HCC Prevention

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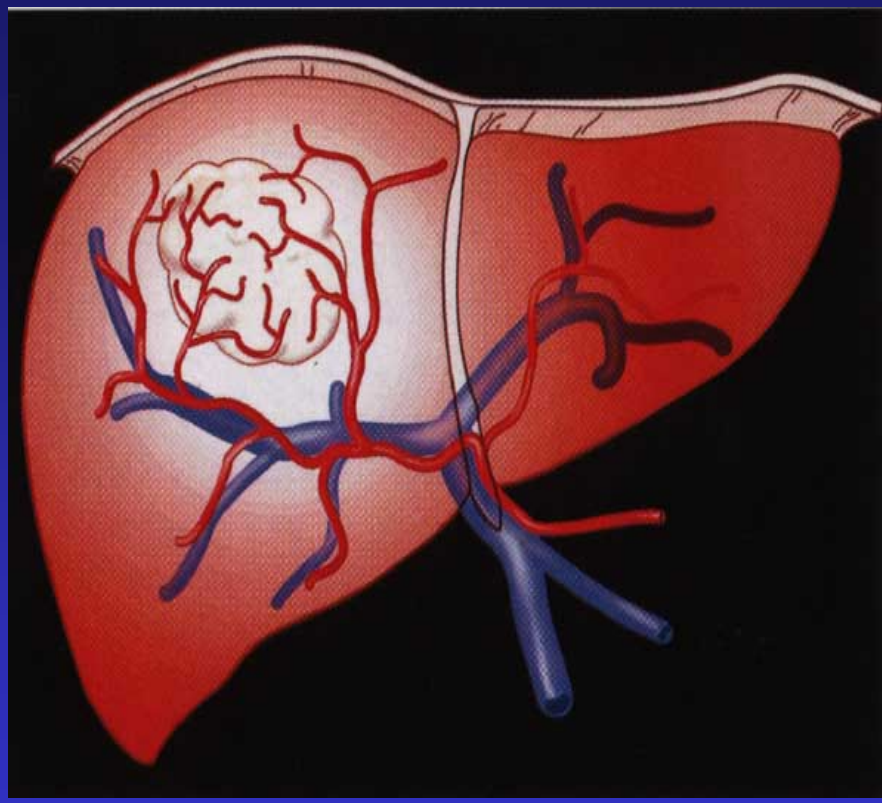
TCC, HCC Prevention, 26 Nov, 2011

Outline

- Pathogenic and Risk Factors



- HBV
  - Primary
  - Secondary
- HCV
  - Primary
  - Secondary
  - Tertiary

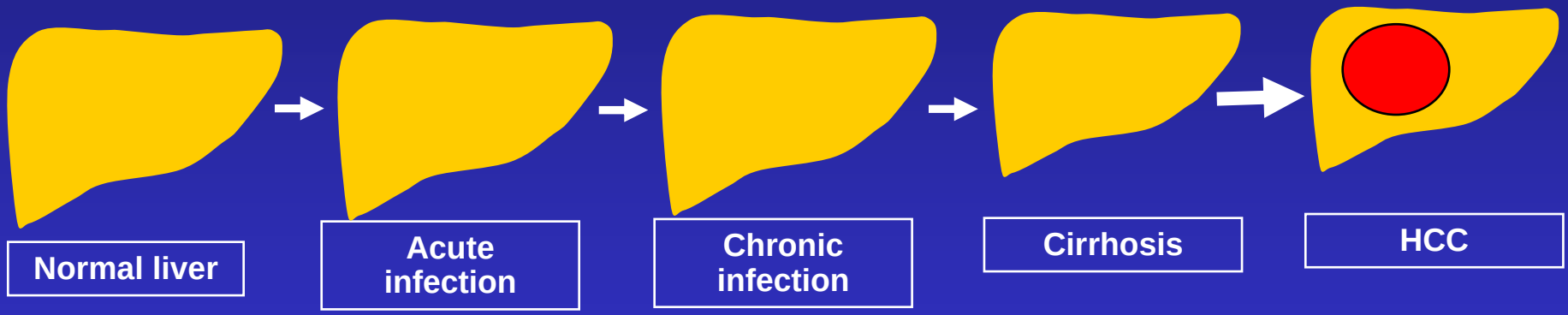
Risks

Surveillance recommended	Incidence of HCC (%/yr)
Asian male hepatitis B carriers >40 y/o	0.4-0.6
Asian female hepatitis B carriers >50 y/o	0.3-0.6
Hepatitis B carrier with family history of HCC	-
hepatitis B cirrhosis	3-8
Hepatitis C cirrhosis	3-5
Other cirrhosis	?
Surveillance benefit uncertain	
Hepatitis B carriers <40 y/o (males) or <50 y/o (females)	< 0.2
Hepatitis C and stage 3 fibrosis	< 1.5
Non-cirrhotic NAFLD	< 1.5

Bruix J. 2010 Hepatology

Pathogenic and risk factors for HCC

- Necroinflammation
- Cellular injuries
- Mitosis
- Regeneration



- Chromosomal intergration
- Genetic transactivation

- HBV/HCV/HDV Coinfection
- Male
- Age
- Family history
- Alcohol
- Aflatoxin
- BMI
- DM

Risk Factors of HCC

- **APASL Recommendations:**

- ✓ **Patients with cirrhosis due to HBV or HCV are at the highest risk for HCC (2a).**
- ✓ **The incidence of HCC was significantly higher in those who were HBeAg positive or have HBVDNA with high loads ($>10^4$ copies/mL) and older than 40 years (2a).**
- ✓ **Coinfection with HBV and HCV may have synergistic effect on the development of HCC (2b).**
- ✓ **Male sex, aging, and familial history are independent risk factors for HCC (2a).**
- ✓ **Chronic and heavy alcohol intake, BMI>25 and DM leading to liver disease increases the risk for HCC (2b).**

Hepatol Int 2010

Prevention for HBV-related HCC
- Primary Prevention

- Necroinflammation
- Cellular injuries
- Mitosis
- Regeneration

Primary Prevention

Normal liver → Acute infection → Chronic infection → Cirrhosis → HCC

- Chromosomal intergration
- Genetic transactivation

- HCV/HDV Coinfection
- Male
- Age
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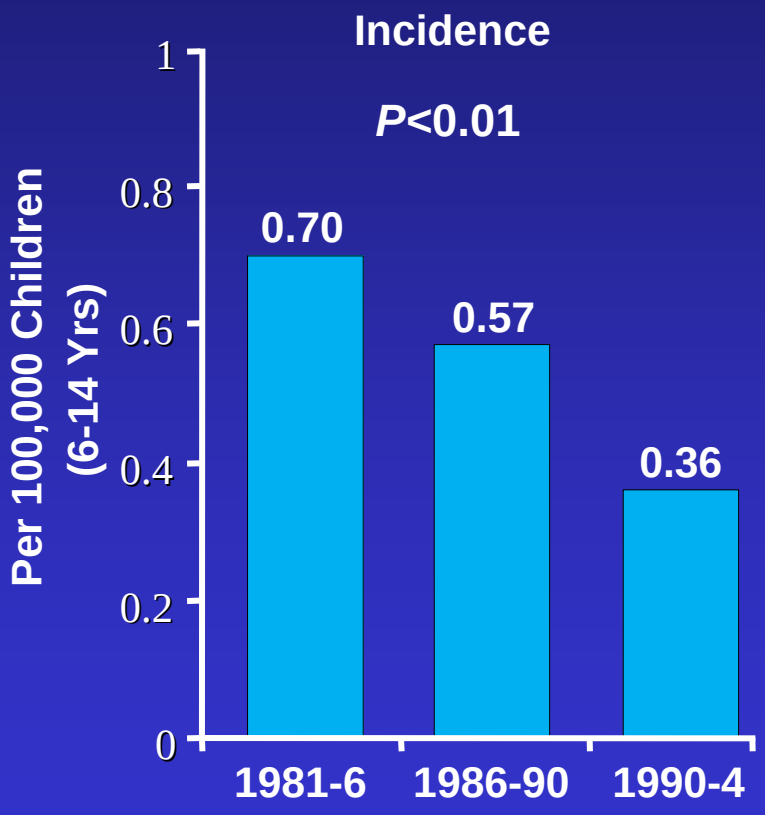
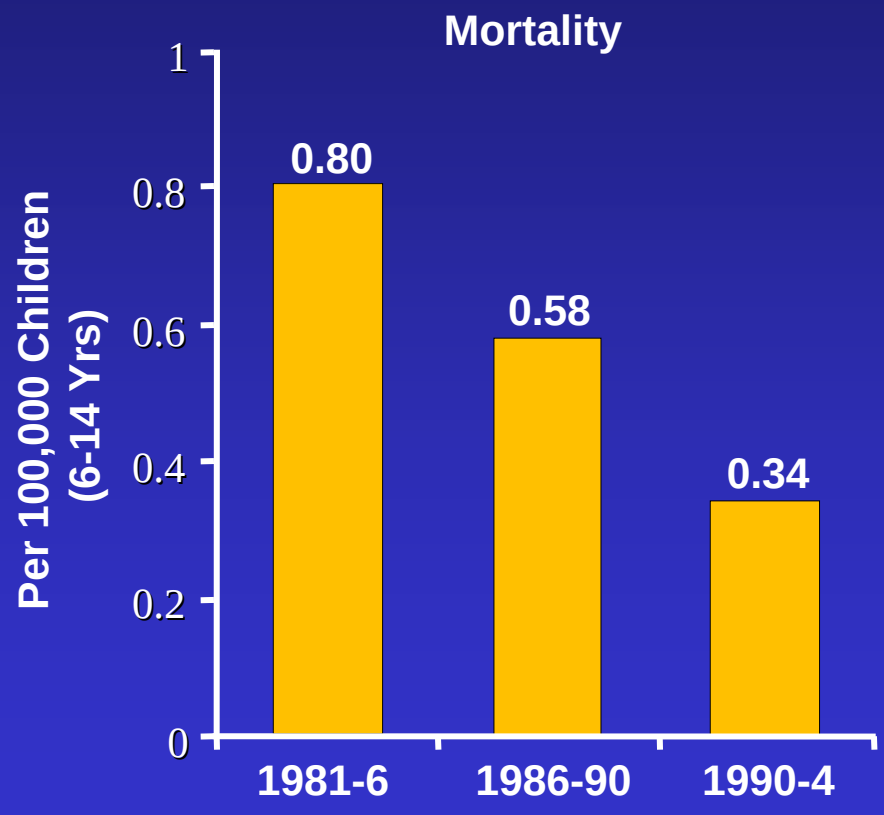
HBV Vaccination: Effect on HCC Incidence and Mortality

Nationwide vaccination in Taiwan, implemented since July 1984.

