First International Course on Translational Hepatology

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The burden of HCV-related HCC in the 3rd millennium and the impact of anti-HCV therapy

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Global incidence and mortality rates of HCC overlap

	Men		Women	
Geographical area	**#**	**AAIR***	**#**	**AAIR**
Developed countries				
Incidence	73,270	8.71	33,270	2.86
Mortality	68,992	8.07	36,657	3.01
Developing countries				
Incidence	325,108	17.43	132,298	6.77
Mortality	314,611	16.86	129,305	6.57

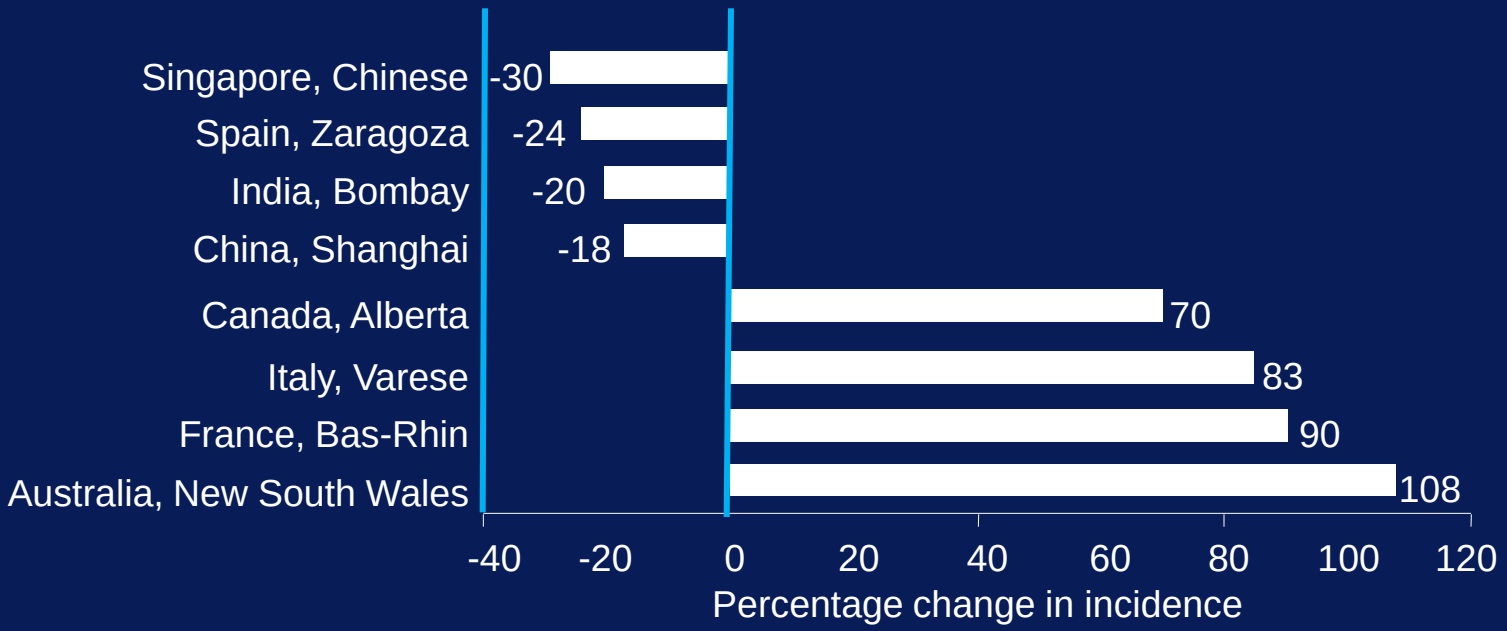
Bosch FX, et al. Clin Liver Dis. 2005;9:191-211.

