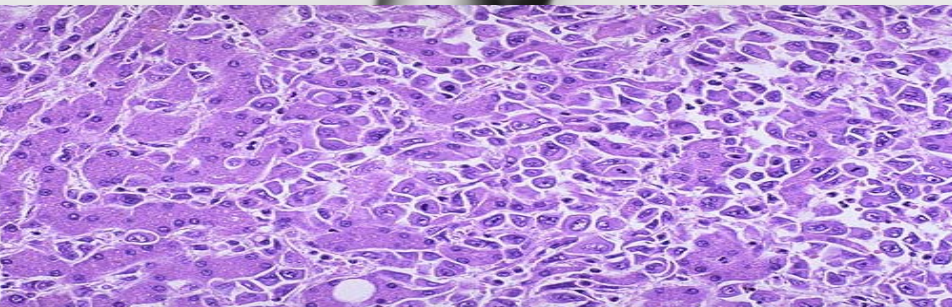
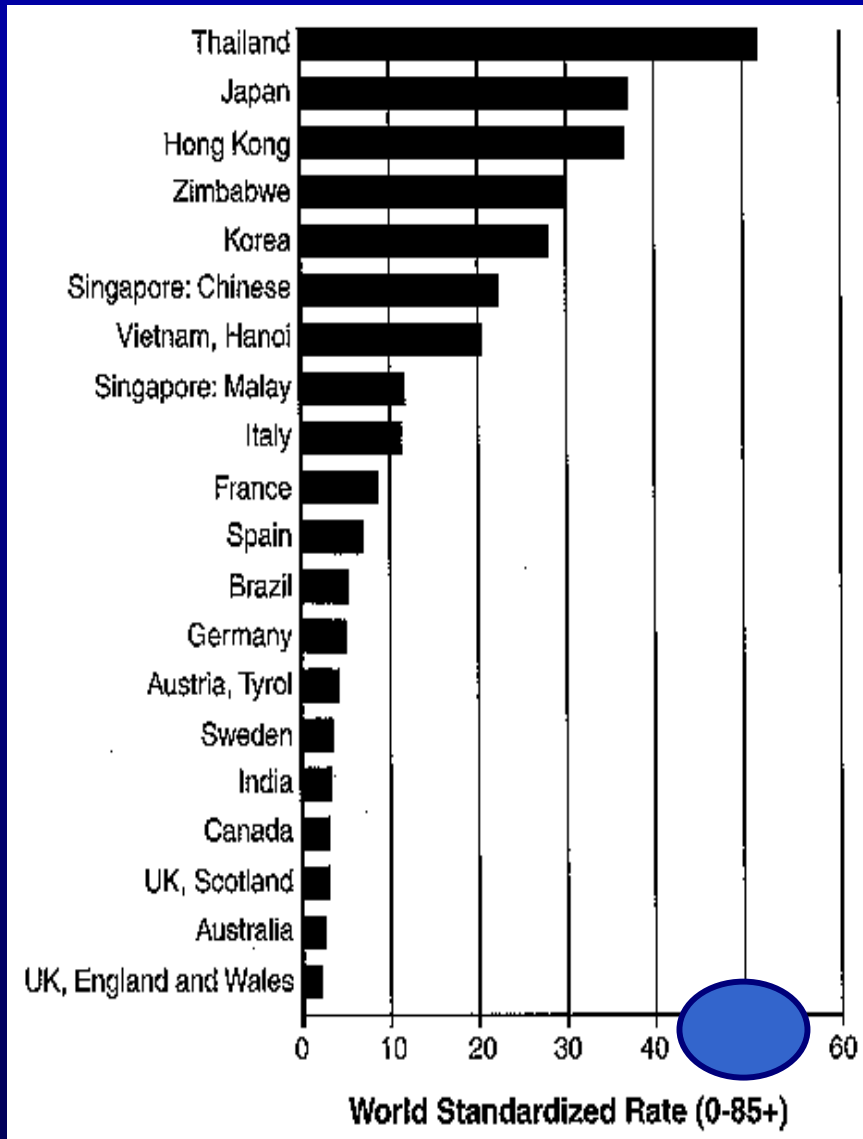