Carrier rate: 9.8% in 1984, 1.3% in 1994, 0.7% in 1999





Chang MH, et al. N Engl J Med. 1997
Ni YH, Chang MH, et al. Ann Intern Med 2001

Factors Affecting Disease Progression in CHB

HBV Factors

- Persistent presence of HBeAg
- Persistent high viral load
- HBV genotype C> B
- Genome mutations

Host Factors

- Age>40 years
- Male
- Immune status
- Family history (cirrhosis, HCC)
- Cirrhosis
- BMI, DM etc

Other Factors

- Habitual alcohol
- Smoking
- Aflatoxin
- HCV, HDV, HIV
- Others

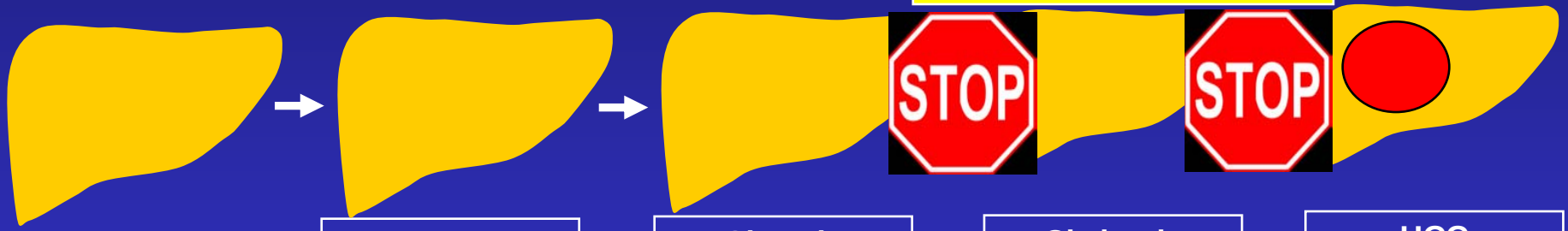
Cirrhosis and/or HCC

Liaw YF. Liver Int 2009; Kao JH. Hepatol Int 2007

Prevention for HBV-related HCC
- Secondary Prevention

- Necroinflammation
- Cellular injuries
- Mitosis
- Regeneration

Secondary Prevention



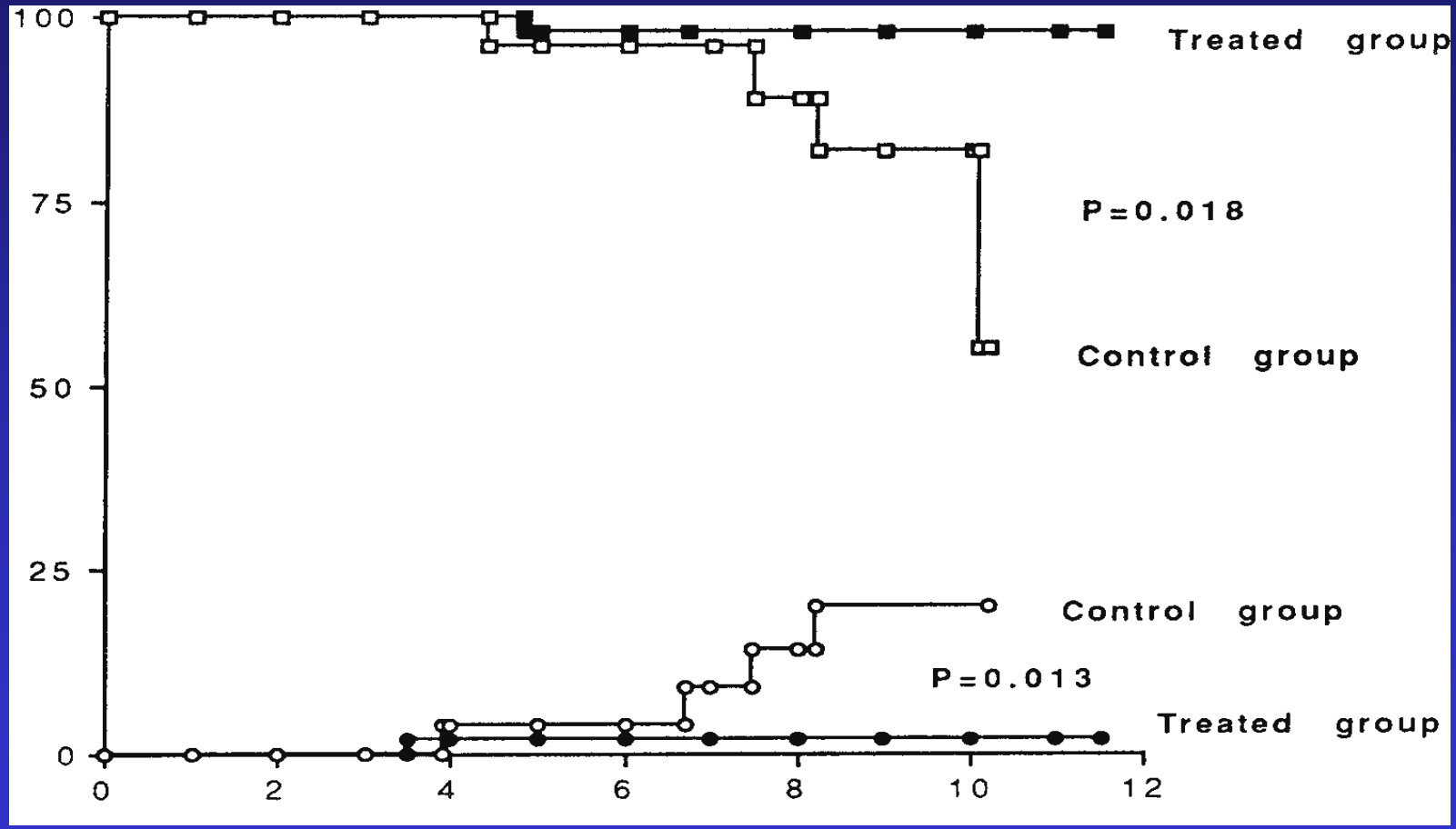
Normal liver → Acute infection → Chronic infection → Cirrhosis → HCC

- Chromosomal intergration
- Genetic transactivation

- HCV/HDV Coinfection
- Male
- Age
- Family history
- Alcohol
- Aflatoxin
- BMI
- DM

IFN therapy reduces the risk of HCC and increases survival in CHB patients

IFN, N=67 (31IFN alone, 36 Pred/IFN) Placebo, N=34; median follow-up 8.2 years (1.1 to 11.5 years)

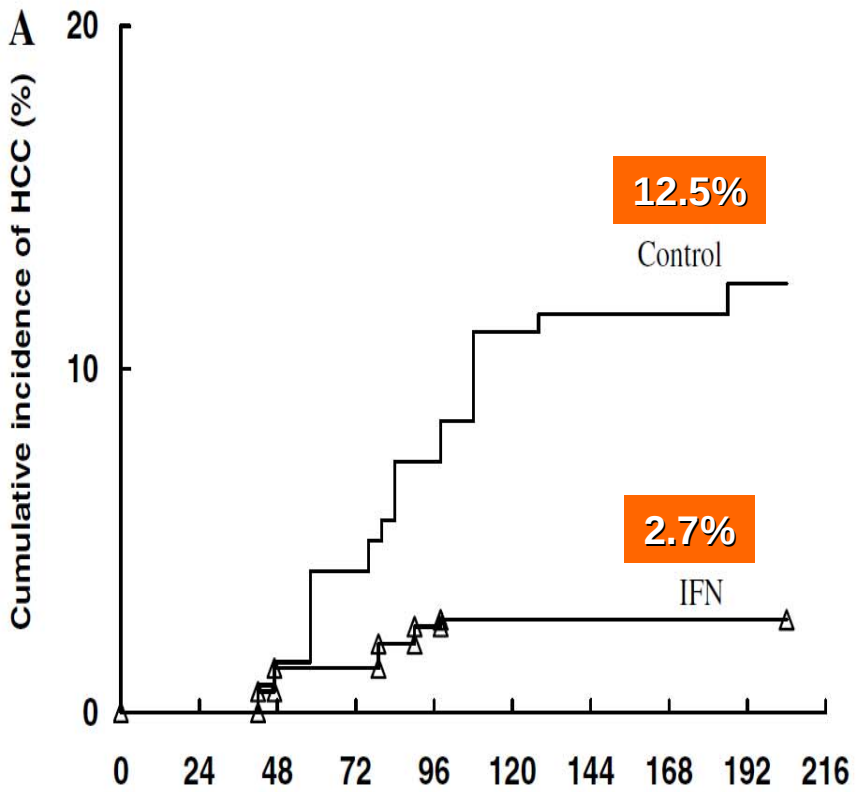


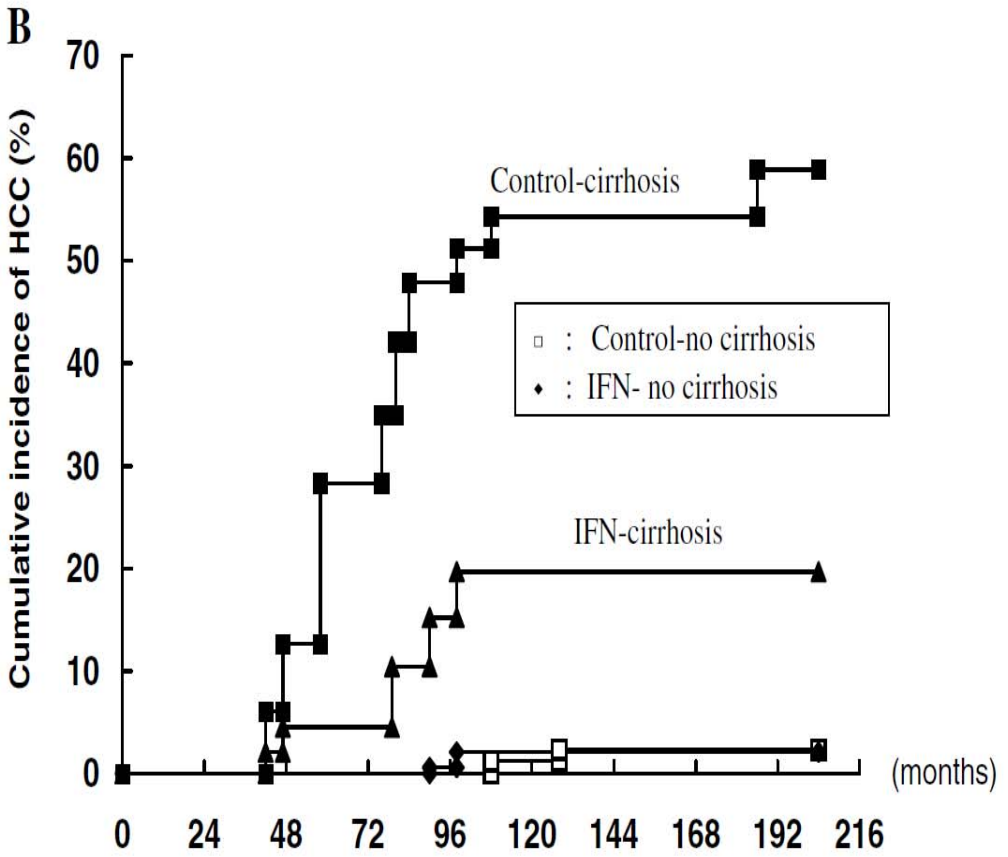
Response was defined as HBV-DNA and HBeAg seroclearance during treatment and/or within 12 months after the end of therapy.

