Controversies in Hepatocellular Carcinoma and Cholangiocarcinoma Surveillance

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First Annual Conference

The Non Controversies

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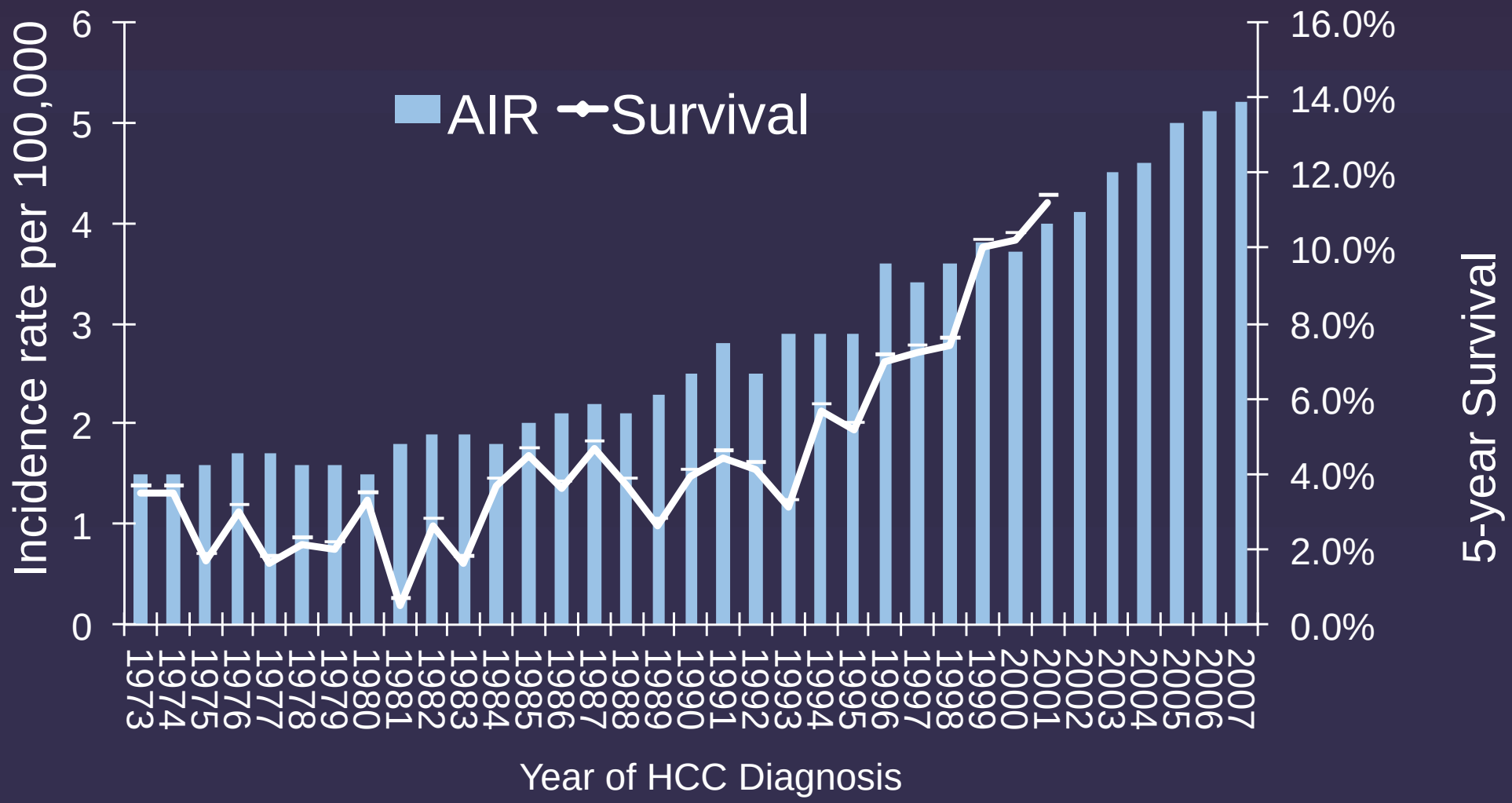
The Incidence and 5-Year Survival of HCC in United States



El-Serag HB. *N Engl J Med* 2011

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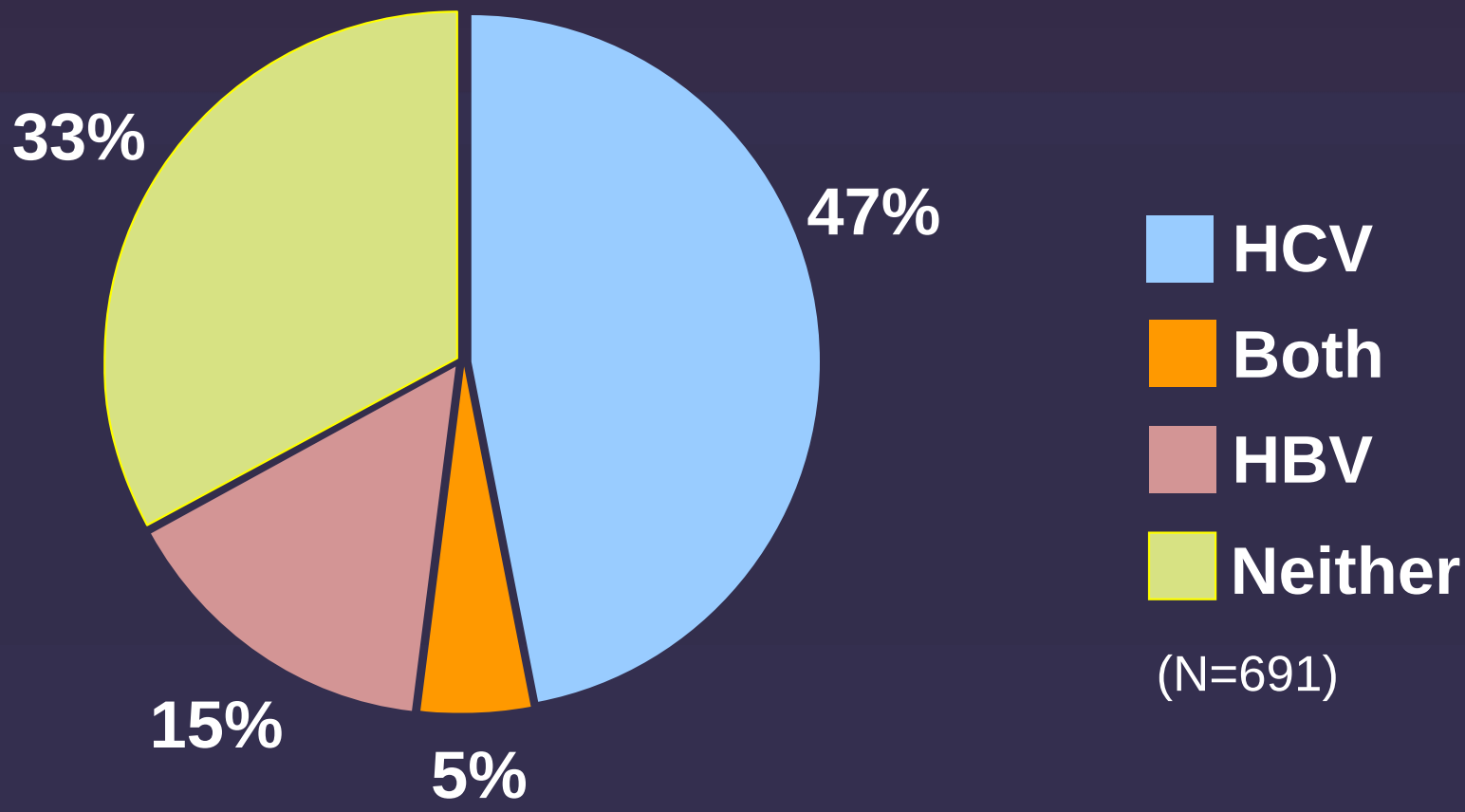
HCV is the Dominant Risk Factor for HCC in the United States