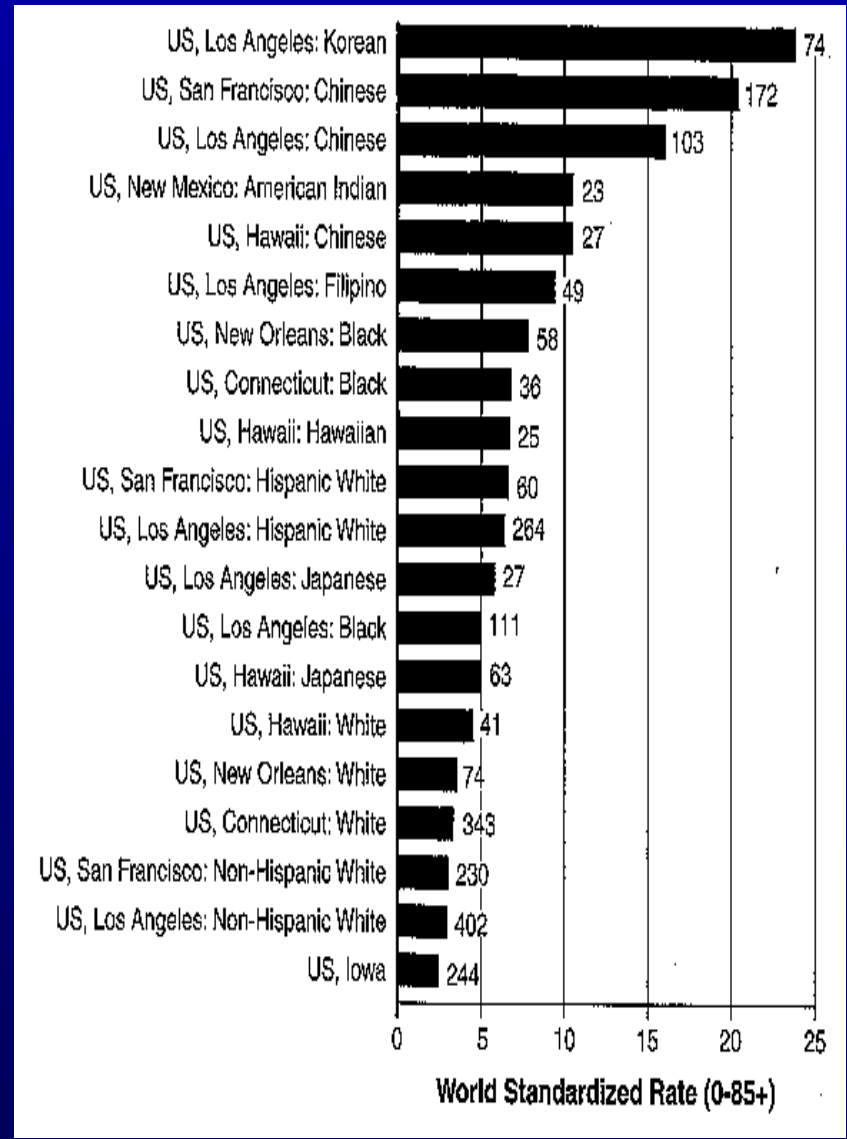
A



# Worldwide



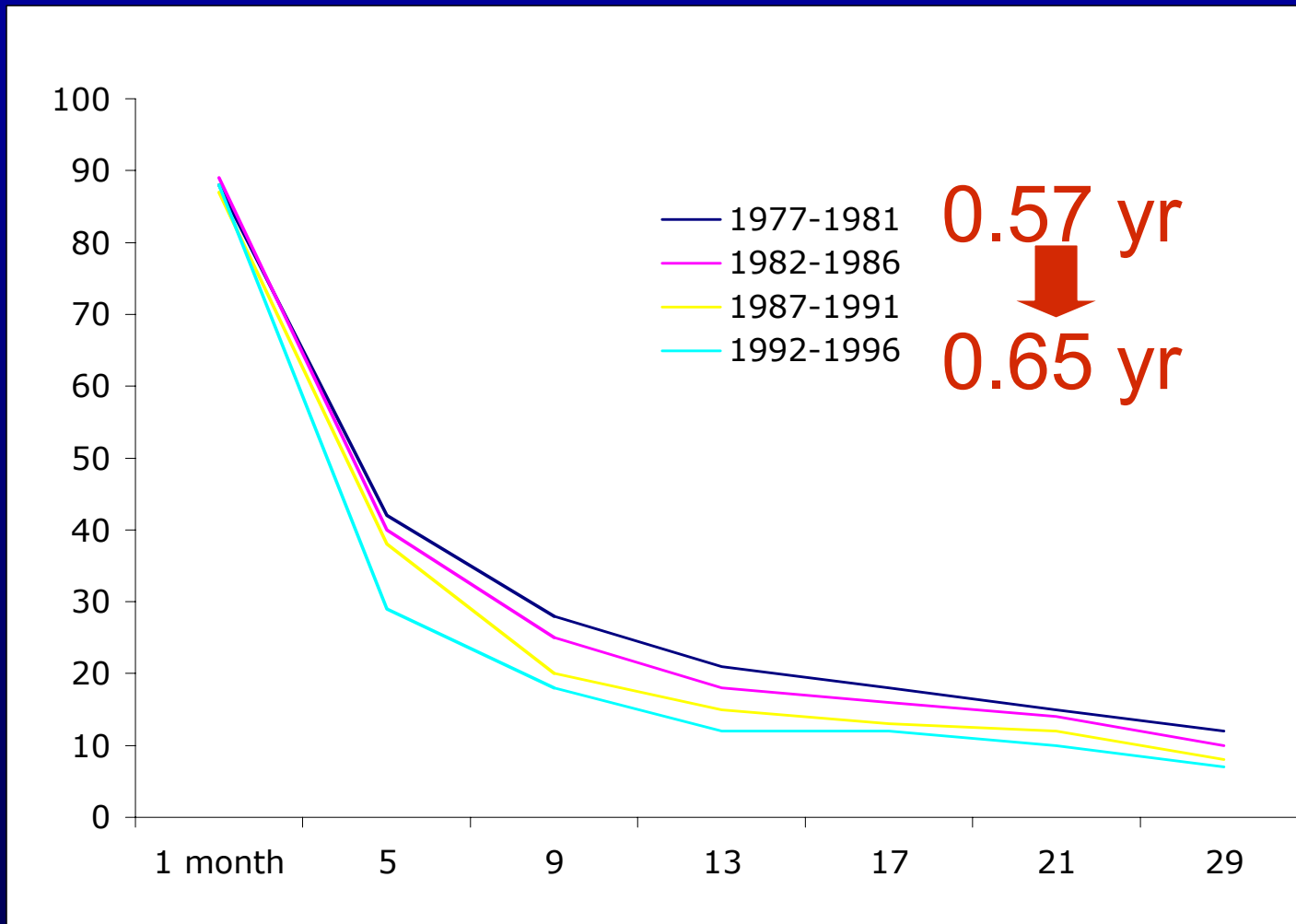
# United States



# Clinical Presentation

- Encephalopathy, SBP, hepatorenal
- Finger Stick: 5
- Hematocrit: 42
- Blood Pressure: 160/100

# Poor Median Survival



# Topics

- What are the important risk factors for HCC in the United States?
- Are there pharmacological therapies to prevent HCC?
- Is screening effective?


# Incidence: SEER, VA, NCHS



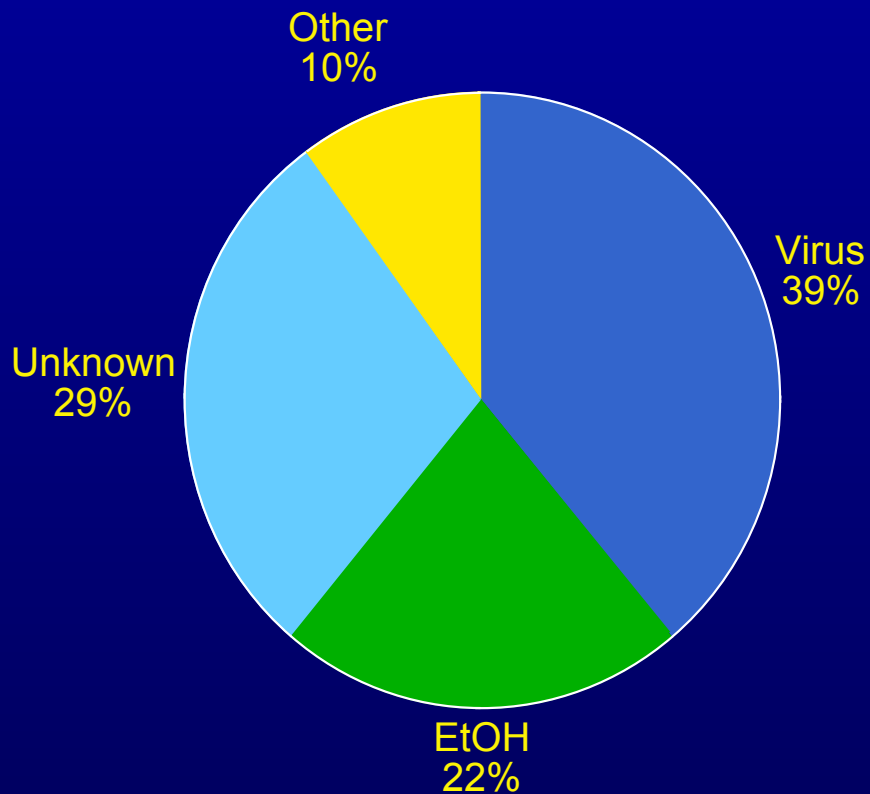
3.0

# HCC Affects Younger Patients

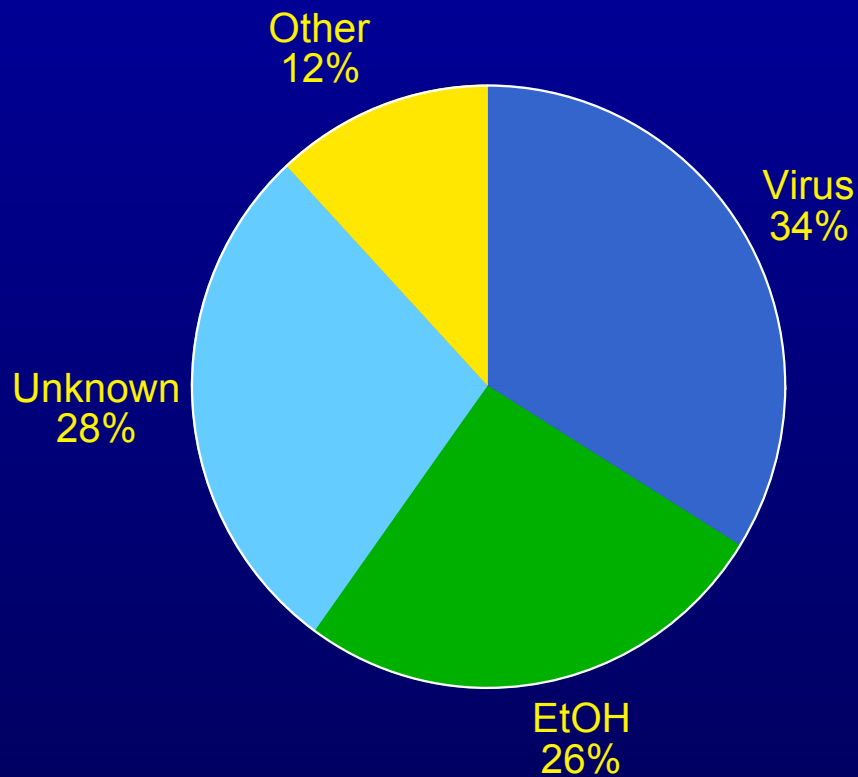
QuickTime™ and a  
TIFF (Uncompressed) decompr  
are needed to see this picture