Lin SM. Hepatology 1999

IFN Therapy Reduces Risk of HCC, Particularly in the Cirrhotics

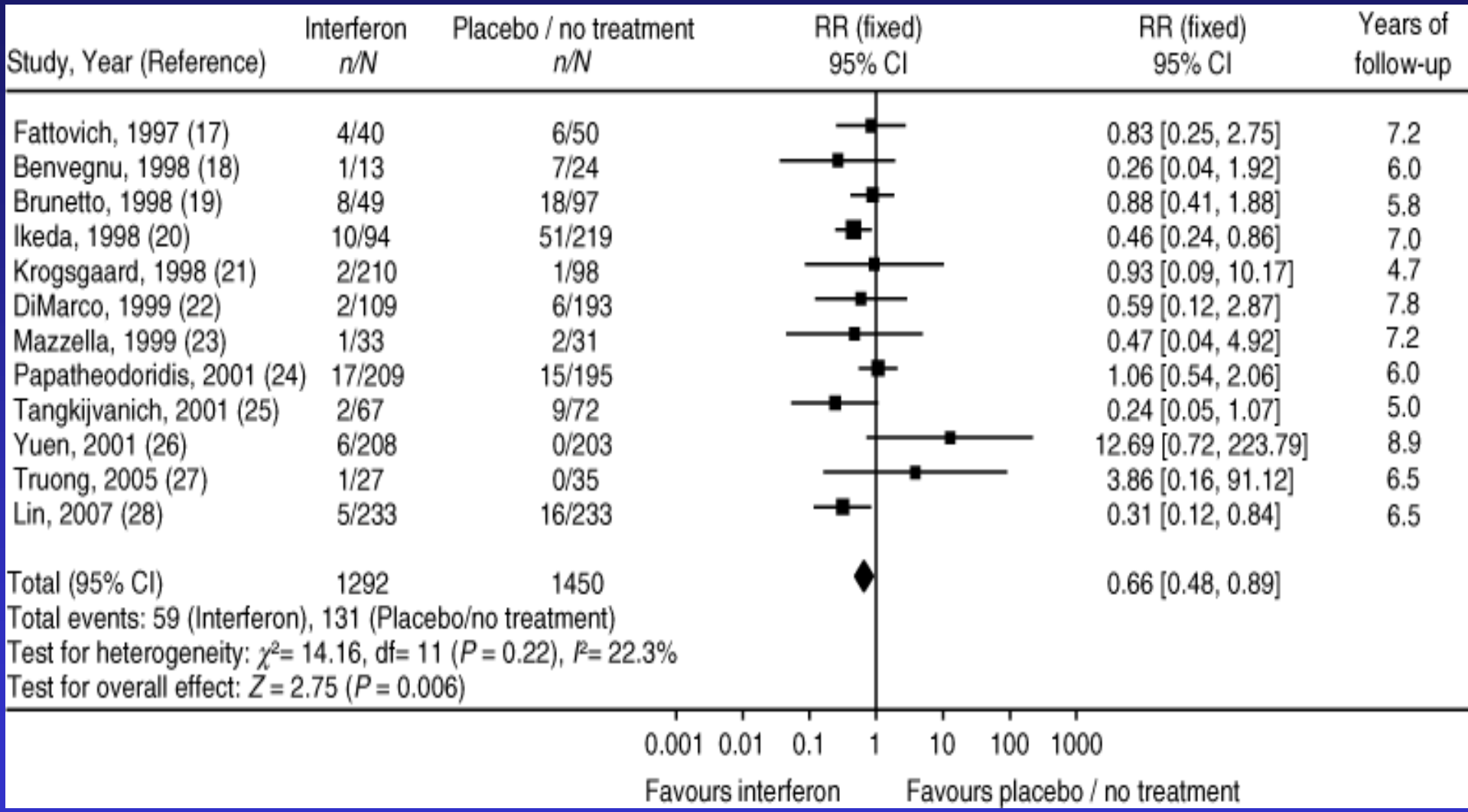
IFN N=233, Control N=233, median follow-up 6.8 yrs (1.1–16.5 yrs)





Lin SM, et al. J Hepatol 2007.

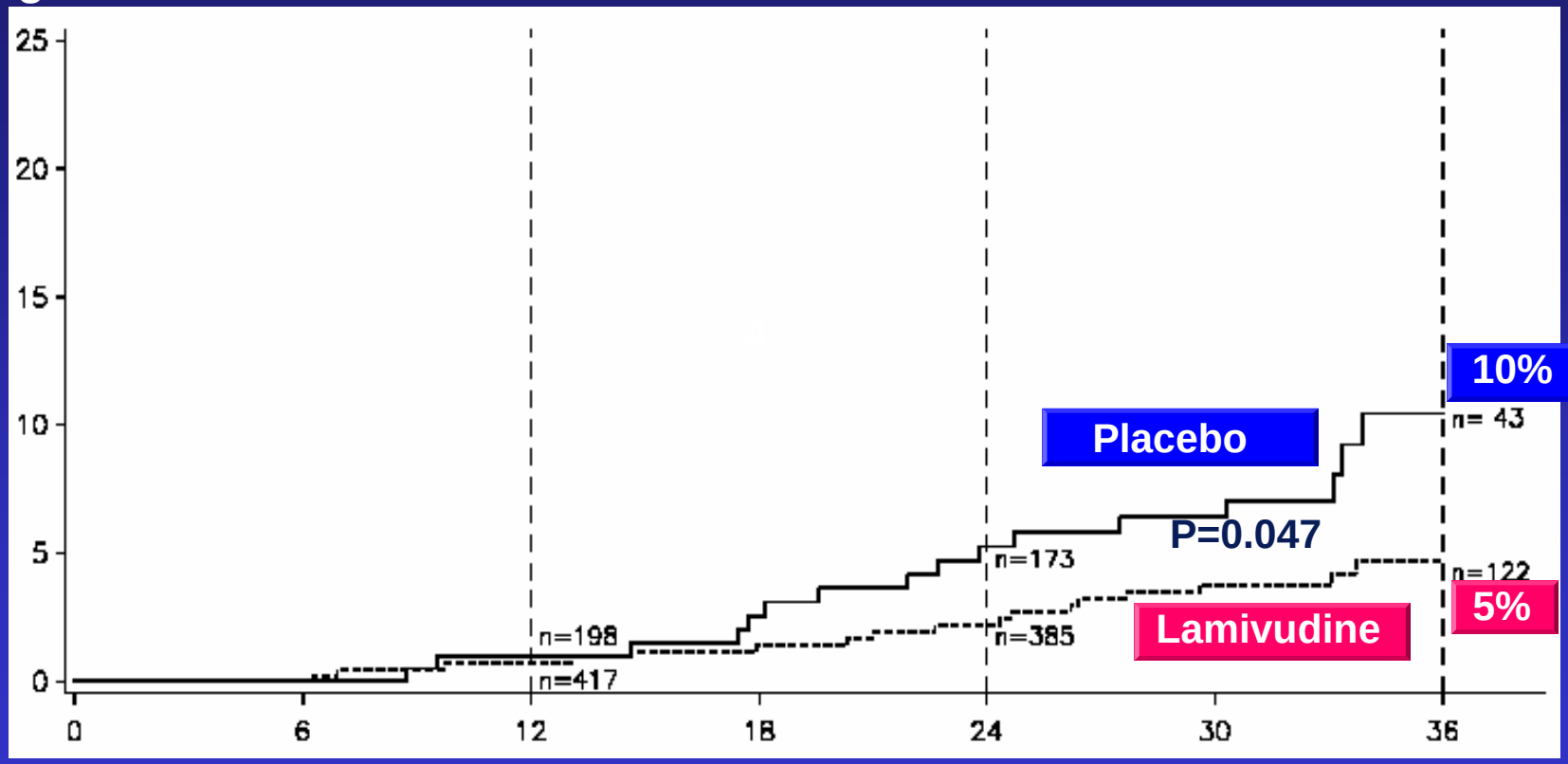
IFN Therapy Reduces HCC Risk by 34%



Sung JJY, et al. Aliment Pharmacol Therap 2008

Time to Diagnosis of HCC

Percentage with Diagnosis of HCC



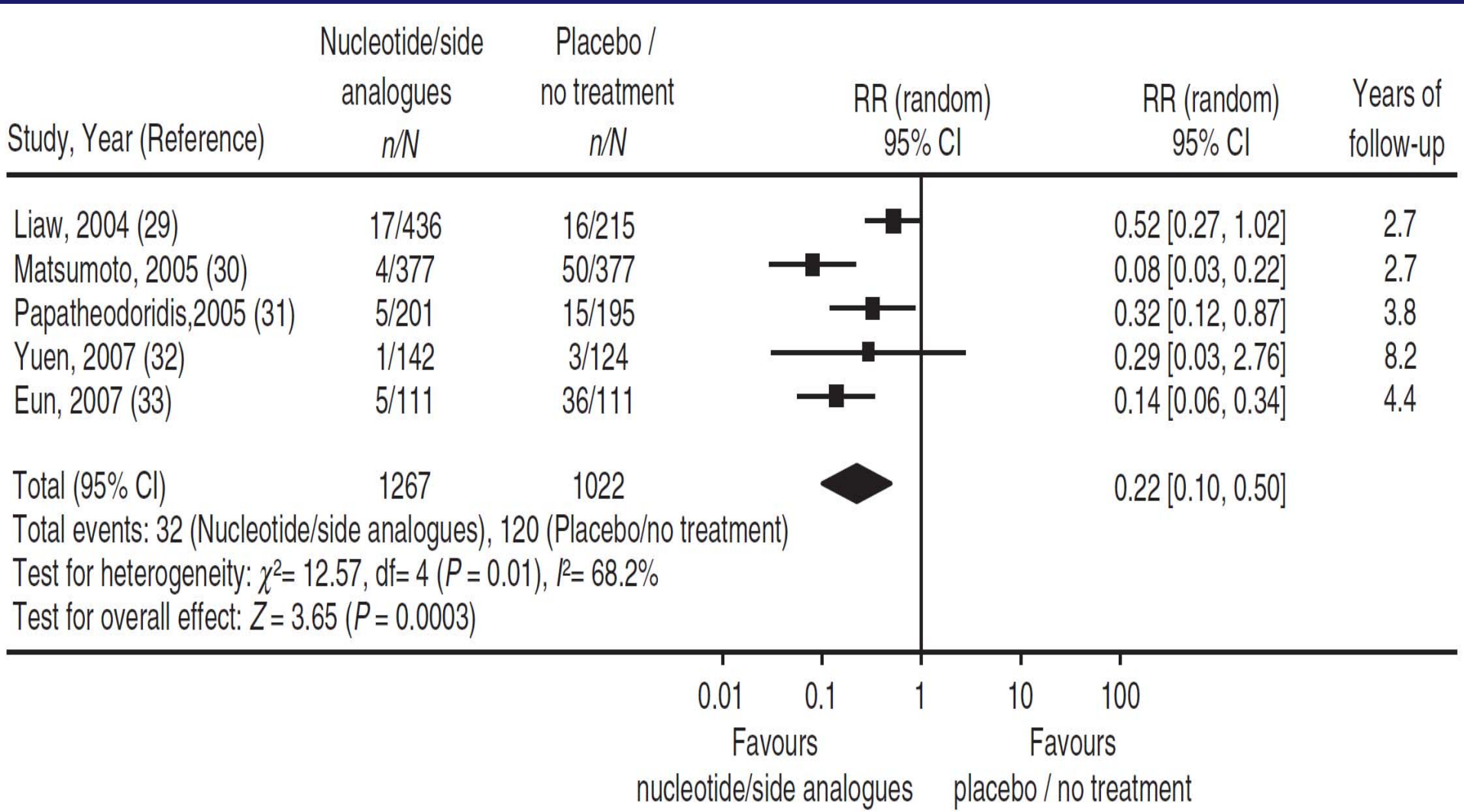
Time to Disease Progression (Months)

