Imperial College London

Imperial College Healthcare NHS Trust

An Overview of Cholangiocarcinoma

Prof Shahid A Khan

Imperial College London

AMMF's Cholangiocarcinoma Patients and Carers Information Day

29th October 2020

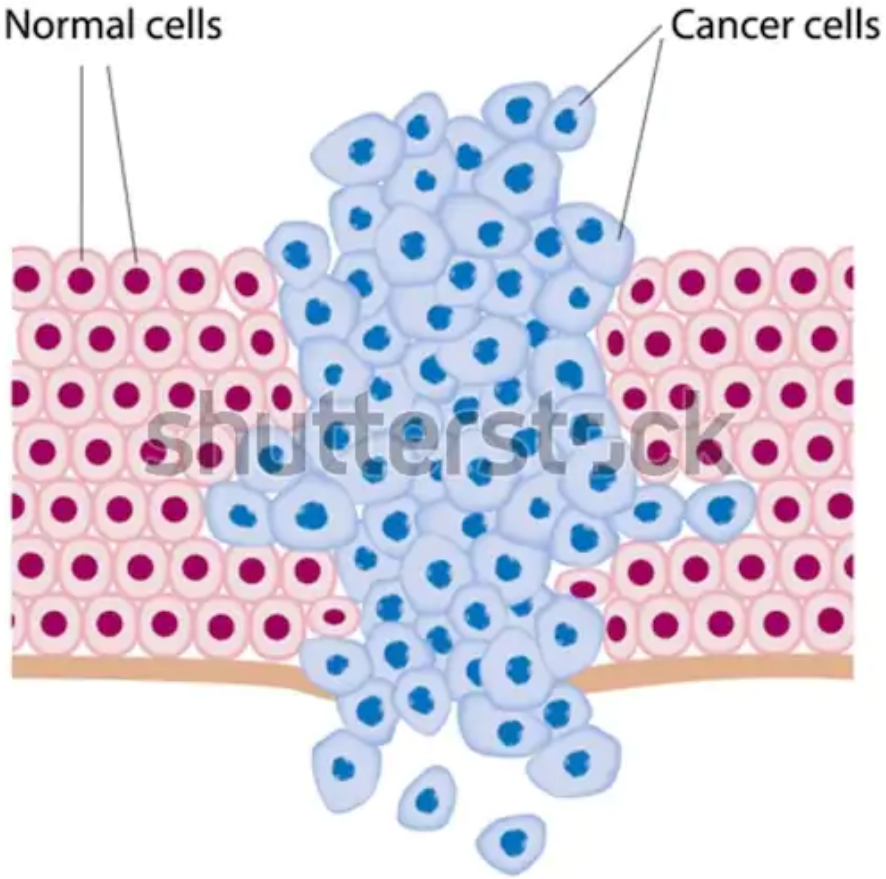
CHOLANGIOCARCINOMA (CCA)

General Overview of Cholangiocarcinoma (CCA)

- What is CCA?
- What symptoms does CCA cause?
- How common is CCA?
- What are the Risk factors for CCA?
- Major Challenges with CCA
- Q & A

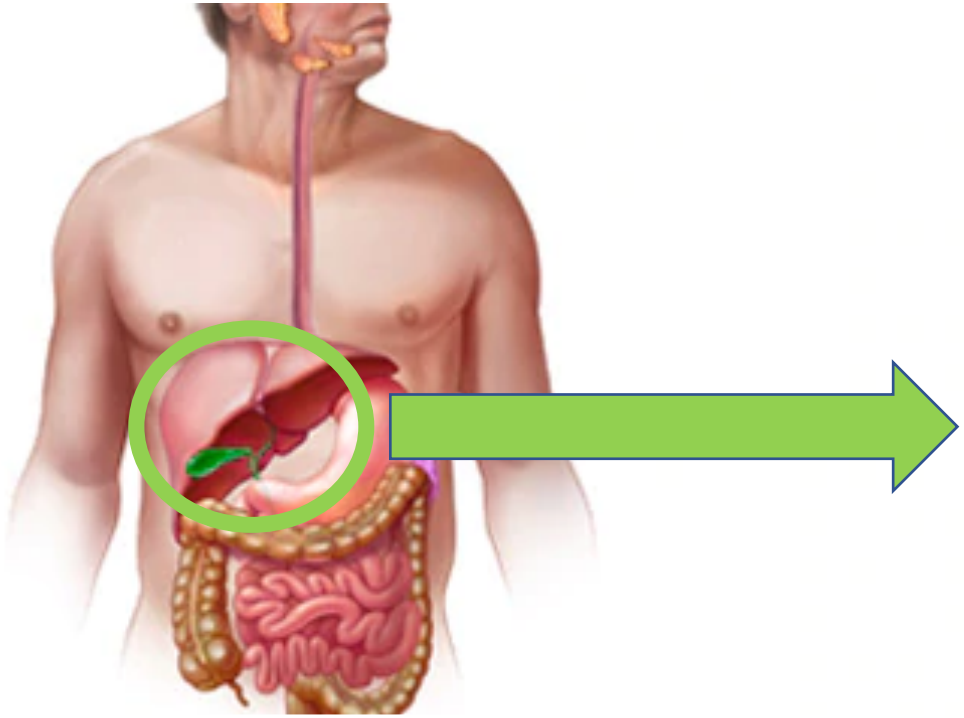
Cholangiocarcinoma (CCA) – What is it?

