

# Hepatocellular Carcinoma for NNN Cancer Webinar Series

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# Disclosures

\* None



# Outline of Talk

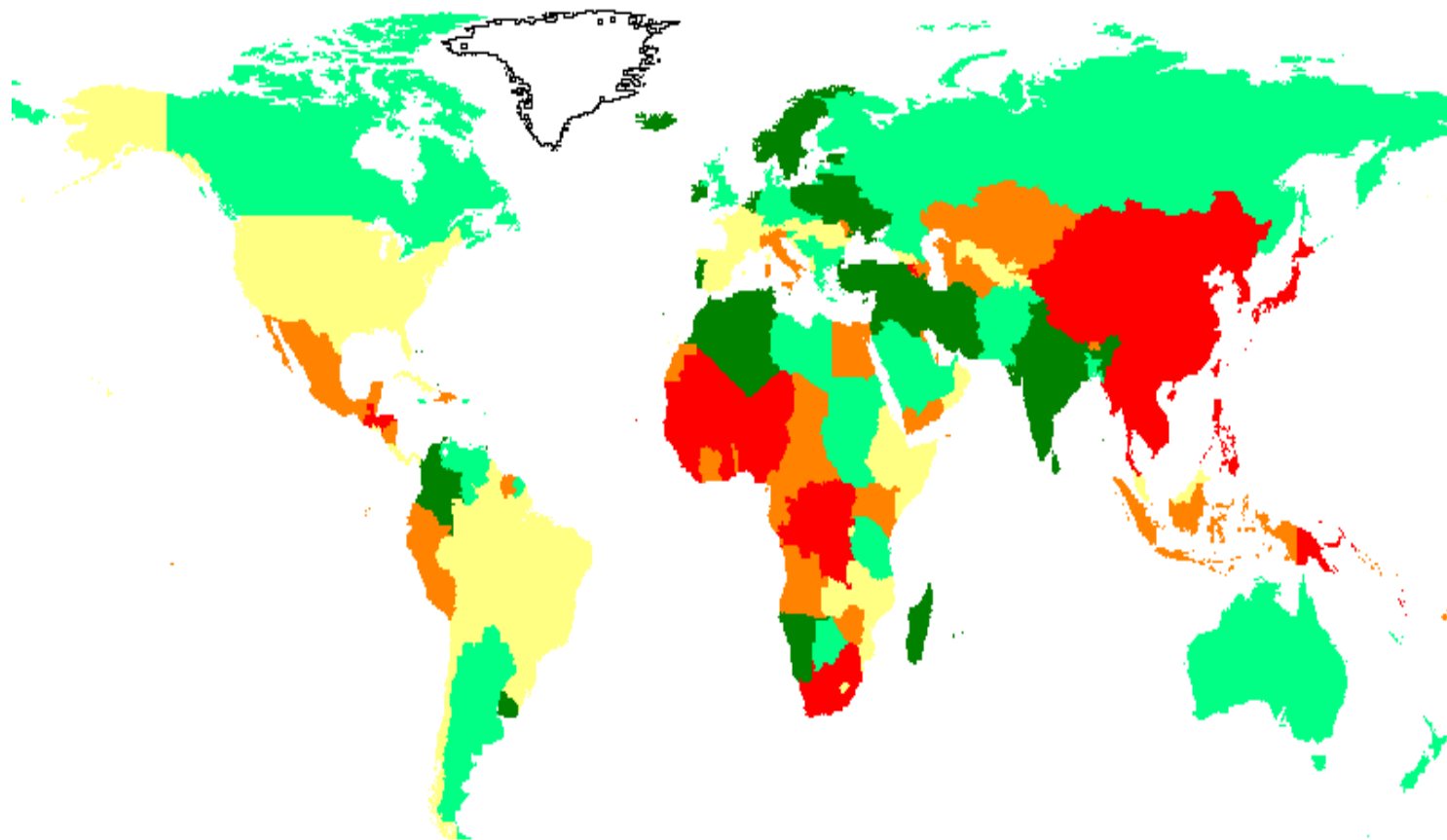
- \* Epidemiology of Hepatocellular Carcinoma (HCC) in the World, US and American Indian/Alaska Native (AI/AN) Peoples
- \* Etiologies of HCC
- \* Risk Factors for HCC
- \* Prevention of HCC
- \* Screening (surveillance) for HCC
- \* Treatment of HCC

# Global View of HCC

- \* Primary liver cancer increased from 437,408 cases in 1990 to 714,600 in 2002
- \* Incidence and mortality rates
  - \* Decreasing in areas of high and intermediate incidence, including China and Japan
  - \* Increasing in low-incidence areas, including the United States and Canada

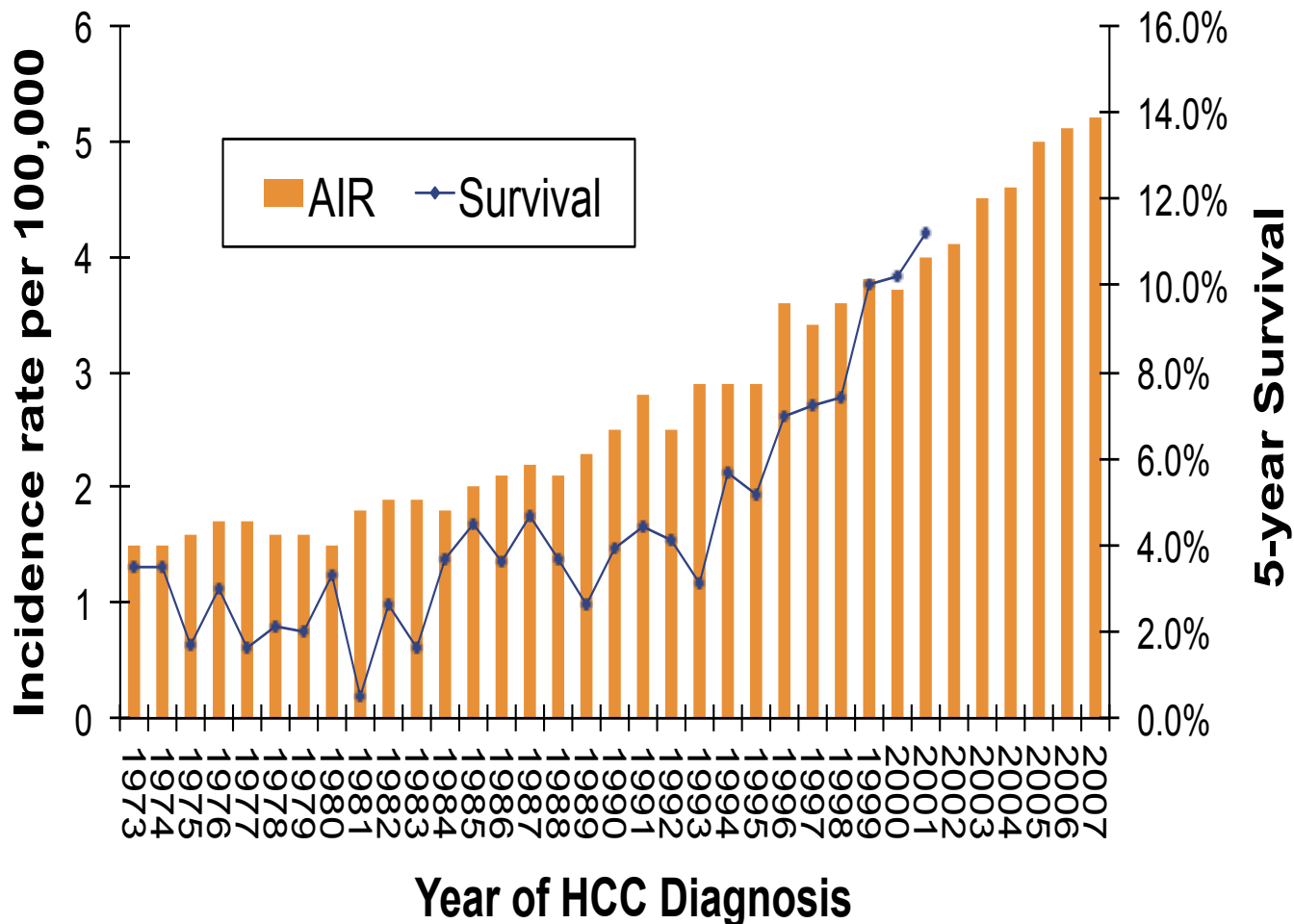
# HCC: Age Standardized Incidence Rates

2005 (Men and Women)

