Causes of cirrhosis
  • Cryptogenic (NASH)
  • Viral hepatitis
  • Alcoholic liver disease
• Distribution of these causes varies worldwide
Hepatocellular carcinoma – Risk factors

Viral hepatitis
50% HCC cases – HBV, 20% - chronic HCV

- **Hepatitis B virus** — Factors other than cirrhosis include:
  - High viral load (ie, HBV DNA levels $>10^6$ copies /mL)
  - HBeAg positivity (an indicator of a prolonged replication phase)
  - HBsAg levels $>1000$ IU/mL in patients with HBeAg negative chronic HBV with low viral load (ie, inactive chronic HBV)
  - HBV genotype C
  - Male sex (for patients who are HBsAg positive)
  - Viral coinfection (HCV or hepatitis D virus)
  - Coinfection with HEV reduces risk compared to HBV alone
  - HBsAg clearance – does not eliminate the risk of HCC but lower compared to HBsAg positive

- Contributing factors in addition to HBV
  - Age – Young age of HBV acquisition or older age among those with chronic infection
  - Lifestyle factors – Alcohol or tobacco use.
  - Blood group B (in males only)
  - Family history of HCC
Hepatocellular carcinoma – Risk factors

• **Hepatitis C virus** - cirrhosis as well as other risk factors:
  • Genotype – HCV genotype 1b, compared with genotypes 2a/c)
  • Viral coinfection (HBV or human immunodeficiency virus infection)
  • Lifestyle factors – Alcohol or tobacco use
  • Metabolic factors – Diabetes mellitus, obesity

• **Hepatitis D virus** — coinfection with HBV increases risk
Hepatocellular carcinoma – Epidemiology

• Geographic variation
  • Asia (72%), Europe (10%), Africa (8%), North America (5%), Latin America (5%)
  • Highest incidence - Mongolia (93.7 per 100,000)
  • Different exposure to viruses and environmental agents

• Sex and race
  • Men > Women (3:1)
  • In USA, incidence in Asia-Pacific Islanders (7.8) > Black Americans (4.2) > Native Americans/Alaska Natives (3.2) > White Americans (2.6)
  • Year of birth - HCV highest prevalence in birth years 1945-65 – highest mortality for liver cancer
Estimated age-standardized incidence and mortality rates (World) in 2020, liver, all ages

Data source: GLOBOCAN 2020
Graph production: Global Cancer Observatory (http://gco.iarc.fr/)
© International Agency for Research on Cancer 2022
Highest incidence in Mongolia (68.4) and Egypt (22.7)

ASR (per 100,000) in India

Overall 2.6
Males 3.6
Females 1.6
Estimated age-standardized mortality rates (World) in 2020, liver, both sexes, all ages

**ASR (per 100,000) in India**

- Overall: 2.5
- Males: 3.5
- Females: 1.5

GLOBOCAN 2020
Liver: Comparison of AAR of 28 PBCRs

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Papumpare</td>
<td>35.2</td>
<td>14.4</td>
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<tr>
<td>West Arunachal</td>
<td>21.5</td>
<td>8.0</td>
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<tr>
<td>Aizawl</td>
<td>12.2</td>
<td>5.9</td>
</tr>
<tr>
<td>Mizoram</td>
<td>10.0</td>
<td>5.9</td>
</tr>
</tbody>
</table>

Annual percent change

<table>
<thead>
<tr>
<th>Districts</th>
<th>Males:</th>
<th>Crude rate 1988</th>
<th>Crude rate 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kamrup urban</td>
<td>+11.0%</td>
<td>2.5</td>
<td>6.2</td>
</tr>
<tr>
<td>Thiruvananthapuram</td>
<td>+7.2%</td>
<td>4.5</td>
<td>9.3</td>
</tr>
<tr>
<td>Mumbai</td>
<td>Males: +4.0%</td>
<td>2.1</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td>Females: +4.2%</td>
<td>1.4</td>
<td>3.2</td>
</tr>
</tbody>
</table>
3y observational study on HCC patients: KMC Manipal