- HBV most frequent in Asians
- HCV most frequent in whites and blacks

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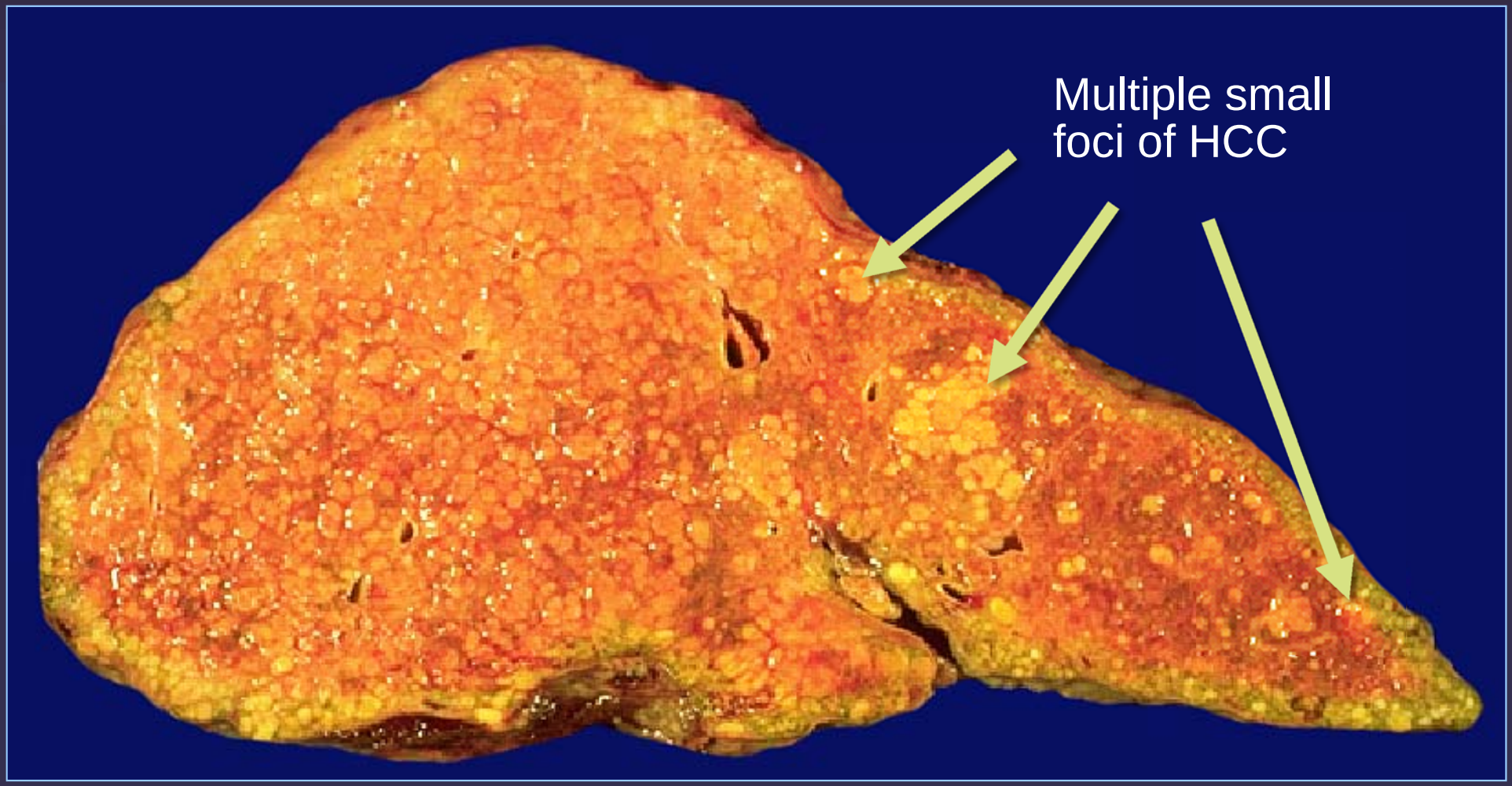
HCV Cirrhosis and HCC



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Controversy #1
IN WHOM?

- High risk groups that need to be targeted for HCC screening?
- NAFLD without cirrhosis?
- HCV after cure?

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Recommended Groups for HCC Surveillance

Population Group	Threshold Incidence for Efficacy of Surveillance (%/year)	Incidence of HCC (%/year)
Asian male hepatitis B carriers > age 40	0.2	0.4–0.6
Asian female hepatitis B carriers > age 50	0.2	0.3–0.6
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African/North American Blacks	0.2	HCC occurs at a younger age
Cirrhotic hepatitis B carriers	0.2–1.5	3–8
Hepatitis C cirrhosis	1.5	3–5

Sherman M. *Semin Liver Dis.* 2010;30(1):3-16.

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Groups in Whom the Risk of HCC is Increased, but in Whom Efficacy of Surveillance Has Not Been Demonstrated

Population Group	Threshold Incidence for Efficacy of Surveillance (%/year)	Incidence of HCC (%/year)
Hepatitis B carriers <40 (males) or 50 (females)	0.2	<0.2
Hepatitis C and stage 3 fibrosis	1.5	<1.5
Noncirrhotic NAFLD	1.5	<1.5

Sherman M. *Semin Liver Dis.* 2010;30(1):3-16.

