Cholangiocarcinoma: Epidemiology & Aetiology
What don't we know & how can we find out?

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London

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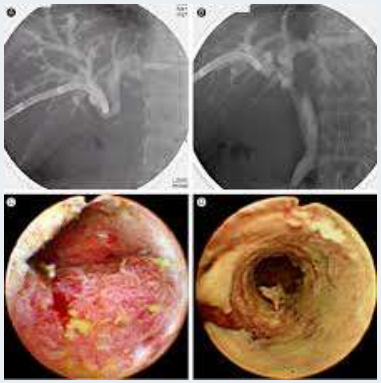
Cholangiocarcinoma (CCA)



- Second commonest primary liver tumour after HCC
- Up to 10% of all primary liver cancers
- Peak age seventh decade
- Slight male preponderance
- **Overall 5 year survival 5%**

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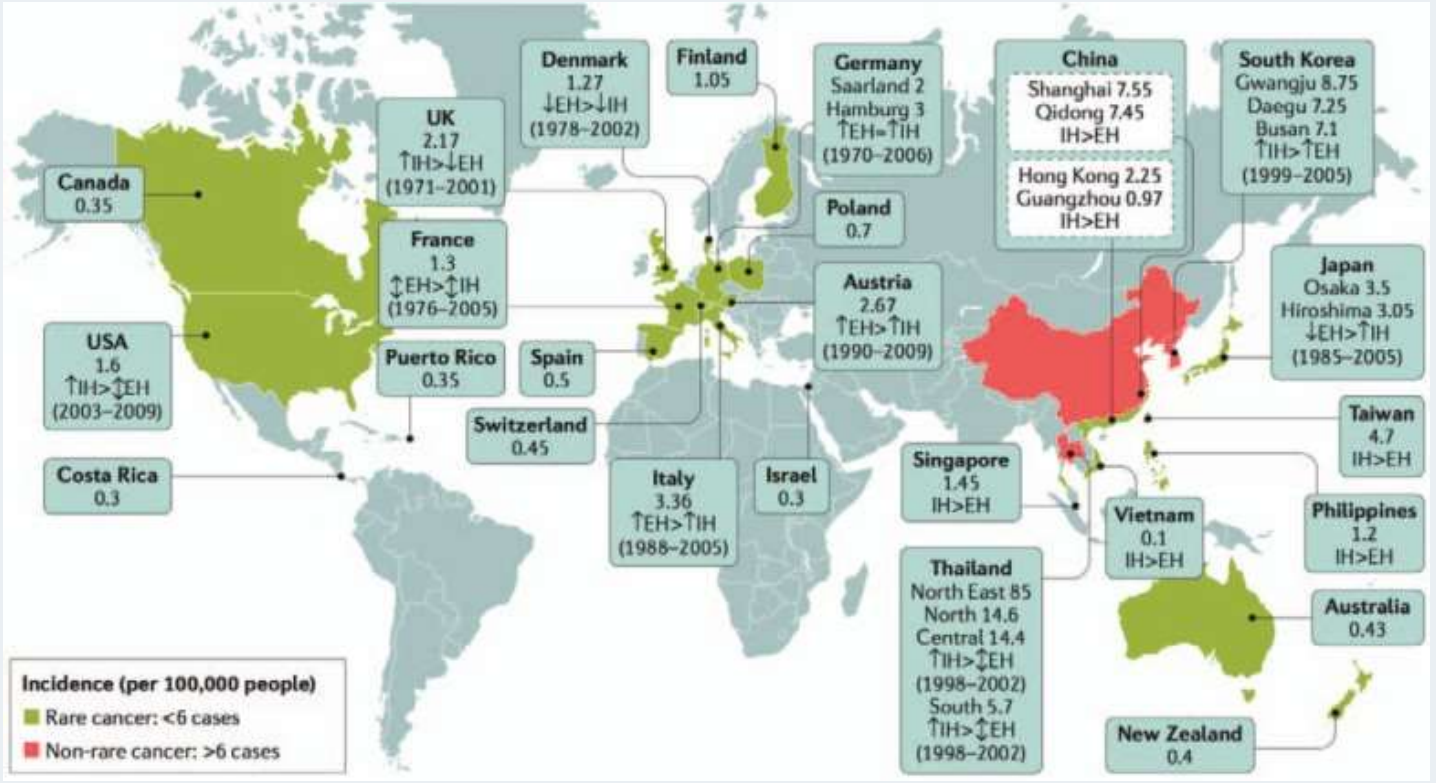