- 73.2% had cirrhosis
- Diabetes mellitus (DM) was present in 44.2%
- BCLC stages C and D - 62.4%
- Only 26.6% of cirrhotic HCC patients were diagnosed during surveillance
- Patients in non-cirrhotic HCC group
  - higher age
  - larger lesion size
  - lower MELD score

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptogenic</td>
<td>51.3</td>
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<tr>
<td>Alcohol</td>
<td>19.4</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>17.4</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Musunuri B, et al. Profile of patients with hepatocellular carcinoma: An experience from a tertiary care center in India. Indian J Gastroenterol. 2022
Hepatocellular carcinoma - Protective factors

- **Vaccination against HBV**
- **Antiviral therapy for viral hepatitis** due to HBV or HCV
- **Medications**
  - **Statins** (hydroxymethylglutaryl CoA reductase inhibitors) – OR 0.63; 95% CI 0.52-0.76 - effect most profound in East Asian males with chronic HBV
  - **Aspirin and other NSAIDs**
  - **Metformin**
- **Lifestyle factors**
  - **Coffee** – possibly due to antioxidants
  - **Diet** – consumption of white meat, fish, omega-3 fatty acids, vegetables, dietary intake of Vit E
  - **Physical activity** – effect of exercise on glucose or lipid metabolism or on improving NAFLD
  - **Other factors** — For patients with NASH & obesity, **bariatric surgery** has lower HCC rates
Hepatitis C has greater contribution in West while Hepatitis B in East Asia and Africa
HBV-associated cancer incidence correlates inversely with HBV vaccination coverage
• 3% of all GI cancers
• Incidence – difficult to interpret, usually clubbed with liver (intrahepatic) or GB (extrahepatic)
  • Highest in Thailand, China (40-fold higher than USA)
• US SEER data
  • 15% of intrahepatic and 33% of extrahepatic lesions are cholangiocarcinomas
  • Incidence 1.26 per 100,000 (2/3 are intrahepatic)
• Incidence increasing for both intra- and extrahepatic
• Factors: higher detection, concomitant increase in risk factors (cirrhosis, alcoholic liver disease, HCV)
Cholangiocarcinoma – Risk factors

**Susceptible host**
- Age (median 50-70y)
  - PSC, Choledochal cysts – 20y earlier
- Gender
  - M > F (? higher PSC)
- Genetic disorders
  - Lynch syndrome
  - BAP1 tumor predisposition syndrome
  - Multiple biliary papillomatosis
  - Cystic fibrosis

**Environment / lifestyle**
- Infections
- Medications
  - DPP-4 inhibitors for DM
  - Long term OCP (>9y)
- Toxic exposures
  - Thorotrast
  - Occupational exposures (auto, rubber, chemical, wood-finishing)
  - Smoking (extrahepatic), alcohol (intrahepatic)
  - Iron overload

**Local factors**
- Primary hepatobiliary disease
  - Primary sclerosing cholangitis
  - Fibropolycystic liver disease
  - Cholelithiasis, cholecystitis, and hepatolithiasis
  - Chronic liver disease
Cholangiocarcinoma – Risk factors

**Primary hepatobiliary disease**

- **Primary sclerosing cholangitis** — leads to strictures of intrahepatic and/or extrahepatic bile ducts
  - Contribute to 30% cholangio
  - Lifetime risk of cholangio 5-15% (0.6-1.5% per annum)
  - Age of diagnosis younger than other cholangio (30-50 years) and diagnosis is difficult
  - Risk unrelated to duration of inflammation (30% diagnosed within 2 years of PSC diagnosis)
  - History of smoking and alcohol increase risk of cholangio

- **Fibropolycystic liver disease**
  - Congenital abnormalities of the biliary tree (Caroli syndrome, congenital hepatic fibrosis, choledochal cysts)
  - 15% risk of malignant change (average age at diagnosis 34y)
Cholangiocarcinoma – Risk factors