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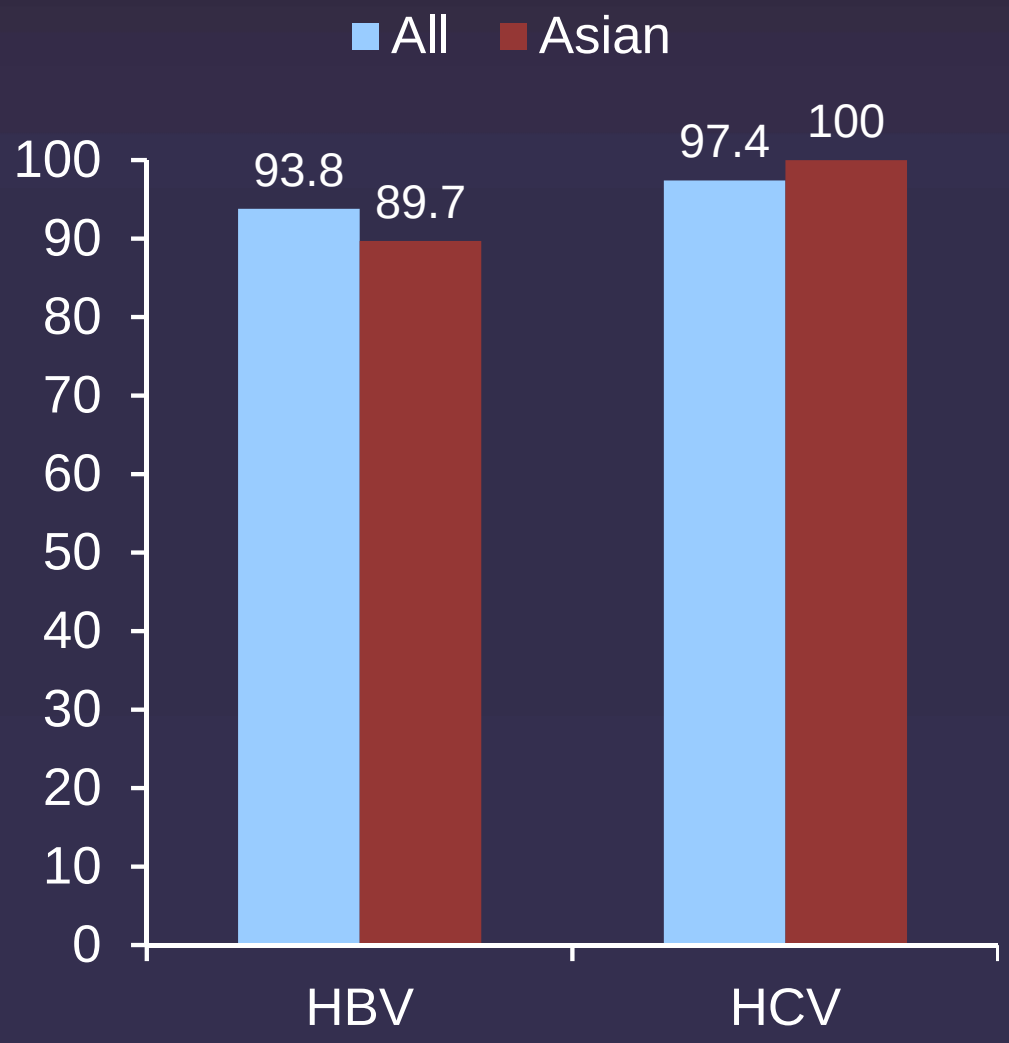
Cirrhosis in Background of HCC



- Majority of HCC occurs in the setting of cirrhosis
- Nearly all HCV patients have cirrhosis
- Lower % with HBV have cirrhosis, especially in Asians

Yang *CGH* 2011;64

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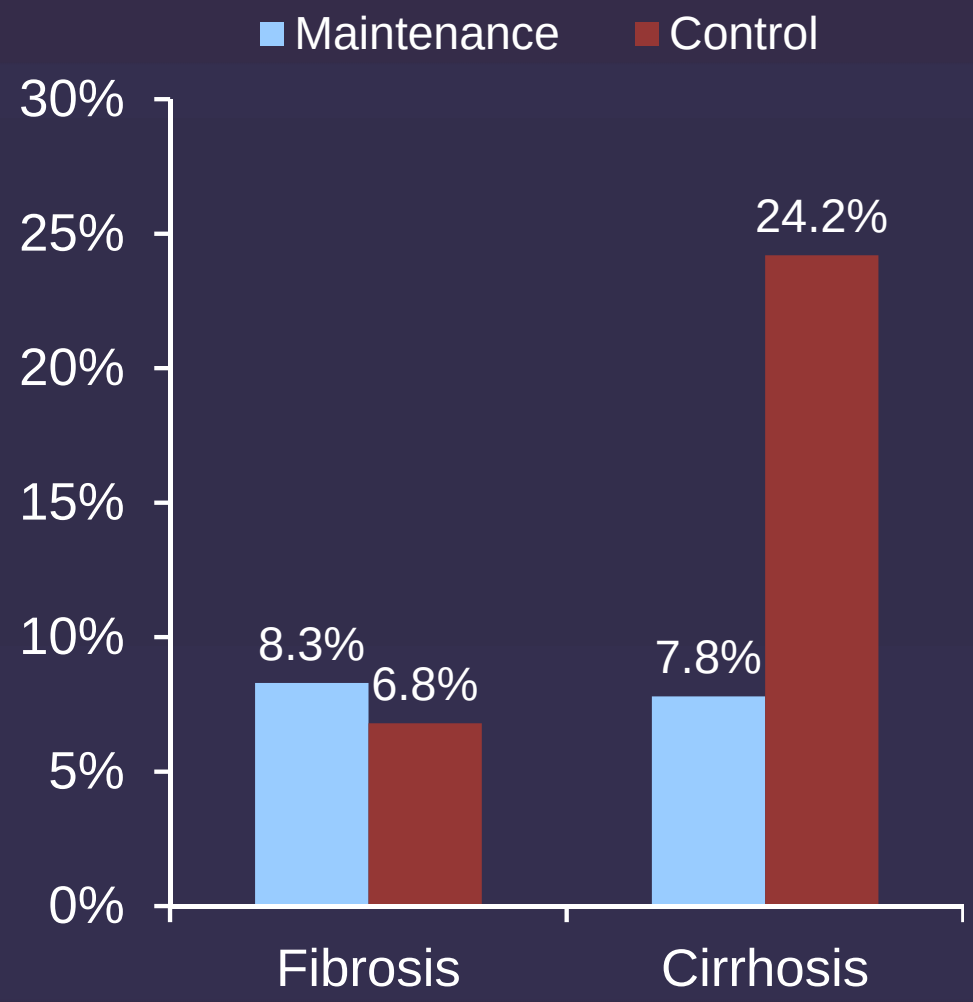
HALT-C: Incidence of HCC after 7 years (fibrosis vs. cirrhosis)



- 1048 patients with cirrhosis (40%) or bridging fibrosis (60%) who failed at least 24 weeks of peg-IFN + RBV
- 4 years of maintenance therapy with peg-IFN
- Median f/u 6.1 yrs (0-8.7)