Risk Factors of Hepatocellular Carcinoma: Estimates of the Attributable Fractions (%)

Risk factors	Europe / US	Japan	Africa / Asia
Hepatitis B virus	22 (4-58)	20 (18-44)	60 (40-90)
Hepatitis C virus	60 (12-72)	63 (48-94)	20 (9-56)
Alcohol	45 (8-57)	20 (15-33)	- (11-41)
Tobacco	12 (0-14)	40 (9-51)	22 -
Aflatoxin	limited	limited	high exposure
Other	< 5	-	< 5

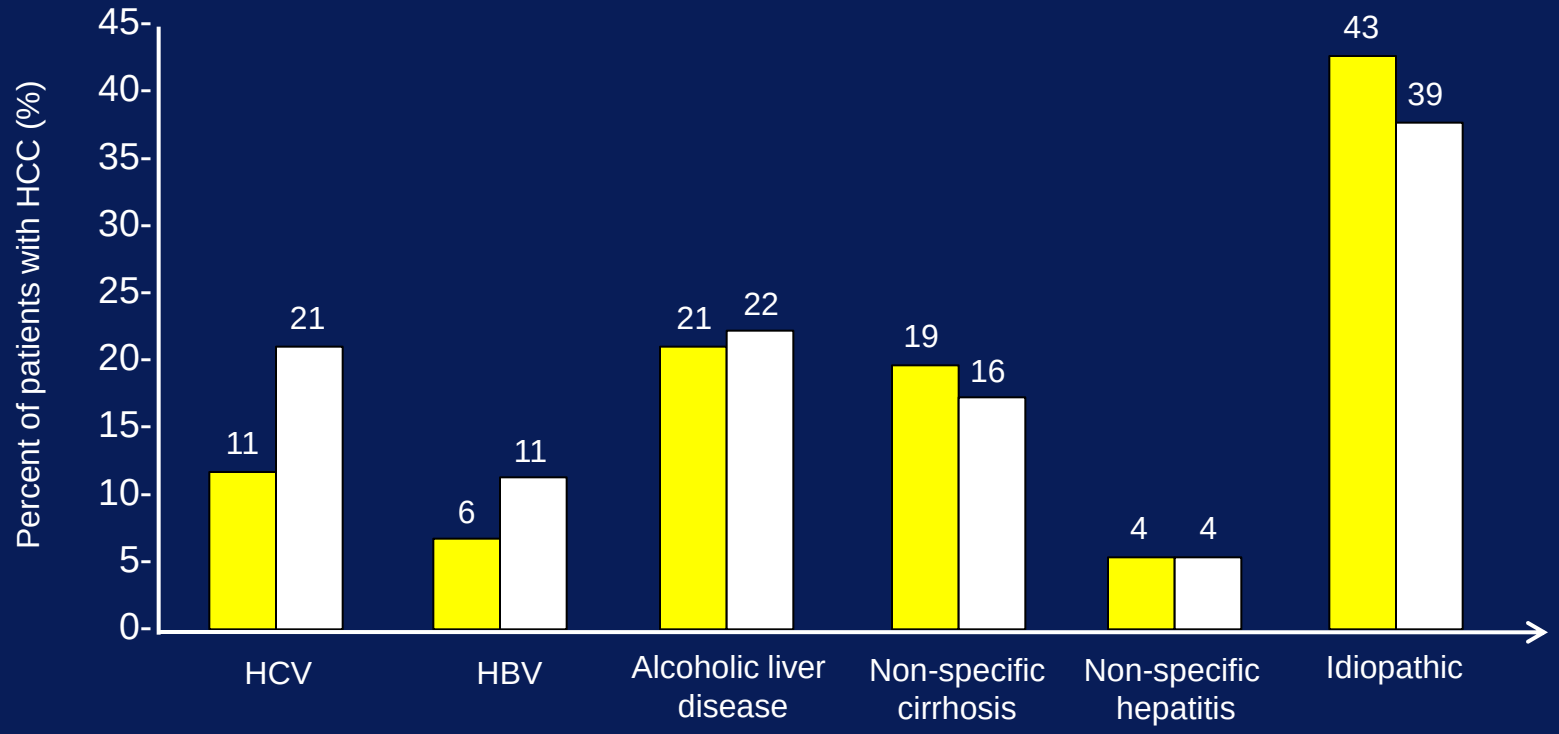
Adapted from Bosch & Ribes, Viruses and Liver Cancer 2002:1-15