• **Cholelithiasis, cholecystitis, and hepatolithiasis**
  • Risk of cholangio lower than Ca GB for GSD
  • Hepatolithiasis or recurrent pyogenic cholangitis – higher incidence in Southeast Asia than West. 50-70% cholangios in Taiwan and 6-18% in Japan have associated hepatolithiasis
  • Diagnosis of cholangio should be suspected in a patient >40y who has a long history of hepatolithiasis, weight loss, high SAP, CEA >4.2 ng/mL, and hepatolithiasis in either the right or both lobes of the liver

• **Chronic liver disease** - more for intrahepatic cholangio
  • HCV (3.5% at 10y, RR 2.55)
  • HBV (less common than HCV)
  • Cirrhosis regardless of etiology
  • Alcoholic liver disease
  • **Precursor lesions** — intraductal papillary neoplasm of bile ducts, intraductal tubulopapillary neoplasm of the bile ducts (rare), and biliary intraepithelial neoplasia
Cholangiocarcinoma – Risk factors

Infections

- **Parasitic infection** — Liver flukes (Clonorchis, Opisthorchis) in Thailand through consumption of undercooked fish – intrahepatic/
  - Carcinogens produced by bacteria in fish and other foods, smoking, alcohol, and HBV infection may act as cofactors
- HIV infection
- H. pylori infection

Other factors

- **Elevated blood glucose** — DM (RR 1.60) – both intrahepatic and extrahepatic cholangiocarcinomas. High risk in higher sugar consumption in Swedish registries (HR 1.69).
- Obesity — intrahepatic cholangiocarcinoma
- **Metabolic syndrome** — intrahepatic cholangiocarcinoma (OR 1.56)
Pancreatic adenocarcinoma

- Worldwide, pancreatic cancer is the 7th leading cause of cancer deaths in both men and women (4th in USA)
- Deemed a disease of developed world
- Early diagnosis in Western countries
  - Average age at diagnosis lower by 3.5 y
  - More cancers detected in IA stage
  - Improved OS in early stage
    - OS in IA: 45% (2004) → 84% (2012)
Pancreas – Risk factors

2017 Global Burden of Disease Study: deaths related to pancreatic cancer were primarily attributable to
- Smoking (21%)
- High fasting plasma glucose (8.9%)
- High body mass index (6.2%)

80% cancers – sporadic mutations
- Family history
- Germline BRCA mutations
- Hereditary pancreatitis
- Chronic pancreatitis
- Lynch syndrome
- Ataxia telangiectasia
- Diabetes mellitus
- Peutz-Jeghers syndrome
- Familial breast-ovarian cancer syndrome
- Familial atypical multiple mole melanoma
- Familial adenomatous polyposis
- Cystic fibrosis

Susceptible host
- Age (peak 65-75 y)
- Male gender (M:F 3:1)
- Black ethnicity
- Non-O blood group
- Diabetes, abnormal glucose metabolism, insulin resistance

Genetic factors

Environment / lifestyle
- Cigarette smoking
- Obesity and physical inactivity
- Infections
  - H pylori, HBV, HCV
- Western diet – saturated fat, smoked meats, low lycopene/selenium, coffee & heavy alcohol use
- NSAIDs /Aspirin/Vit D - ? Reduce risk
Pancreas - Epidemiology

• Age
  • Pancreatic cancer is rare before the age of 45. Peak incidence in men is at age 65-69 and in women at 75-79
  • Median age in USA 79 years
  • In India, the disease peaks in the 6th decade

• Gender
  • In India, M:F ratio is 1.5-2 : 1
  • Gender differences confounded by habits like smoking; undiscovered genetic factors may contribute

• Extent
  • Most cases are locoregionally advanced; only 15-20% are potentially resectable at presentation

• Geography
  • Highest incidence in high-income North America, high-income Asia Pacific, and Western and Central Europe
  • Lowest incidence in South Asia and eastern and central Sub-Saharan Africa
  • USA: African-Americans > Caucasians > Asian Americans and Pacific Islanders
Pancreas – Risk factors