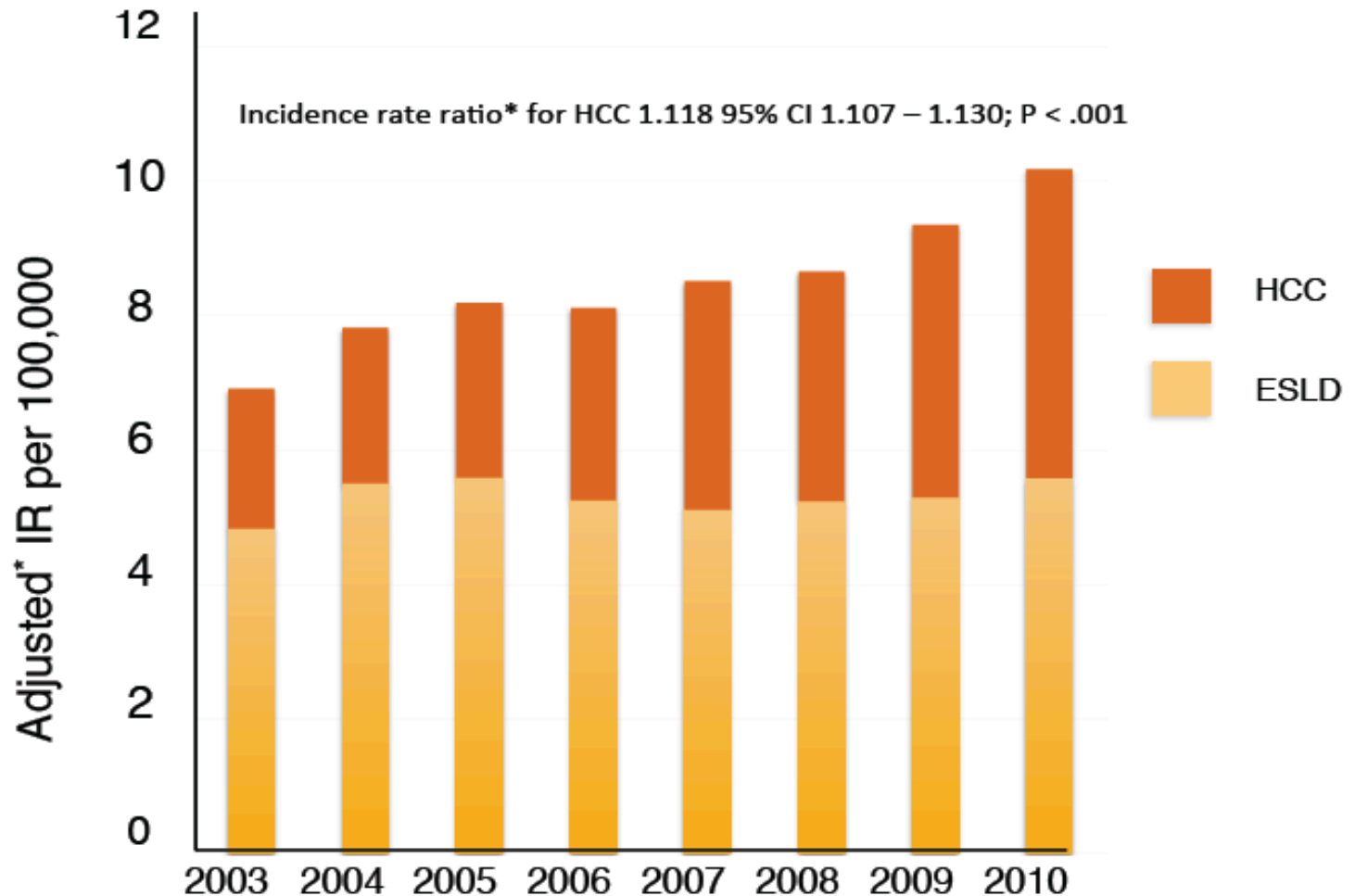


■ < 2.5   ■ < 4.0   ■ < 6.0   ■ < 9.3   ■ < 94.4

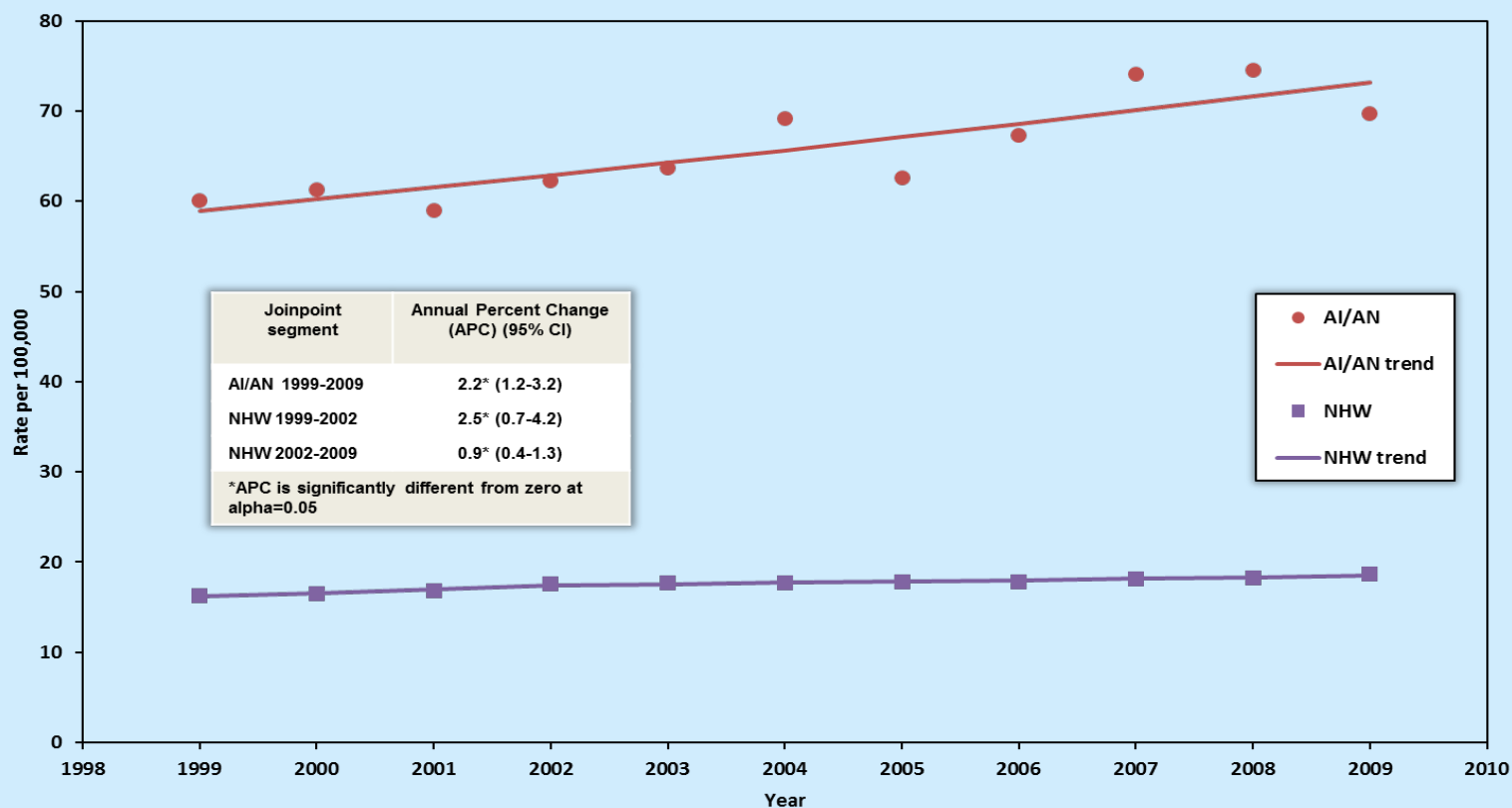
# The Incidence and 5-Year Survival of HCC in United States



## Hepatocellular carcinoma is increasingly the indication liver transplant listing among HCV infected patients in the United States

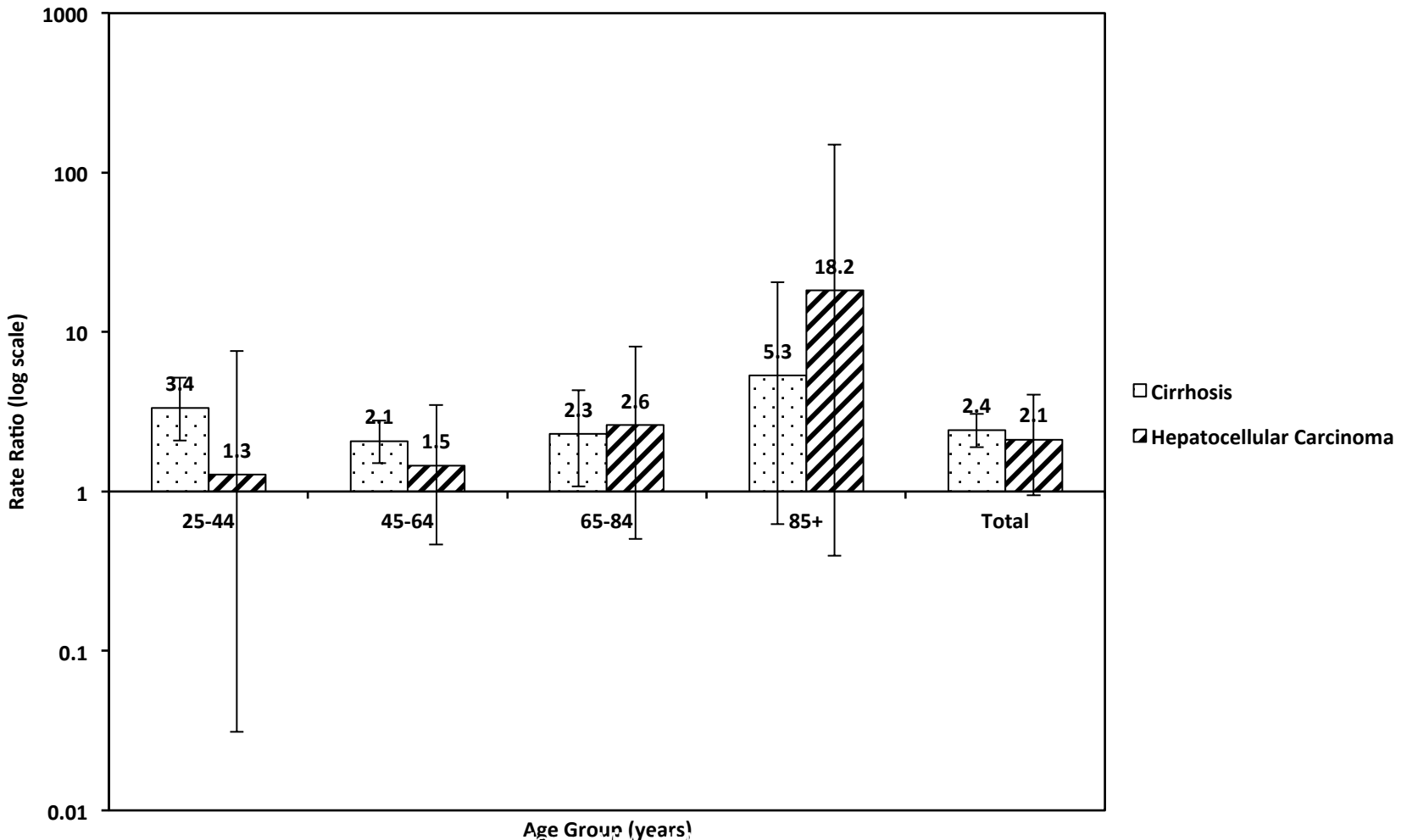


# CLD Death Rate Trends in AI/ANs and NHWs: 1999–2009





# Age-Specific CLD Death Rate Ratios, AI/ANs:NHWs, Hepatitis B-Related CLD



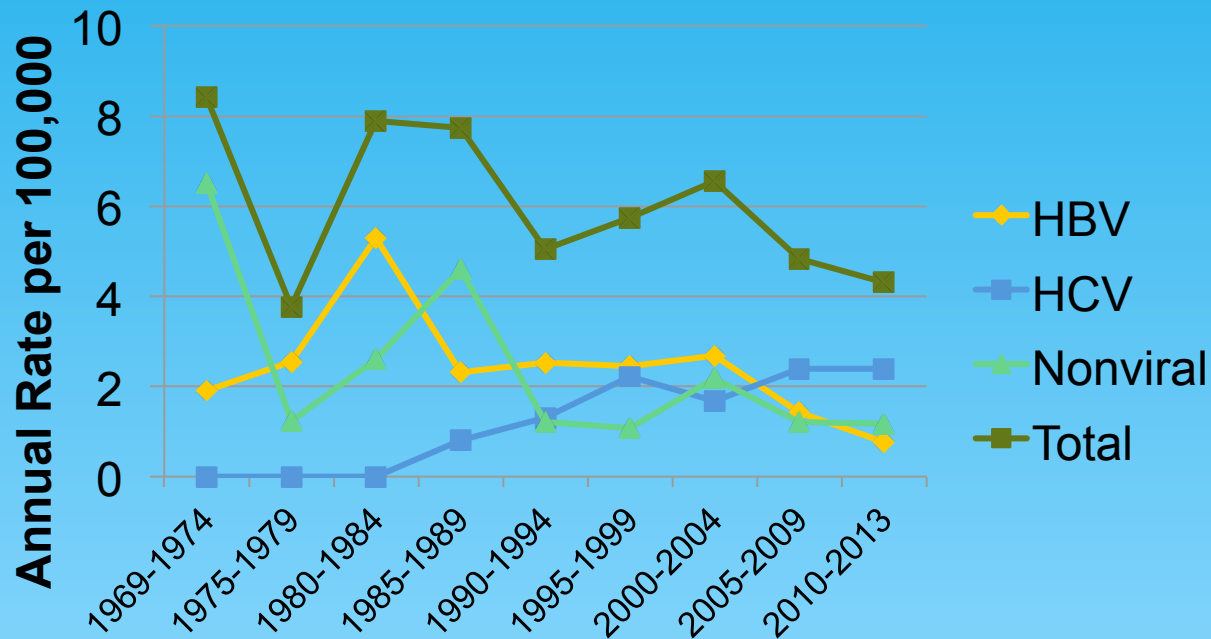
# Annual Incidence of HCC in Different Liver Diseases

- \* Chronic Hepatitis B
    - \* Females >50
    - \* Males >40
    - \* HBV with cirrhosis
  - \* Cirrhosis
    - \* Chronic HCV
    - \* Alcoholic (ALD)
    - \* NAFLD
    - \* AIH
    - \* PBC
- \* Incidence HCC/yr.
    - \* 0.3-0.6%
    - \* 0.2-0.6%
    - \* 3-8%
    - \* 3-6%
    - \* Unknown
    - \* Unknown
    - \* Unknown
    - \* 3-5%

# Causes of HCC In Alaska Natives

- \* Chronic Hepatitis B with or without cirrhosis
- \* Alaska Native Patients with cirrhosis with following etiologies have been identified:
  - \* Chronic Hepatitis C
  - \* Non-Alcoholic Liver Disease
  - \* Alcoholic liver disease
  - \* Autoimmune hepatitis
  - \* Primary Biliary Cirrhosis

## HCC in Alaska Natives, 1969-2013, Age-adjusted rate



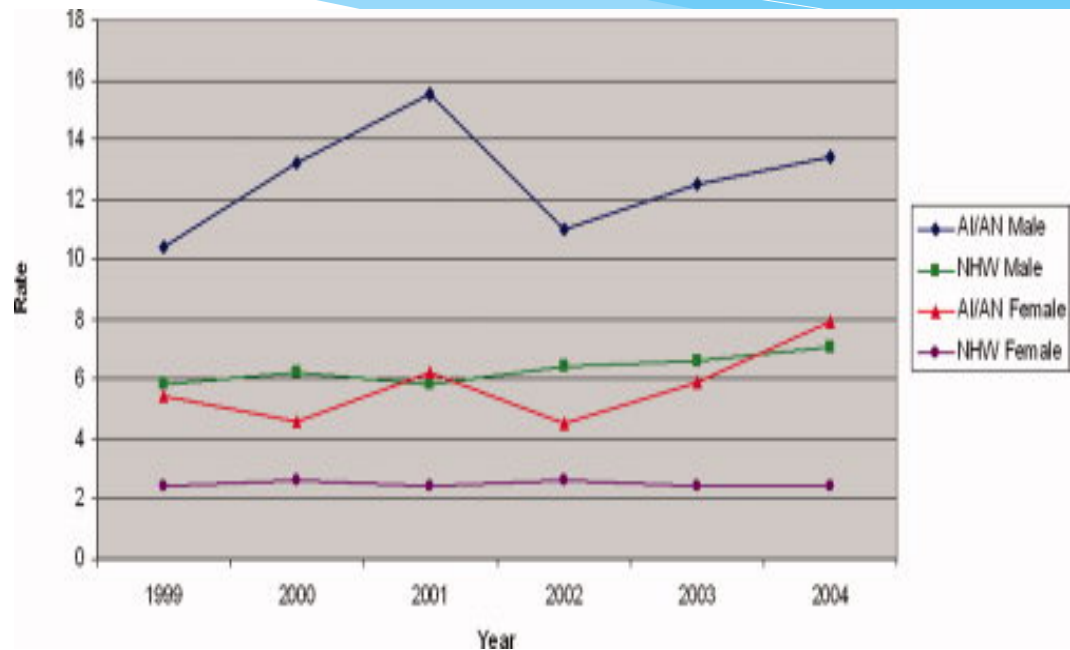
Decrease incidence of HBV associated HCC over time  $p=0.048$ —unpublished data