Lok et al. *Gastro* 2011;140:840-49

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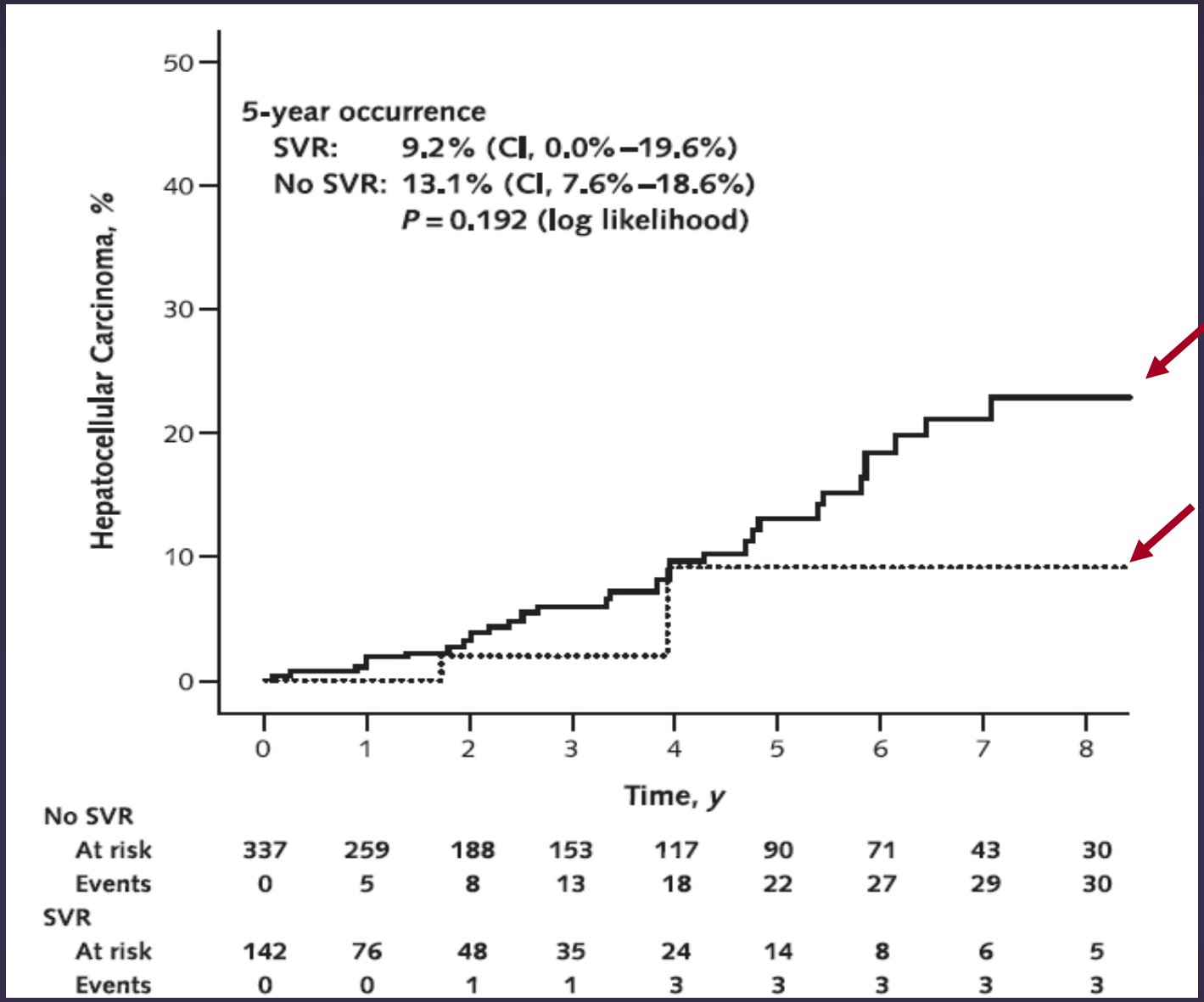
Sustained Response to Interferon Therapy: HCCs Still Occur



No SVR									
At risk	337	259	188	153	117	90	71	43	30
Events	0	5	8	13	18	22	27	29	30
SVR									
At risk	142	76	48	35	24	14	8	6	5
Events	0	0	1	1	3	3	3	3	3

Veldt, Heathcote, Wedemeyer et al., *Ann Inn Med* 2007

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NAFLD and HCC: Summary of Epidemiological Evidence

- Two population-based cohort studies of patients with NAFLD/NASH
  - No HCC in one study
  - 0.3% over 6 years in another
- Three clinic based cohort studies of NAFLD or NASH (not restricted to cirrhosis)
  - Between 0 and 6% absolute risk of HCC in approximately 20 year follow up
  - Lower relative risk compared to alcohol or HCV

White D, Kanwal F, El-Serag. *Clin Gastro Hep* 2012

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NAFLD and HCC

- Clinic based cohorts without control group studies
  - Cumulative HCC mortality rates
    - 0.25% (in 7.6 yrs) in Rochester, MN cohort
    - 1% (in 8.3 yrs) in Cleveland Clinic cohort
    - 2.3% (in 13 yrs) in Swedish cohort study
- Six clinic based cohort studies of NAFLD/NASH cirrhosis c/w an internal control group
  - Increased HCC incidence and mortality
  - Consistently a lower HCC risk than viral-related cirrhosis

White D, Kanwal F, El-Serag. *Clin Gastro Hep* 2012

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Presenting Features and Outcomes of HCC Are Worse in Patients With Non-Viral Liver Disease

Mohsen W, Rodov M, Prakoso E, Bowen D, Koorey DJ, Shackel NA, McCaughan GW, Strasser SI

Many patients with HCV and HBV undergo regular surveillance to detect early HCC; however screening in those with non-viral liver disease, particularly due to alcohol and NASH is less consistent.