ENS-CCA consensus statement. *Nat Rev Gastroenterol Hepatol* 2016

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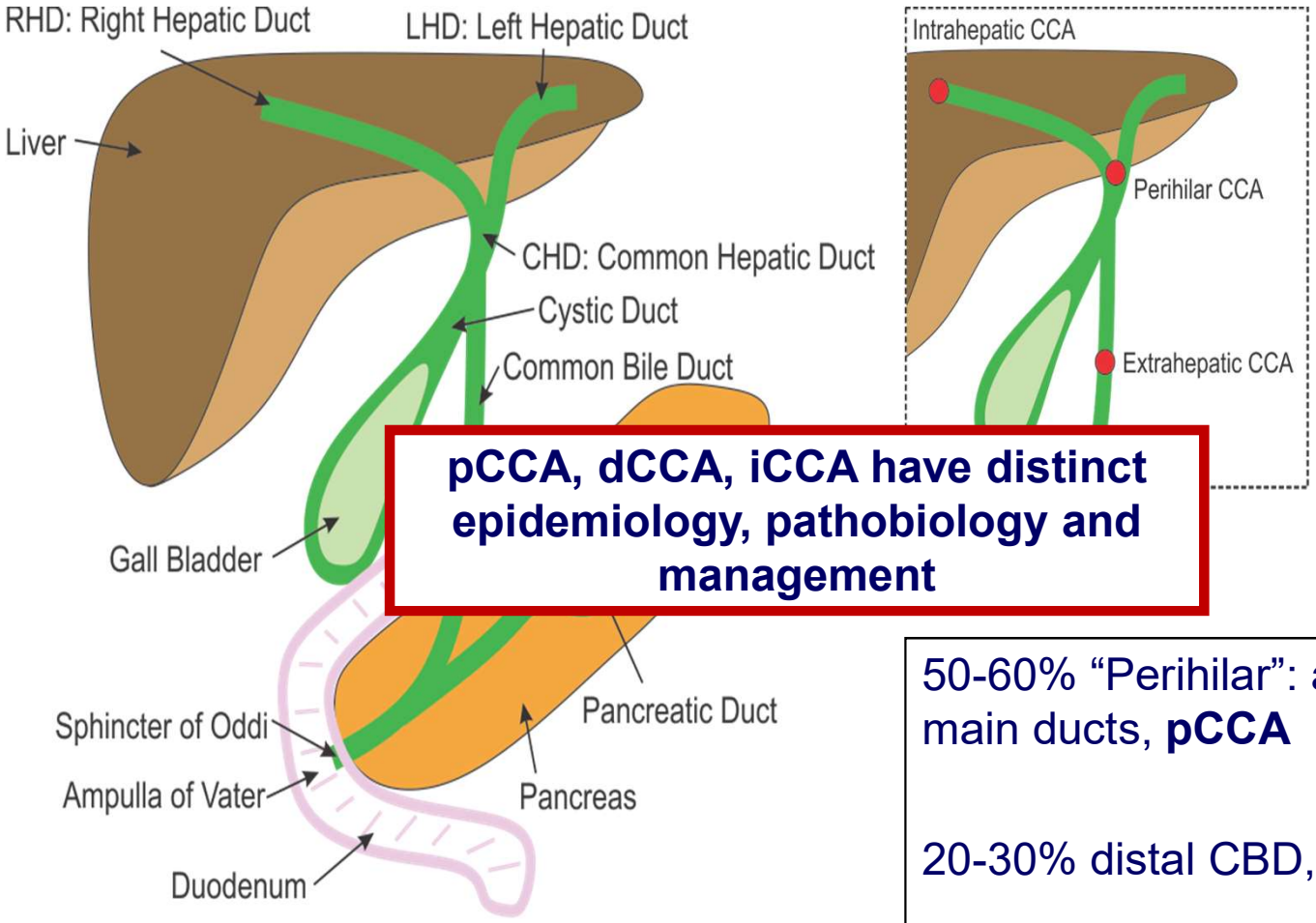
Cholangiocarcinoma (CCA) sub-types: Intrahepatic/ Perihilar/ Extrahepatic



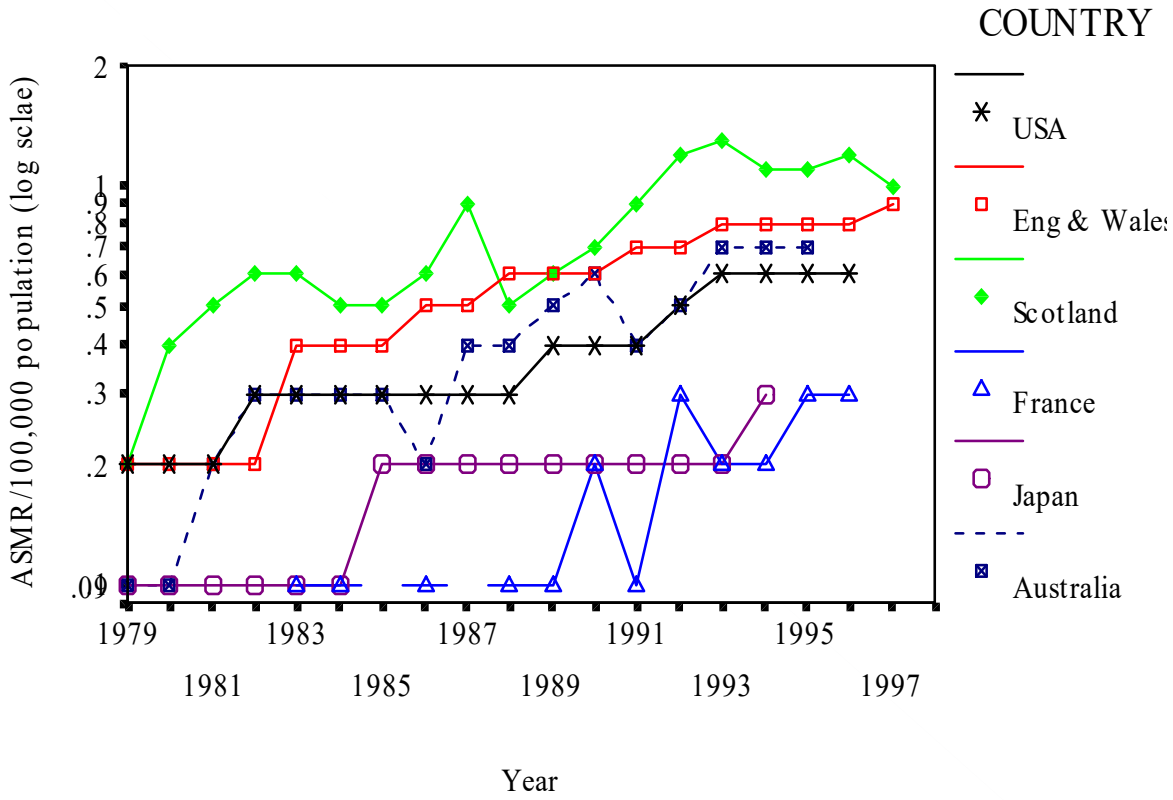
pCCA, dCCA, iCCA have distinct epidemiology, pathobiology and management