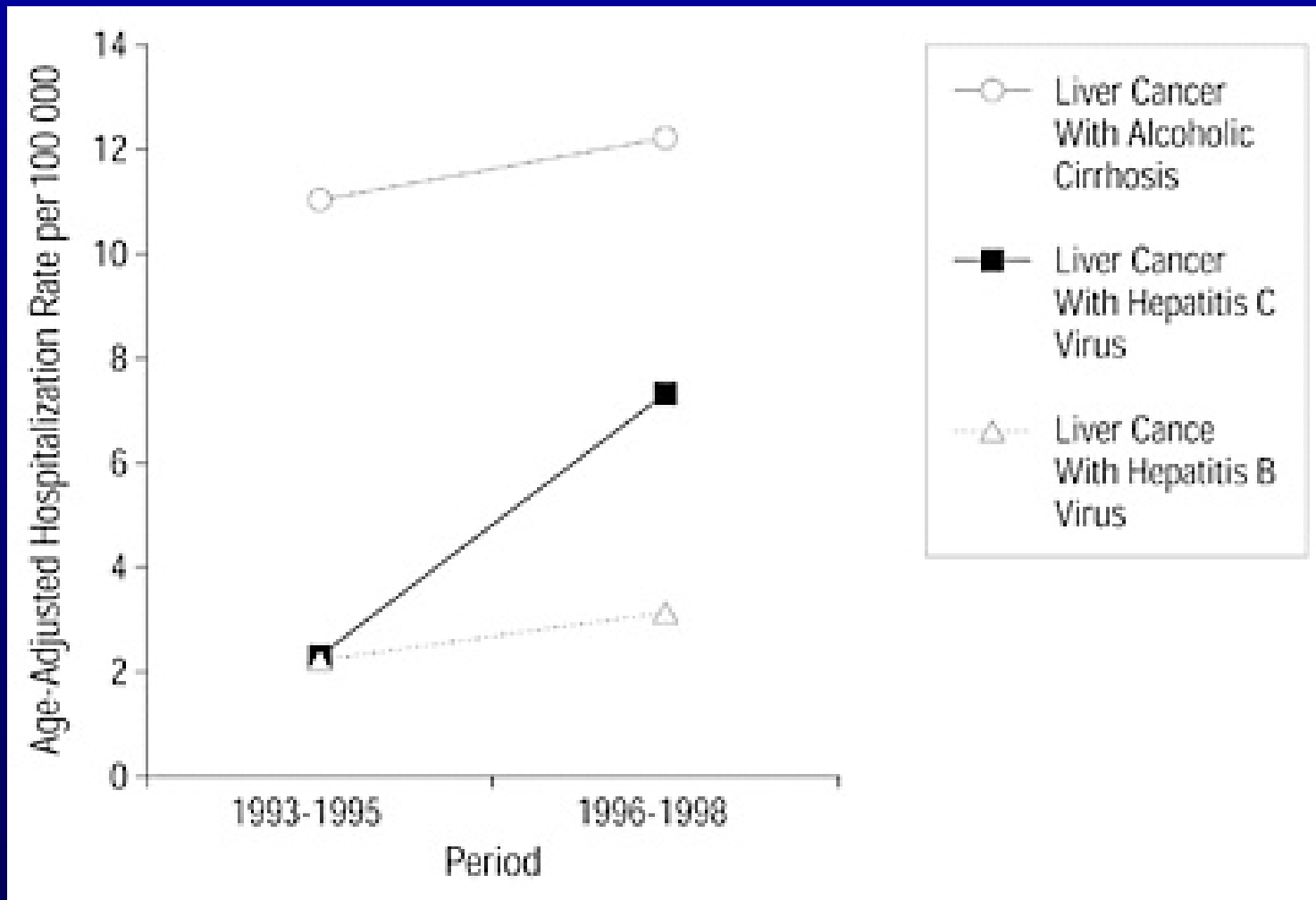
# Michigan



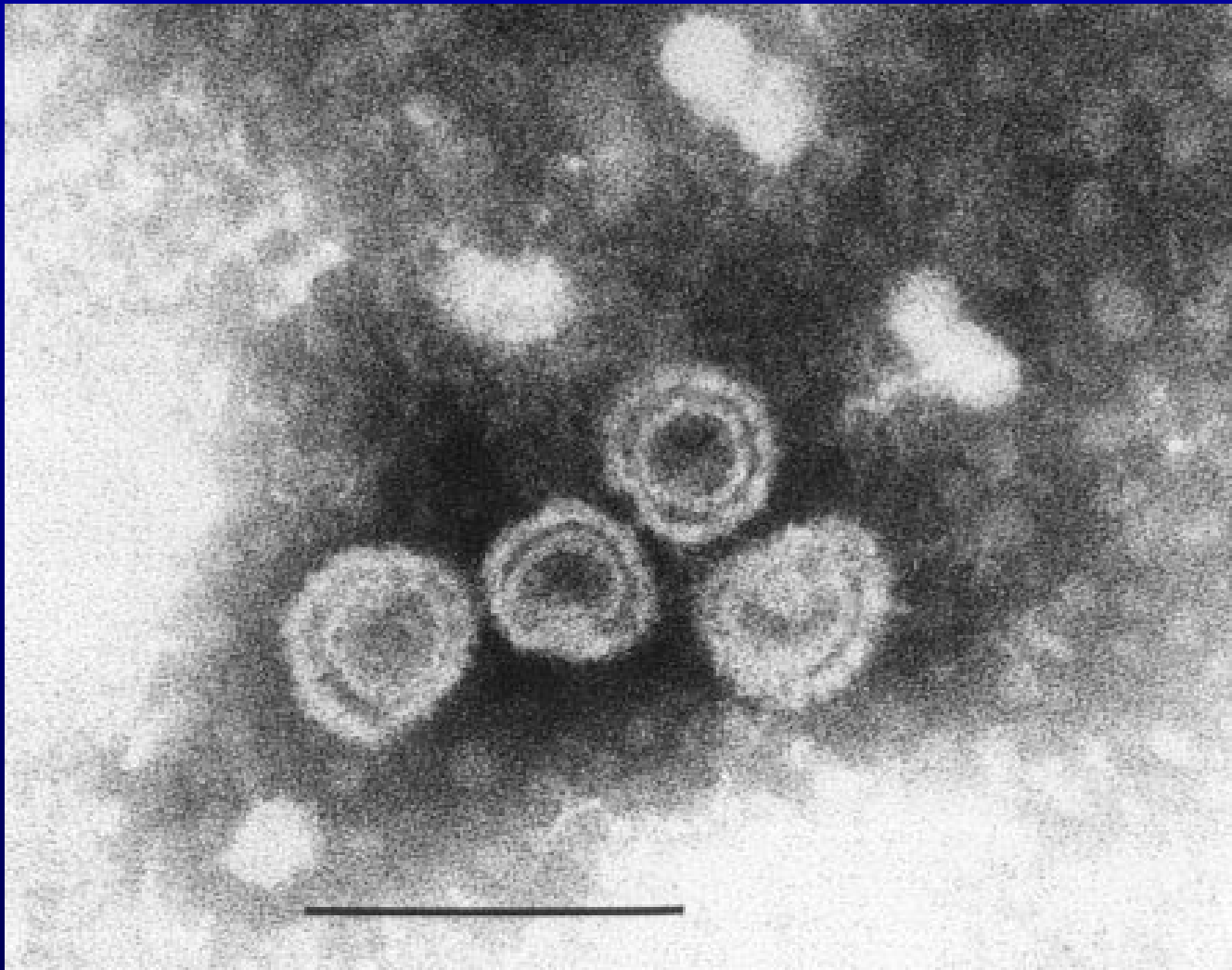
# VA



# HCC: 1993-98 VA-PTF

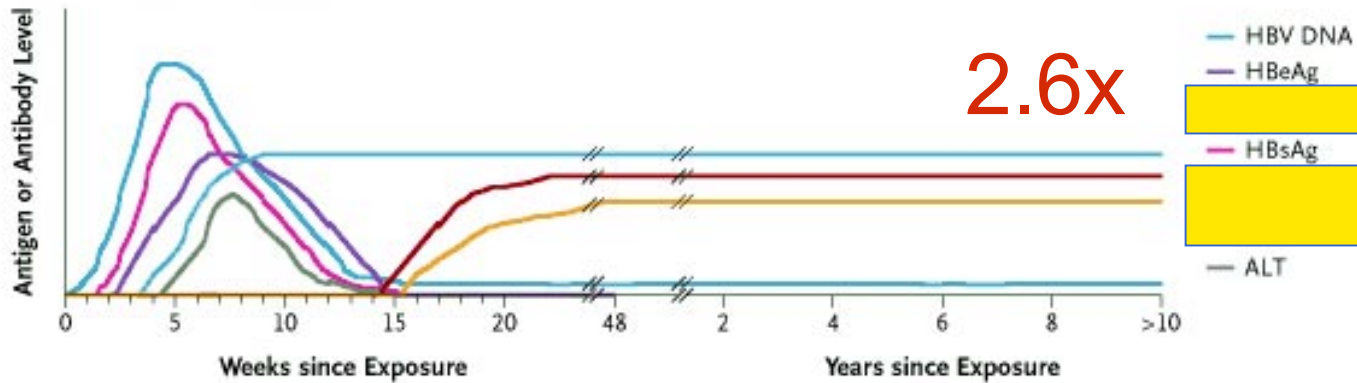


# Hepatitis B Virus (HBV)

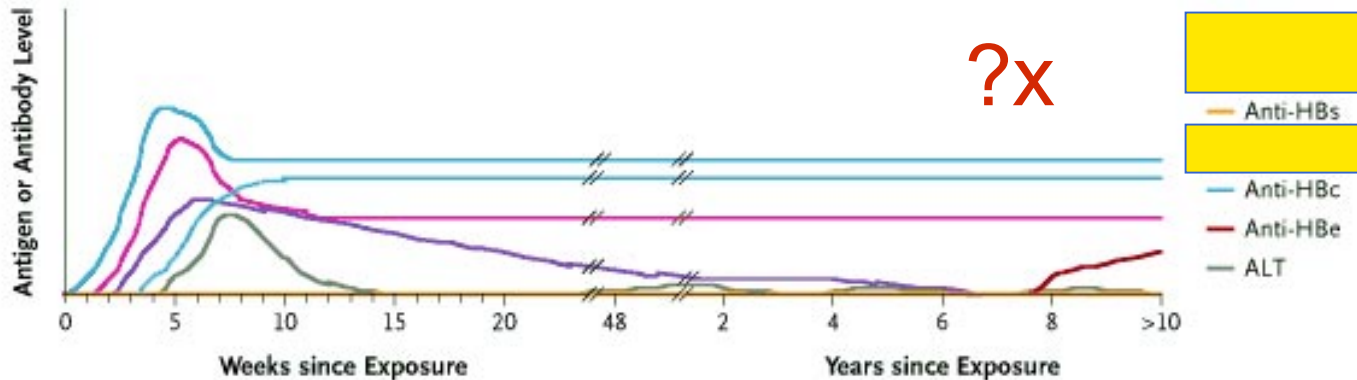


# HBV sAb, cAb, sAg, eAg

A Acute Self-Limited HBV Infection



B Chronic HBV Infection



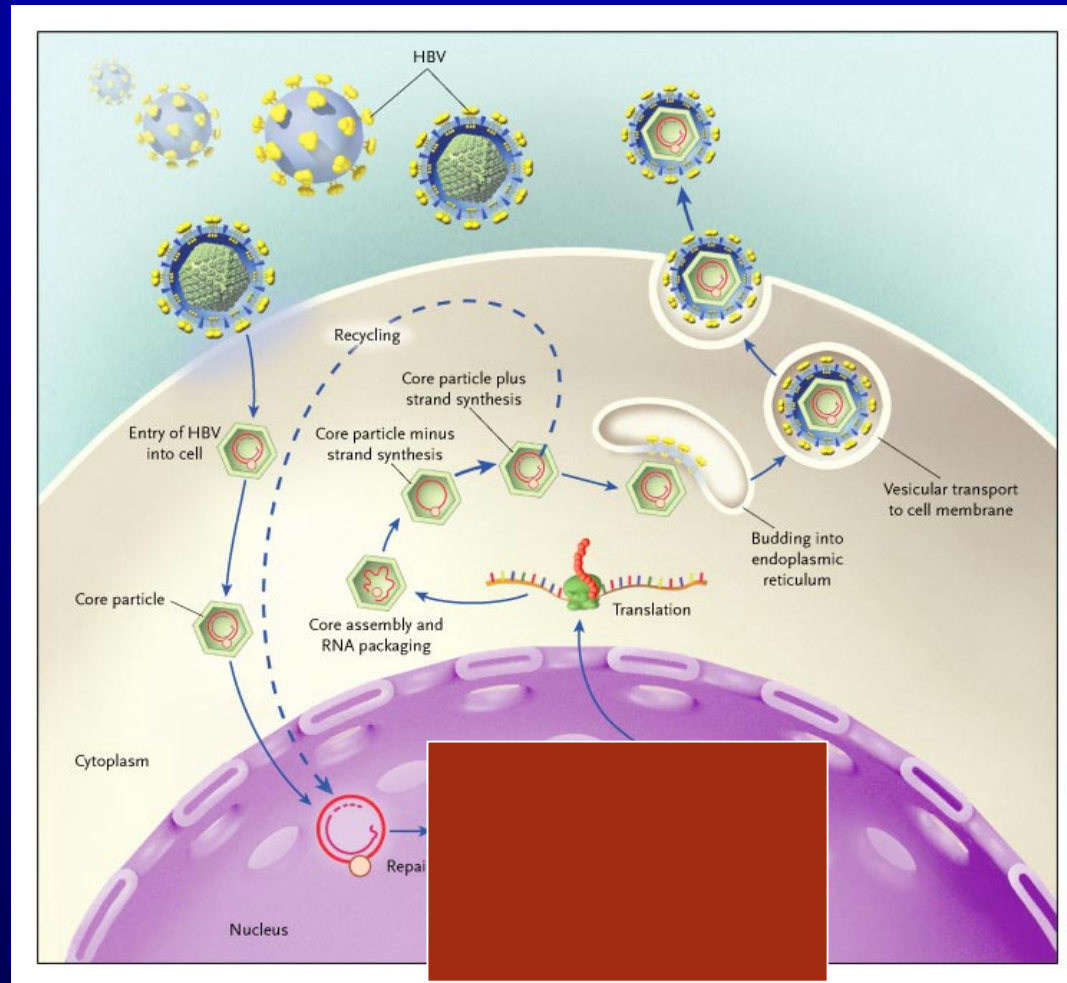
**HBV eAg:** 10,000 patients, followed for 10 years - 60 fold increased risk

60x

QuickTime™ and a  
TIFF (Uncompressed) decompressor  
are needed to see this picture.