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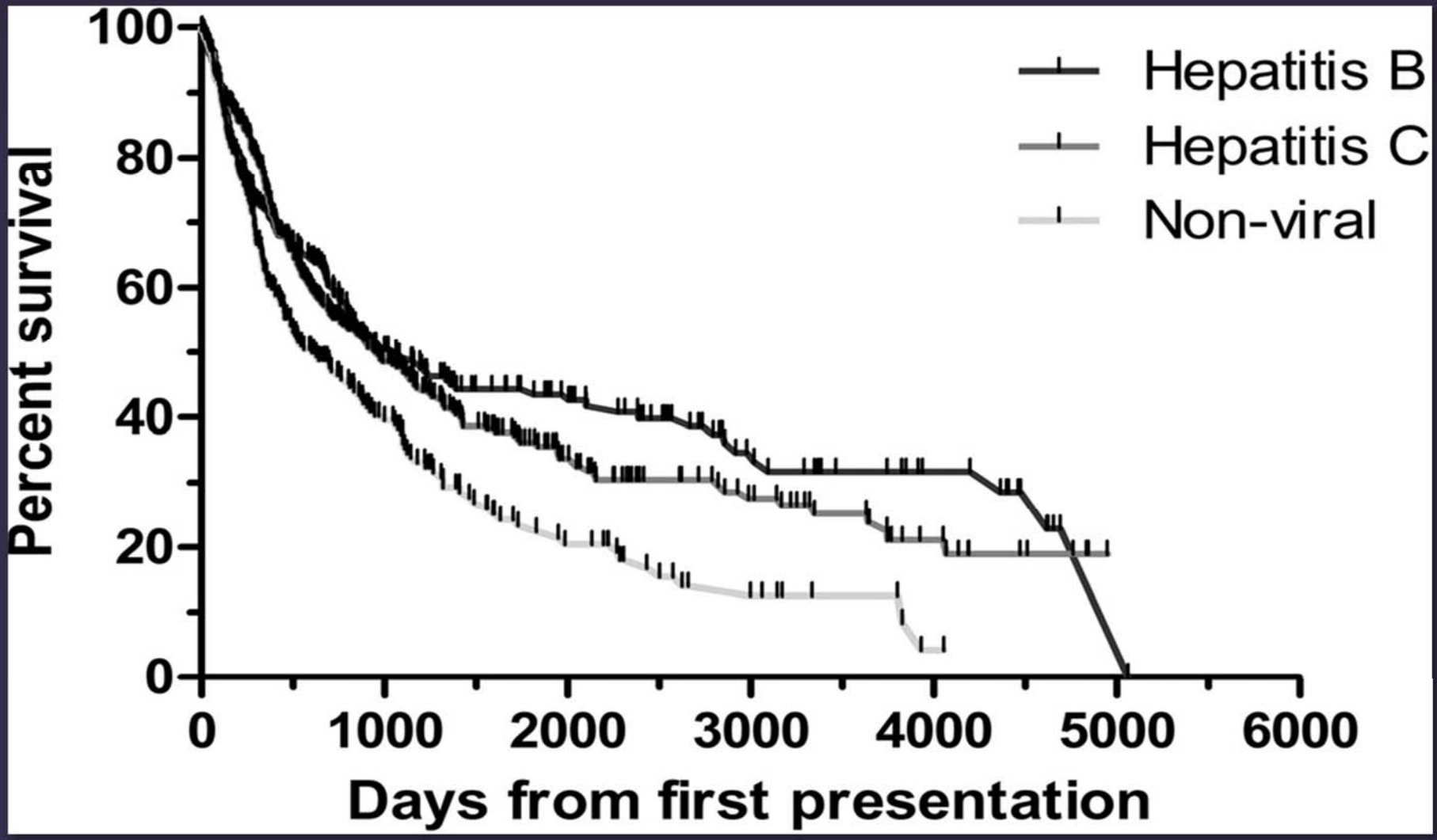
Presenting Features and Outcomes of HCC Are Worse in Patients With Non-Viral Liver Disease



Mohsen W. et al., DDW 2013

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Controversy #2: HOW?

- AFP or no AFP?

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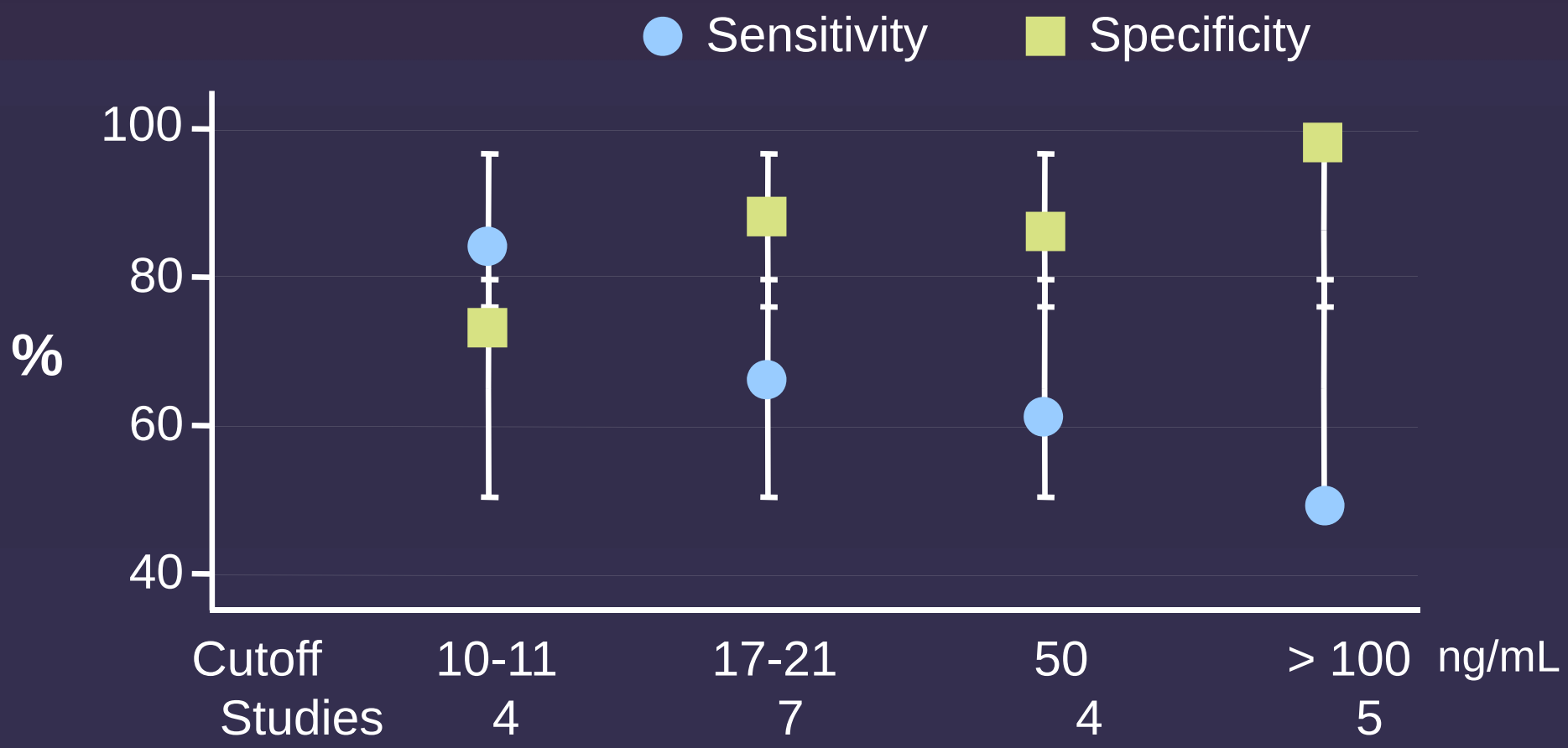
Performance Characteristics of AFP Based on Cutoff Level