——— Placebo (n= 215)
····· Lamivudine (n= 436)

Excluding 5 cases in yr1: HR=0.47; P=0.052

Liaw YF, et al, NEJM 2004

NA Therapy Reduces HCC Risk by 78 %



Sung JJY, et al. Aliment Pharmacol Therap 2008

Prevention of HBV-related HCC

- **APASL Recommendations**:

✓ Universal hepatitis B vaccination should be implemented in the countries where HBV infection is endemic or hyperendemic (2a, A).

✓ Interferon (IFN) therapy in adult with active hepatitis may be effective in reducing the incidence of HBV-related HCC (2b, B).

✓ Maintained HBV suppression by oral antiviral agent(s) can reduce the risk of HCC (1b, A).

Hepatol Int 2010

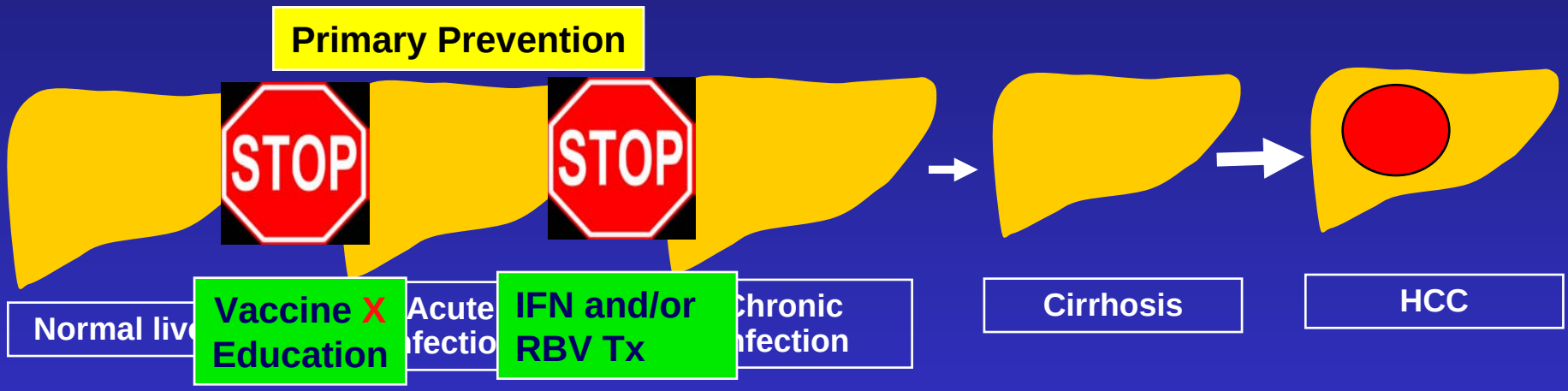
Prevention of HBV-related HCC

- **JSH Consensus Statements:**
- Among patients with type B chronic liver disease, the incidence of HCC is high in those with a high HBV DNA level.
- NAs are useful for preventing HCC in patients with chronic hepatitis B or compensatory liver cirrhosis B.

Dig Dis 2011

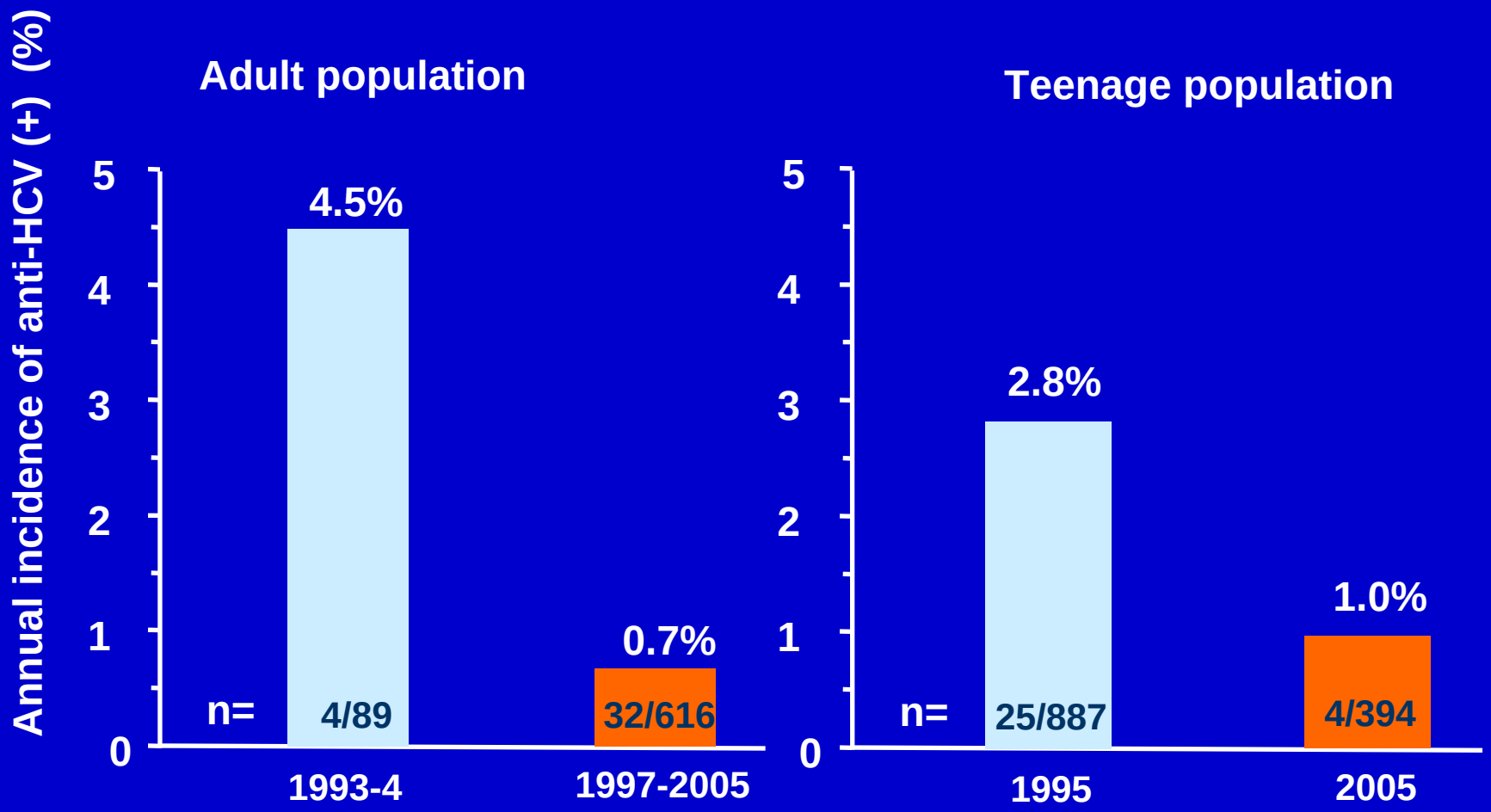
Prevention for HCV-related HCC
- Primary Prevention

- Necroinflammation
- Cellular injuries
- Mitosis
- Regeneration



- HBV/HIV Coinfection
- Male
- Age
- Family history
- Alcohol
- Aflatoxin
- BMI
- DM

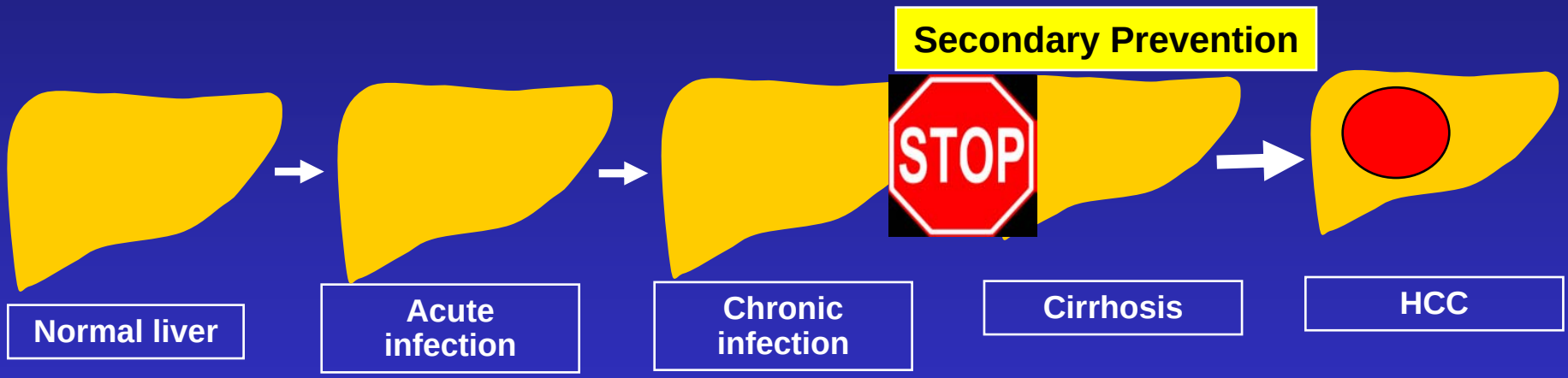
Changing Prevalence of Anti-HCV (+) with the Implementation of Screening



Lu SN, Huang JF, et al. Kaohsiung J Med Sci 1997
Tsai PS, Lu SN, et al. Liver Int 2010
Huang JF, Lu SN, et al. Epidemiol Infect 2001
Huang CF, Huang JF, Lu SN, et al. Trans R Soc Trop Med Hyg 2008