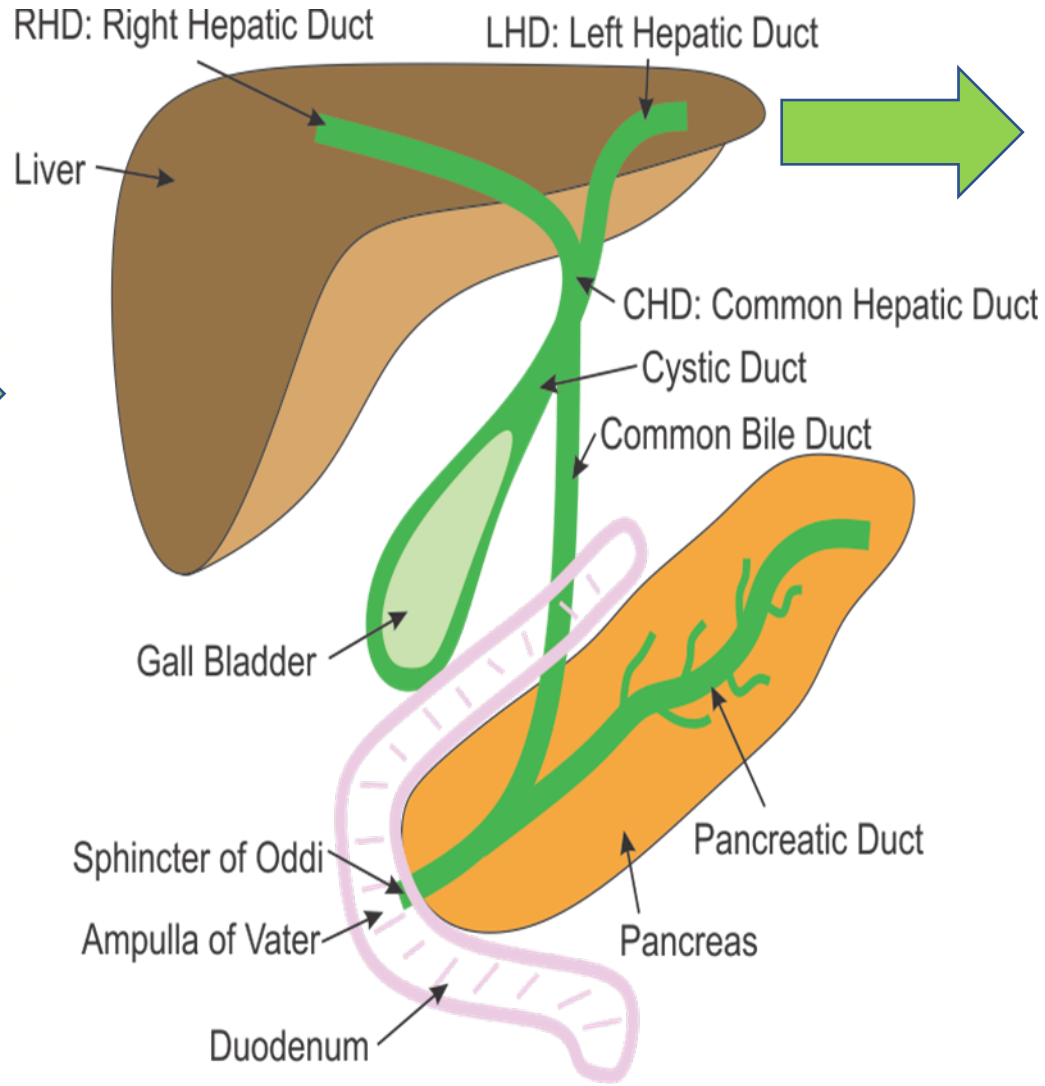
- CCA is a **cancer** which arises from somewhere in the **biliary system**
- What is **cancer**?
- Cancer is a condition where cells in a specific part of the body grow and reproduce uncontrollably
- The cancerous cells can invade and destroy surrounding healthy tissue, including organs
- A cancer sometimes begins in one part of the body but later spreads to other areas. This process is known as metastasis.



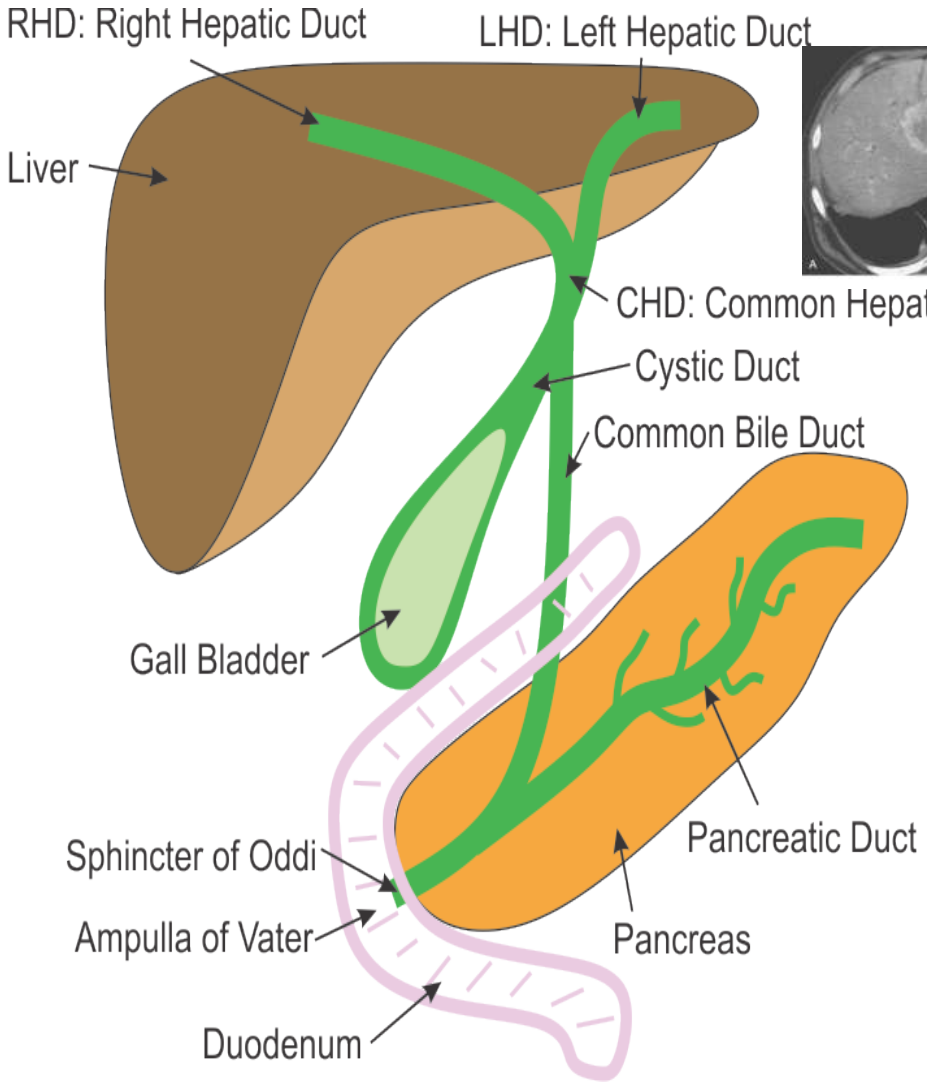
Cholangiocarcinoma (CCA) – What is it?