• Genetic factors
  • African Americans
    • Advanced disease, lesser access to surgery
    • Genetic predisposition
      • higher rates of K-ras mutations to valine
      • lower rates of K-ras mutations to cysteine
      • lower expression of Fas
      • trend towards higher HER2 positivity
  • Chinese patients
    • different expressions of K-ras and p53 than Western or Japanese patients
  • Asian patients
    • less aggressive tumors and better survival rate than non-Asian patients
Estimated age-standardized incidence and mortality rates (World) in 2020, pancreas, all ages

- WHO Europe (EURO)
- WHO Americas (PAHO)
- WHO Western Pacific (WPRO)
- World
- WHO East Mediterranean (EMRO)
- WHO Africa (AFRO)
- WHO South-East Asia (SEARO)

Data source: GLOBOCAN 2020
Graph production: Global Cancer Observatory (http://gco.iarc.fr)
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ASR (World) per 100 000
Highest incidence in Hungary and Uruguay (9.2 & 8.9)

ASR (per 100,000) in India

Overall  0.94
Males    1.2
Females  0.69
Estimated age-standardized mortality rates (World) in 2020, pancreas, females, all ages.

Highest mortality in Hungary and Uruguay (10.2)

ASR (per 100,000) in India

- Overall: 0.90
- Males: 1.1
- Females: 0.66
ILBS data

Table 2: Distribution by diagnosis of registered patients (n=502)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients, n (%)</th>
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<tbody>
<tr>
<td>Carcinoma gall bladder</td>
<td>149 (29.7)</td>
</tr>
<tr>
<td>HCC</td>
<td>87 (17.3)</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>44 (8.8)</td>
</tr>
<tr>
<td>Periampullary carcinoma</td>
<td>31 (6.2)</td>
</tr>
<tr>
<td>Carcinoma pancreas</td>
<td>35 (6.8)</td>
</tr>
<tr>
<td>NET</td>
<td>11 (2.2)</td>
</tr>
</tbody>
</table>

Ca GB: 75% stage IV, 44% had gallstones, M:F ratio 1 : 1.6
HCC: 65.5% were BCLC C, M:F ratio 7.7 : 1

6m OS was 56.5% for biliary cancers, 71.4% for HCC
WHO Encyclopedia of carcinogens
IARC monographs

- To date, IARC has classified 120 agents as carcinogenic to humans
- Agents classified in 4 groups
- Group 1: carcinogenic to humans

<table>
<thead>
<tr>
<th>LIVER (HEPATOCELLULAR CARCINOMA)</th>
<th>GALLBLADDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflatoxins</td>
<td>Thorium-232 and its decay products</td>
</tr>
<tr>
<td>Alcoholic beverages</td>
<td>BILIARY TRACT</td>
</tr>
<tr>
<td>Estrogen-progestogen contraceptives</td>
<td>Chlonorchis sinensis</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>1,2-Dichloropropane</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>Opisthorchis viverrini</td>
</tr>
<tr>
<td>Plutonium</td>
<td></td>
</tr>
<tr>
<td>Thorium-232 and its decay products</td>
<td></td>
</tr>
<tr>
<td>Tobacco smoking (in smokers and in smokers’ children)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LIVER (ANGIOSARCOMA)</th>
<th>PANCREAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinyl chloride</td>
<td>Smokeless tobacco</td>
</tr>
<tr>
<td></td>
<td>Tobacco smoking</td>
</tr>
</tbody>
</table>
Both incidence and mortality in India expected to rise in next 20 years
Similar trends in World
Relatively smaller rise in USA
Conclusion

• Complex interplay of host and environmental factors for disease risk and epidemiology
• All HPB malignancies rising in the World as well as India
• No screening programme – only surveillance for high risk populations
• Ca GB – small problem for the World but of high relevance in North India – high incidence, advanced stage, rarely curable
• Possible remedies
  • Ca GB: improve socioeconomic conditions, access to cholecystectomy for GB disease
  • HCC: Discourage alcohol, Hepatitis B vaccination
  • Cholangiocarcinoma: surveillance of high risk patients
  • Pancreas: Discourage smoking, control DM/obesity, healthy diet