Prevention for HCV-related HCC
- Secondary Prevention

- Necroinflammation
- Cellular injuries
- Mitosis
- Regeneration



- HBV/HIV Coinfection
- Male
- Age
- Family history
- Alcohol
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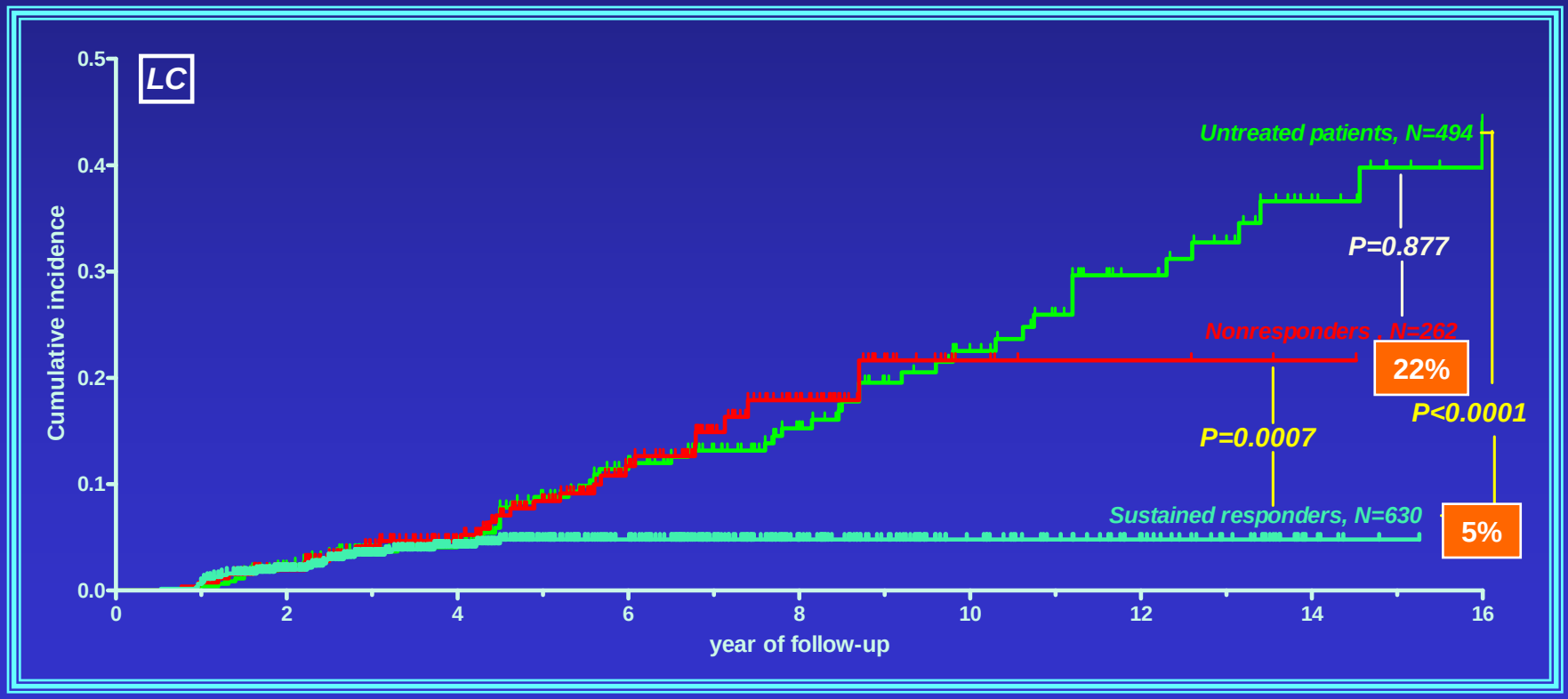
- BMI
- DM

Reducing Risk of LC in non-cirrhotic CHC Patients with IFN-based Therapy

Benefit only in patients with SVR

- 1386 pts from LK-CGMH, KCGMH, KMUH
- IFN-based therapy, 896; untreated, 494
- mean FU, 5.16 y (1-16 y)

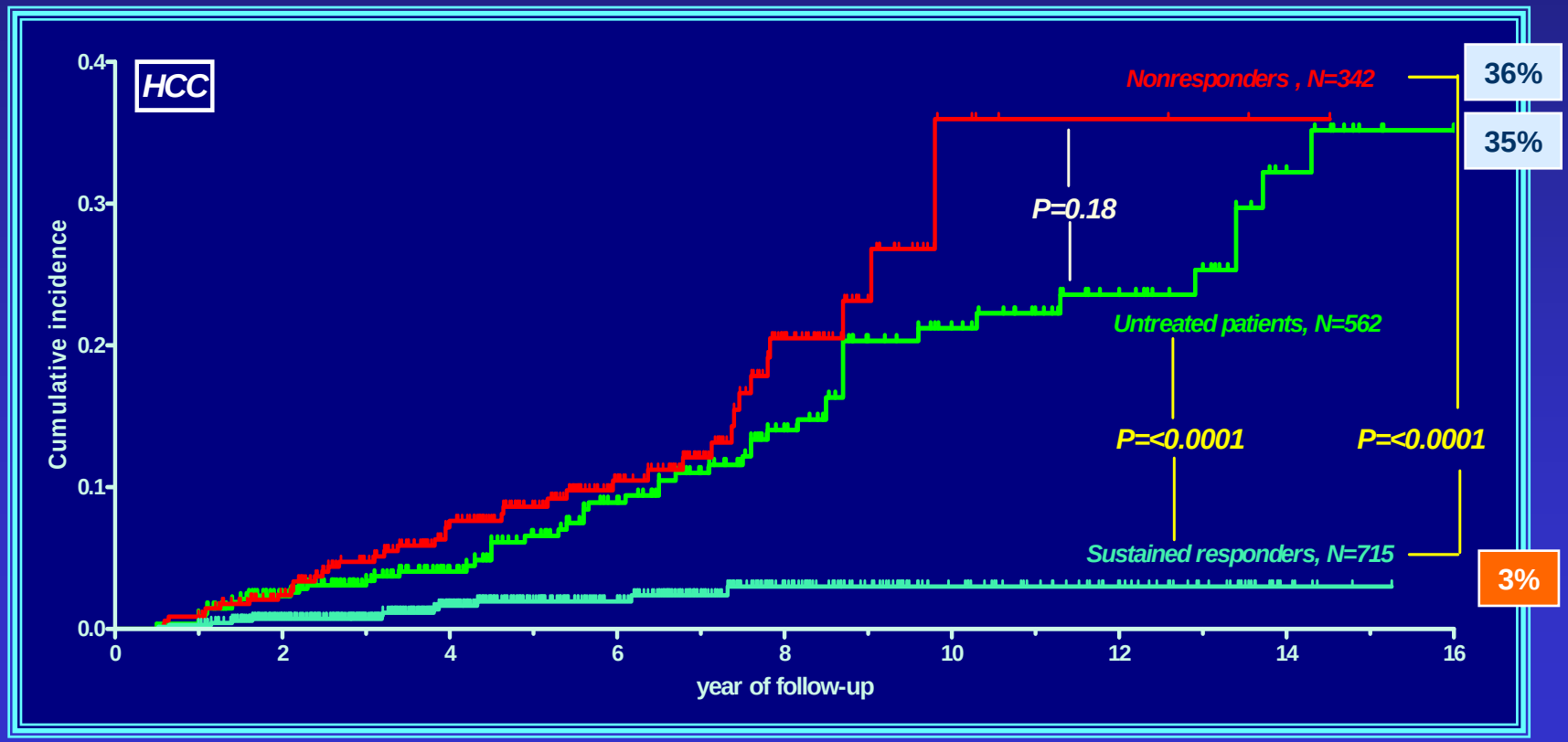


Huang JF, Yu ML, et al., Aliment Pharmacol Ther. 2007;25:1029-37.

Reducing Risk of HCC in CHC Patients with SVR to IFN-based Therapy

Benefit only in patients with SVR

- 1619 pts from LK-CGMH, KCGMH, KMUH
- IFN-based therapy, 1057; untreated, 562
- mean FU, 5.16 y (1-16 y)

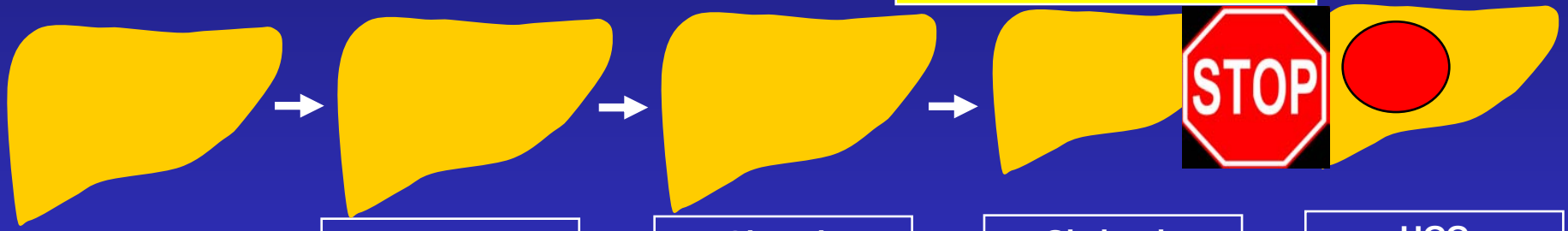


Yu ML, et al., Antiviral Therapy, 2006;11:985-94.
Yu ML, et al., Hepatology, 2006;44:1086-97.