10x

# Non-Cirrhotic HBV Related HCC's: 20%



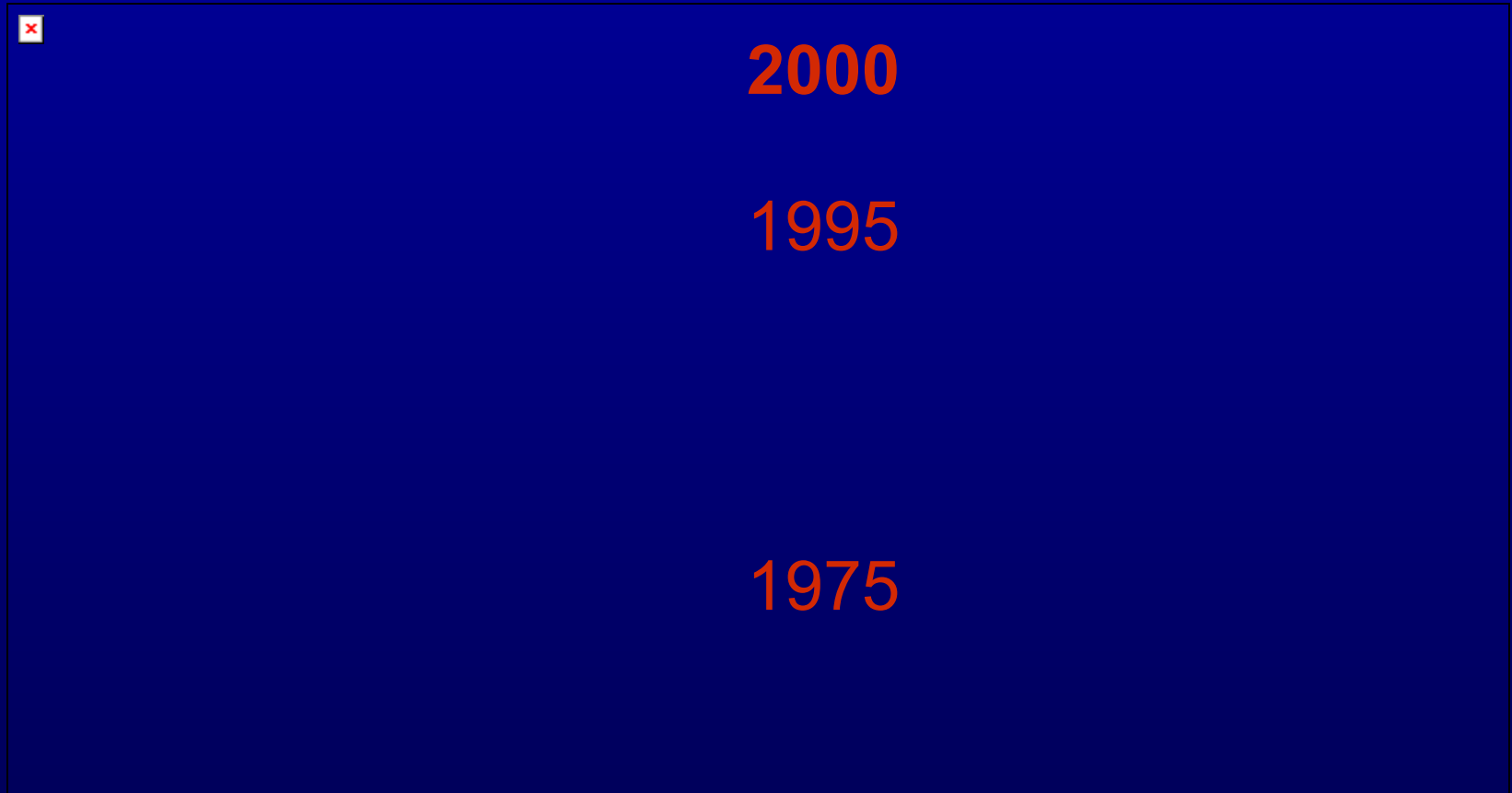
# Hepatitis C (HCV): 1988-1994

**TABLE 2.** PREVALENCE OF ANTIBODY TO HCV (ANTI-HCV) ACCORDING TO AGE AND RACE OR ETHNIC GROUP IN NHANES III.\*

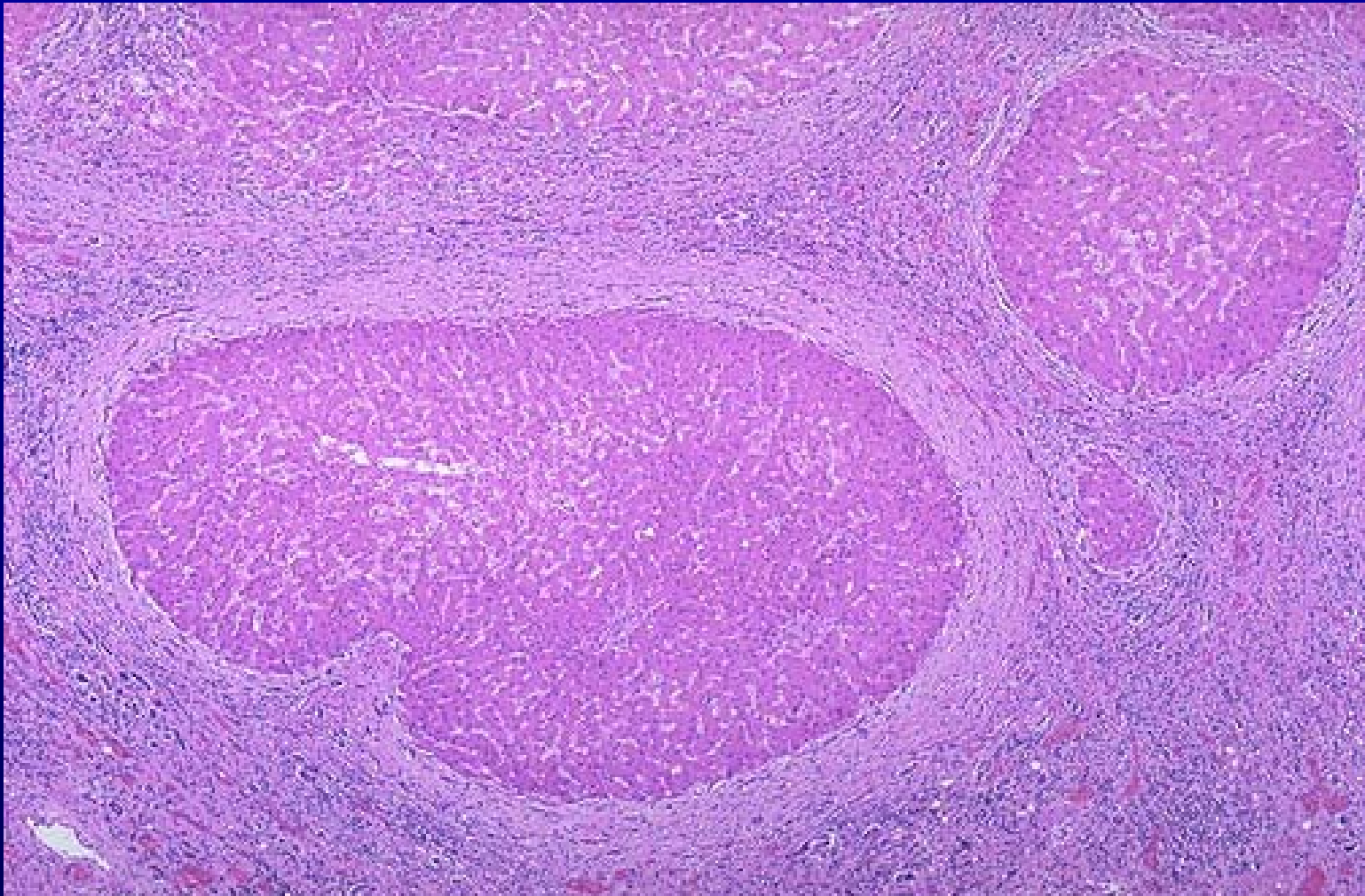
AGE	TOTAL POPULATION		NON-HISPANIC WHITES		NON-HISPANIC BLACKS		MEXICAN AMERICANS	
	NO. TESTED	PREVALENCE OF ANTI-HCV (95% CI)	NO. TESTED	PREVALENCE OF ANTI-HCV (95% CI)	NO. TESTED	PREVALENCE OF ANTI-HCV (95% CI)	NO. TESTED	PREVALENCE OF ANTI-HCV (95% CI)
		%		%		%		%
6-11 yr	2762	0.2 (0.04-0.6)	732	0.2 (0.02-1.2)	895	0.2 (0.1-0.8)	1014	0.4 (0.1-2.8)
12-19 yr	2905	0.4 (0.2-0.9)	746	0.2 (0.02-1.2)	1017	1.2 (0.4-4.0)	995	0.4 (0.1-1.2)