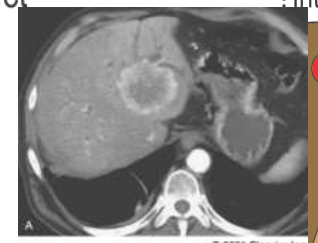
- CCA is a **cancer** which arises from somewhere in the **biliary system**
- What is the "**biliary system**"?
- The liver makes bile, which flows through the biliary ducts and eventually into the intestine
- Bile helps with digestion and also is a route of getting rid off waste products and toxins
- Where is the "biliary system"?

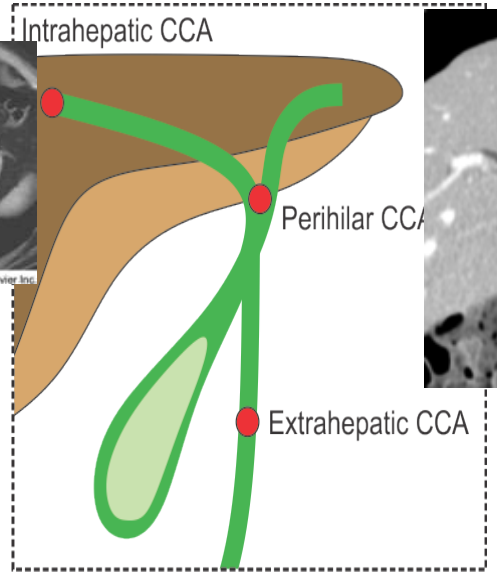


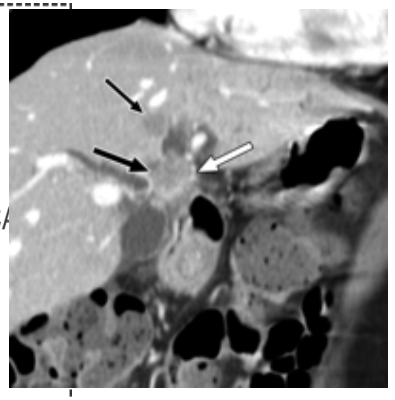

RHD: Right Hepatic Duct
LHD: Left Hepatic Duct
Liver
CHD: Common Hepatic Duct
Cystic Duct
Common Bile Duct
Gall Bladder
Pancreatic Duct
Sphincter of Oddi
Ampulla of Vater
Pancreas
Duodenum

Cholangiocarcinoma (CCA) sub-types: Intrahepatic/ Perihilar/ Extrahepatic









The three subtypes have differences in occurrence, symptoms, risk factors, clinical diagnosis, and treatment

50-60% “Perihilar”: arise at bifurcation of main ducts, **pCCA**

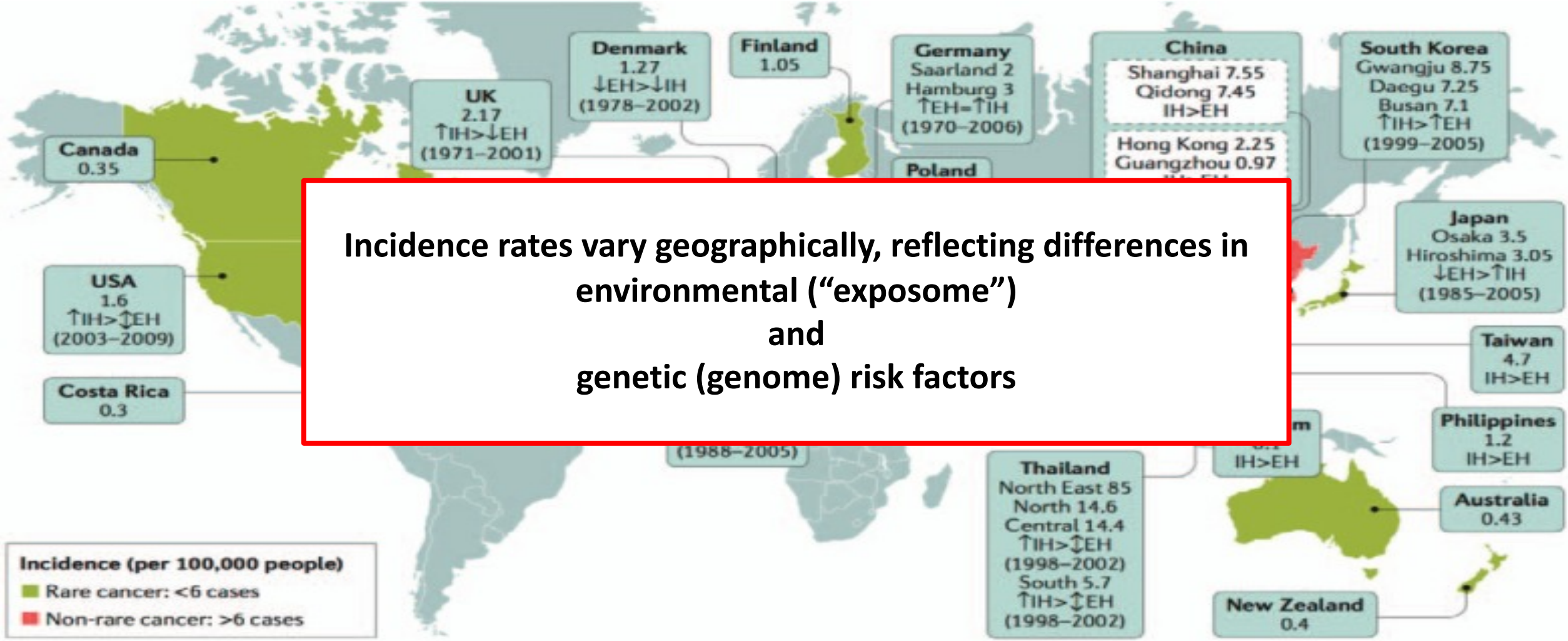
20-30% distal/extrahepatic CBD, **dCCA**

10-20% arise in intrahepatic ducts, **iCCA**

Cholangiocarcinoma – presenting symptoms

- Most patients > 50 years old and have no family history of liver disease
- Around 20-30% patients have a history of Primary Sclerosing Cholangitis (PSC)
- Many patients may have abnormal liver function blood tests
- Presenting features depend on CCA location
- Perihilar or distal/extrahepatic CCA typically present with biliary obstruction:
  - painless jaundice - pale stools - dark urine - pruritus (itching)
- Intrahepatic CCA usually present with non-specific symptoms:
  - malaise - unintentional weight loss - abdominal discomfort

Cholangiocarcinoma – How Common is it?