Prevention for HCV-related HCC
- Secondary Prevention

- Necroinflammation
- Cellular injuries
- Mitosis
- Regeneration

Secondary Prevention



Normal liver → Acute infection → Chronic infection → Cirrhosis → HCC

- HBV/HIV Coinfection
- Male
- Age
- Family history
- Alcohol
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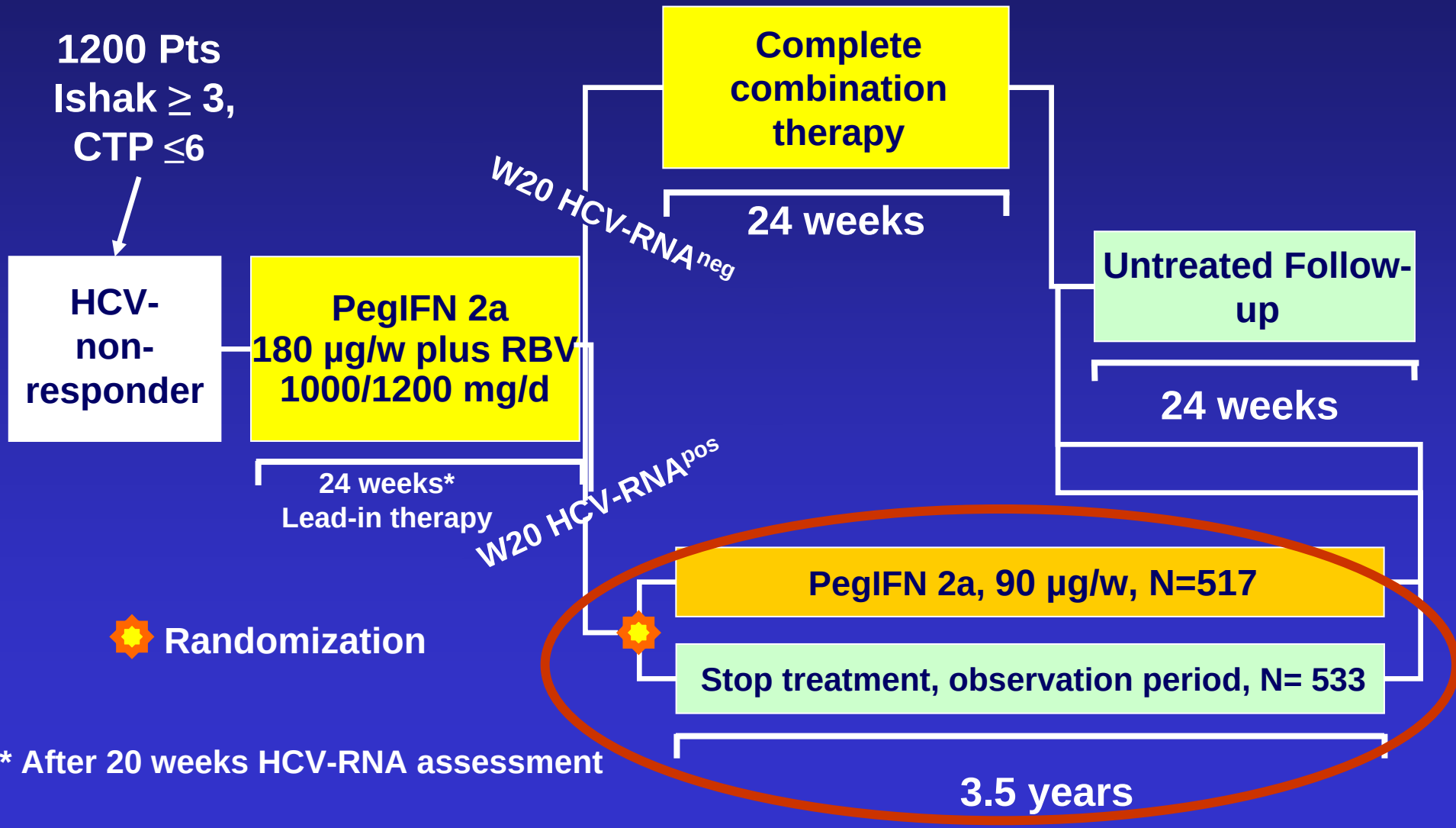
- BMI
- DM

IFN monotherapy reduces risk of HCC in cirrhotic CHC patients

	Pts	F/U, M (range)	Comparison, n/N (%)		RR (95%CI)
			IFN-treated	untreated	
Nishiguchi et al., Lancet. 1995.	LC	53 (24-86)	2/45 (4)	17/45 (38)	0.12 (0.04-0.37)
Mazzella et al., J Hepatol. 1996.	LC	32 (12-71)	5/193 (3)	9/92 (10)	0.12 (0.04-0.38)
Fattovich et al., Gastroenterol. 1997.	LC	60 (1-153)	7/193 (4)	16/136 (12)	0.12 (0.04-0.39)
Serfaty et al., Hepatology. 1998.	LC	40 (6-72)	4.4% at 4 y	23% at 4 y	0.12 (0.04-0.41)
IIHCSG, Lancet. 1998.	LC	NA	21/232 (9)	48/259 (19)	0.12 (0.04-0.42)
Valla et al., Hepatology. 1999.	LC	40 (37-53)	5/45 (11)	6/39 (15)	0.83 (0.27-2.54)

Yu ML et al., Oncology 2007;72(suppl 1):16–23.

HALT-C Study – Non-responders to IFN ± RBV



* After 20 weeks HCV-RNA assessment

Lok AS, et al. Gastroenterology. 2009;136:138-148.

HALT-C for HCC risk

- 4.8% of pts (n = 48) developed HCC during median FU of 4.6 yr (max: 6.7 yr)
- Incidence of HCC similar in peginterferon and no-treatment groups

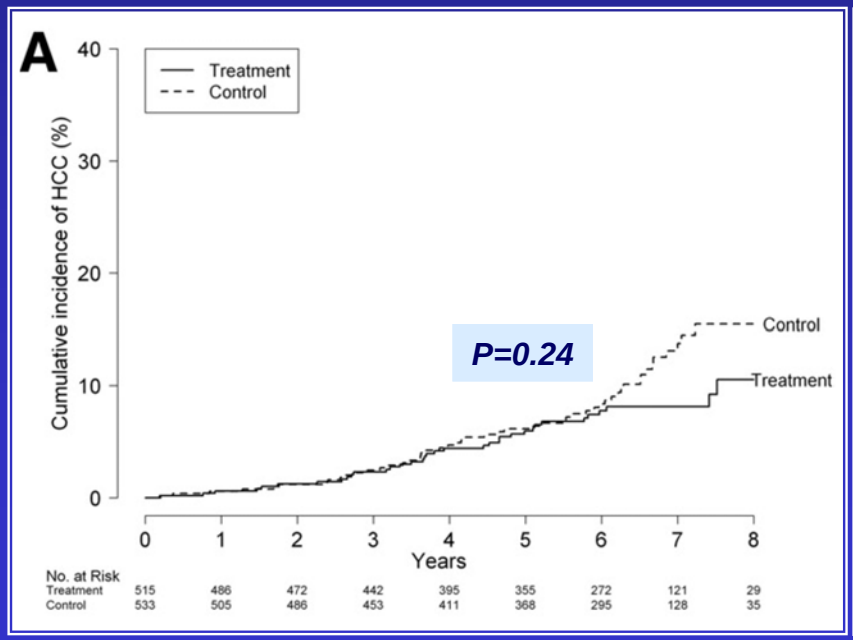
Outcome, %	PegIFN (n = 495)	No Tx (n = 510)
Overall HCC incidence	4.5	4.9
• Patients with fibrosis	5.0	2.7
• Patients with cirrhosis	4.1	8.1
Annual incidence	1.1	1.0
Cumulative incidence		
• 3 yrs	1.9	1.9
• 5 yrs	5.4	5.0

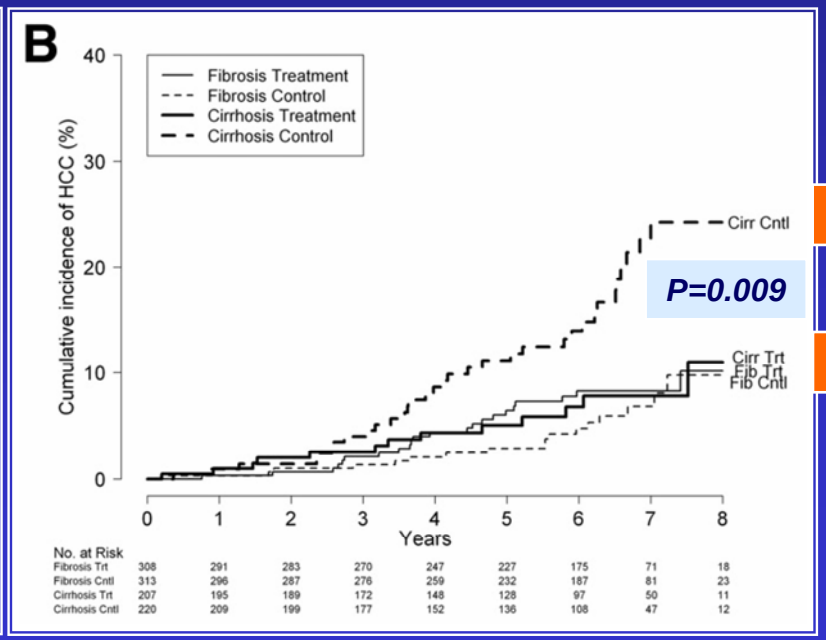
Variable	Hazard Ratio	*P* Value
Age	1.050	.01
Black race	2.044	.04
Alkaline phosphatase	1.006	.01
Esophageal varices	2.164	.02
Ever smoked	2.114	.07
Platelet count	0.989	.001

Lok AS, et al. Gastroenterology. 2009;136:138-148.

Extended Follow-up of the HALT-C

- Peginterferon or no treatment controls for 3.5 years and followed up for a median of 6.1 (max, 8.7) years
- Long-term peginterferon therapy does not reduce the incidence of HCC among patients with advanced hepatitis C who did not achieve SVRs.
- Patients with cirrhosis who received peginterferon treatment had a lower risk of HCC than controls





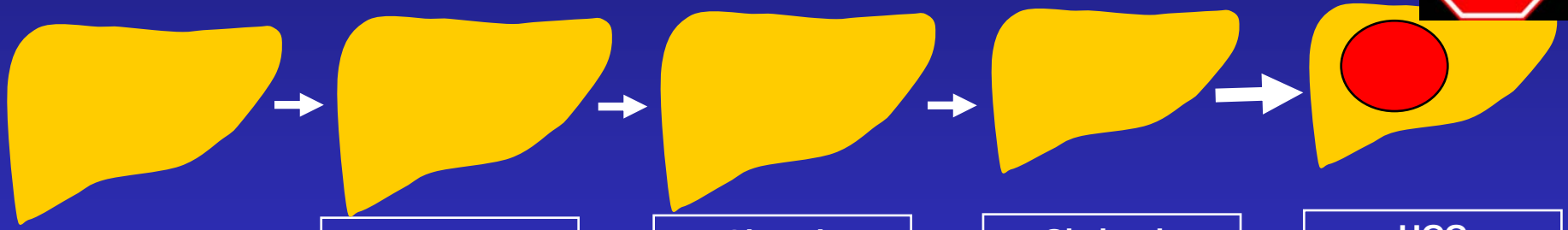
Lok A. et al. GASTROENTEROLOGY 2011;140:840–849