# Primary Liver Cancer in AI/AN

- \* Using registries from National Program of Cancer Registries of CDC and SEER Program of NCI linked with IHS enrollment records
- \* AI/AN Peoples had higher incidence of HCC than non-Hispanic Whites (NHW)
- \* Incidence rates in males ranged from:
  - \* 7.3 (95%CI; 3.8-12.6) in East Tribes to 17.2 (95%CI 10.4-26.3) in Alaska
- \* Incidence in females ranged from:
  - \* 3.8 (95%CI; 1.2-8.2) in East to 6.9 (95%CI; 3.6-11.6) in Alaska
- \* Increasing trend in AI/AN but did not reach significance except for Alaska
- \* AI/AN less likely to be diagnosed with localized HCC except Alaska

# Primary liver cancer incidence among American Indians and Alaska Natives, US, 1999–2004

Rates/100,000 Age Adjusted to 2000 Standard US Population



Jim et al. Primary Liver Cancer in AI/AN

Cancer

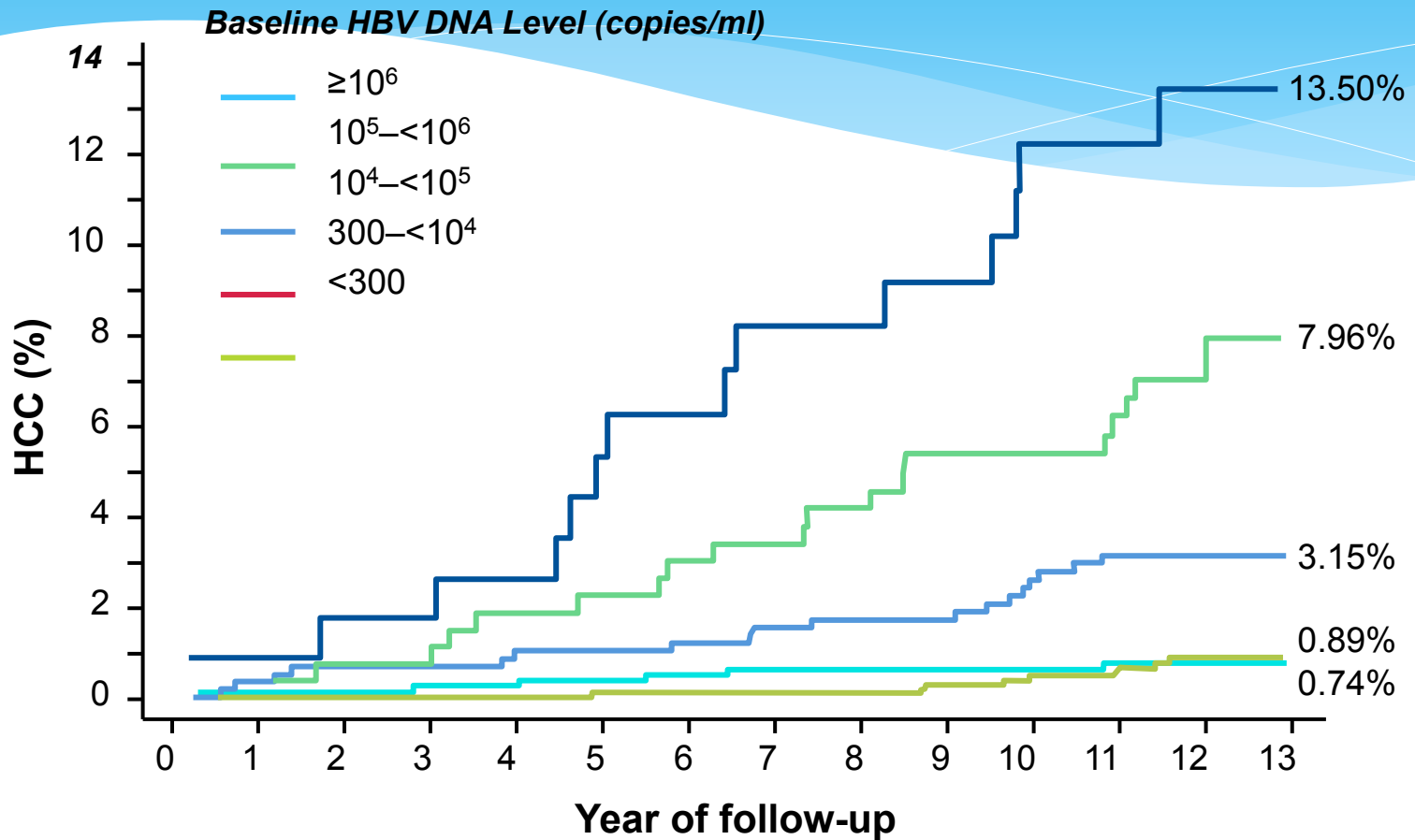
Volume 113, Issue S5, pages 1244-1255, 20 AUG 2008 DOI: 10.1002/cncr.23728

<http://onlinelibrary.wiley.com/doi/10.1002/cncr.23728/full#fig2>

# Risk Factors for HCC in HBsAg-Positive Carriers

- \* HBV acquisition at birth or early childhood
- \* >40 years of age males; > 50 years females
- \* Cirrhosis > no cirrhosis
- \* Family History of HCC
- \* Aflatoxin exposure
- \* HBeAg-positive carriers
- \* High HBV DNA level in persons >40 years
- \* HBV genotype C and F
- \* HBV precore (decrease), core promoter (increase)
- \* Co-infection with HCV or HDV

# Hepatitis B: Association Between Viral Load and Incidence of HCC



HBeAg negative, **normal ALT**, no liver cirrhosis at entry (n=2,925)

Chen CJ et al. *JAMA*. 2006;295:65-73



# Risk Factors for HCC in Persons with HCV

- \* Advanced Fibrosis: Cirrhosis or Bridging Fibrosis
  - \* Risk is minimal in patients with mild or no fibrosis
- \* HBV/HCV co-infection
- \* Other risk factors of weaker quality of evidence
  - \* HCV + HIV

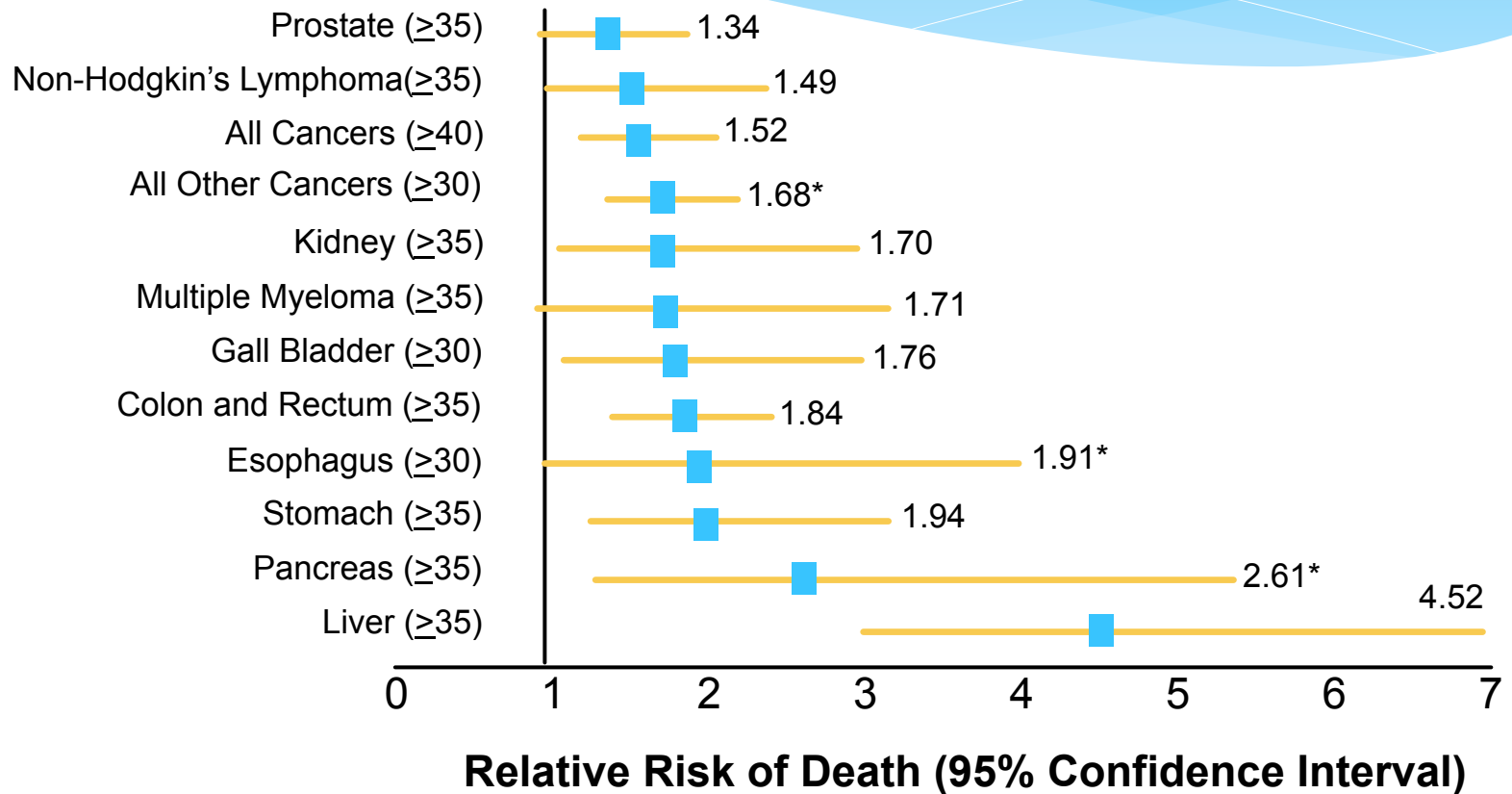
# Other Risk Factors from Case-Control Studies in both HBV and HCV

- \* Heavy alcohol intake: likely due to synergistic effect on development of cirrhosis
- \* Tobacco use
- \* Diabetes and obesity