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

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

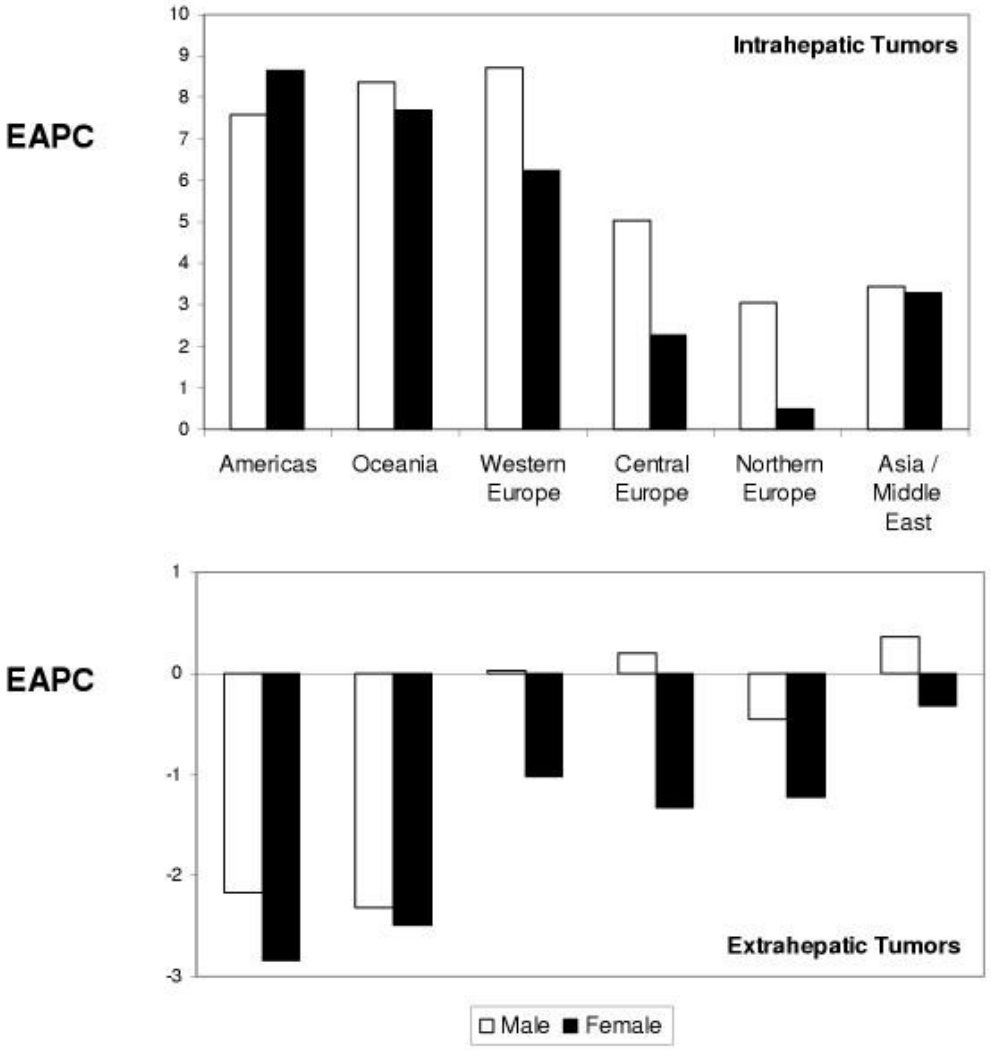
10-20% arise in intrahepatic ducts, **iCCA**