20-29 yr	3275	1.6 (1.0-2.5)	849	1.6 (0.8-2.9)	1029	1.8 (1.1-2.8)	1255	2.0 (1.4-2.8)
50-59 yr	1762	1.4 (1.0-2.1)	865	0.4 (0.1-1.0)	447	3.6 (2.2-6.1)	357	6.0 (3.4-10.4)
60-69 yr	2194	0.9 (0.5-1.7)	952	0.7 (0.3-1.9)	527	2.5 (1.8-3.4)	638	1.5 (0.7-3.4)
≥70 yr	2768	1.0 (0.7-1.4)	1945	0.9 (0.6-1.2)	412	2.8 (1.4-5.4)	339	0.2 (0.1-1.0)

\*NHANES III denotes the third National Health and Nutrition Examination Survey, and CI confidence interval. Totals include subjects whose race or ethnic group was "other."

# HCV: From Cirrhosis to HCC



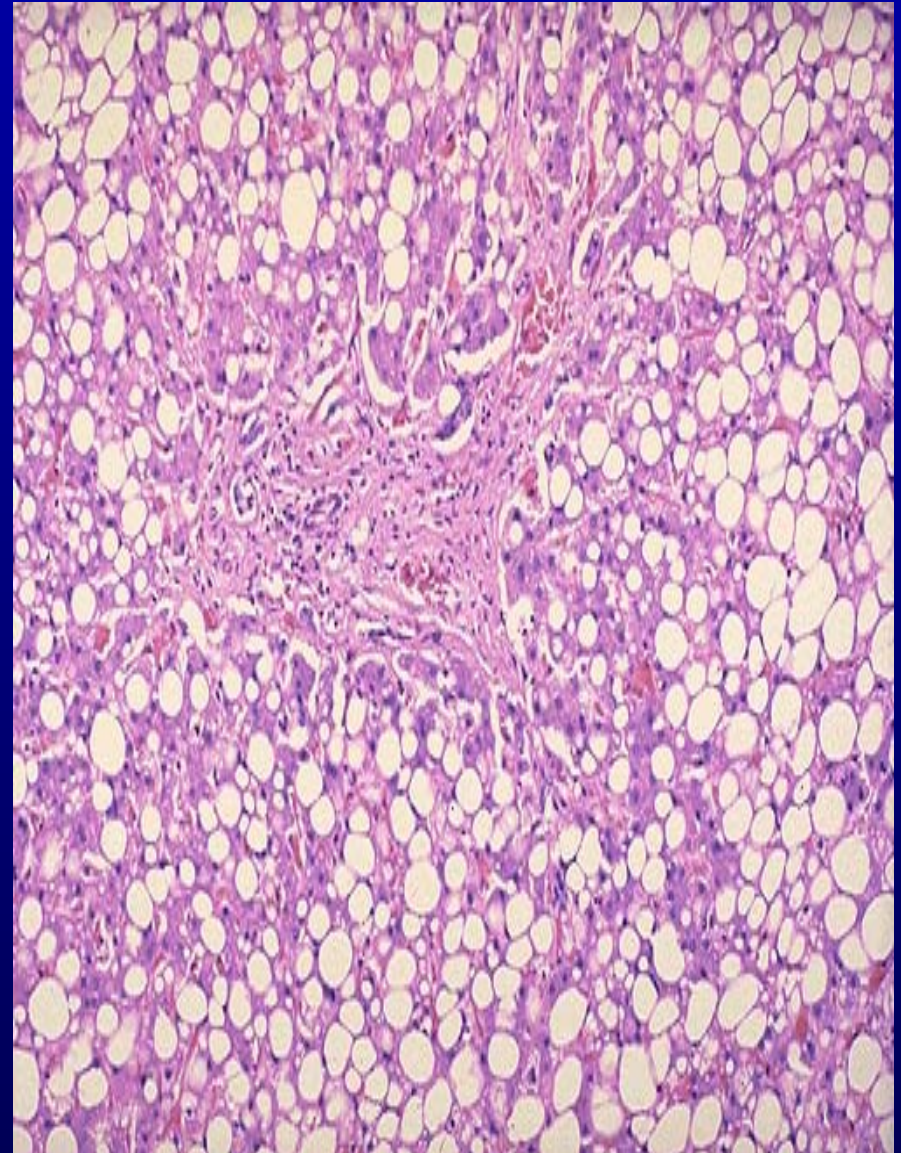
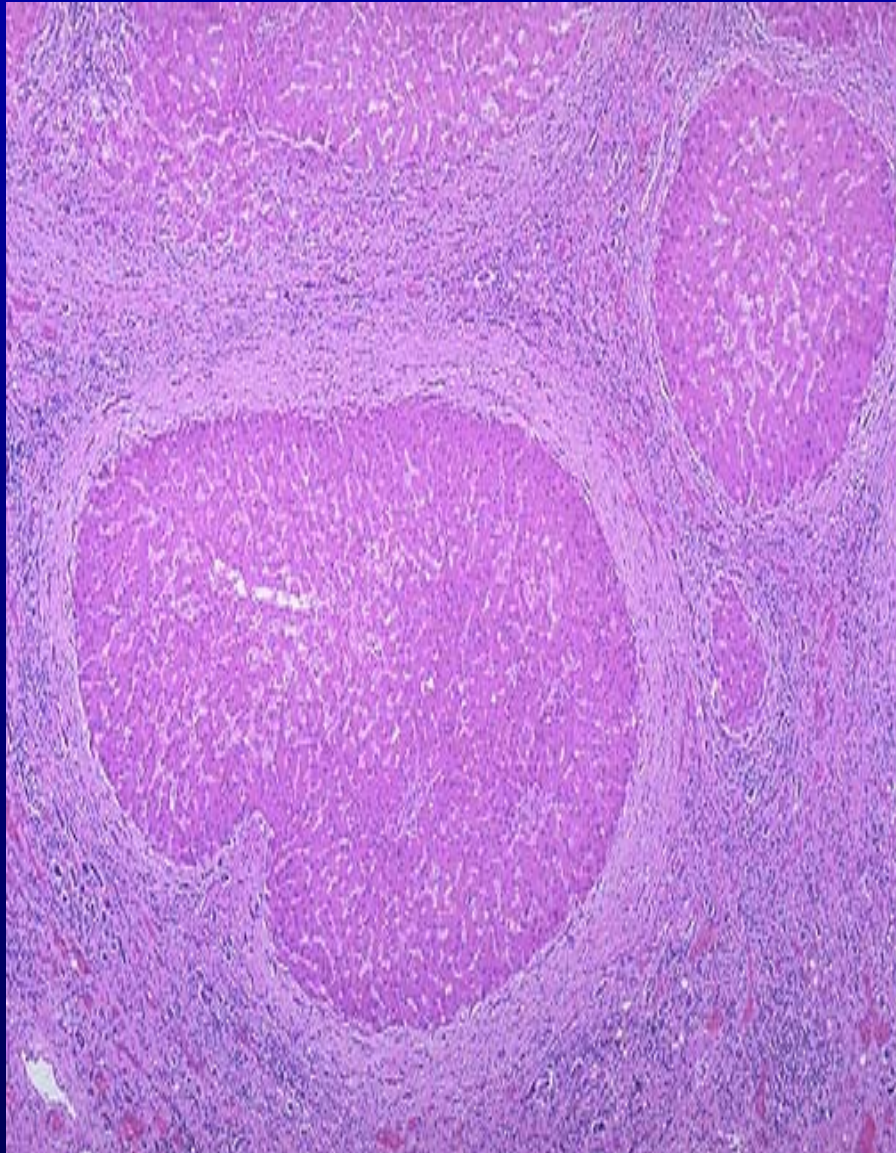
# Cryptogenic Cirrhosis (CC)?