Incidence rates vary geographically, reflecting differences in environmental ("exposome")
and
genetic (genome) risk factors

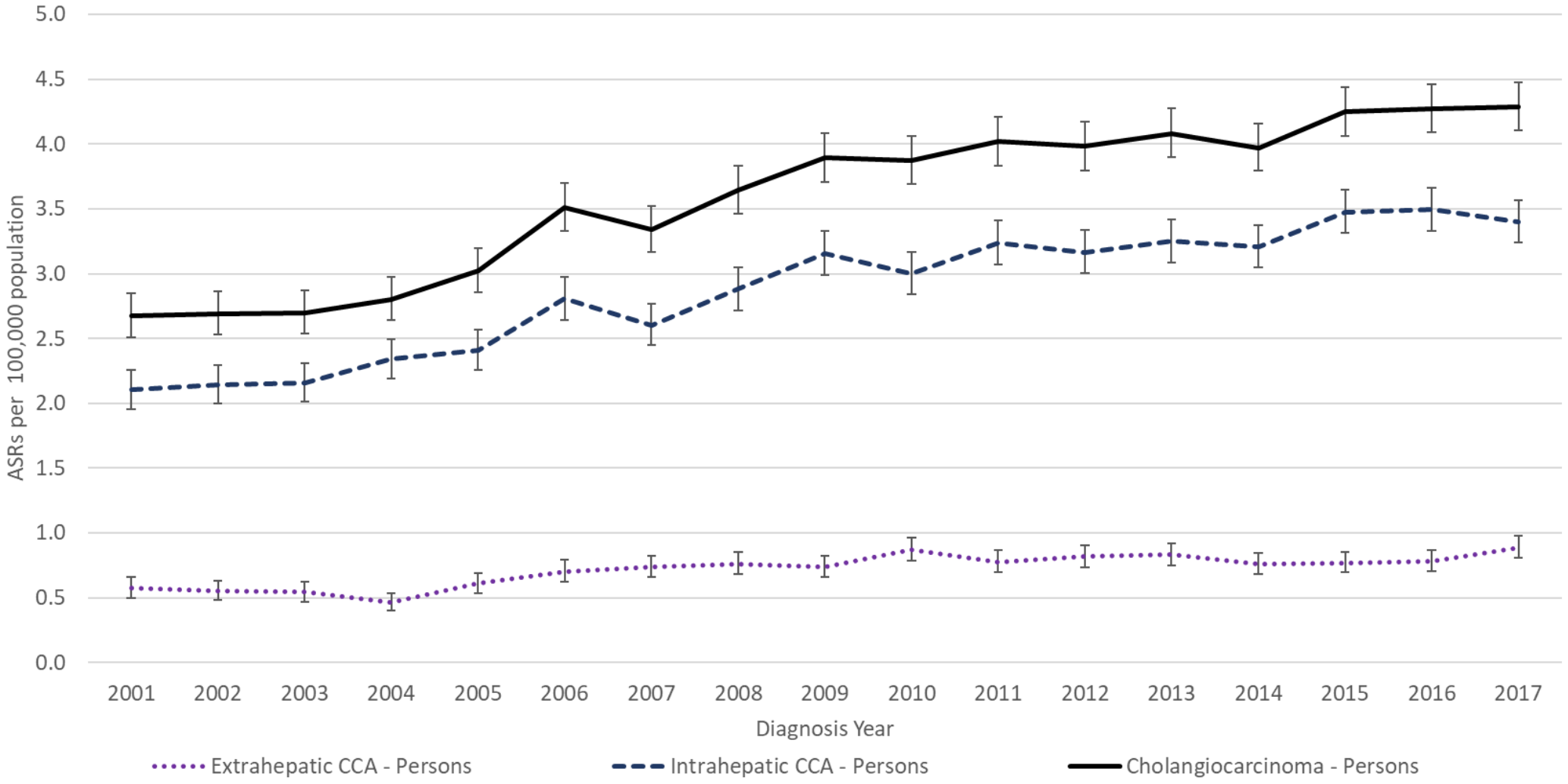
Banales et al. European Network for the Study of Cholangiocarcinoma (ENS-CCA) *Nat Rev Gastroenterol Hepatol.* 2016

CCA: Project on Epidemiology of CCA in England

- AMMF, in partnership with Cholangiocarcinoma-UK and Imperial College London (SA Khan, MB Toledano) &
- National Cancer Registration & Analysis Service (NCRAS) of Public Health England (PHE)

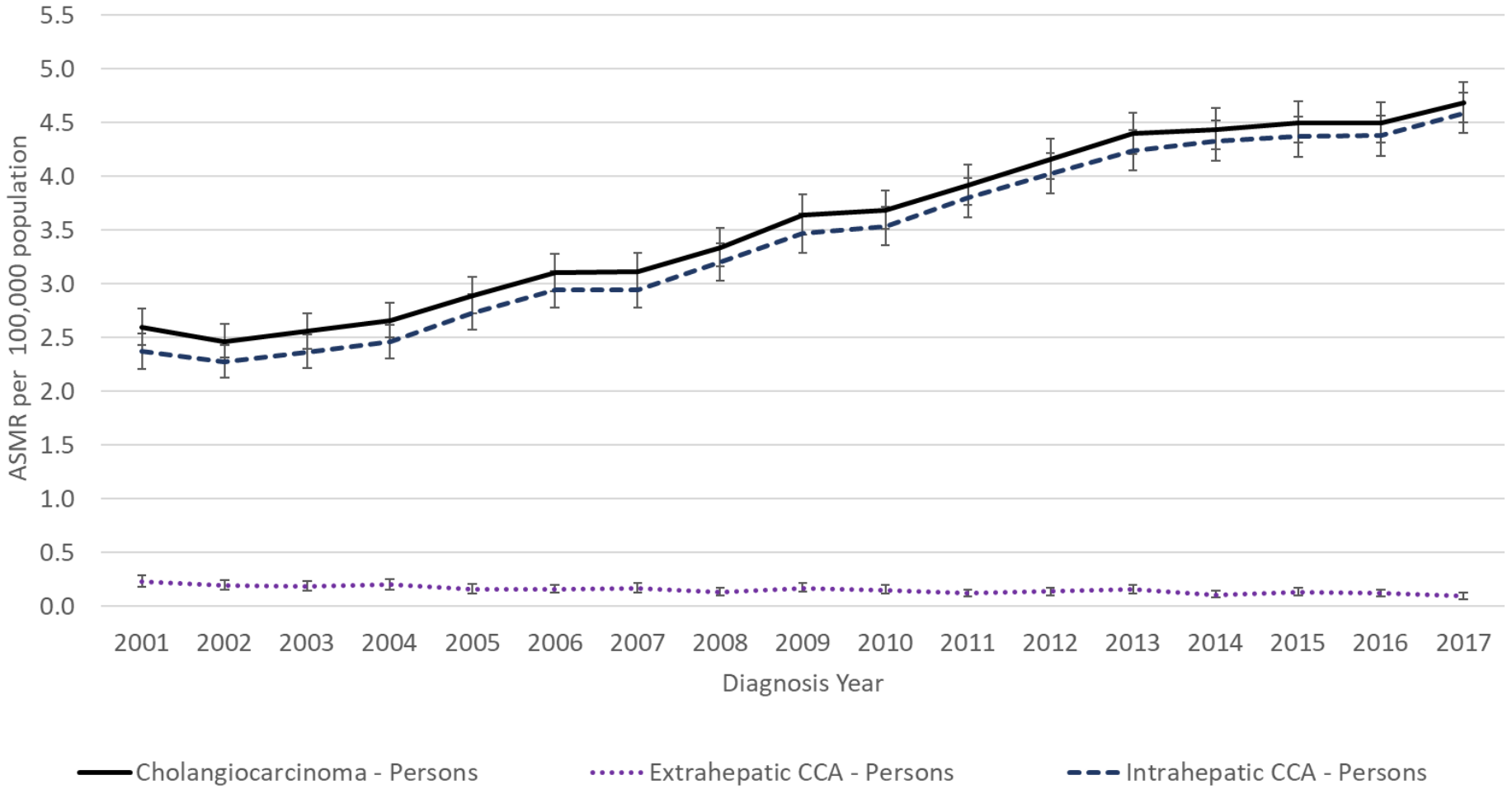
- Age-standardised incidence and mortality rates of CCA sub-types