Colli A, et al. *Am J Gastro* 2005

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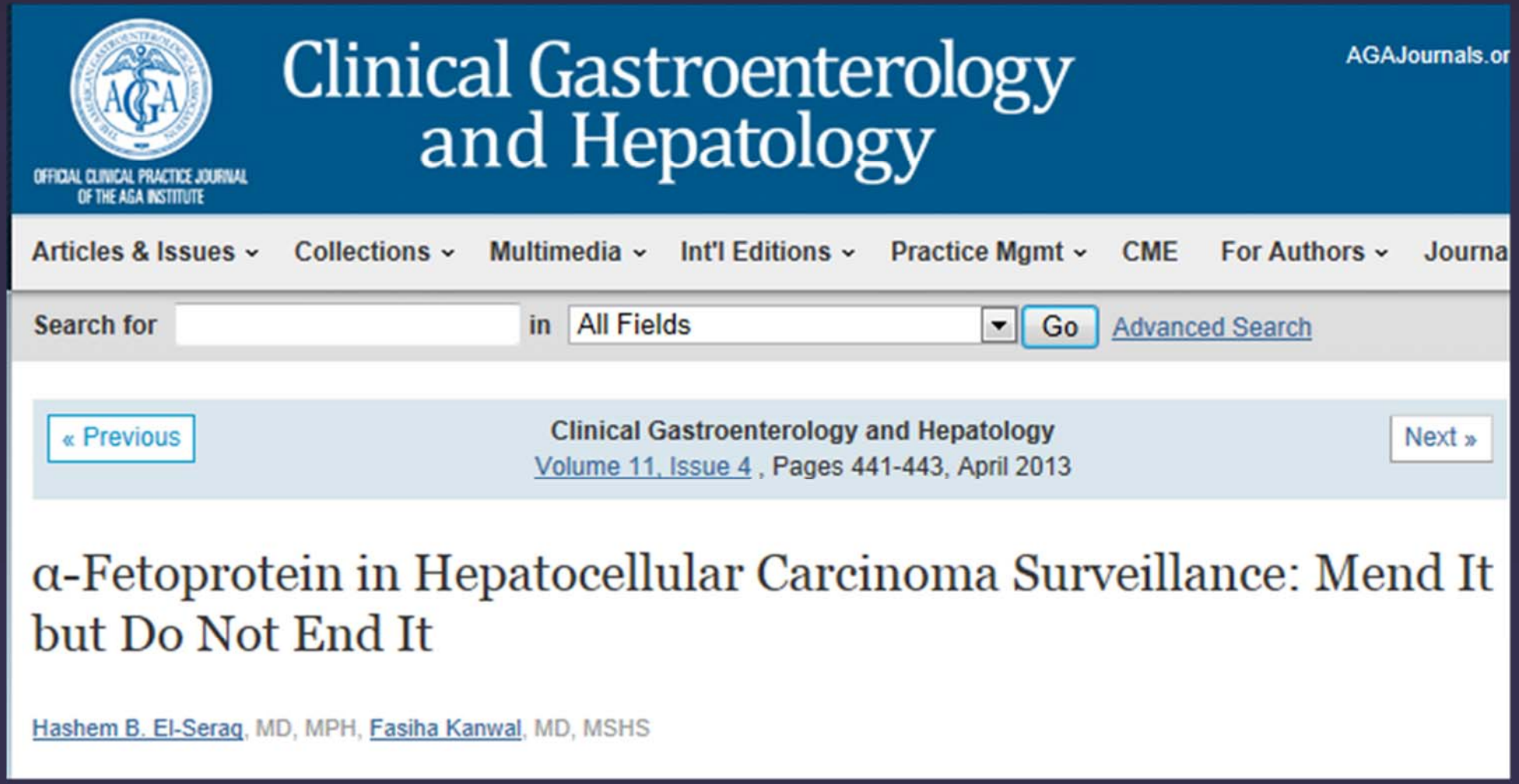

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α-Fetoprotein in Hepatocellular Carcinoma Surveillance: Mend It but Do Not End It

Hashem B. El-Serag, MD, MPH, Fasiha Kanwal, MD, MSHS

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Patterns Of AFP Tests Identify More Accurately HCV + Patients Most Likely To Develop HCC

- HALT-C cohort
- Incorporate
  - Standard deviation of AFP
  - Rate of AFP increase
  - Patient-specific risk factors
- Improved the prognostic accuracy
  - From 0.76 when only the most recent AFP level was used to AUC of 0.81

Lee E, et al. *Clin Gastro Hepatol* 2013

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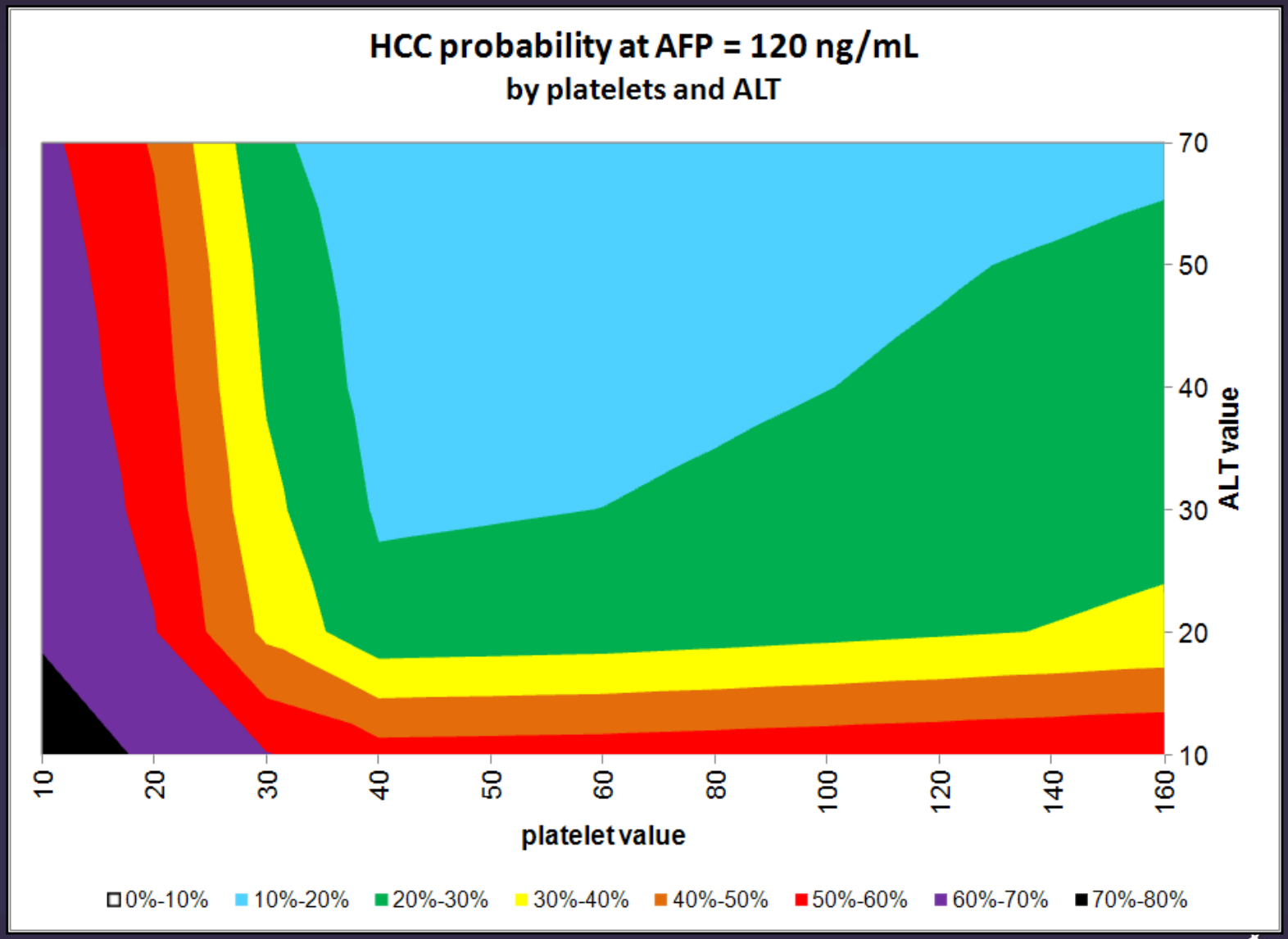
Adjusted AFP Algorithm