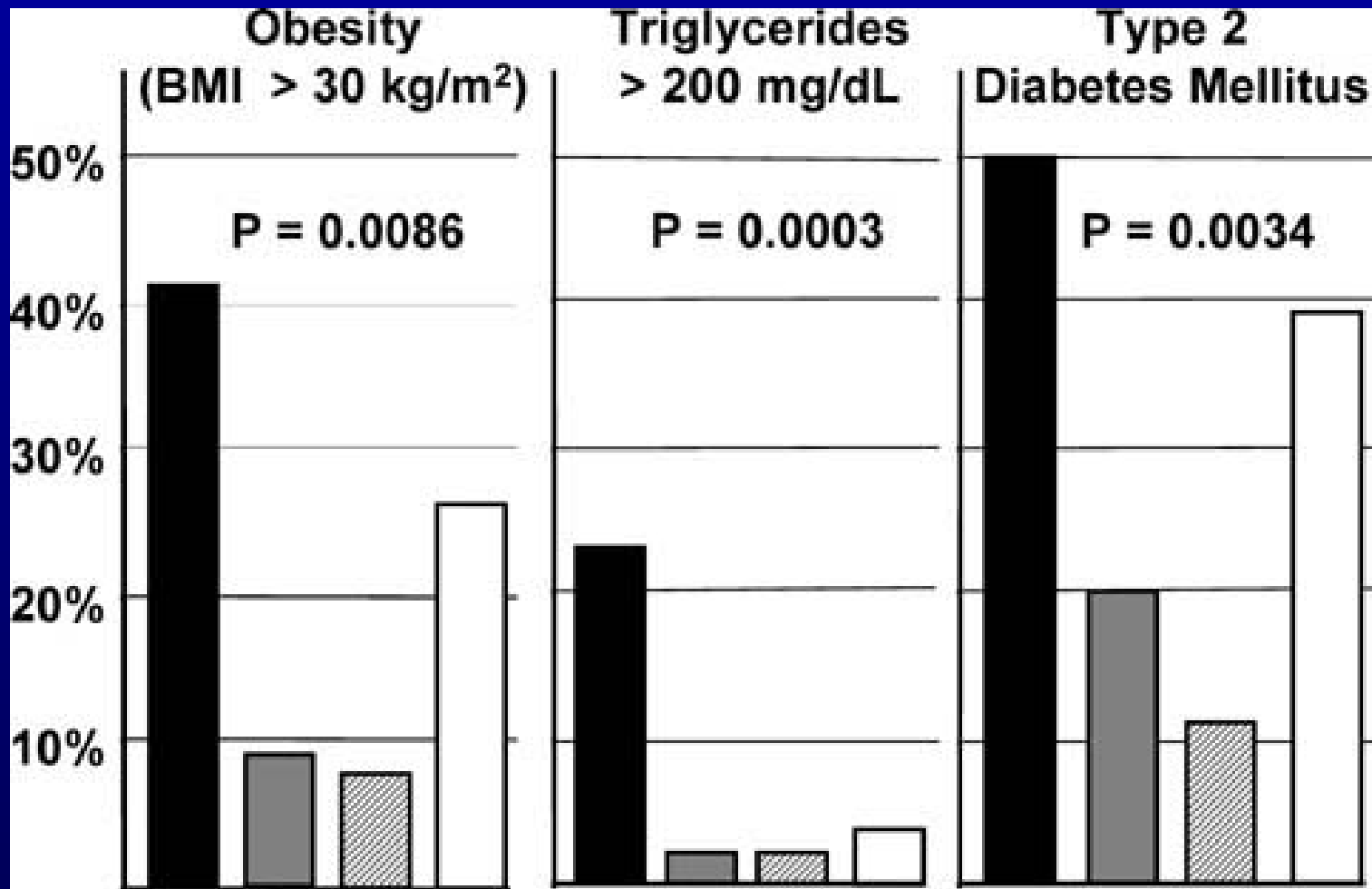
Cryptogenic Cirrhosis

≈

NAFLD/NASH

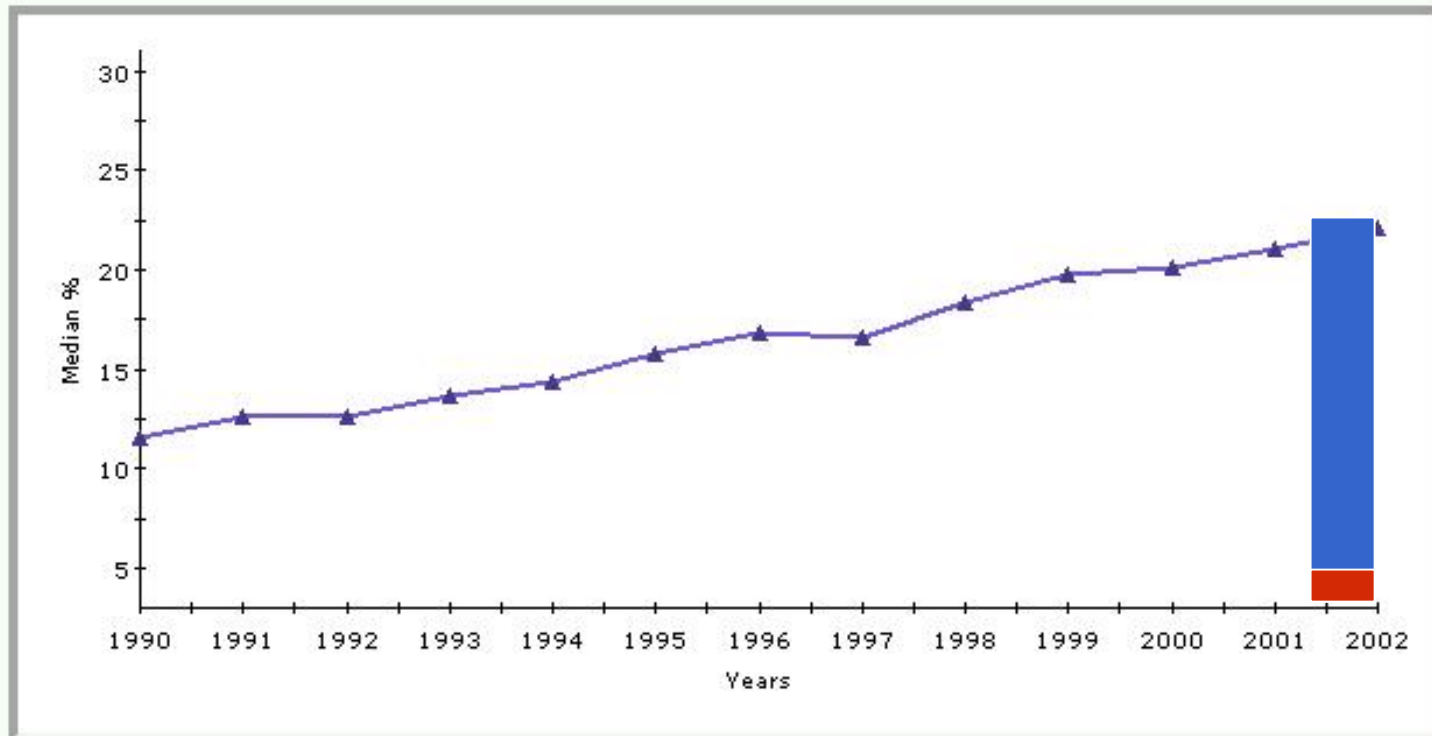


# Indirect Evidence



# The Obesity Epidemic

Obesity: By Body Mass Index  
Nationwide



# CC ≈ Occult Viral Hepatitis

- 1999 Occult hepatitis B virus infection in patients with chronic HCV. N Engl J Med 1999;341:22-26.**
- 2004 Hepatitis B maintains its pro-oncogenic properties in the case of occult hepatitis B. Gastroenterology 2004;126: 102-110.**
- 2004 Occult hepatitis C infection in patients in whom etiology of persistent elevated liver function tests is unknown. J Inf Diseases 2004;189:7-14.**

# Other Risk Factors

- Alcohol: BAD with concurrent virus
- Iron: hemachromatosis
- Aflatoxin: 3x

Virus, NASH, EtOH, Aflatoxin, Iron, etc.