Rizvi S, Khan SA et al. Nat Rev Clin Oncol 2017



Internationally increasing age standardized mortality rates (ASMR) for intrahepatic CCA in men

Khan *et al*. J Hepatol 2002



Global mean estimated annual % change (EAPC) in ASMR from

- IHBT (top)
and
- gall bladder + EHBT (bottom)

Patel T *BMC Cancer 2002*

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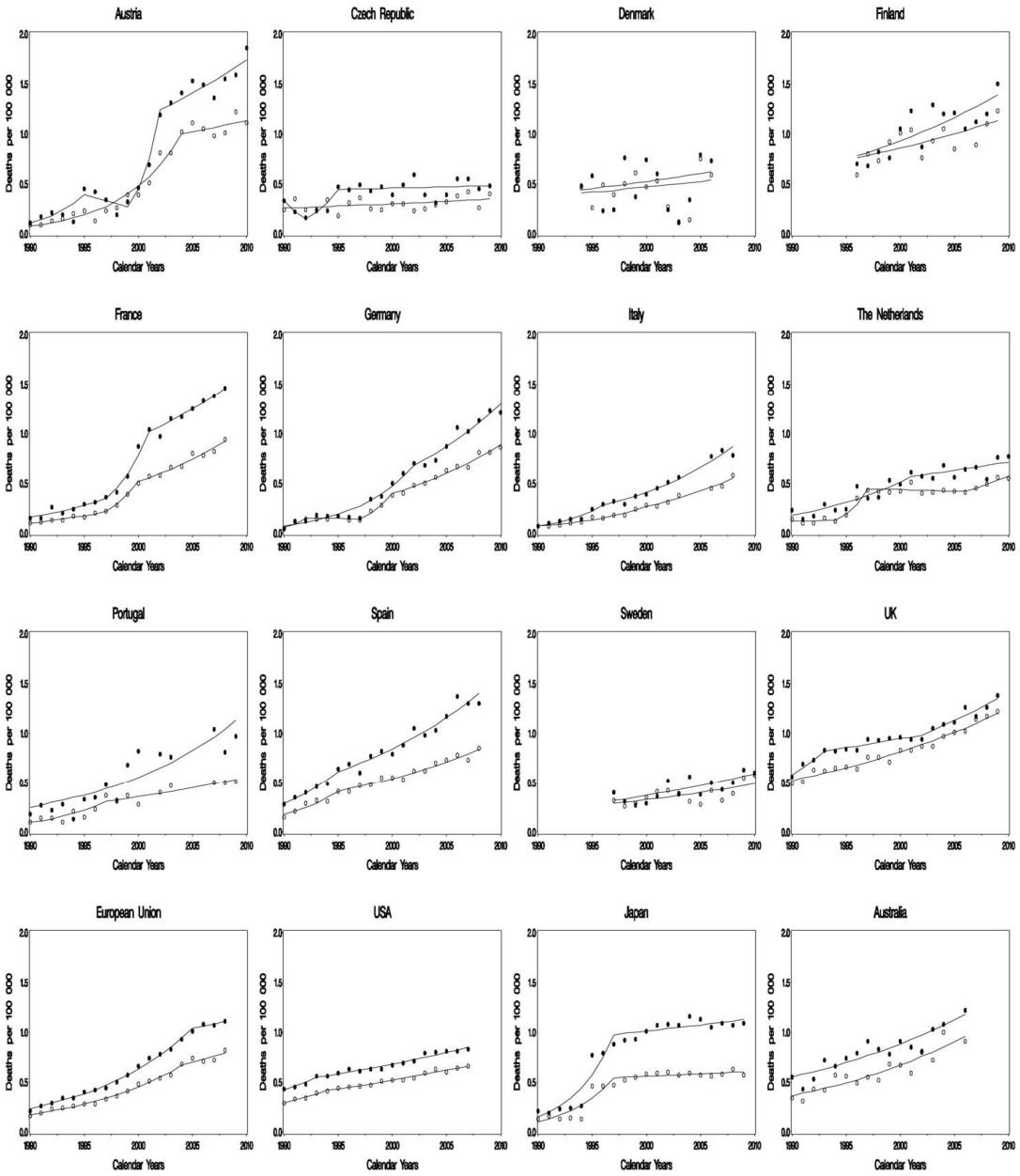