Richardson P. *DDW* 2013

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AFP Should Not Be Excluded As Part of Surveillance for HCC in the Real World Setting

Tablante M, Sollano JD, Wong SN

- Out of 341 patients with elevated AFP
  - 41 (12%) had a normal ultrasound
- Most (30/41) were ruled out to have HCC through dynamic imaging or long-term follow-up
- Of the 11 patients diagnosed with HCC despite no tumor on the initial ultrasound
  - All had typical findings of HCC on dynamic imaging
  - Mean tumor size was 8.3 cm and 4 were infiltrating

Tablante M et al., DDW 2013

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Evidence for Surveillance of HCC in HCV: HALT C Trial

- Sensitivity of US was 58%
- 28 HCC *early stage* cases in the nested case-control study
  - 40%: Ultrasound indicating a nodule
  - 20%: Rising AFP
  - 20%: Rising AFP and US indicating a nodule
- Conclusions: AFP and US complementary

Lok AS, et al. *Gastroenterology* 2010

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HCC Surveillance Recommendations

- US is central
- Not AFP alone
- Premature to recommend dropping AFP
- RCTs used AFP + US
- Only population based cohort used AFP
- ~20% of HCC cases are detected based only on an increase in AFP (with normal results from US analysis)
- Most of the current community-based surveillance is either nothing or AFP

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Controversy #3

- Effectiveness of HCC Screening in Practice?

Prevention of HCC (Antiviral Treatment or Surveillance)

Efficacy in Clinical Trials and Research Centers

≠

Effectiveness in Community Practice

↓

Efficacy x Access x Correct Diagnosis x Recommendation x Acceptance x Adherence

El-Serag HB. et al. *Gastroenterology*. 2007;132:8-10.

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Efficacy and Effectiveness

A Demonstration of the Multiplicative Effect of Factors

Example 1: Rx "X"	
Efficacy of Rx "X"	60%
Access	x 80%
Correct diagnosis	x 85%
Recommend	x 85%
Acceptance	x 85%
Adherence	x 70%
Effectiveness of Rx "X"	= 21%

Example 2: Rx "Y"	
Efficacy of Rx "X"	80%
Access	x 80%
Correct diagnosis	x 85%
Recommend	x 85%
Acceptance	x 85%
Adherence	x 70%
Effectiveness of Rx "Y"	= 28%

Example 3: Rx "X" Modified	
Efficacy of Rx "X"	60%
Access	X 90%
Correct diagnosis	x 90%
Recommend	X 90%
Acceptance	x 90%
Adherence	X 80%
Effectiveness of Rx "X" modified	= 32%

El-Serag HB. *Gastroenterology*. 2007;132:8-10.

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Is HCC Screening Effective?

- The pieces are present:
  - Increasing fatal disease
  - High risk population: liver cirrhosis (and HBV-infected patients)
  - OK tests: US and AFP
  - Recall strategy available (imaging, biopsy)
  - Treatment available: curative and palliative
- The whole thing?

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Utilization of Hepatocellular Carcinoma Surveillance Among American Patients: A Systematic Review

- Nine studies
- The pooled surveillance rate 18.4% (95%CI 17.8%-19.0%)
- Surveillance rates higher in patients followed in subspecialty gastroenterology compared to primary care clinics (51.7% vs. 16.9%)

Singal AG et al. *J Gen Intern Med*. 2012

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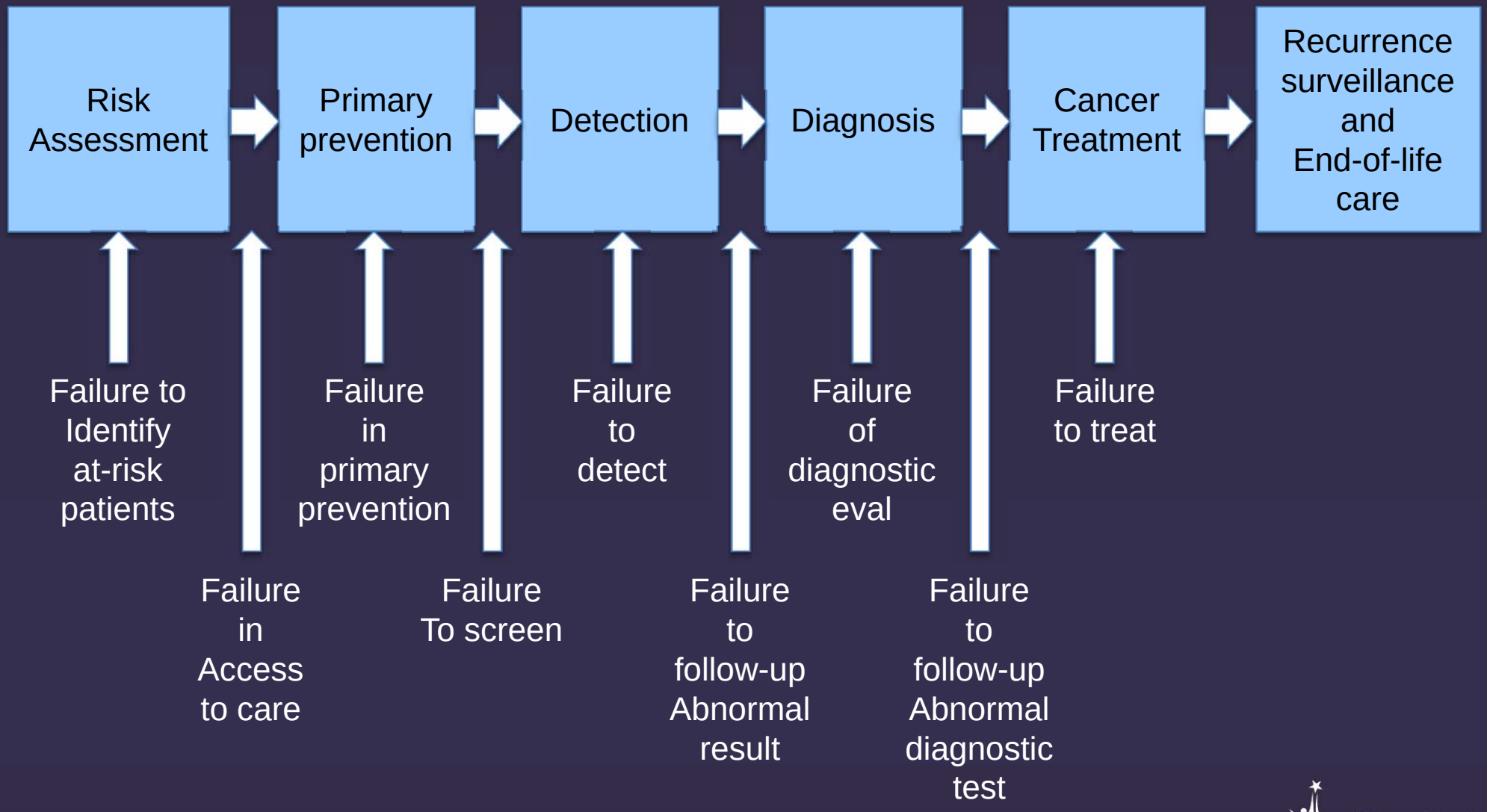
The Quality in the Continuum of Cancer Care (QCCC) Conceptual Framework