Prevention for HCV-related HCC
- Tertiary Prevention

- Necroinflammation
- Cellular injuries
- Mitosis
- Regeneration

Tertiary Prevention

HCC recurrence



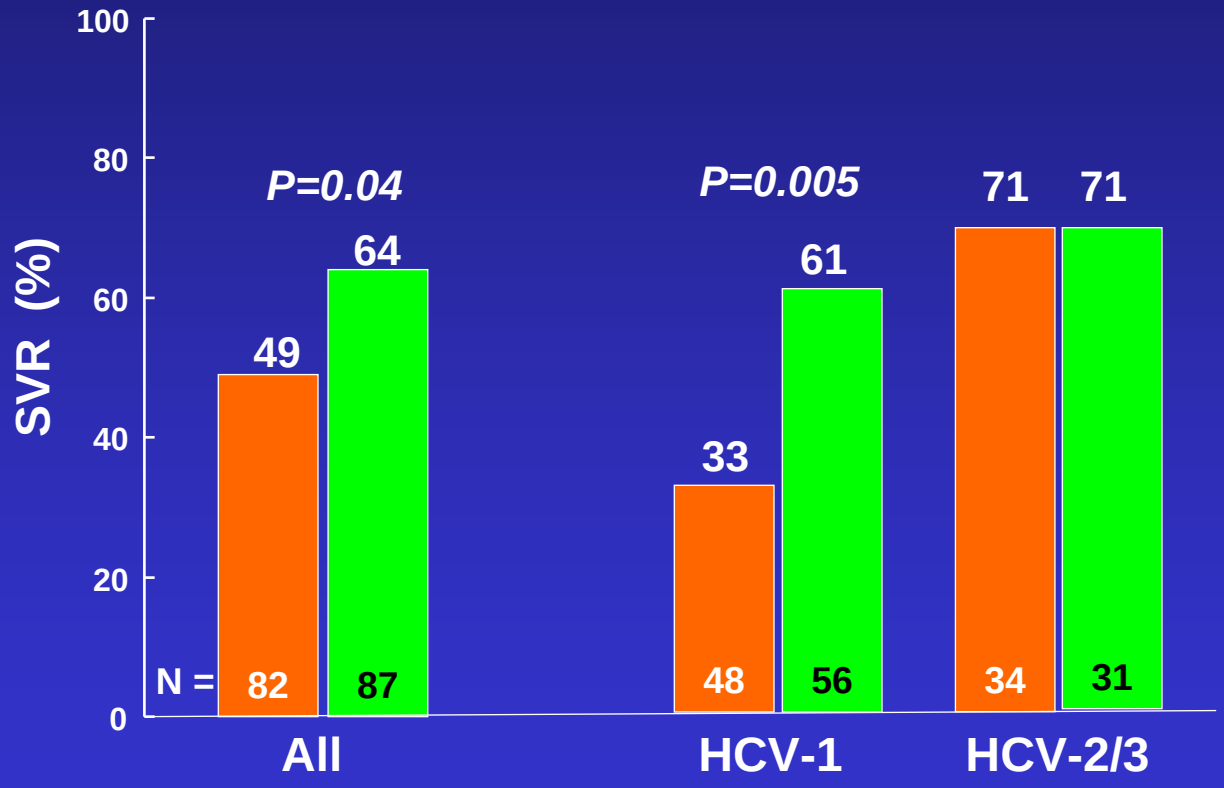
Normal liver → Acute infection → Chronic infection → Cirrhosis → HCC

- HBV/HIV Coinfection
- Male
- Age
- Family history
- Alcohol
- Aflatoxin
- BMI
- DM

HCV-HCC post Curative Therapies vs. Cirrhosis Response to PegIFN/RBV

HCC group, post surgery, RFA, or PEI LC group, Child A

SOC with Peg-IFNα-2a plus RBV

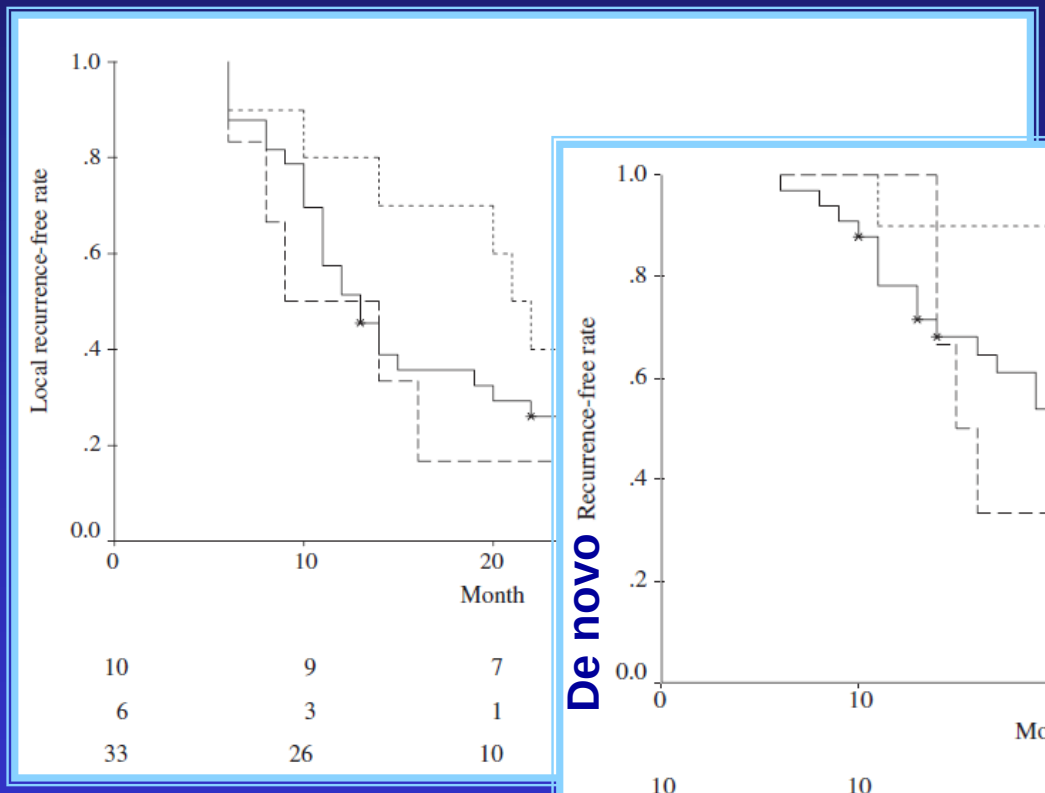


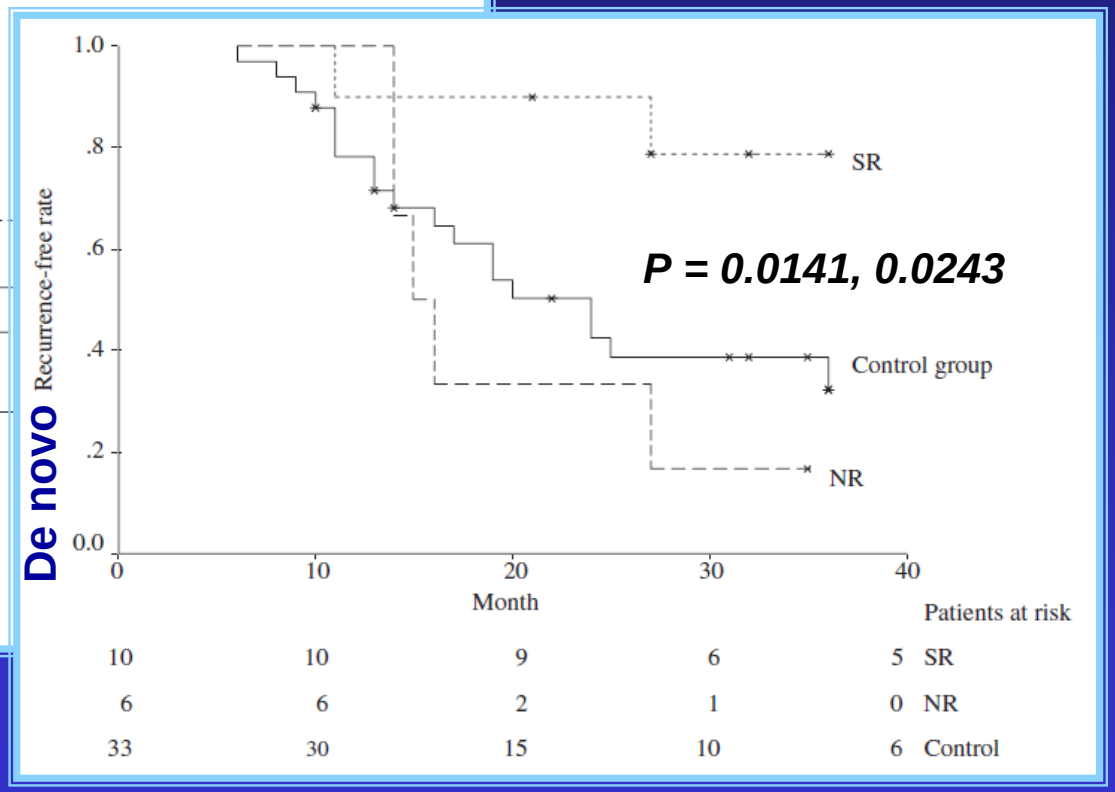
SAE (HCC vs. LC, 11% vs 13%), correlated to Bil (T) > 1.5 mg/dl (OD= 4.7, CI=1.5-15)

Huang JF, Yu ML, et al. J Hepatol 2011; 54: 219–226

Reducing Risk of *de novo* HCC Development in HCV-HCC post Local Curative Therapies post IFN/RBV

IFNα-2b, 3-5 MU tiw, plus RBV 24-48 w, n = 16 vs. control = 33





Hung CH, et al. J Gastroenterol Hepatol, 2005; 20: 1553-9.

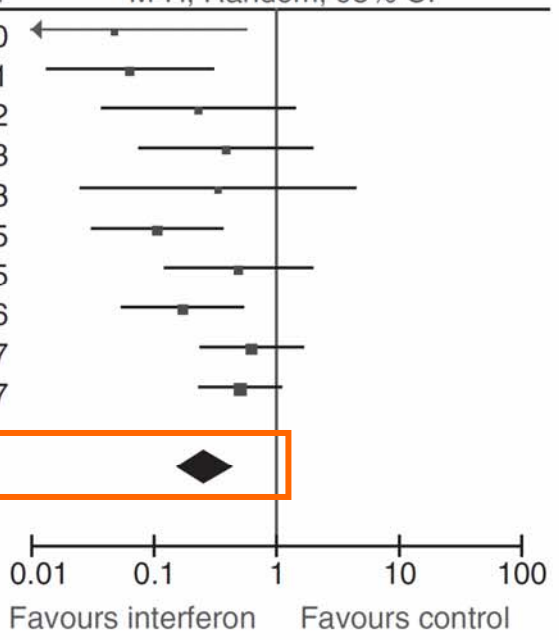
Benefit of IFN in reducing risk of *de novo* HCC recurrence after curative treatment of HCC in HCV-related LC

- 10 studies (n = 645, 301 treated with IFN) on the use of IFN after resection or ablation of HCV-associated HCC
- The benefit of IFN was stronger with SVR compared with non-SVR for HCC recurrence [0.19 (0.06–0.60); P = 0.005] and survival [0.31 (0.11–0.90); P = 0.03].