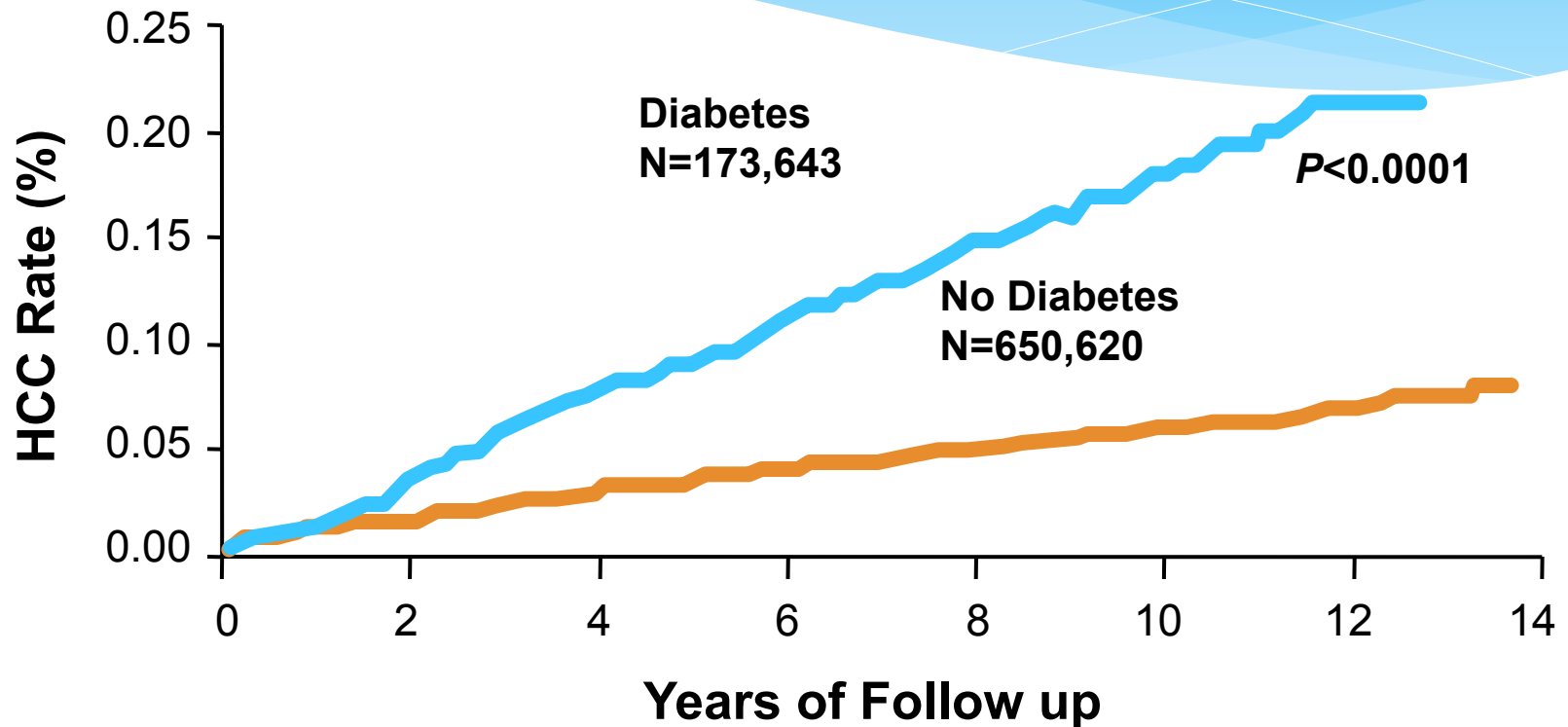
# Mortality from Cancer in Obese US Men (n=900,053)

Men

Type of Cancer  
(Highest BMI Category)



# Diabetes Is Associated with a Two-fold Increase in Risk of HCC



# HCC Risk Factors:

Prevalence, Risk Estimates, Attributable Fraction?

	Prevalence in general population	Risk estimate of HCC	Current prevalence in HCC cases	Population attributable fraction
HBV	0.5-1%	20-25	10-15%	5-10%
HCV	1-2%	20-25	30-60%	20-25%
Alcoholic liver disease	10-15%	2-3	20-30%	20-30%
Metabolic syndrome	30-40%	1.5-2.5	20-50%	30-40%

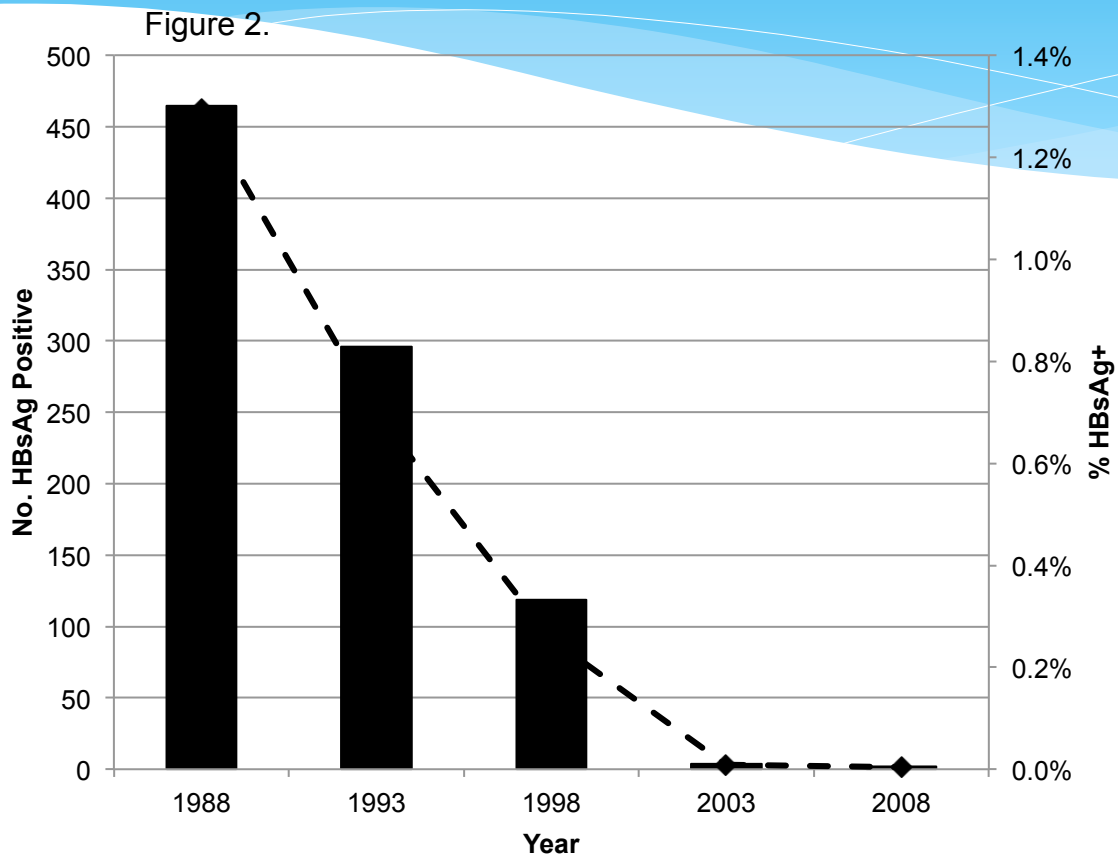
# Prevention of HCC

- \* Prevention: HBV vaccination
  - \* Decrease risk of HCC in childhood in Taiwan, Thailand and Alaska from universal infant/childhood vaccination
- \* Decrease Risk:
  - \* Treatment of underlying liver disease
  - \* Coffee
  - \* Statins
  - \* Metformin
- \* Prolonged survival: Surveillance for HCC

# Prevention of or Reduction of Risk for HCC

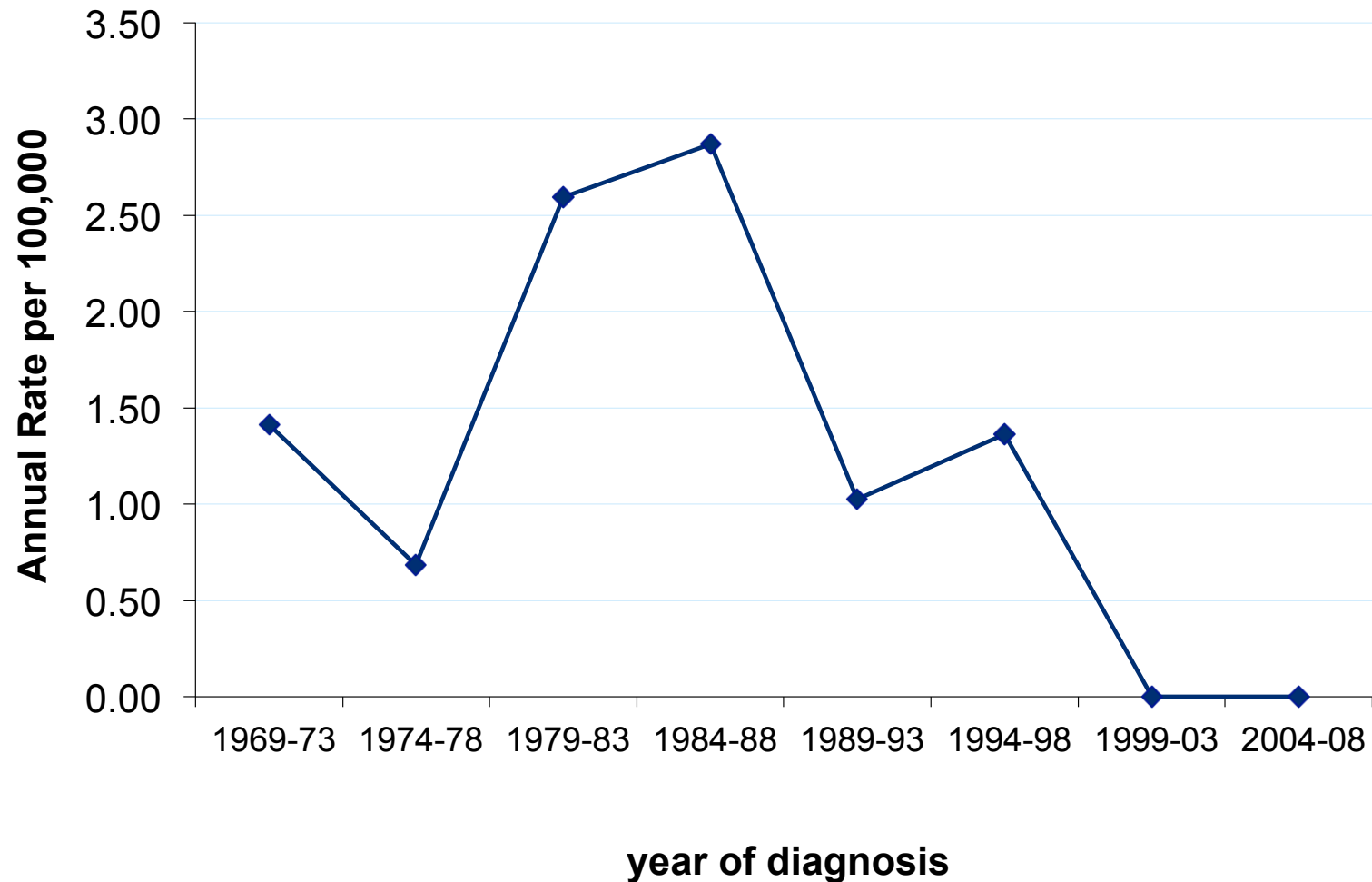
- \* Treat underlying cause of cirrhosis or hepatitis
  - \* Vaccination against HBV
  - \* Antiviral therapy for HBV for those who meet criteria
    - \* Lok, McMahon AASLD Guideline for HBV at [aasld.org](http://aasld.org)
  - \* Cure of hepatitis C with Direct Acting Antivirals (DAA)
  - \* Weight loss/exercise for persons with metabolic syndrome
  - \* Abstinence for alcoholic cirrhosis
  - \* Targeted therapy for Autoimmune hepatitis or PBC