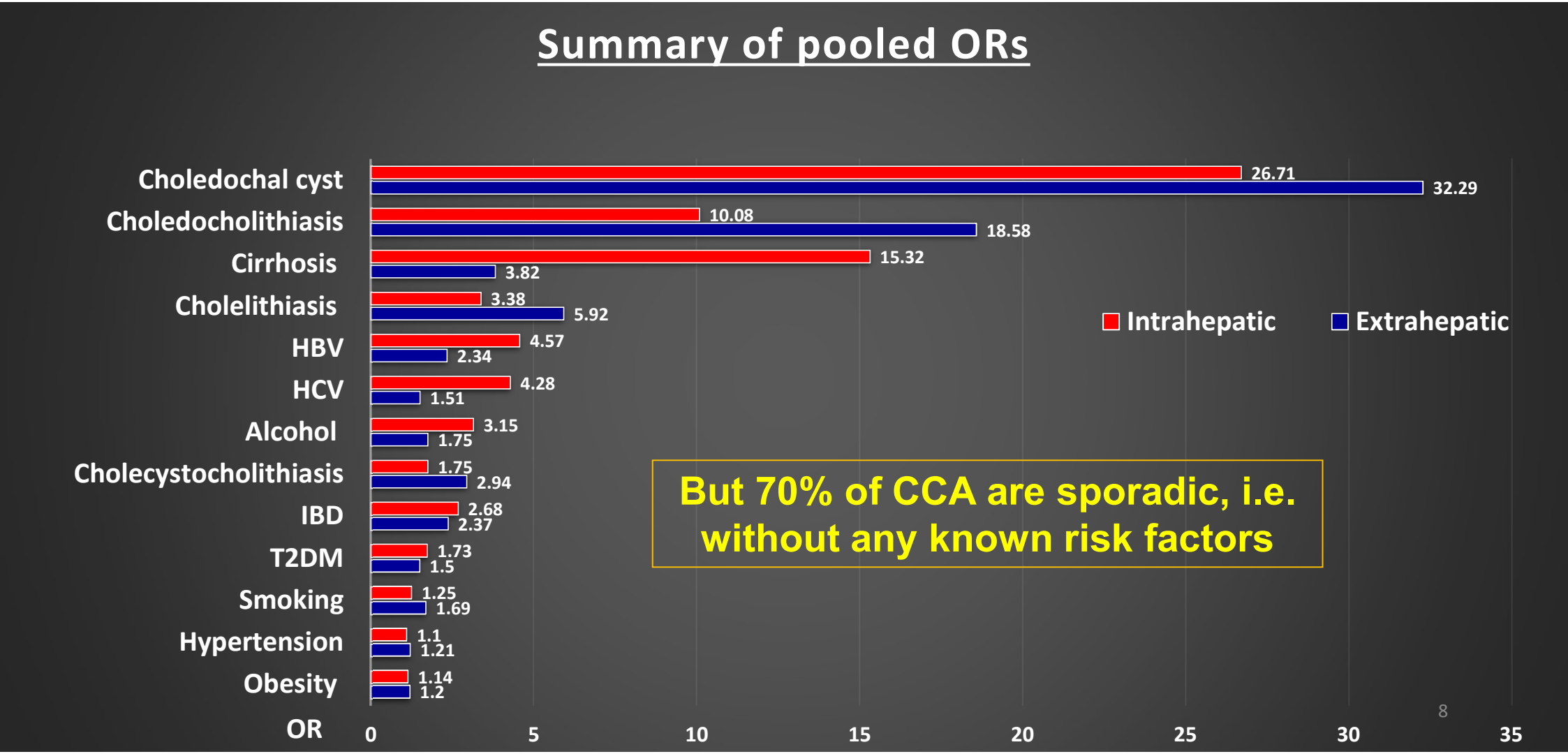
Intrahepatic CCA ASMR **increased** 9% in M & F, 1990-2008 to:

1.1/100,000 M
0.75/100,000 F

Highest rates in UK, Germany, and France (1.2–1.5/100,000 M, 0.8–1.1/100,000 F)

Bertuccio P et al. Ann Oncol 2013

Meta-analysis of Risk factors for Intrahepatic & Extrahepatic CCA;
Clements O, Eliahoo J & Khan SA (manuscript in prep), 25 studies, ILCA 2018



Intrahepatic CCA rates are increasing

Extrahepatic CCA rates are decreasing

Overall, CCA is increasing

Is it really iCCA that's increasing? Or pCCA? Or dCCA?

Better diagnosis? Awareness? Coding changes?

Current coding systems do NOT accurately record CCA data

- ICD-10 list all known medical diagnoses, cancer and non-cancer
- WHO owns ICD-10 & updates, next (ICD-11) is due out 2019/20
- IARC, Lyon, is the specialized cancer agency of the WHO
- ICD-10 (and ICD-11) list **topography** codes, which describe the **anatomical** site of origin of a tumour, and updates every few years
- IARC: separate ICD for Oncology (ICD-O) exists for cancers only, consists of **two coding** systems, which together describe the tumour:
  - **topographical** code: describes anatomical site of tumour,

  and
  - **morphological** code: describes cell type/histology of tumour, and if malignant or benign
- ICD editions change every few years and are adopted by countries at different times

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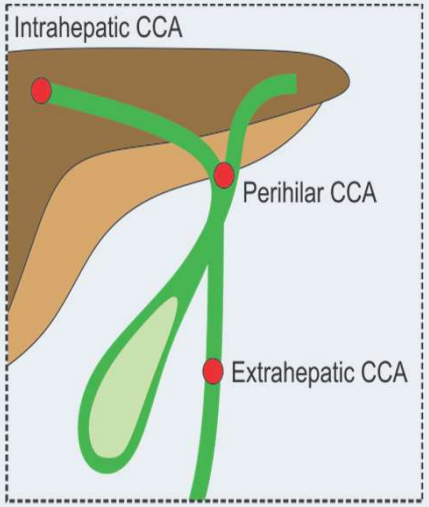
Coding of (Peri)Hilar (Klatskin) CCA: Intrahepatic or Extrahepatic?