Age-standardised Incidence Rates for CCA Subtype in England (2001 to 2017)



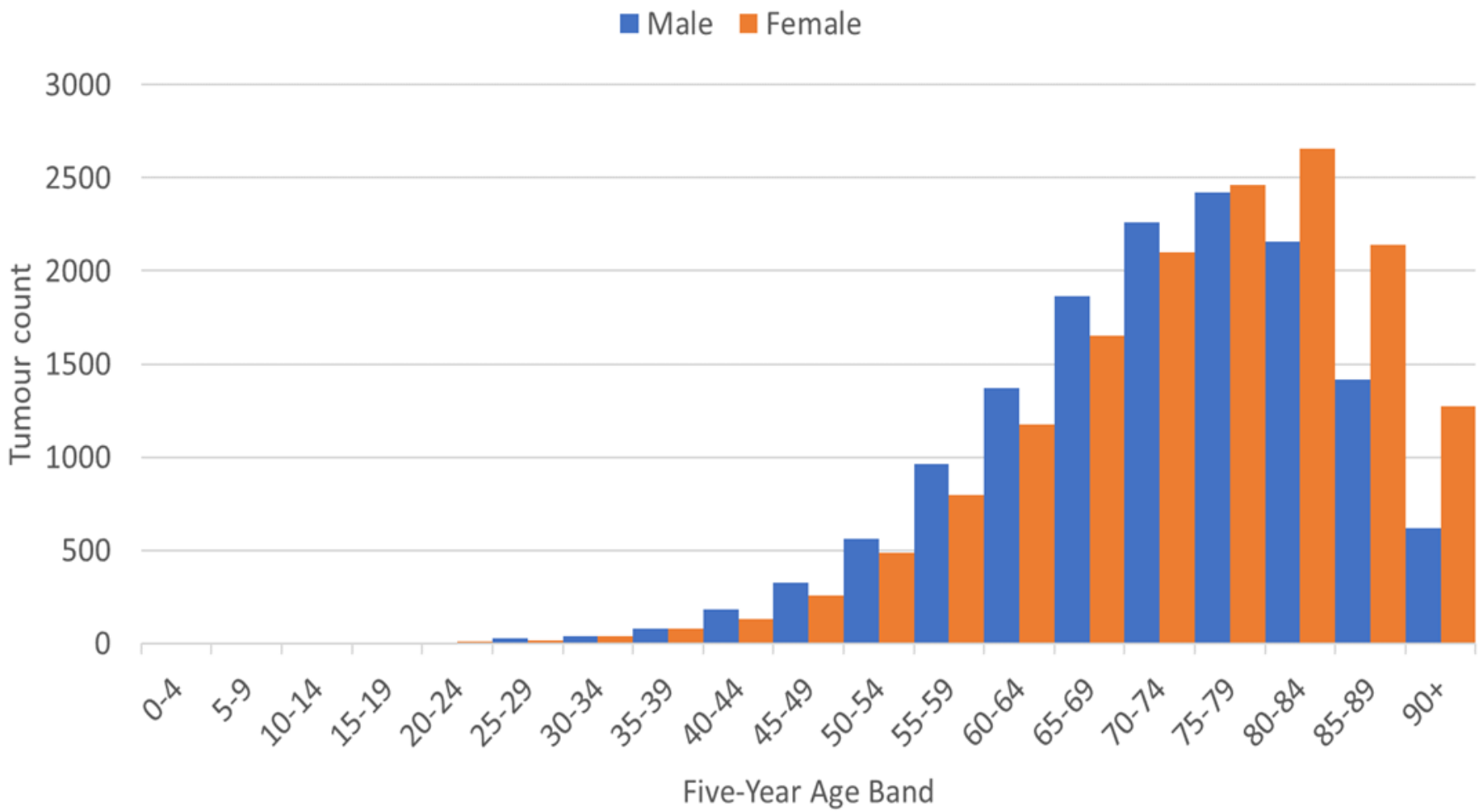
Genus et al 2020 (EASL)

Age-standardised Mortality Rates for CCA Subtype in England (2001 to 2017)



Genus et al 2020 (EASL)

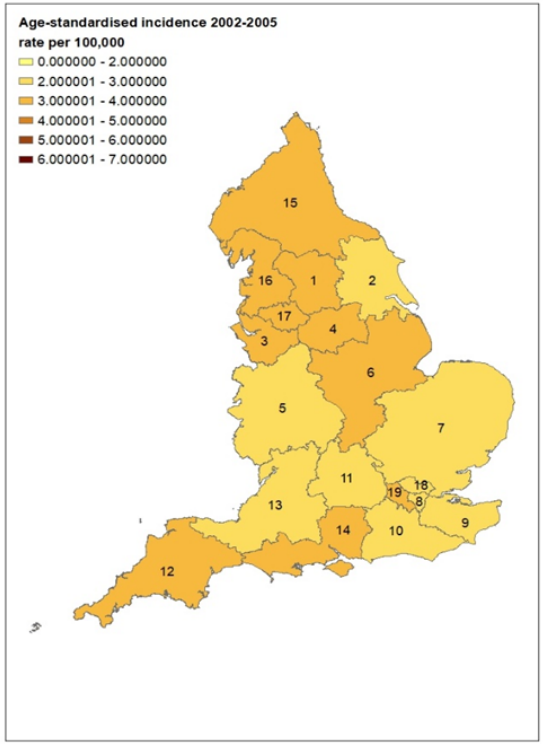
Distribution of Cholangiocarcinoma by Age and Gender (2001 to 2017)