# Number of Alaska Native Children Under 20 Years of Age who Tested Positive for Hepatitis B: 1988-2008

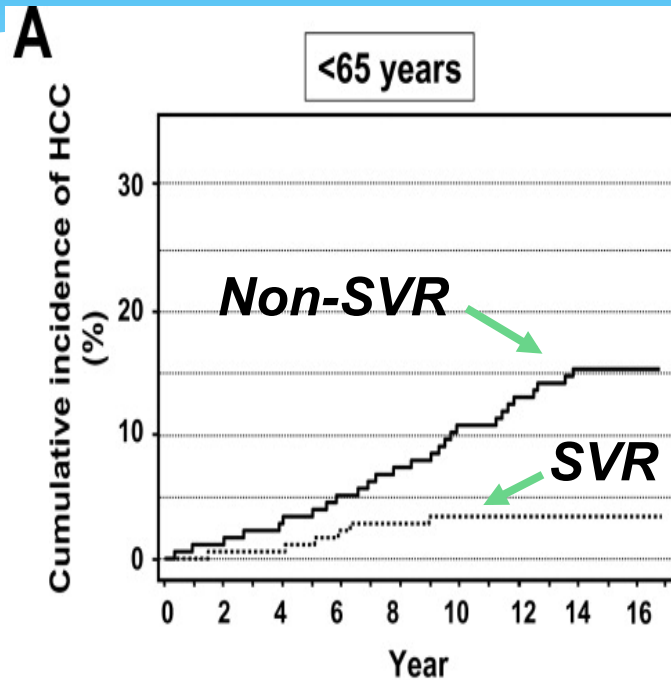




## Hepatocellular Cancer in Alaska Native Children <20 Years Old, 1969-2008

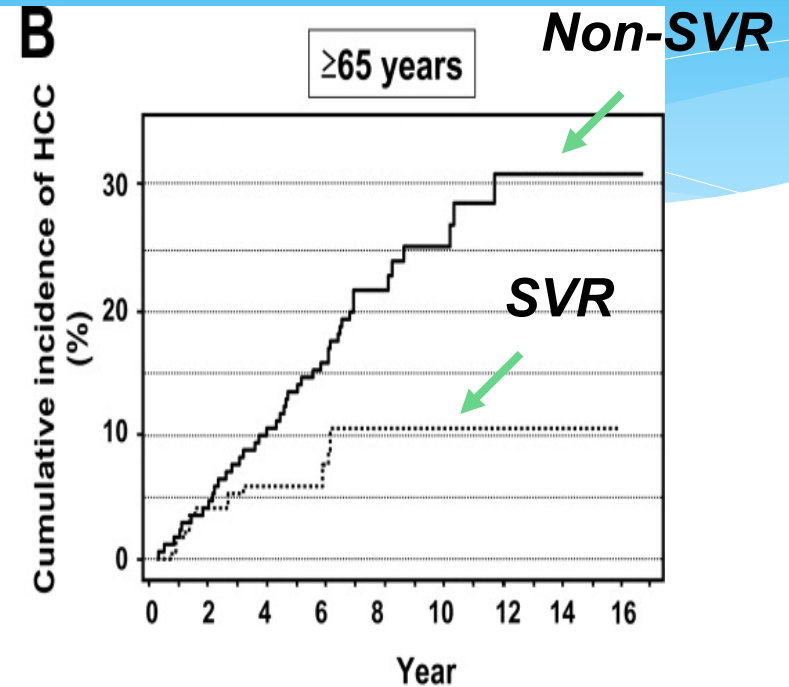


# HCC and Hepatitis C Treatment



	0	5 yrs.	10 yrs.	15 yrs.	
SVR	Patients with HCC	0	6	12	12
	Patients at risk	565	376	164	56
	Cumulative incidence of HCC	0%	1.2%	3.3%	3.3%

	0	5 yrs.	10 yrs.	15 yrs.	
Non SVR	Patients with HCC	0	33	72	85
	Patients at risk	980	723	345	141
	Cumulative incidence of HCC	0%	3.6%	10.9%	15.5%

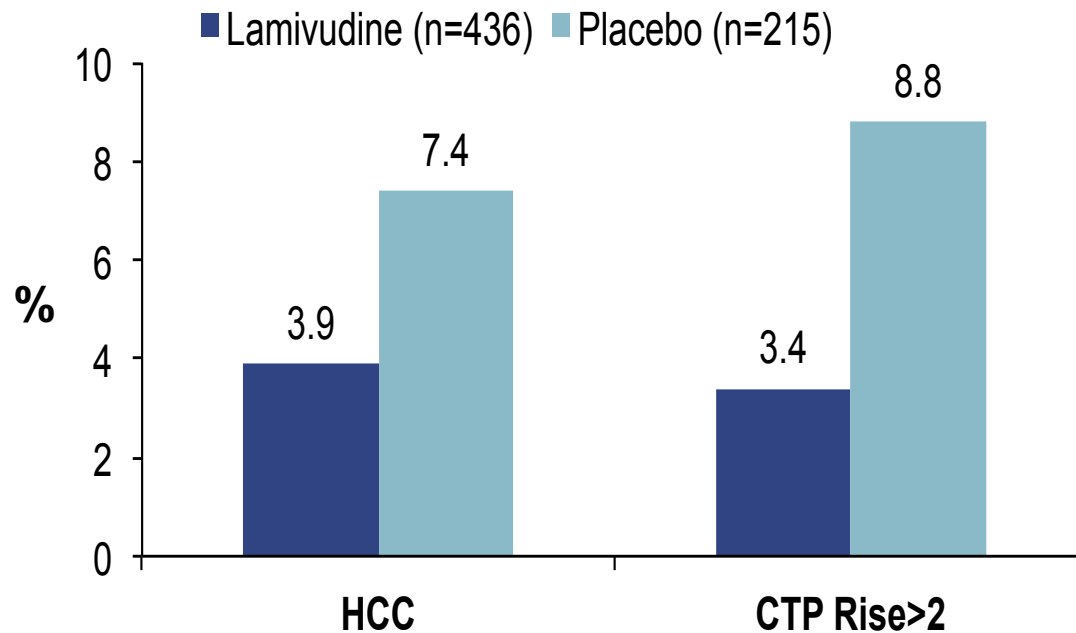


	0	5 yrs.	10 yrs.	15 yrs.	
SVR	Patients with HCC	0	7	10	10
	Patients at risk	121	67	21	5
	Cumulative incidence of HCC	0%	6.0%	11.0%	11.0%

	0	5 yrs.	10 yrs.	15 yrs.	
Non SVR	Patients with HCC	0	46	61	64
	Patients at risk	376	179	43	25
	Cumulative incidence of HCC	0%	14.1%	25.5%	31.1%

# Impact of HBV Treatment on HCC

- \* Randomized controlled trial comparing lamivudine versus placebo
  - \* Patients with advanced fibrosis or cirrhosis
  - \* HBV-DNA ( $>10^5$  copies/mL) or HBeAg+
  - \* Study terminated prematurely by DSMB (median Tx=32.4 mo)



# AASLD Recommendations for Screening for HCC

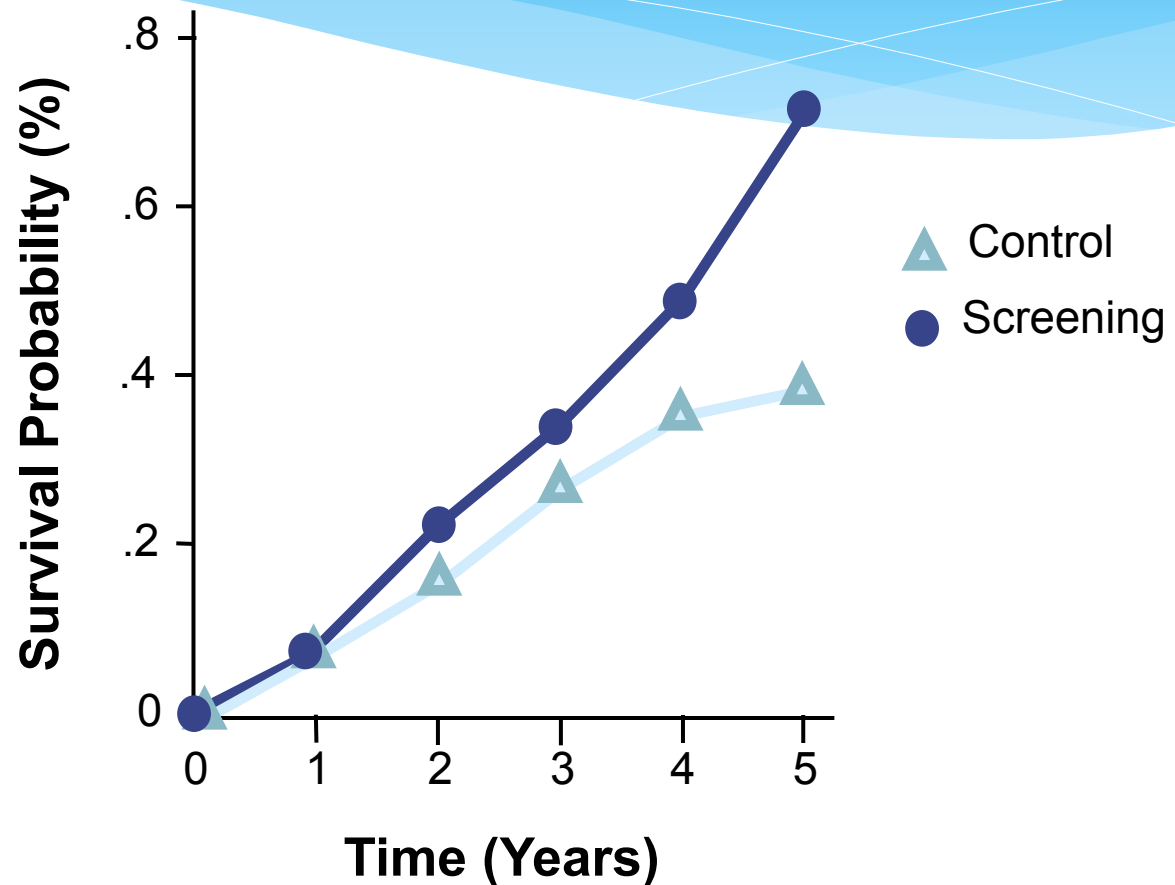
- \* Surveillance for HCC should be performed using ultrasonography (level II).
- \* Patients should be screened at 6 month intervals (level II).
- \* The surveillance interval does not need to be shortened for patients at higher risk of HCC (level III).

# HCC Surveillance: Randomized Controlled Trials

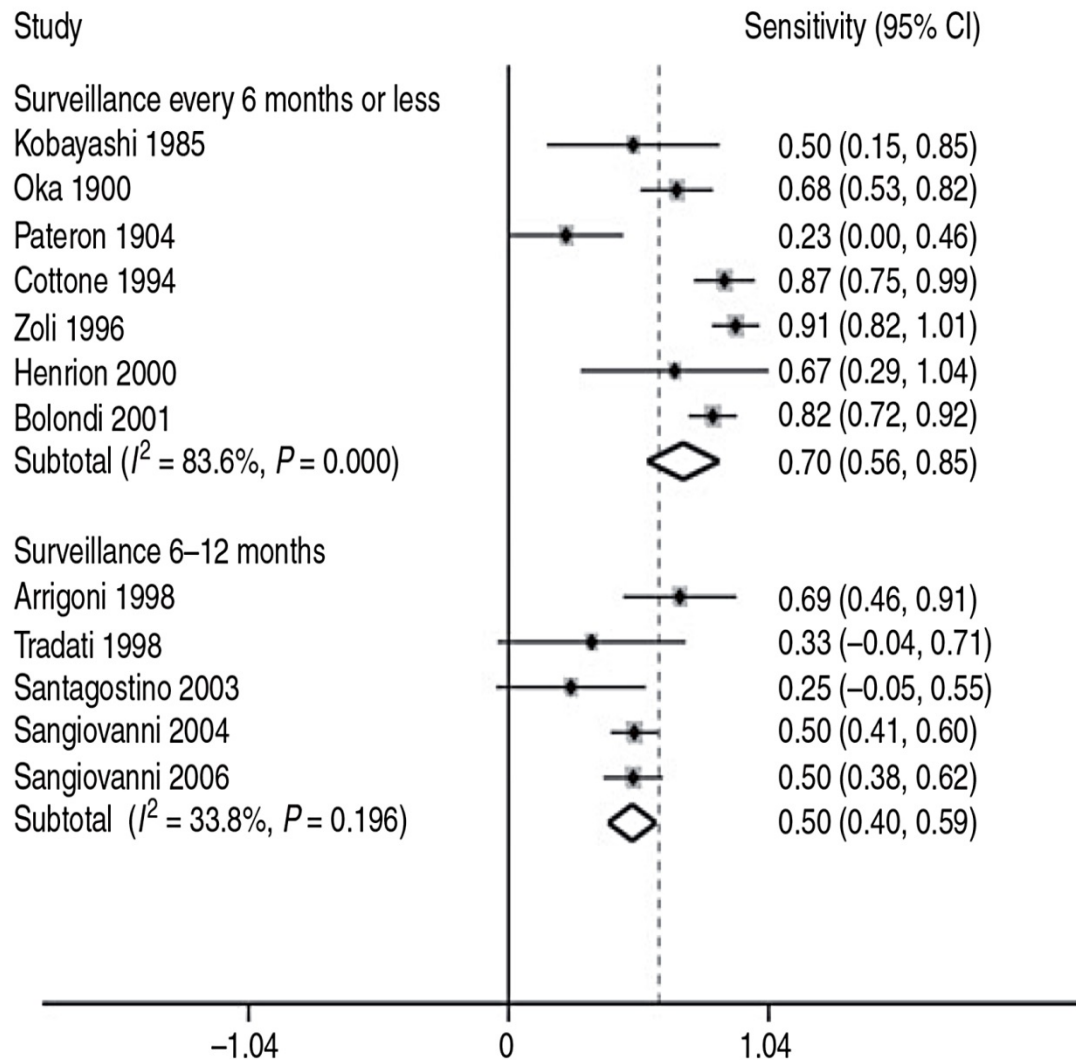
- \* Cirrhosis (NONE)
- \* Hepatitis C infection (NONE)
- \* Hepatitis B infection carriers
  - \* China
  - \* Two trials
  - \* One showed benefit (Zhang et al. 2004)
  - \* One did not show benefit (Chen et al. 2003)