Hilar/Klatskin CCA are extrahepatic but are not specifically differentiated in routine data

ICD-O-1:
- "Klatskin" CCA not assigned specific morphology/histology code & could be classed as intra (C22.1) **or** extrahepatic (C24.0)

ICD-O-2:
- Klatskin CCA given unique histology code, 8162/3, BUT this was **cross referenced to topography code for *intra*-** NOT extrahepatic CCA
- ICD-O-2 adopted in USA 1991; Eng &Wales 1995

ICD-O-3:
- Klatskin CCA (8162/3) cross referenced to intra *or* extrahepatic
- ICD-0-3 adopted in USA 2001; UK 2008



50-60% of CCA are, **pCCA**

20-30% are distal CBD, **dCCA**

10-20% are intrahepatic **iCCA**

So, perihilar CCA may have been misclassified in ALL versions of ICD-O, esp to intrahepatic during ICD-O2

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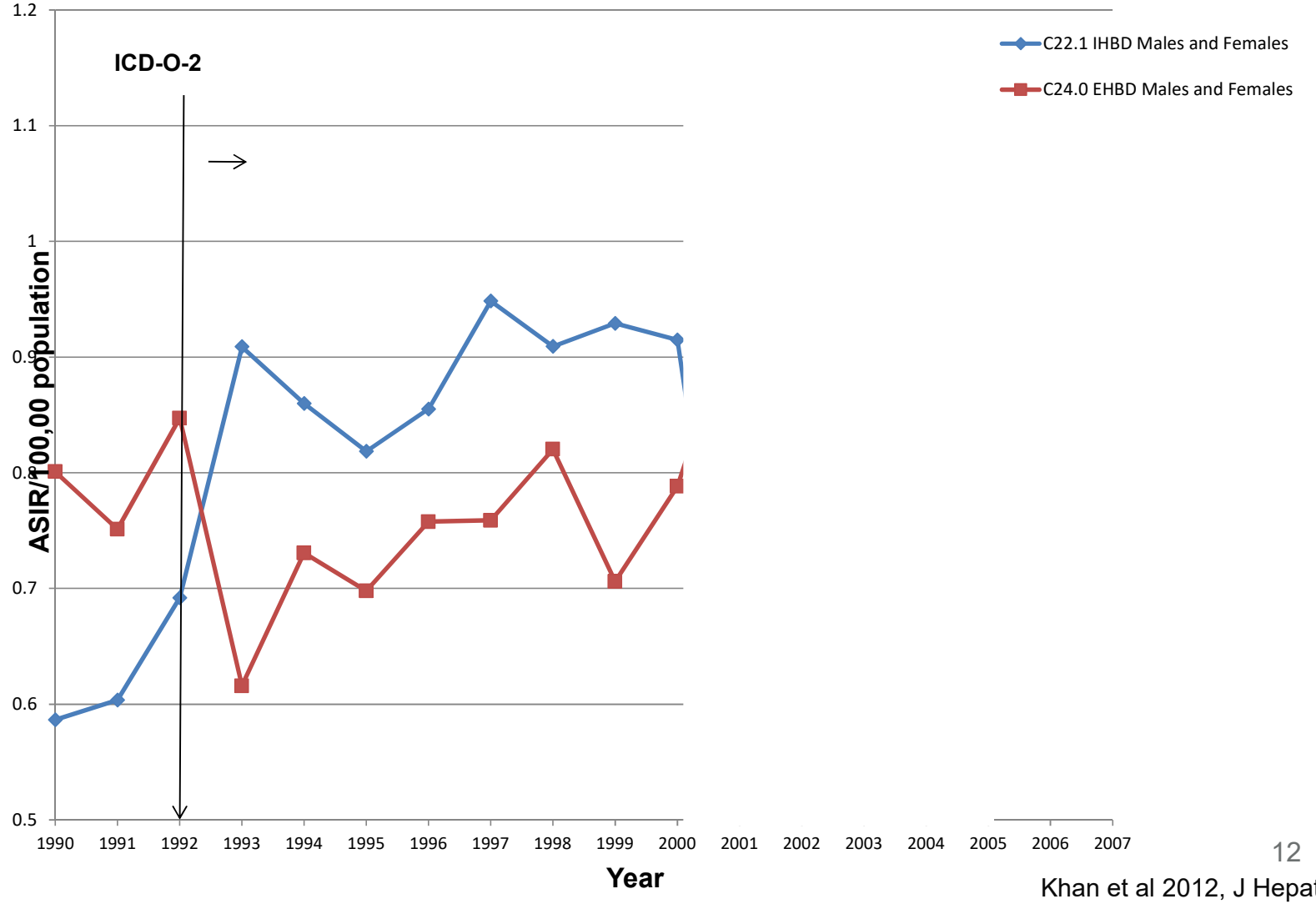
Trends in ASIR for tumours coded to **C22.1 (iCCA) & C24.0 (eCCA)** 1990-2007 & when ICD-O-2 & ICD-O-3 were introduced in **USA** (SEER Data)