Singal A. *Clin Gastro Hepatol* 2013

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HCC Summary

- High risk groups?
  - Cirrhosis including NASH related
  - Advanced fibrosis
    - Irrespective of cause or cure of underlying etiology
  - Some groups of non cirrhotic HBV
- AFP or no AFP?
  - US combined with AFP
  - Mended AFP methods
  - Urgent need for biomarkers
- Effectiveness of HCC screening in practice?
  - Low utilization, repeat, recall
  - New integrated models of care needed

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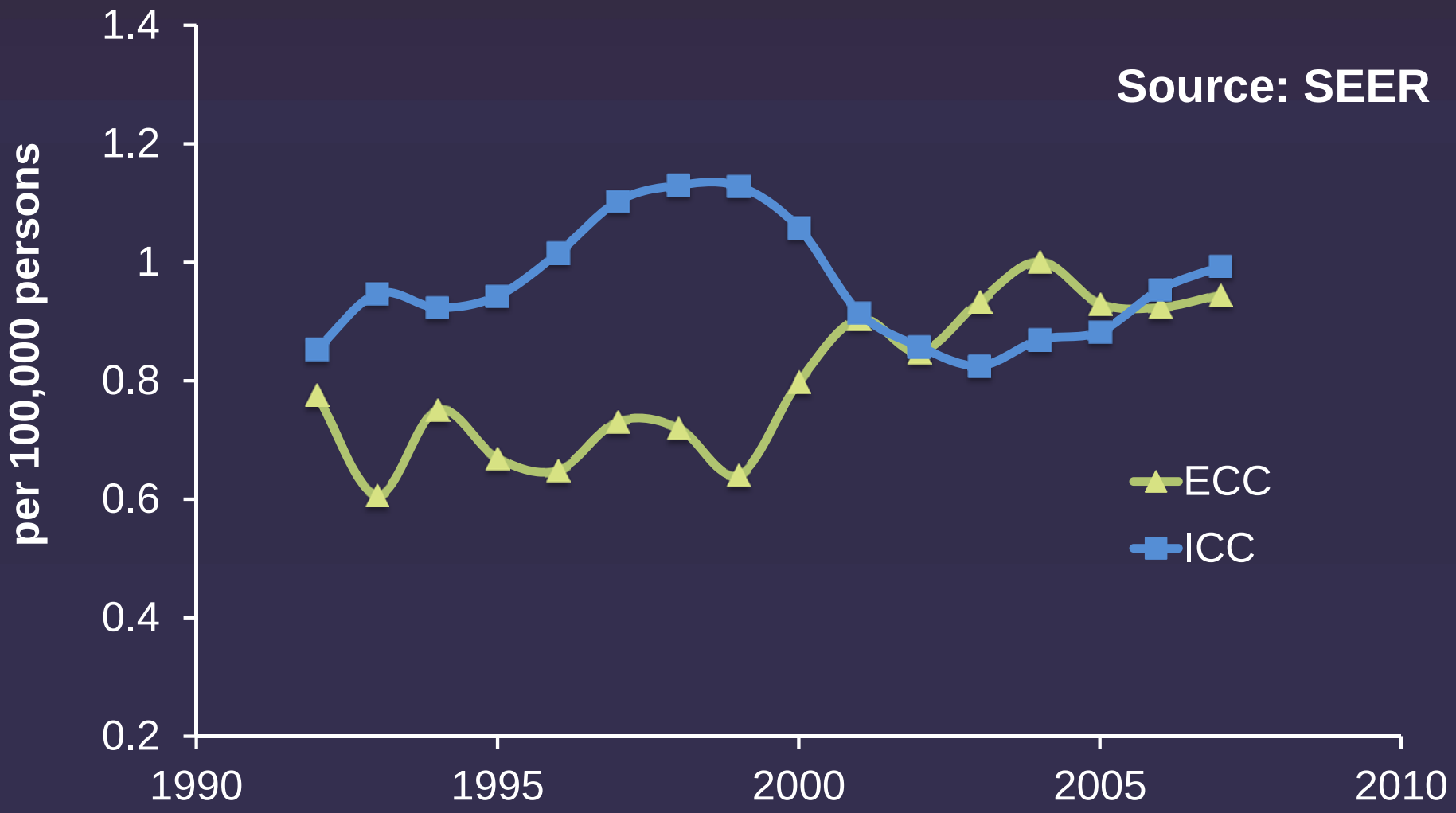
Incidence Rates of Intrahepatic (ICC) and Extrahepatic (ECC) Cholangiocarcinoma



Tyson G et al. 2013 in review

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Risk Factors For CC

Most people, especially in Western countries have no known risk factors

- Established risk factors
  - Parasitic infections:
    - Opisthorchis viverrini (Thailand)
    - Cloronchis sinensis (China,Hong Kong,Korea)
  - Primary Sclerosing Cholangitis
  - Hepatolithiasis (Asia)
  - Congenital bile duct abnormalities (Asia)
    - Choledochal cyst
    - Caroli's disease
  - Toxic Exposure
    - Thorotrast

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Possible Risk Factors For CC

- Cirrhosis
- Viral hepatitis (HCV, HBV)
- Smoking
- Alcohol
- Diabetes
- Obesity
- Inflammatory bowel disease

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HCV and Cholangiocarcinoma

First author	CC Type	Cases (% with risk factor)	Controls (% with risk factor)	Risk Estimate (95% CI)
Shin (Korea)	NS	41 (13.8%)	406 (2.3%)	3.9 (0.9-17.1)
Yamamoto (Japan)	**ICC**	**50 (36%)**	**205 (3%)**	**6.02 (1.5-24.1)**
Shaib (US)	**ICC**	**83 (6%)**	**236 (0.8%)**	**7.9 (1.3-84.5)**
	ECC	163 (3.7%)	236 (0.8%)	2.8 (0.3-35.1)
Welzel (US)	**ICC**	**535 (<0.9%)**	**102,782 (0.1%)**	**4.4 (1.4-14.0)**
	ECC	549 (<0.9%)	102,782 (0.1%)	1.5 (0.2-11.0)
Donato (Italy)	**ICC**	**26 (23%)**	**824 (6%)**	**9.7 (1.6-58.9)**
Lee (Korea)	ICC	622 (1.9%)	2,488 (1.9%)	NS
Zhou (China)	ICC	312 (2.9%)	438 (1.4%)	0.93 (0.3-3.1)

Tyson G and El-Serag HB, *Hepatology* 2011

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