# Surveillance for HCC Reduces Mortality:

A Randomized Controlled Trial of AFP+US q 6 months



# Ultrasound Surveillance in Early HCC: Systematic Review



# AFP & HCC

- \* AFP as a serologic marker has a low sensitivity and specificity for HCC
  - \* AFP can be elevated by active liver inflammation and regeneration
  - \* Persons with AFP elevation are at higher risk of developing HCC in future
- \* AFP has a high negative predictive value for the absence of HCC (AFP <8ng/ml) but a low positive predictive factor



# ANTHC LDHP Program Recommendations for Screening for HCC in Chronic HBV

- \* AFP every 6 months for all persons
- \* US also every 6 months for those
  - \* Cirrhosis
  - \* Family History of HCC
  - \* Previous HCC diagnosis
  - \* Men >40 and women > 50 years who live in community with US available
- \* If AFP > 10mg/ml, then do US initially and if negative, repeat AFP & US in 3 months then every 3-6 months thereafter

# Other Surveillance Considerations to Detect HCC in HBV

- \* Persons for whom liver Ultrasound should be performed if living in a community that has US available
  - \* All Males over 40 years of age
  - \* All Females over 50 years of age
  - \* Persons with HBV genotype C over 40 years of age\*
  - \* Persons infected with HBV genotype F at any age\*
  - \* Persons over age 40 with high viral load (>20,000 IU/ml)

Increase risk of HCC in HBV genotypes C and F in Alaska Native Persons  
Livingston: J Infectious Diseases 2007;195:5-11

# ANTHC LDHP Program Recommendations for Screening for HCC other than HBV

- \* Patients with cirrhosis from HCV, NAFLD, ALD, AIH, PBC or other cause
  - \* AFP and US every 6 months
- \* Patients with HCV in whom liver fibrosis stage is unknown
  - \* AFP every 6 months
    - \* If AFP > 10, do US initially and repeat AFP US in 3 months then every 3-6 months thereafter

# Effectiveness of Surveillance for HCC in Alaska Native Persons

- \* Chronic HBV: Hepatology 2000;32:842-6
  - \* Sensitivity of AFP >15ng/ml: 97%
  - \* Specificity excluding pregnancy: 95%
  - \* Positive Predictive value: 31%
  - \* Significant 5 yr. survival compared to prior to 1982 when no screening done
  - \* 53 cases detected since 1982
    - \* 47 (89%) detected at potentially curable stage
      - \* 34 resected
      - \* 13 treated ETOH injection or RFA

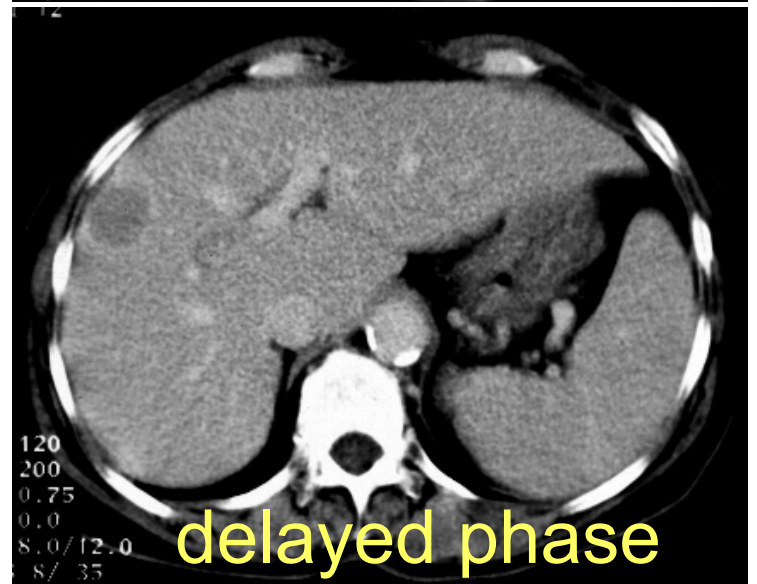
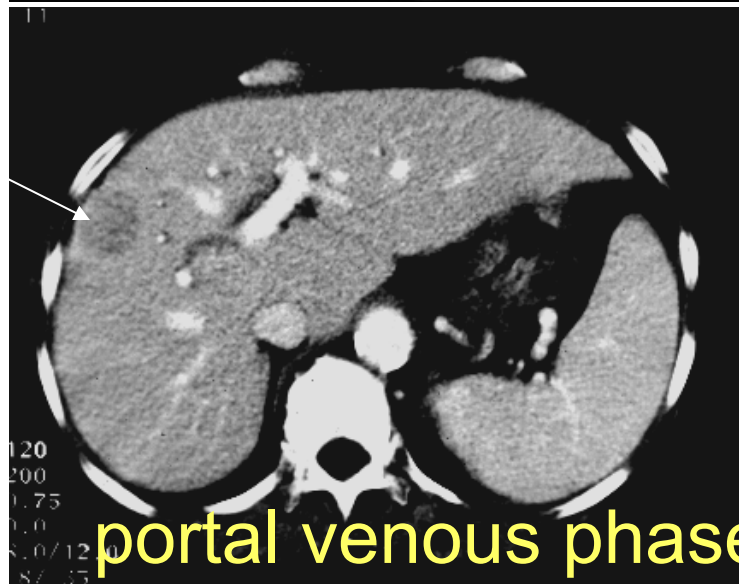
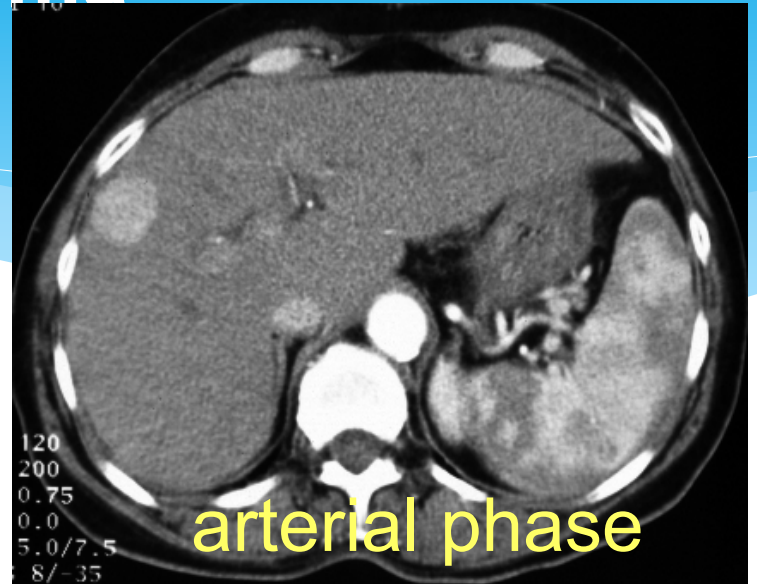
# HCC and AFP in Alaska Natives with Chronic HCV

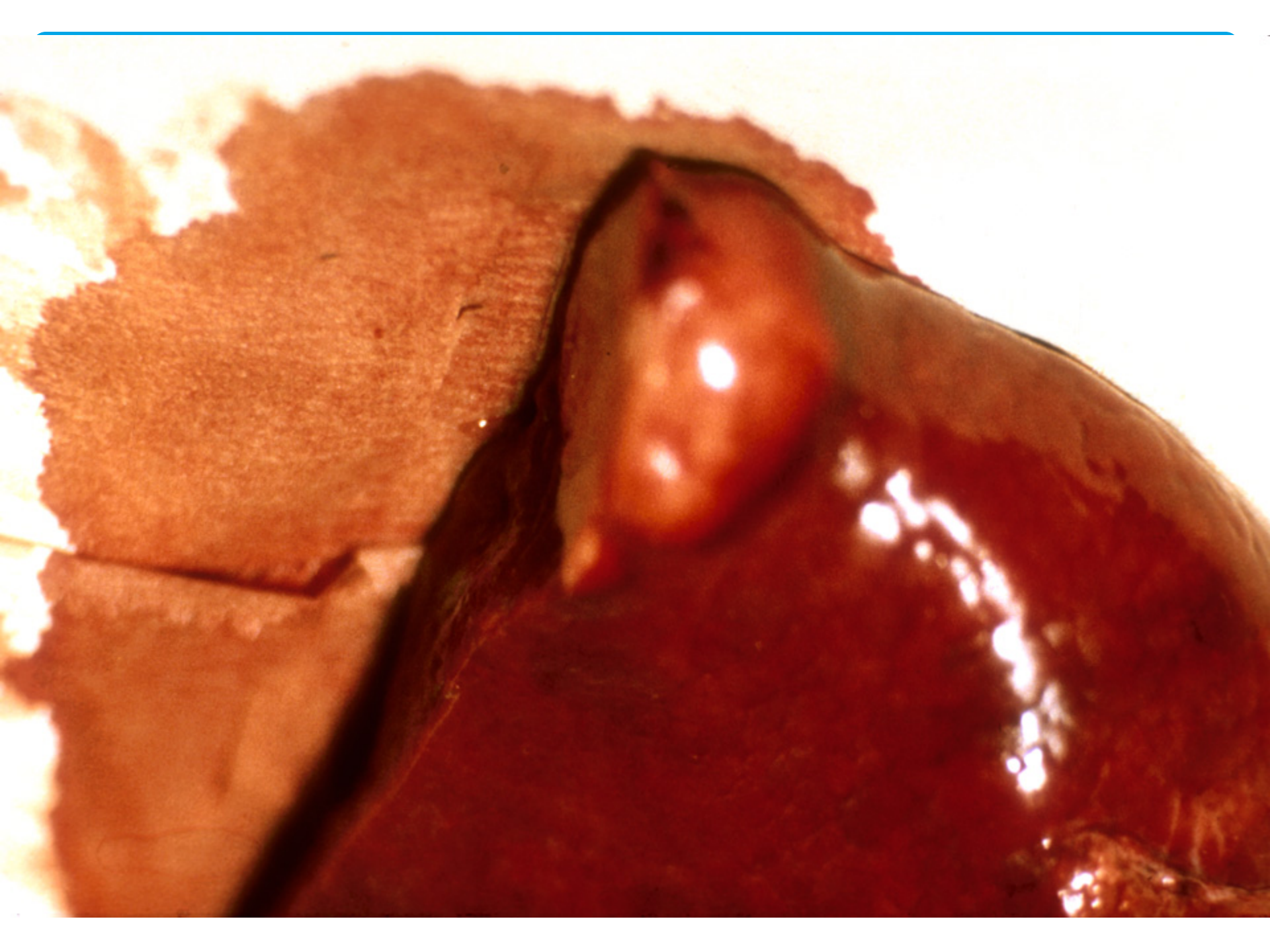
- \* Effectiveness of AFP to use to determine who needs liver ultrasound additionally
  - \* No patient with AFP persistently  $<8\text{ng/ml}$  developed HCC over 6 year period
  - \* AFP  $\geq 8\text{mg/ml}$  had a 39% sensitivity and 95% specificity of detecting advanced fibrosis (Ishak 3-6 = bridging fibrosis or cirrhosis)
  - \* Persons with ESLD or HCC had 158 times the odds of having AFP  $>8\text{ng/ml}$  (95%CI 37-691)