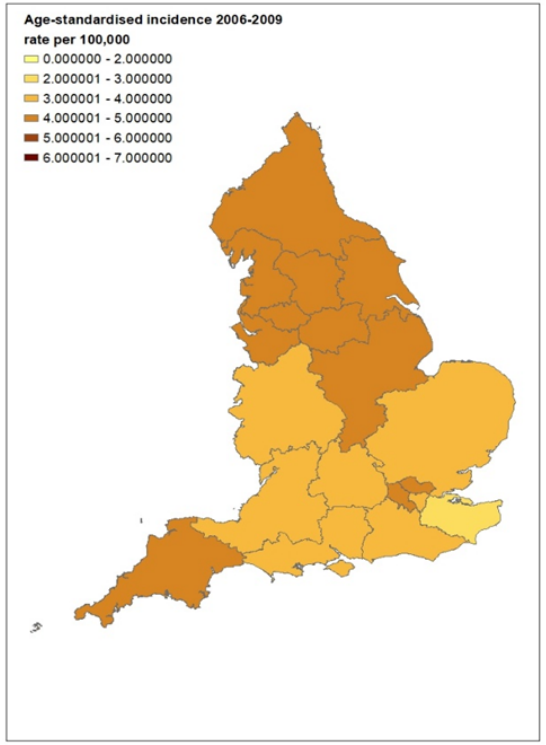
Genus et al 2020 (EASL)

Density maps for Cholangiocarcinoma Incidence in England for:

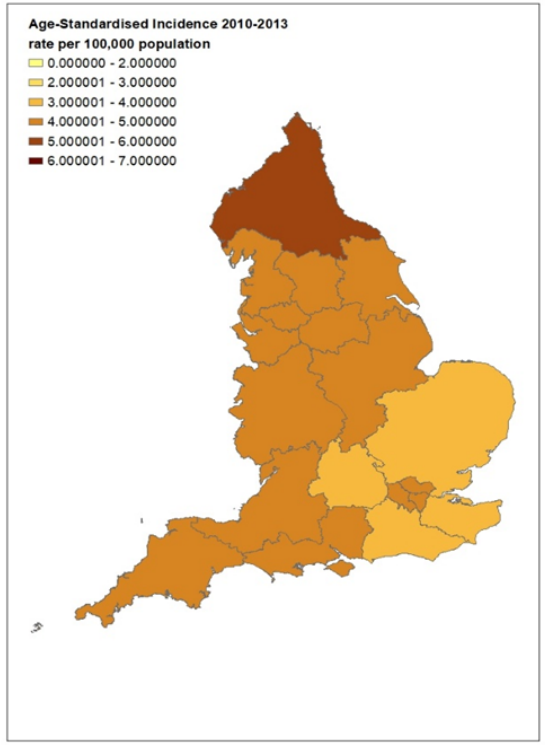
2002-2006



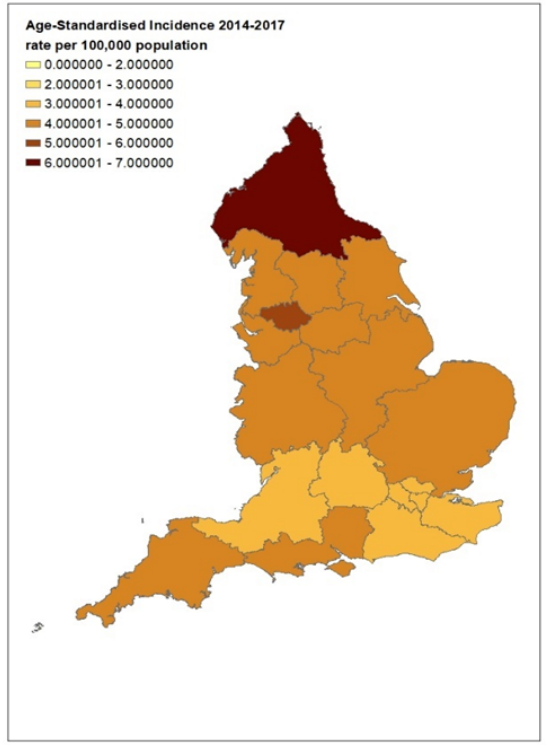
2007-2009



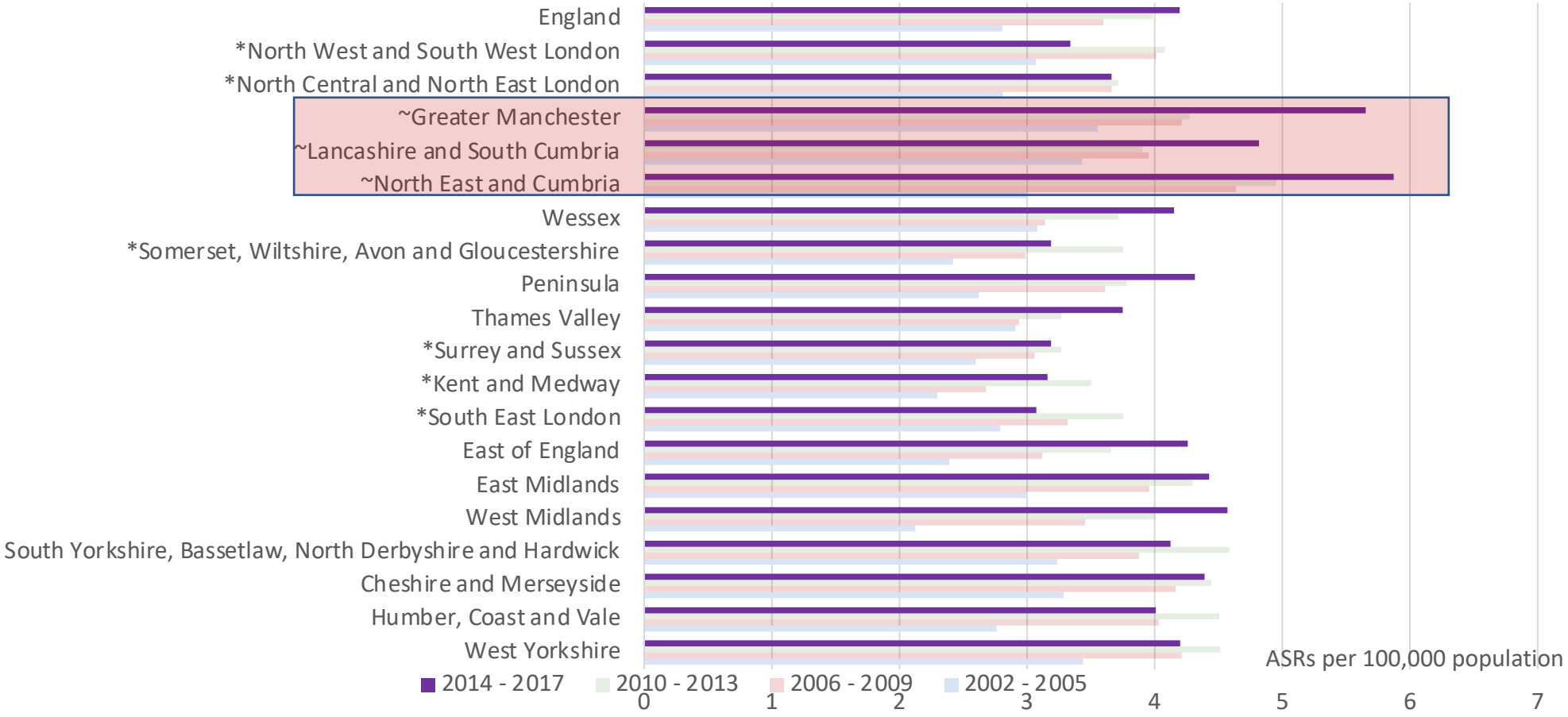
2010-2013



2014-2017



Age-standardised incidence rates for CCA by Cancer Alliance



~ significantly higher than national rate

* significantly lower than national rate

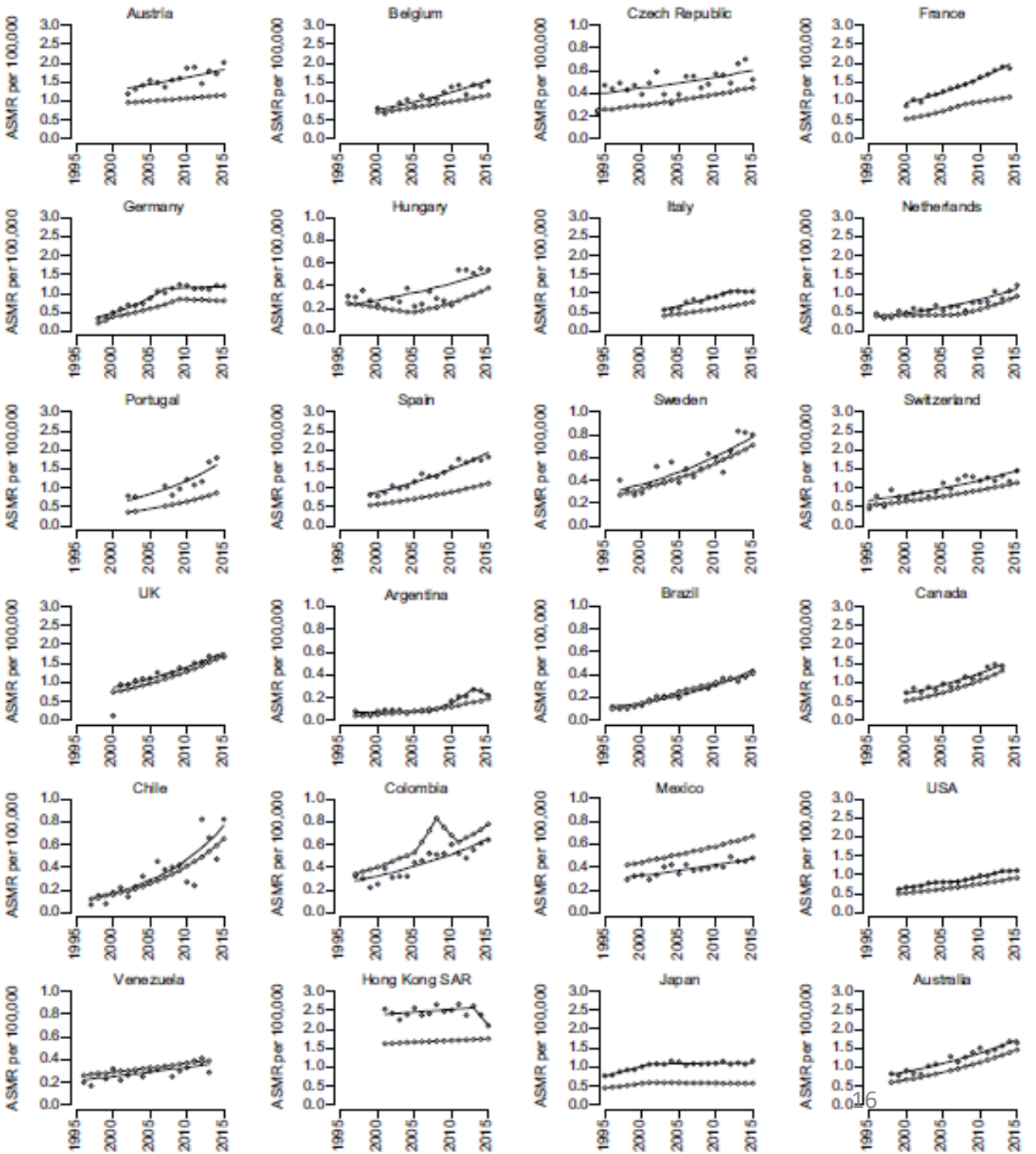
iCCA increasing/eCCA decreasing globally for decades

- *Taylor-Robinson et al 2001*
- *Khan et al 2002, 2005, 2012, 2019*
- *Patel et al 2002*
- *West et al 2007*
- ***Bertuccio** et 2013, **2019***

- Highest rates iCCA (1.5-2.5/100,000 M; 1.2-1.7 F) in France, Spain, UK, Aus

- Lowest rates (0.2–0.6/100,000 M & F) in Latin American and Eastern Europe

- eCCA Mortality decreased in most countries
- Rates < 1/100,000 in (M & F)



Conclusions from the Epidemiology

- Incidence and mortality rates of CCA in England continue to increase
- This may reflect an increase in risk factors including multiple causes of chronic liver
- However, most cases of CCA in the Western world are sporadic – no known risk factors
- Regional variation in incidence and mortality exists, which has worsened over time
- ?Due to differences in risk factors, clinical service – or a combination?
    - **Given the ongoing rise in CCA incidence and mortality, further research into risk factors, aetiopathogenesis, early diagnosis and systemic Rx are a priorities**

Cholangiocarcinoma – What are the Risk Factors?