Khan et al 2012, J Hepatol

CCA Epidemiology – other problems with the data

- Studies do not differentiate between eCCA: namely pCCA, dCCA and GB
- UK Cancer registries reported that if a tumour site is unspecified, most would classify as intrahepatic *(Khan 2012)*
- Study of concordance between cancer registries and the patient register: systematic underreporting of Biliary tract cancers *(Kilander 2014)*
- Sweden: most liver cancer deaths are classified by the Cancer Register as “unspecified” and hepatocellular carcinoma is likely underreported *(Duberg 2017)*
- Misclassification between HCC and iCCA may be confounding
  + heterogeneity and 10% overlap *(Rizvi 2017)*

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CCA Epidemiology: Need Consistency

- Need **international consistency in classification of CCA, to allow accurate monitoring of disease rates**
- Bile duct cancers should be sub-classified as
  Intrahepatic, **Perihilar** or **Distal** (abandon “Klatskin”)
- These have different epidemiology, pathobiology, clinical presentations and management
- CCA/Biliary Tract Cancer trends need to be interpreted with caution
- Data needs to be recorded uniformly and accurately
- The responsibility to do so lies with clinicians and cancer registries

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CCA Epidemiology: changes in the UK

- UK (AMMF + S Khan): discussions with Head of Cancer Datasets, National Cancer Registration and Analysis Service, of Public Health England (PHE)
- From 2020, COSD v9 in the UK will define the three types of CCA clearly:

LIVER – DIAGNOSIS: CHOLANGIO-CARCINOMA (CCA)	CCA CATEGORY	State where the CCA is present	1	Intrahepatic
			2	Perihilar
			3	Extrahepatic
			9	Not known

Need International Consistency in Classification of CCA – to allow accurate monitoring of epidemiology

ICD11 (2019/20) will resolve this. Proposed:

- **2C18.0 Hilar Cholangiocarcinoma**
- **2C12.10 Intrahepatic cholangiocarcinoma**
- **2C15.0 Extrahepatic cholangiocarcinoma: Adenocarcinoma of biliary tract, distal bile duct**

- **Similar needed for ICD-O 4 i.e. three separate topography/morphology codes for iCCA, pCCA and dCCA**

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CD-11 for Mortality and Morbidity Statistics
earch Cholangiocarcinoma hilar
biliary tract, cystic duct
2C14.Z Malignant neoplasms of proximal bi
tract, cystic duct, unspecified
2C15 Malignant neoplasms of biliary tract, distal bile duct
2C15.0 Adenocarcinoma of biliary tract, distal bile duct
2C15.1 Mucinous cystic neoplasm with associated invasive carcinoma of distal bile duct
2C15.2 Neuroendocrine neoplasms of distal bile duct
2C15.Y Other specified malignant neoplasms of biliary tract, distal bile duct
2C15.Z Malignant neoplasms of biliary tract, distal bile duct, unspecified
2C16 Malignant neoplasms of ampulla of Vater
2C17 Malignant neoplasms of other or unspecified parts of biliary tract
2C18 Malignant neoplasms of perihilar bile duct
2C18.0 Hilar cholangiocarcinoma
associated invasive carcinoma of perihilar bile duct
2C18.2 Neuroendocrine neoplasm of perihilar bile duct
2C18.Y Other specified malignant neoplasms of perihilar bile duct
2C18.Z Malignant neoplasms of perihilar bile duct, unspecified
2C1Z Malignant neoplasms of digestive organs, unspecified
Malignant neoplasms of middle ear, respiratory or intrathoracic organs
Malignant neoplasms of skin


CD-11 for Mortality and Morbidity Statistics
earch Cholangiocarcinoma hilar
2C12.0Y Other specified malignant neop
of liver
2C12.1 Malignant neoplasm of intrahepatic bile ducts
2C12.10 Intrahepatic cholangiocarcinoma
2C12.1Y Other specified malignant neoplasms of intrahepatic bile ducts
2C12.Z Malignant neoplasms of liver or intrahepatic bile ducts, unspecified
2C13 Malignant neoplasms of gallbladder
2C14 Malignant neoplasms of proximal biliary tract, cystic duct
2C14.0 Adenocarcinoma of proximal biliary tract, cystic duct
2C14.1 Mucinous cystic neoplasm with associated invasive carcinoma of cystic duct
2C14.2 Neuroendocrine neoplasms of cystic duct
2C14.Y Other specified malignant neoplasms of biliary tract, cystic duct
2C14.Z Malignant neoplasms of proximal biliary tract, cystic duct, unspecified
2C15 Malignant neoplasms of biliary tract, distal bile duct
2C15.0 Adenocarcinoma of biliary tract, distal bile duct
associated invasive carcinoma of distal bile duct
2C15.2 Neuroendocrine neoplasms of distal bile duct
2C15.Y Other specified malignant neoplasms of biliary tract, distal bile duct
2C15.Z Malignant neoplasms of biliary tract, distal bile duct, unspecified
2C16 Malignant neoplasms of ampulla of Vater