# Diagnosis of HCC

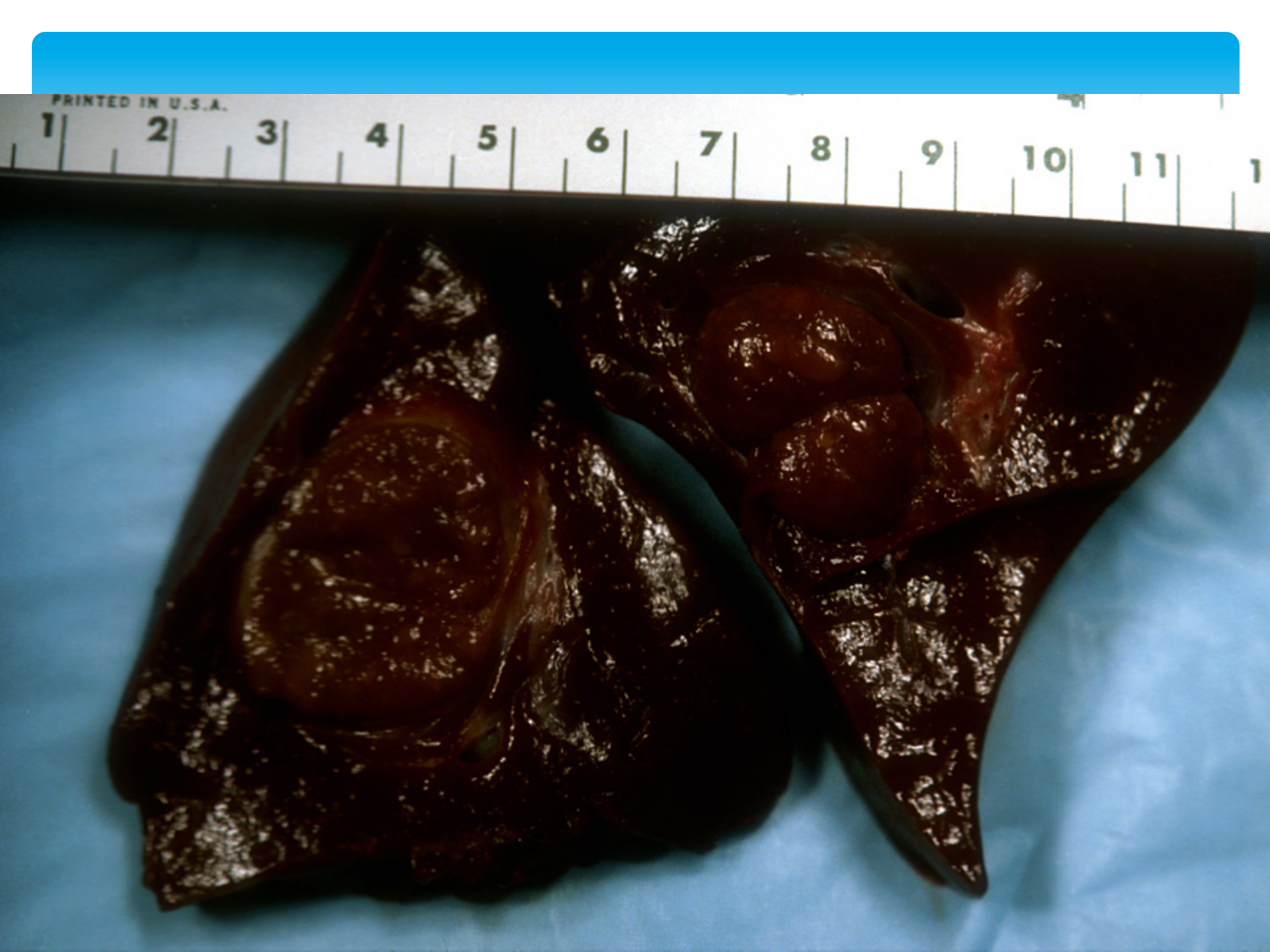
- \* Barcelona Criteria:
  - \* Two imaging studies with compatible lesion
    - \* Hypoechoic lesion on US
    - \* Lesion that lights up on arterial phase of tri-phasic or Quadra-phasic CT
      - \* Don't order non-contrast/contrast CT for HCC: you'll miss many small lesions
    - \* Compatible lesion on MRI with Gadolinium
  - \* One compatible image plus an AFP >400 mg/ml