Some risk factors are known but

>60% of CCA cases in West have NO known risk factors

Cholangiocarcinoma: Known Risk Factors

EAST: Parasitic Infection with liver flukes (*O viverrini*, *C sinensis)*

WEST: Primary sclerosing cholangitis (PSC)

- Patients with PSC are at particularly increased risk for CCA
- The annual incidence of CCA in patients with PSC is estimated to be 0.5%-1.5%, with a reported lifetime incidence of 15 - 20%

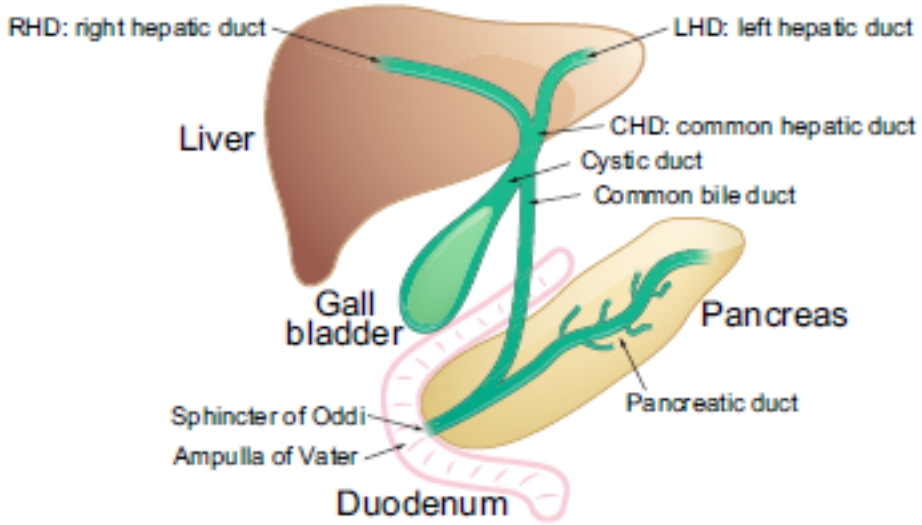
Toxins? Thorotrast

OTHERS:

- **Age:** More than 60 percent of bile duct cancer patients are 65 years or older.
- **Obesity:** Being obese may increase the risk some cancers, including bile duct cancer.
- **Family history:** Although a family history of bile duct cancer may increase a person's bile duct cancer risks, the risk is low because this is a rare disease. Most cases of bile duct cancer do not appear to a have a familial link

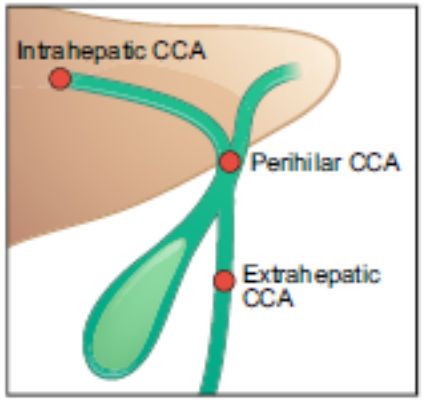
Cholangiocarcinoma: other Risk Factors

>60% of CCA cases in West have NO known risk factors



Intrahepatic CCA risk factors:

- Choledochal cysts (OR 26.71)
- Choledocholithiasis (OR 10.08)
- Cirrhosis (OR 15.32)
- Cholelithiasis (OR 3.38)
- HBV (OR 4.57)
- HCV (OR 4.28)
- Alcohol (OR 3.15)
- Cholecystocholithiasis (OR 1.75)
- IBD (OR 2.68)
- T2DM (OR 1.73)
- Smoking (OR 1.25)



Extrahepatic CCA risk factors:

- Choledochal cysts (OR 34.94)
- Choledocholithiasis (OR 18.58)
- Cirrhosis (OR 3.82)
- Cholelithiasis (OR 5.92)
- HBV (OR 2.11)
- Alcohol (OR 1.75)
- Cholecystocholithiasis (OR 2.95)
- IBD (OR 2.37)
- T2DM (OR 1.50)
- Smoking (OR 1.69)

- Choledochal cysts most strongly associated with both iCCA & eCCA
- Cirrhosis is a big risk, iCCA > eCCA
- Choledocholithiasis, eCCA > iCCA
- Eastern countries, cirrhosis and HBV conferred a greater risk of iCCA than in Western countries
- Could part of the rising global incidence of iCCA be linked to increases in T2DM, cirrhosis, alcoholic liver disease and cholelithiasis?

Challenges in Cholangiocarcinoma (CCA)

- High mortality (5-year Survival <10%) and rising incidence
- Most cases “sporadic”, i.e. no known risk factors; no proven screening group/test
- The patient’s clinical presentation is often non-specific
- Diagnosis/getting histology (sample tissue) can be difficult
- Lack of accurate diagnostic biomarkers
- Surgery is the only cure but most patients are diagnosed too late
- Even if patients get to surgery and all visible cancer is removed, there is high recurrence
- Lack of effective non-surgical treatments: diverse molecular/mutational drivers
- Deemed to be a rare disease and funding not forthcoming

CHOLANGIOCARCINOMA (CCA)

General Overview of Cholangiocarcinoma (CCA)

- What is CCA?
- What symptoms does CCA cause?
- How common is CCA?
- What are the Risk factors for CCA?
- Major Challenges with CCA
- Q & A

Imperial College London

Acknowledgments

- AMMF
- National Cancer Registration and Analysis Service, Public Health England
- Cholangiocarcinoma UK and BASL
- UK National Institute for Health Research (NIHR) Biomedical Facilities at Imperial College London.

- *This work used data provided by patients and collected by the NHS as part of their care and support. The data is collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of Public Health England (PHE)*

- All my Research Fellows, Students, Co-authors and Co-workers

Imperial College London

Imperial College Healthcare NHS Trust

An Overview of Cholangiocarcinoma

Prof Shahid A Khan

Imperial College London

AMMF's Cholangiocarcinoma Patients and Carers Information Day

29th October 2020