Study or Subgroup	Interferon Events	Interferon Total	Control Events	Control Total	Weight	Odds ratio M-H, Random, 95% CI	Year
Ikeda *et al.*	1	10	7	10	4.2%	0.05 [0.00, 0.56]	2000
Suou *et al.*	4	18	18	22	8.6%	0.06 [0.01, 0.30]	2001
Kubo *et al.*	9	15	13	15	6.9%	0.23 [0.04, 1.41]	2002
Shiratori *et al.*	40	49	23	25	8.2%	0.39 [0.08, 1.94]	2003
Lin *et al.*	5	8	5	6	3.9%	0.33 [0.03, 4.40]	2003
Sakaguchi *et al.*	6	24	25	33	11.8%	0.11 [0.03, 0.36]	2005
Hung *et al.*	11	16	27	33	10.1%	0.49 [0.12, 1.94]	2005
Mazzaferro *et al.*	57	76	70	74	12.8%	0.17 [0.06, 0.53]	2006
Jeong *et al.*	28	42	32	42	15.2%	0.63 [0.24, 1.63]	2007
Kudo *et al.*	24	43	60	84	18.3%	0.51 [0.23, 1.09]	2007
Total (95% CI)		301		344	100.0%	0.26 [0.15, 0.45]	
Total events	185		280				

Heterogeneity: Tau² = 0.27; Chi² = 14.41, df = 9 (P = 0.11); I^2 = 38%

Test for overall effect: Z = 4.84 (P < 0.00001)



Singal et al, Aliment Pharmacol Ther 2010; 32: 851–858

Prevention of HCV-related HCC

- APASL Recommendations:

✓ The control of transfusion-related, iatrogenic, and illicit drug userelated viral transmission is of paramount importance (2a, A).

✓ Efficient screening for HCV infection would find patients who require treatment (2b, B).

✓ Interferon therapy is indicated in acute hepatitis C to prevent chronicity (1b, A)

✓ Sustained virologic response to an IFN-based therapy reduces the risk of HCV-related HCC in patients with compensated chronic hepatitis C (1a, A).

Hepatol Int 2010

Prevention of HCV-related HCC

- **JSH Consensus Statements:**

- Among patients with chronic hepatitis C, the incidence of HCC is higher in those with marked fibrosis or liver cirrhosis.
- It is recommended that antiviral therapy with IFN be performed to prevent HCC in patients with chronic hepatitis C. Firstly, virus elimination is important. When it is impossible the liver function must be normalized.

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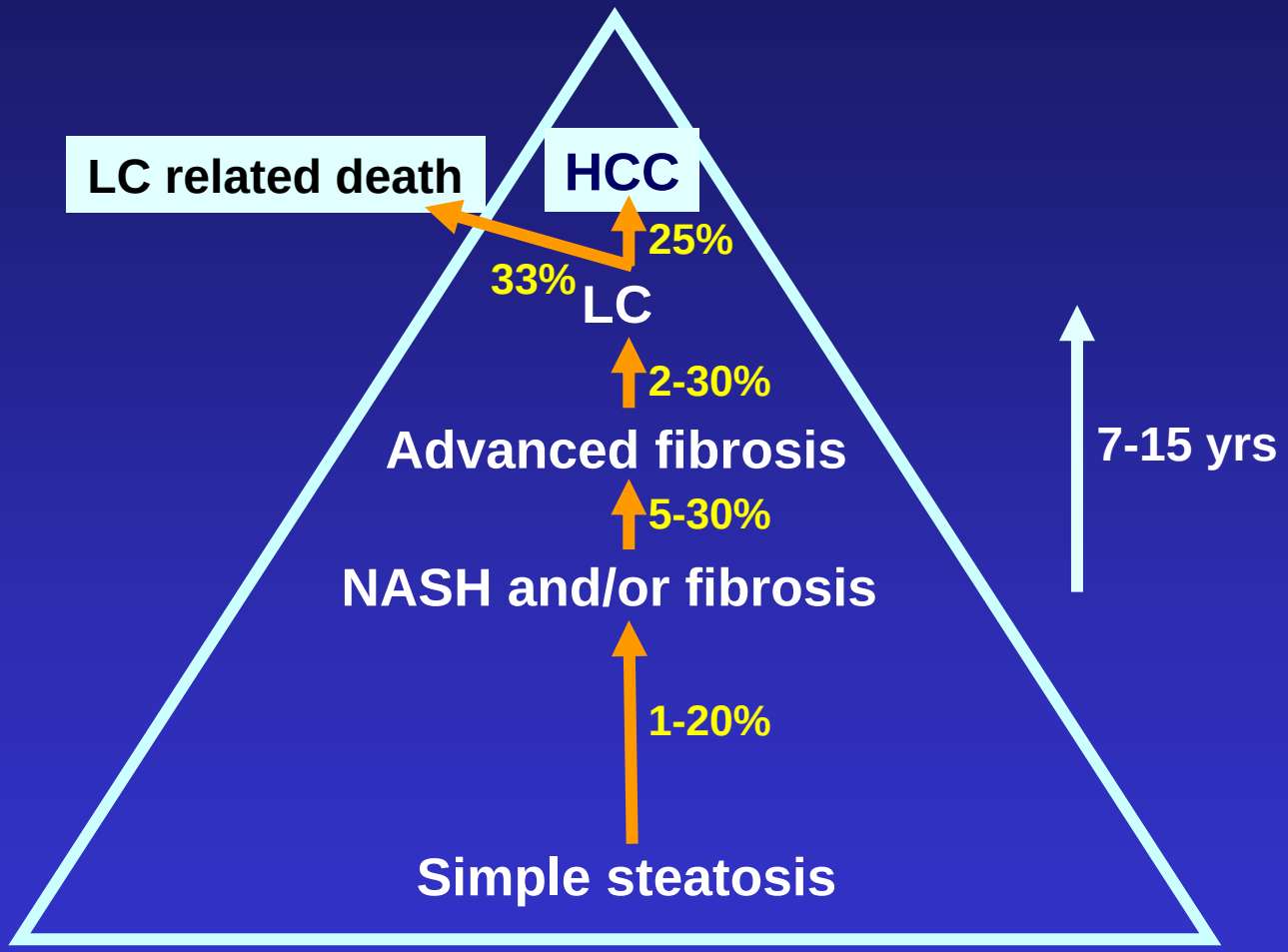
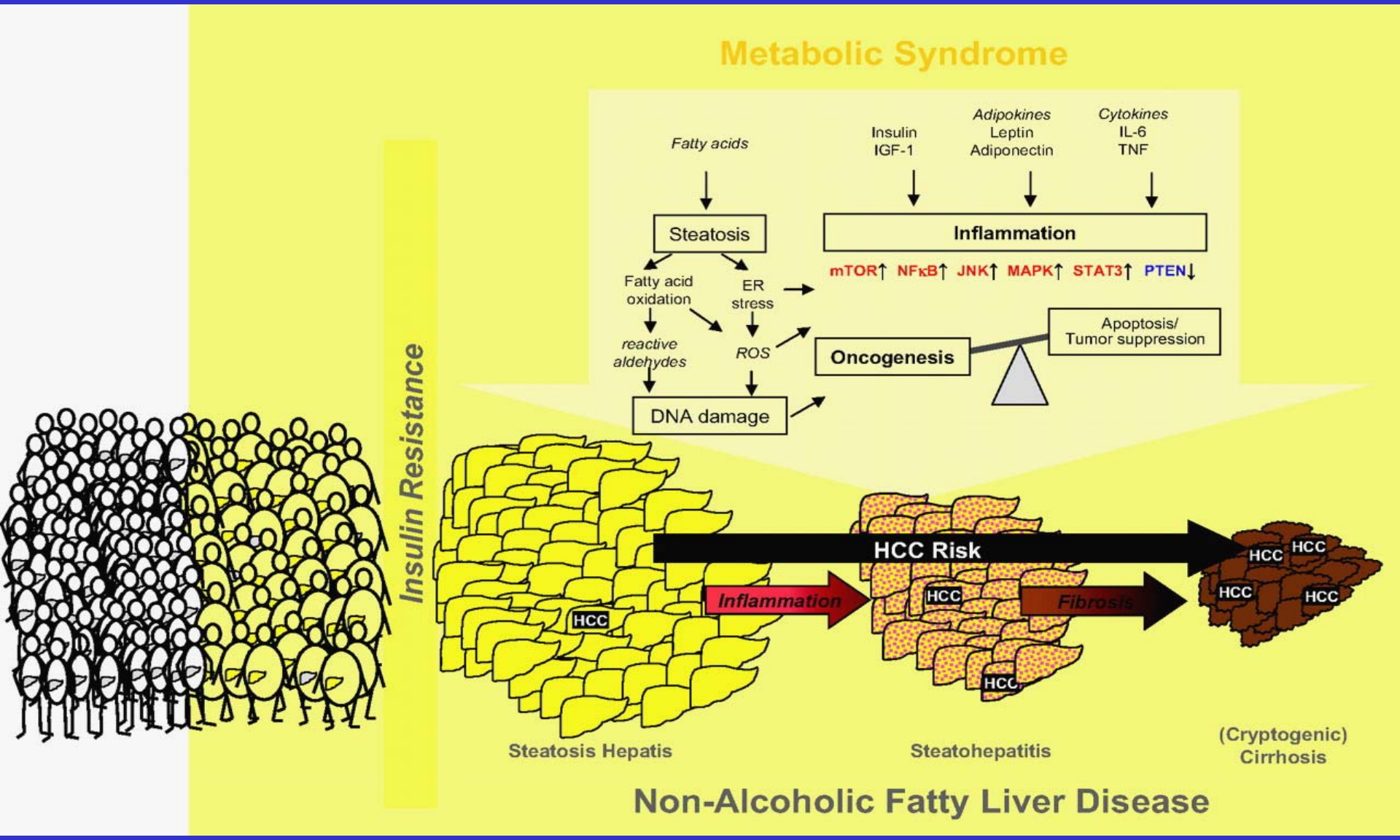
NAFLD / NASH may lead to Cirrhosis / HCC



Adams LA, et al. Gastroenterology 2005;129: 113-121
Ekstedt M, et al. Hepatology 2006; 44: 865-873
Bugianesi E, et al.Gastroenterology 2002; 123: 134-140
Adams LA, et al. J Hepatol 2005;42: 132-138
Angulo P. N Engl J Med 2002;346: 1221-1231
McCullogh AJ.,et al. Blackwell Publishing, 2005: 23-37
Ratziu V, et al. Gastroenterology 2000; 118: 1117–1123
Fassio E, et al. Hepatology 2004; 40: 820–826
Marchesini G, Hepatology 2003; 37: 917–923
Harrison SA,et al.Drugs 2003;63: 2379-2394

Molecular mechanisms linking non-alcoholic fatty liver disease (NAFLD) with the development of HCC



Stickel F , Hellerbrand C Gut 2010

Viral-unrelated Prevention of HCC

- APASL Recommendations:
  - ✓ Prevention of HCC in patients with nonalcoholic steatohepatitis (NASH) is primarily through lifestyle modification with diet and exercise (2, B).

Hepatol Int 2010

Summary (1)

- Risk identification and intervention are important with respect to the prevention of HCC in CHB, CHC and NAFLD.
- Universal hepatitis B vaccination should be implemented for effective prevention of HBV-related HCC.
- IFN and NA therapies may reduce the risk of HCC in CHB patients.

Summary (2)

- IFN-based therapy could reduce the risk of HCC development in CHC patients. The benefits are obtained mainly in those responders.
- The benefits of maintenance PegIFN monotherapy in reducing HCC risk in IFN-resistant CHC patients might exit in subgroup of cirrhotic pts.
- IFN-based therapy is feasible and may reduce de novo recurrence in those CHC-HCC patients after curative treatment.