# Quadra-Phasic CT for Hepatocellular Carcinoma

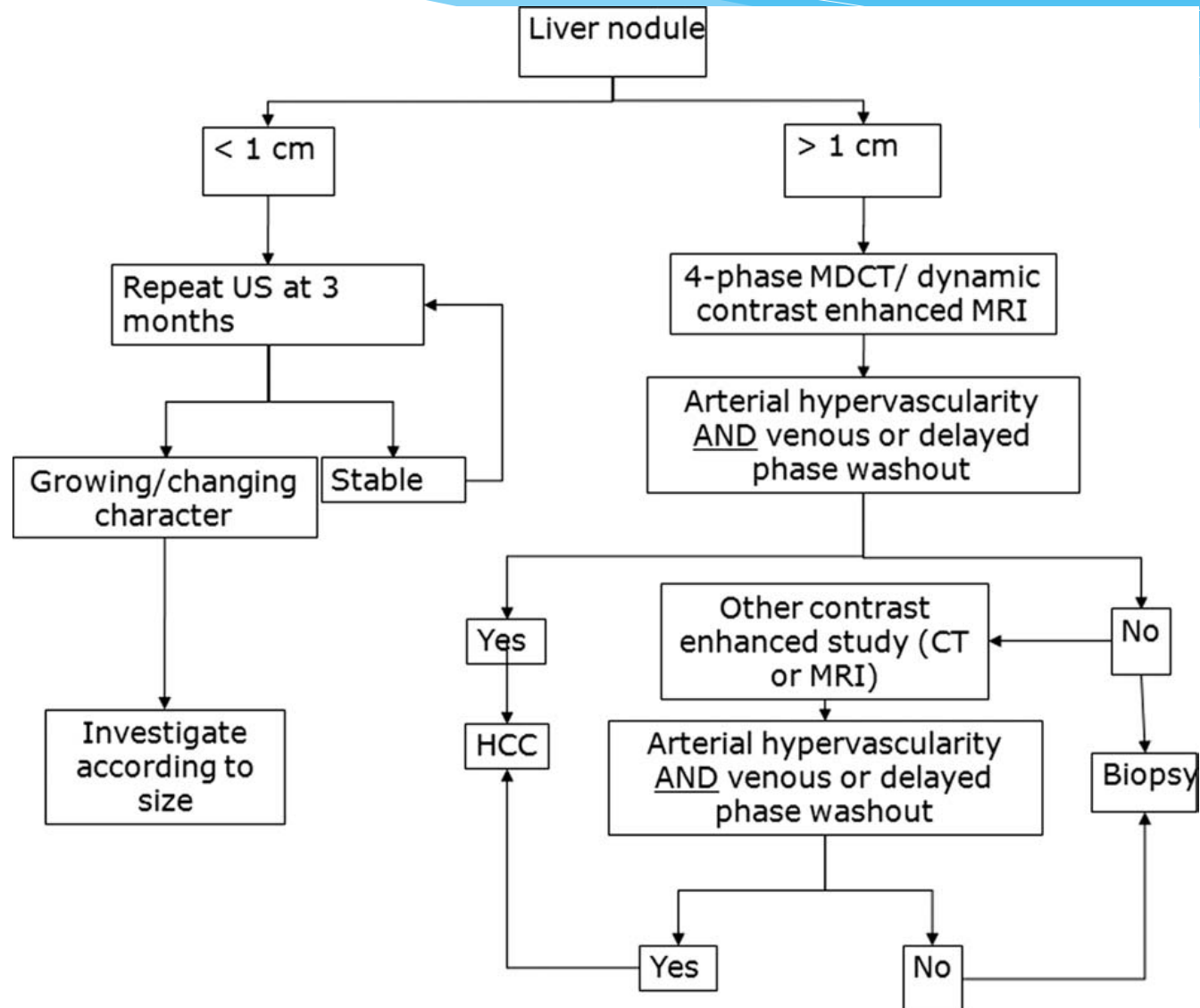




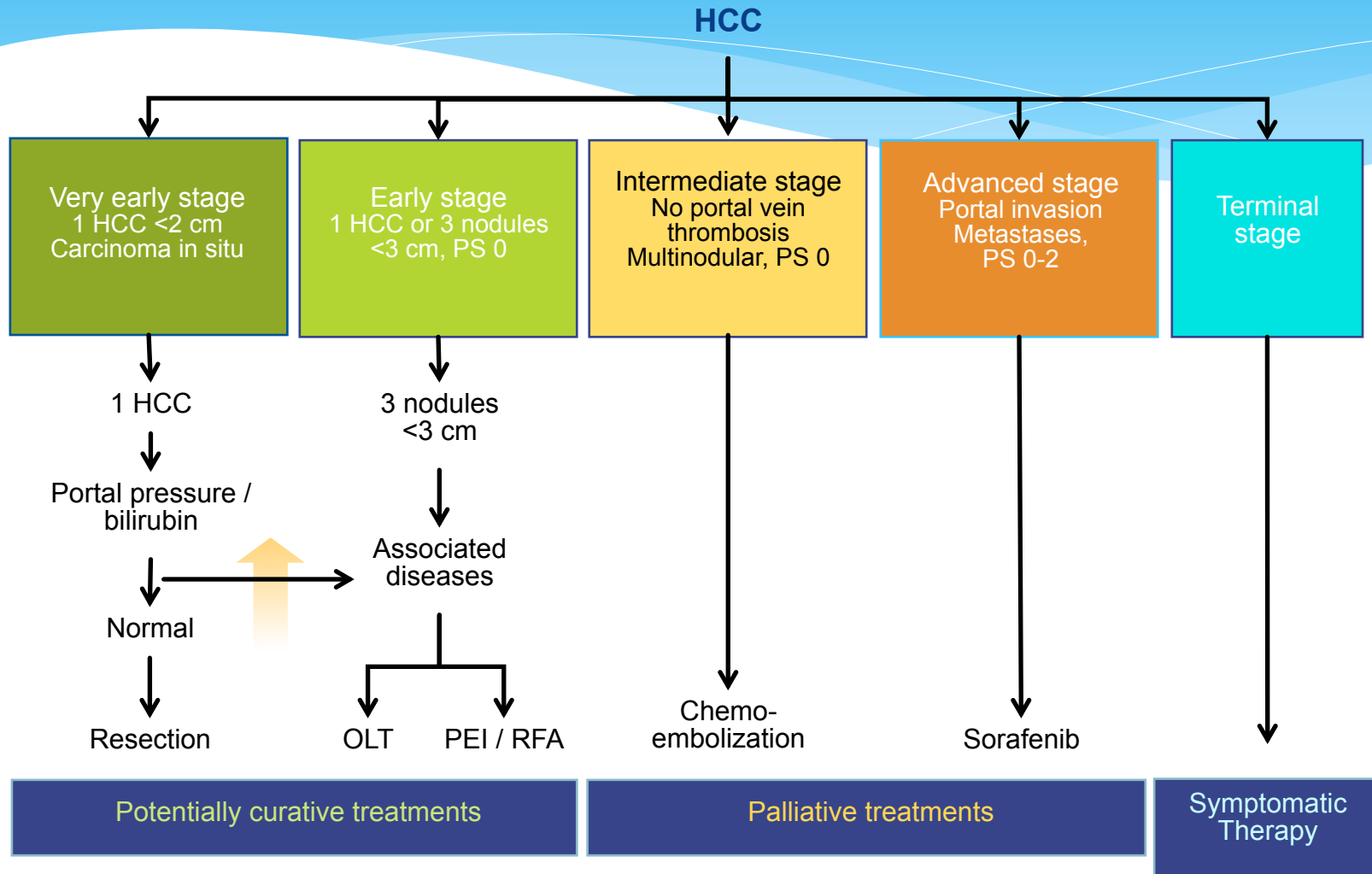




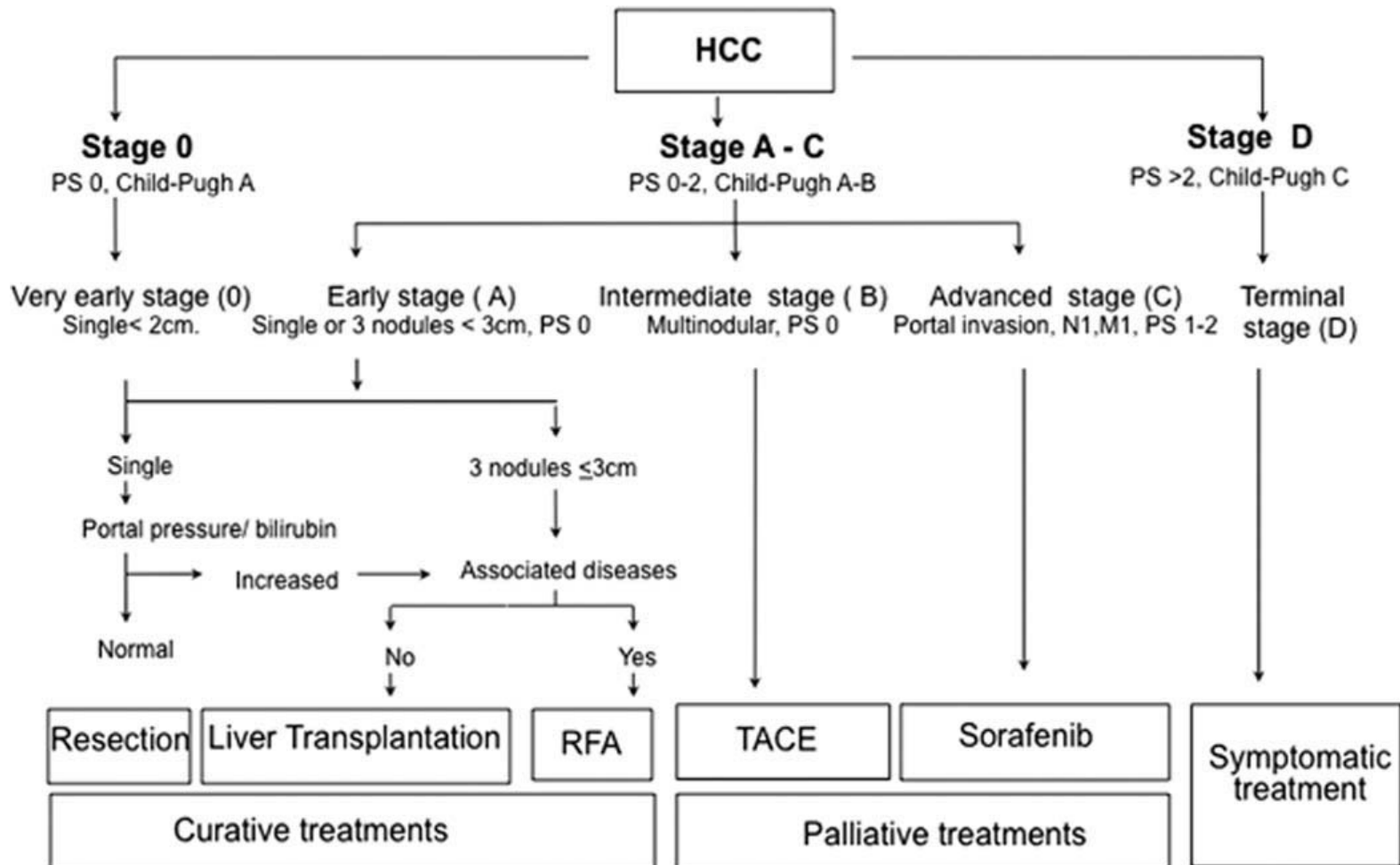
# Diagnostic algorithm for suspected HCC.



# Hepatocellular Carcinoma: Treatment



# The BCLC staging system for HCC



# RFA electrode



# RFA generator



# Hepatocellular Carcinoma: Treatment

## Randomized Trial of RFA versus Resection for Very Early HCC

- \* Study Groups: RFA = 71; Resection = 90
- \* No difference among groups in terms of liver function, performance status and tumor burden (all < 3 cm)
- \* No difference in overall survival
- \* RFA had less morbidity and complications

# Hepatocellular Carcinoma: Treatment

## Transplantation (LT)

- \* Curative for HCC and chronic liver disease
- \* MELD exception points for HCC
- \* Live donor LT considered for HCC progression outside MILAN criteria
- \* UCSF criteria not implemented in current MELD exception allocation policy

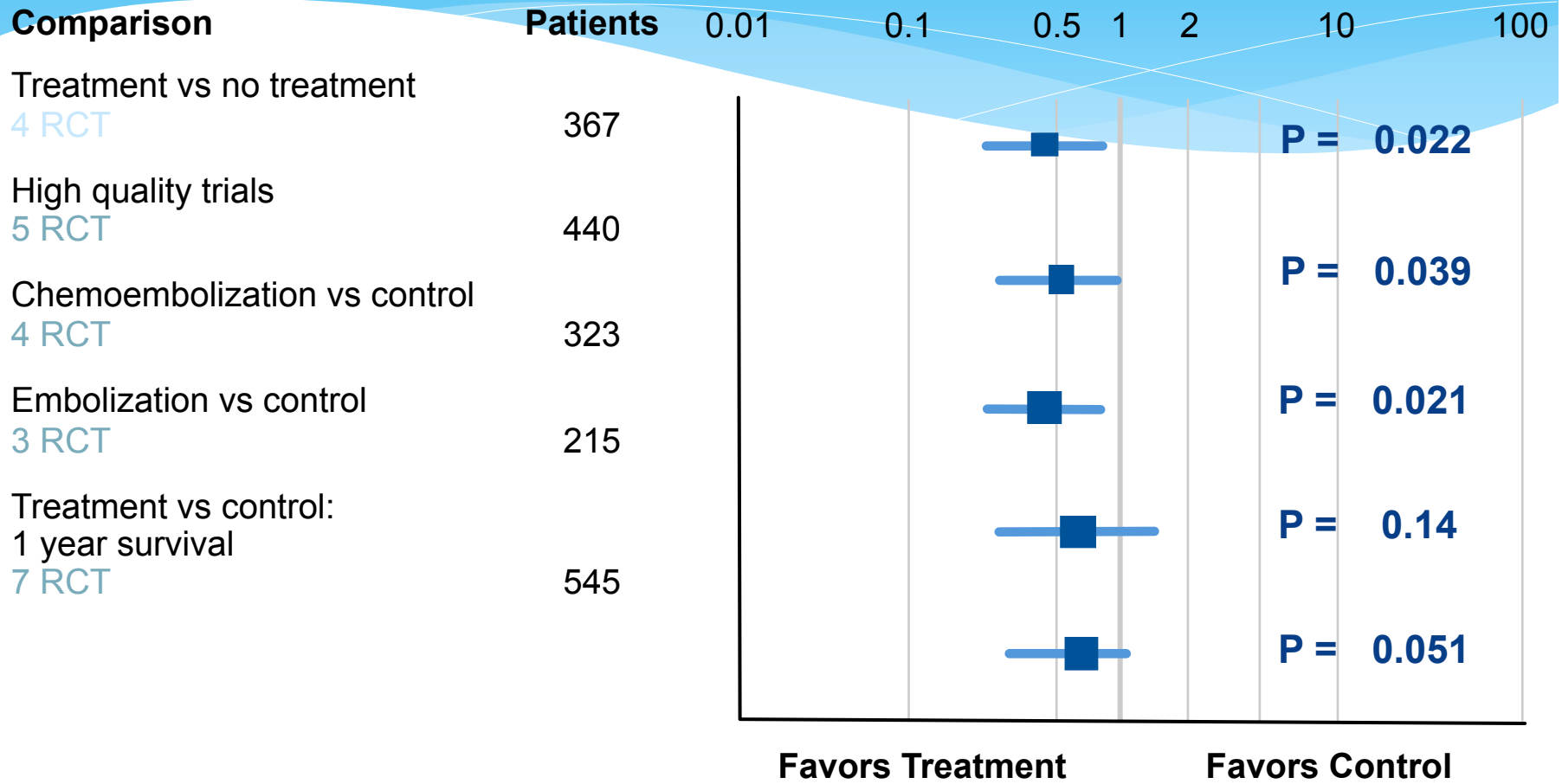
## Survival

1 year	91%
2 year	75%
5 year Milan	>70%
5 year (extended)	~50%

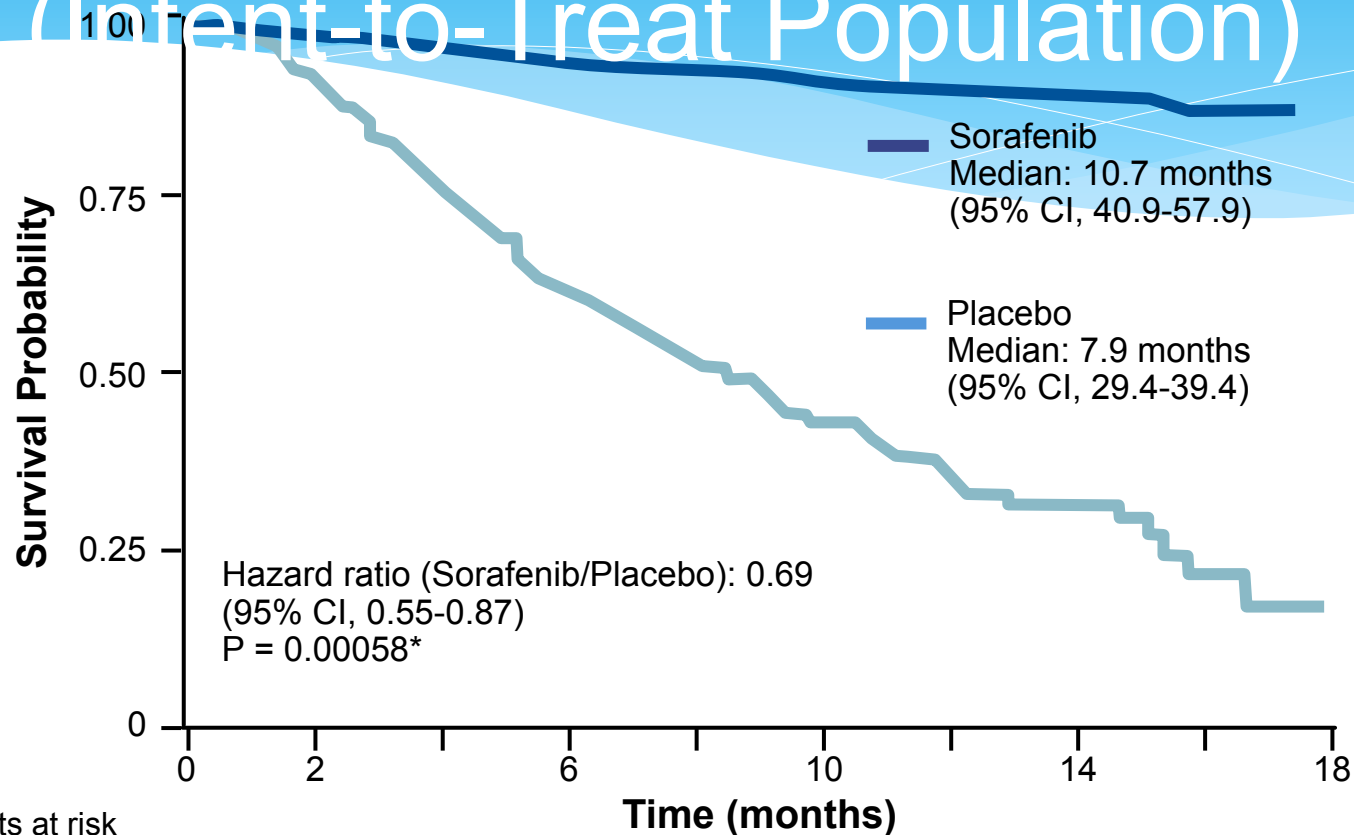


# Sensitivity Meta-Analysis of Core RCTs Reporting

1 or 2-year Survival with Cemoembolization / Embolization: Various Treatment Comparisons



# Phase III SHARP Trial: Overall Survival (Intent-to-Treat Population)



Patients at risk

Sorafenib:

299    274    241    205    161    108    67    38    12    0

Placebo:

303    276    224    179    126    78    47    25    7    2

\*O'Brien-Fleming threshold for statistical significance was  $P = 0.0077$ ; CI=confidence interval

# Problems with Sorafenib

- \* Survival benefit: <3.5 months
- \* Cost: > \$70,000
- \* Side effects: Many patients can't tolerate; can result in poor quality of life for remainder of time patient has, especially if it doesn't work
- \* While it is on our formulary, our oncologists and our Hepatology service have stopped using it as every patient treated asked to stop

# Conclusions

- \* Incidence of HCC is rising in US
  - \* Etiologies of HCC have changed in last 20 yrs.
- \* New risk factors for HCC in HBV have been identified
- \* Surveillance for HCC in HBV with AFP alone is effective 1<sup>st</sup> step in detection but US should also be used if available
- \* AFP is also a surrogate marker for advanced fibrosis in HCV
- \* Better serologic screening tests for HCC are needed

# LiverConnect Videoteleconference

- 1<sup>st</sup> Tuesdays, 8-9am Alaska Standard Time
- Case study presentations from rural providers
- CEUs (1.0 for each session)
- Contact Ebba Paniptchuk to join: +1 907-729-1560
- Questions: Email [liverconnect@anthc.org](mailto:liverconnect@anthc.org) or contact Julia Plotnik, RN +1 907-729-1581 or Jim Gove, RN +1 907-729-1568

# Liver Disease/Hepatitis Program Website

<http://www.anthctoday.org/community/hep/index.html>

- Initial Funding from Government
- Reviewed quarterly by our advisory group of indigenous patients living with HCV
- Contents of Website
  - Patient Information
  - Provider Information
  - Hepatitis C Treatment
  - Publications
  - LiverConnect – Past presentations
  - The website is constantly updated as new treatments