Summary

- Multiple studies report rising incidence rates of iCCA and falling rates of dCCA over last 40 years
- What is happening with pCCA, the commonest form of CCA?
- We need accurate data
- Unclear due to the problems with coding
- ICD-11 and subsequent iterations of ICD-O must have separate topography and morphology codes for iCCA, pCCA and dCCA

However CCA is classified, its incidence seems to be rising.
Urgent studies into its causes & effective therapies are needed

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CCA Epidemiology: Ongoing work in UK

- AMMF/PHE partnership with Imperial : embedded analyst in National Cancer Registration & Analysis Service (NCRAS)

Questions:

- Is CCA truly increasing in England? If so, which age groups/gender(s)?
- Which type(s) of CCA is rising/falling?
- Has adoption of new ICD-codes affected incidence rates?
- Has the route to diagnosis changed over recent years?
- If rising CCA is due to better diagnosis, is stage of disease at diagnosis changing?
- Any regional variations in mortality, reflecting variation in referral practices?
- Are there common co-morbidities in CCA patients?
- Are there regional variations in incidence/case clustering, which may indicate potential underlying risk factors?

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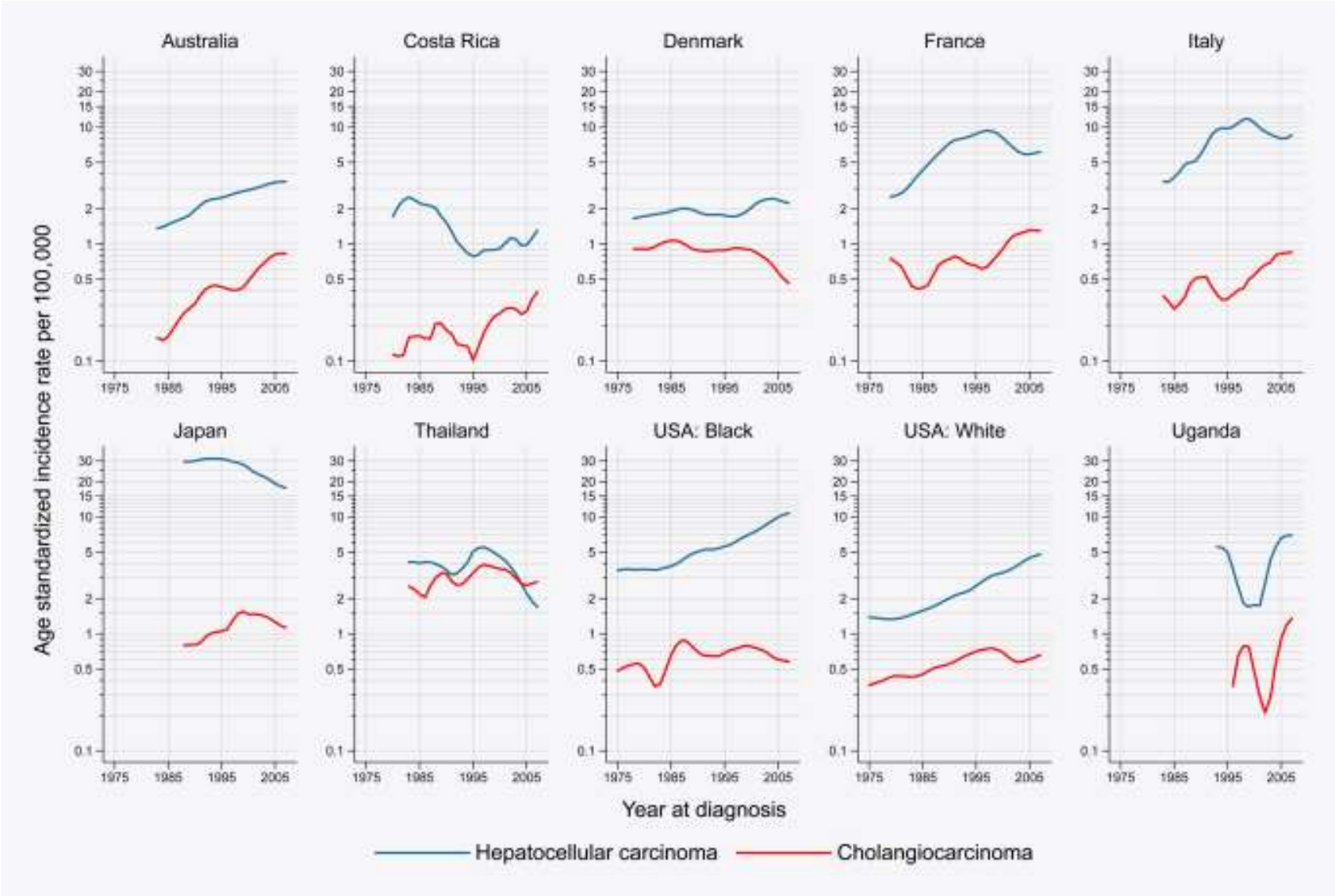

Trends in age-adjusted male incidence rates for HCC and iCCA, 1978–2007

Petrick et al. Int J Ca 2016