# HBV Treatment

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	Interferon (12-24 weeks)	Lamivudine (52 weeks)
Mechanism	Immune modulation	Incorporating into DNA
Loss of eAg	33% vs. 12%	20% vs. 10%
L-T F/U on HCC	?	?

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# Interferon on HCC

- (-) 2001 Interferon: Yuen. *Hepatology* – 5/208  
developed HCC vs. 0/203  
developed HCC, 9 year follow-up.
- (+) 2004 Interferon: Janssen. *Hepatology* –  
2/54 r developed HCC vs. 6/111  
nders, 8.8 year follow-up.

# Lamivudine on HCC

- (+) 2003 Lamivudine: Liaw. *Hepatology*. 651 patients, double blind randomization, 4% on lamivudine developed HCC vs. 7% on placebo (p = 0.047). Early termination.

# HBV Treatment on HCC

	Interferon (12-24 weeks)	Lamivudine (52 weeks)
Mechanism	Immune modulation	Incorporating into DNA chain
Loss of eAg	33% vs. 12%	20% vs. 10%
L-T F/U on HCC	+/-	1+

# HCV: 1995 - 90 Patients Randomized, 4.4 Yr Follow-up

17/45

QuickTime™ and a  
TIFF (LZW) decompressor  
are needed to see this picture.

2/45

# Interferon on HCC:

Study	Untreated		Treated	
	HCC / Cases	%	HCC / Cases	%
Nishiguchi, 1995	17 / 45	38	2 / 45	4.4
Mazzella, 1996	9 / 91	9.8	5 / 193	2.6
Fattovich, 1997	16 / 136	12	7 / 193	3.6
Bruno, 1997	16 / 81	20	6 / 82	7.3
Serfaty, 1998	7 / 44	16	4 / 59	6.8
IIHCSG, 1998	48 / 259	18	21 / 232	9
Imai, 1998	7 / 20	35	8 / 32	25
Benegnu, 1998	20 / 77	26	4 / 75	5.3
Niederrau, 1998	13 / 77	17	3 / 64	4.7
Valla, 1999	9 / 49	18	5 / 45	11
Ikeda, 1999	67 / 452	15	29 / 1191	2.4
Yoshida, 1999	32 / 107	30	33 / 230	14
Okanoue, 1999	22 / 55	40	7 / 40	17.5
Gramenzi, 2001	19 / 72	26	6 / 72	8.3
<b>Total</b>	<b>302 / 1565</b>	<b>19</b>	<b>140 / 2553</b>	<b>5.5</b>

# NASH: Early Trials

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	Intervention	n	Effect
Lavine	Vit E	11	Improvement
Abdelmalek	Betaine	10	Improvement
Laurin	Clofibrate	24	Improvement
Caldwell	Troglitazone	10	Improvement
Marchesini	Metformin	20	Improvement

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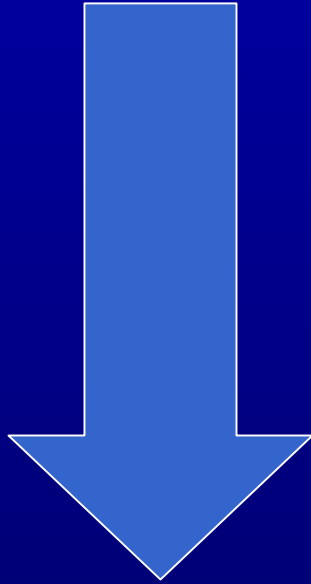
# NASH: Recent Evidence

- Pilot study of pioglitazone, uncontrolled
- 18 non-diabetic biopsy proven NASH
- 30 mg qd for 48 weeks (11 months)
- Histology improvement assessed by less inflammation, injury, and steatosis in 2/3 of patients (  $p < 0.05$  )

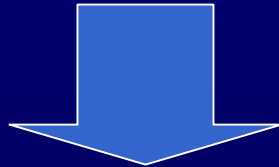
# Others

- Aflatoxin: chlorophyllin, oltipraz
- Hemochromatosis: phlebotomy
- Cox-2 Inhibitors?

Virus, NASH, Aflatoxin, Iron, etc.

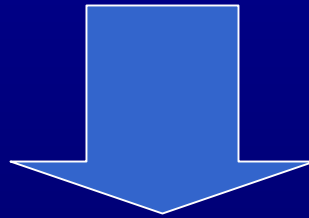
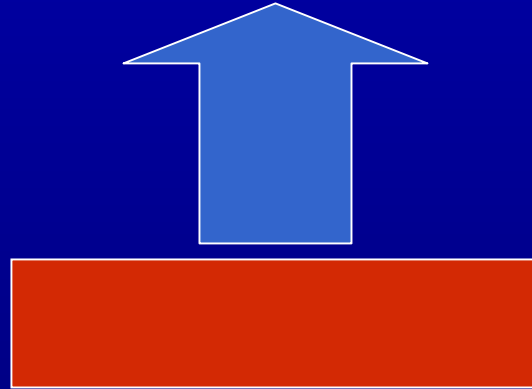


**Cirrhosis**

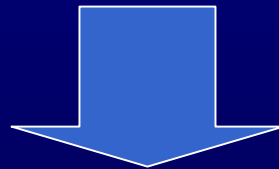


**HCC**

Virus, NASH, Aflatoxin, Iron, etc.



**Cirrhosis**



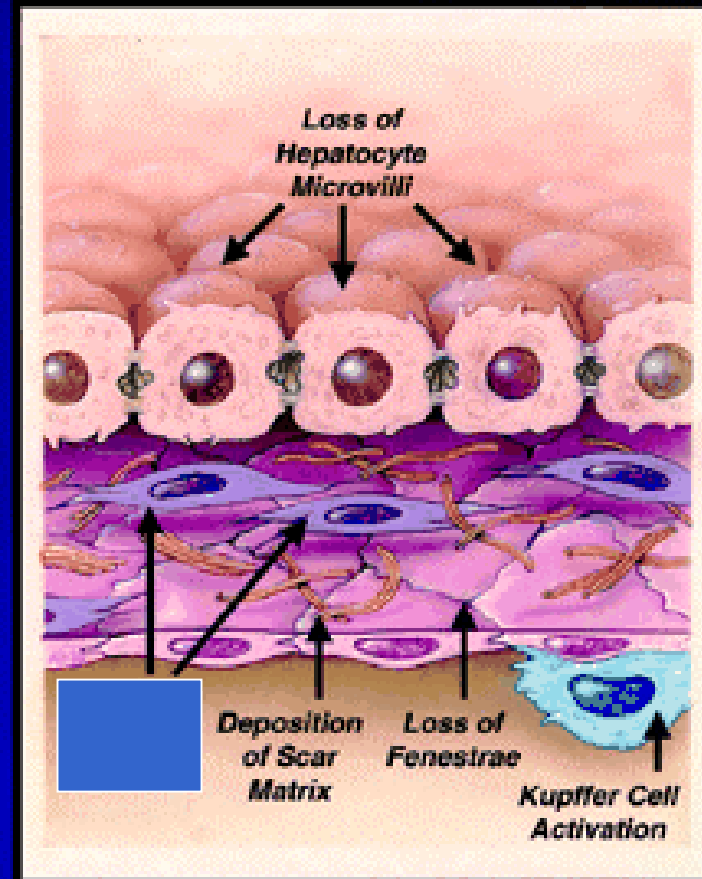
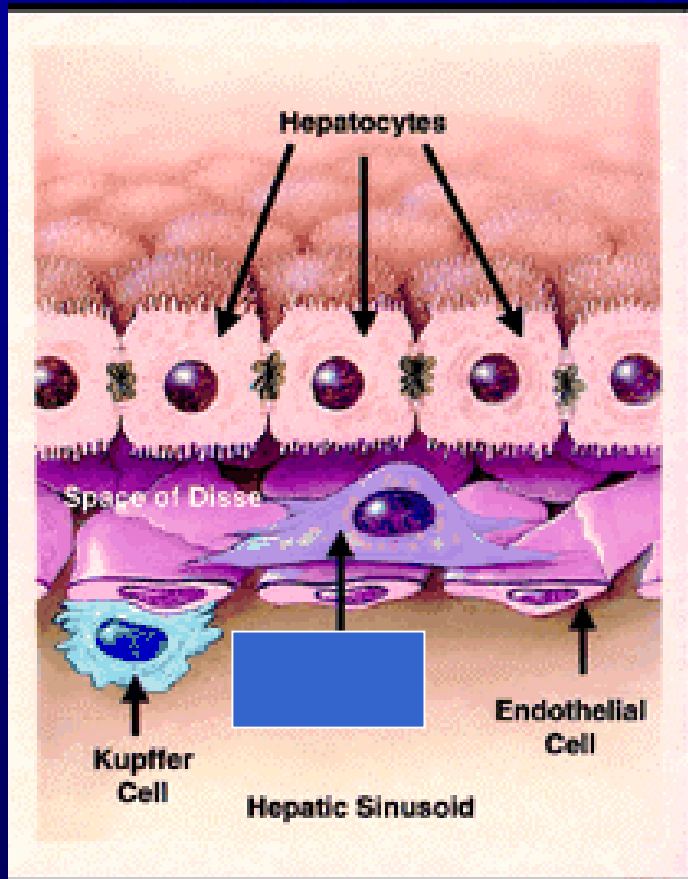
**HCC**

# TGF- $\beta$ , PDGF, IL10, IL13

Normal Liver



Liver Injury



# TJ-9: 1/9 Licorice

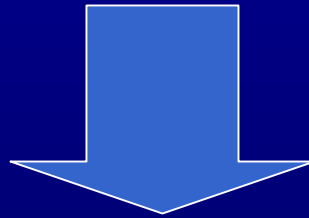
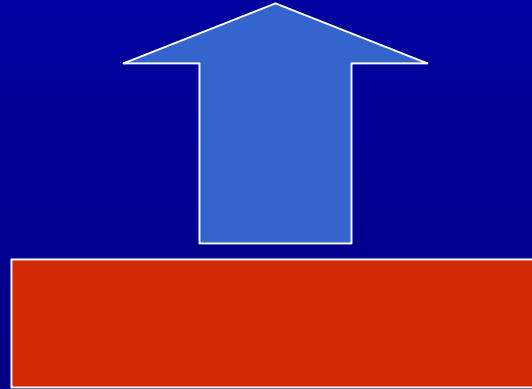


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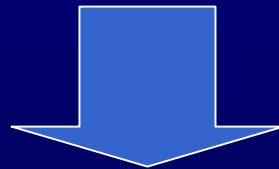
	TJ-9	Control
Total	130	130
Randomized		
Patients with HCC	23	33
Alive with HCC	17	24
Dead with HCC	6	9
Survived	102	89

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Virus, NASH, Aflatoxin, Iron, etc.

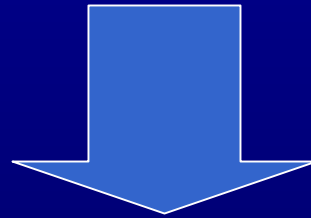
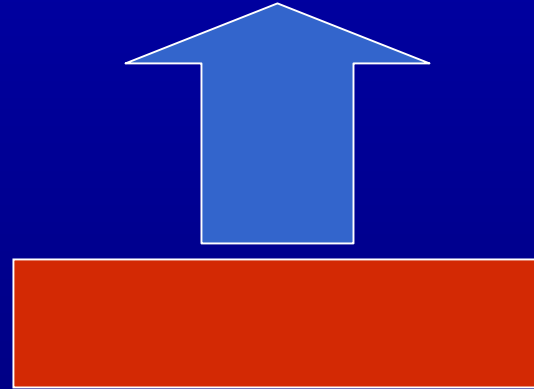


**Cirrhosis**



**HCC**

Virus, NASH, Aflatoxin, Iron, etc.



**Cirrhosis**



**HCC**

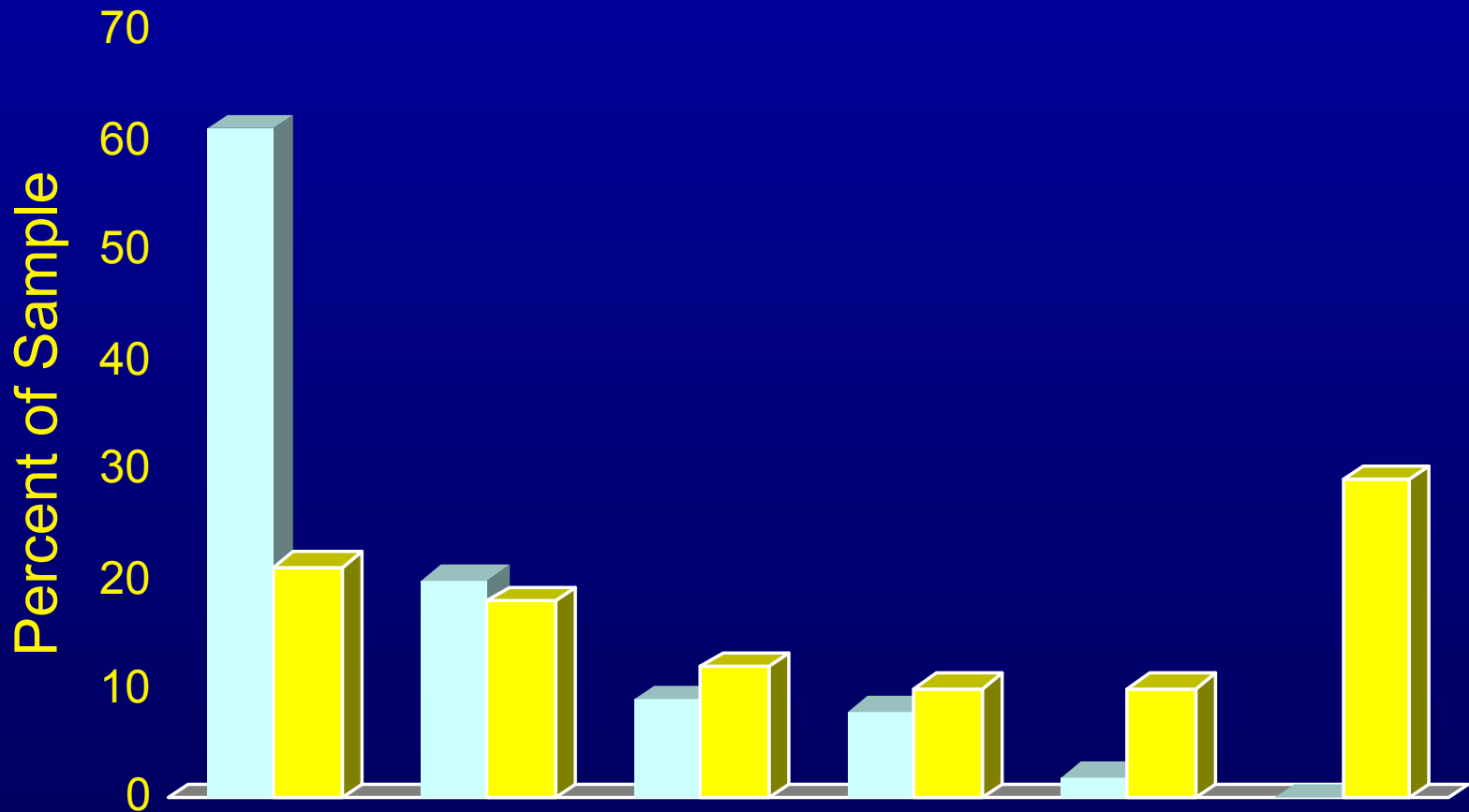


**HCC**

# Screening Controversial

- Lack of sensitive screening tests
- Lack of evidence to suggest improved clinical outcome
- Lack of cost effectiveness

# AFP in HCC and Controls



# Current HCC Screening Tests

	Sensitivity	Specificity	Problems
$\alpha$ FP (10-400 ng/ml)	40-100%	70-100%	cirrhosis, HBV, 30% HCC nl, race/ethnicity
Serum Interleukin 2 receptor, TGF $\beta$ 2, etc.	50-99%	90-100%	Not Available
Ultra-Sound	11-99%	> 90%	Benign nodule, invasive tests
CT, MRI	Unknown	Unknown	Expensive

# Smaller Tumor = Surgery = Survival

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	Localized HCC	Regional Spread	Rest
	24.8%	23.9%	51.4%
Radical Surgery	1.7%	0.4%	0.4%
Palliative Surgery	19.1%	6.7%	29.1%
No Surgery	79.2%	92.2%	92.5%

---

# Efficacy of HCC Screening

- 1995 Tang, *J Gastro Hepatol* 10:683-90 –
- 1995 Sherman, *Hepatology* 22:432-7 –
- 1996 Solmi, *Am J Gastro* 91:1189-94 – In  
CLD patients, 300 screened using AFP and  
U/S vs. 2000 usual care; 75% vs. 16% small  
tumors, no long term follow-up
- 1996 Lee, *Br J Surg* 83:330-3 –
- 2002 Marrero, *Hepatology* 36:1349-54 –

# Cost: \$110,000/Yr Life Saved

	<i>Baseline costs*</i>	<i>Costs in screened pts*</i>	<i>Costs in unscreened pts*</i>
Surveillance programme			
APF	14	40 236	1 456†
Ultrasonography	47	135 078	4 888†
Diagnostic tests			
Computed tomography	1 530	11 322	15 912
Echo guided biopsy	95	5 700	9 025
Treatments			
PEI	1 610	22 540	32 200
TACE‡	3 250	165 750	292 500
Hepatic resection	11 970	47 880	99 850
OLT	54 120	324 720	432 960
Resulting cost		753 226	858 791
Cost for treatable hepatocellular carcinoma		17 934	14 555

\*Costs are those allocated to Bologna University Hospital by National Public Health Service and are converted to US\$.

†Costs are assumed for a single  $\alpha$  fetoprotein (AFP) determination and ultrasonography before our observation.

‡Values account for both diagnostic and therapeutic procedures.

OLT, orthotopic liver transplantation; PEI, percutaneous ethanol injection; TACE, transarterial chemoembolisation.

# AASLD Practice Guidelines

- Chemoprevention of HCC: None
- Screening:
  - High Risk HBV: AFP and U/S q6mo, ie. men > 45 yo, cirrhosis, FH of HCC
  - Low Risk HBV: Maybe AFP.
  - HCV: No screening before cirrhosis; and should screen once cirrhosis develops, but no specific methods.



A