Changes in the Incidence of HCC 1978–92, Males



McGlynn K, et al, Int J Cancer 2001;94:290–296

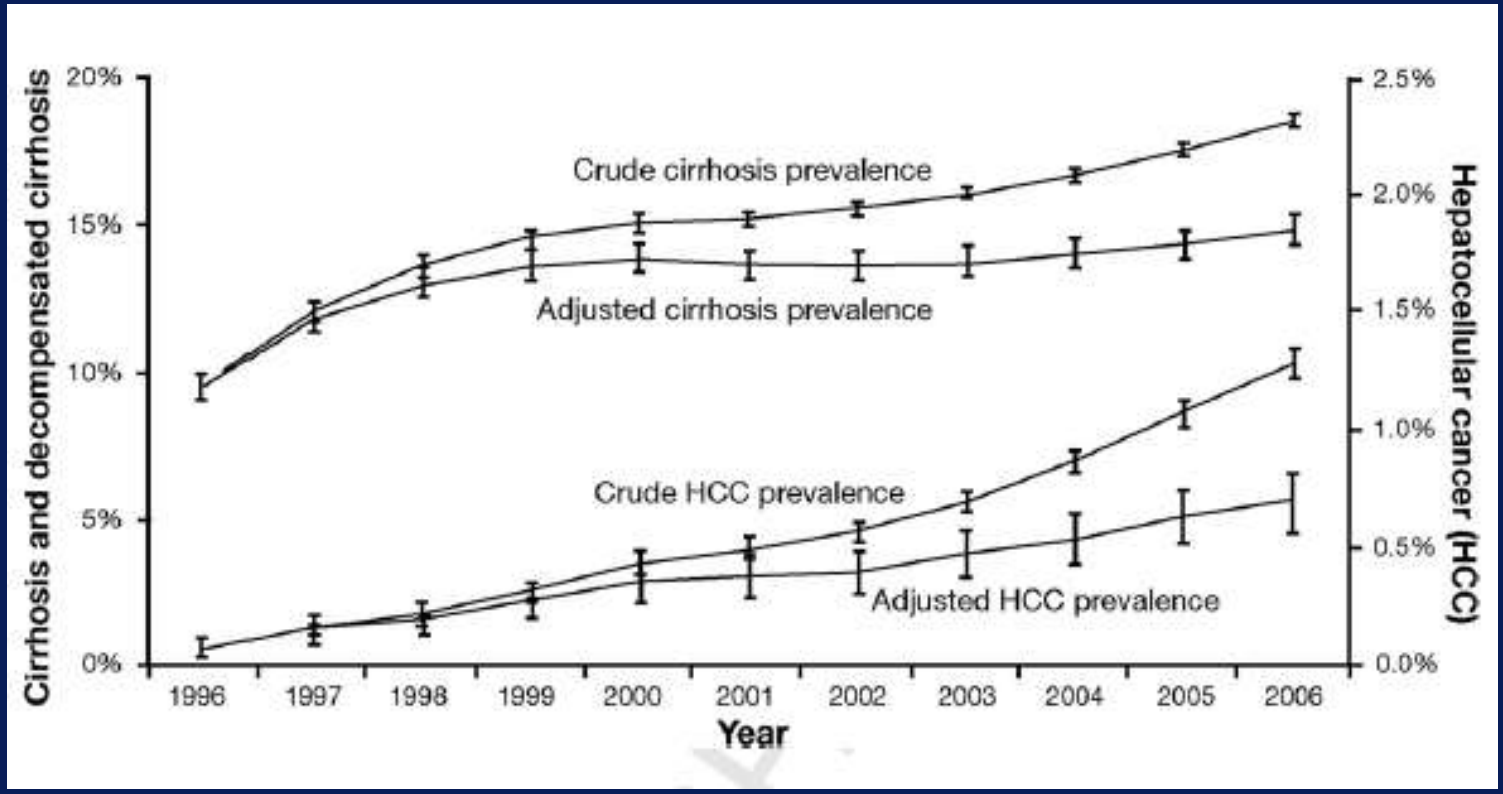
Hepatitis C Infection and the Increasing Incidence of HCC in USA a Population-based Study



Changes in the proportion of HCV, HBV, alcohol-induced liver disease, nonspecific cirrhosis, nonspecific hepatitis, and idiopathic among 2584 patients with HCC over 2 time periods (■ January 1993–June 1996; □ July 1996–December 1999).

Davila Gastroenterology 2004 127 1372-80

Increasing Prevalence of HCC and Cirrhosis in Patients With Chronic Hepatitis C Virus Infection



Kanwal et al, Gastroenterology in press

Cirrhosis Is the Dominant Risk Factor for Hepatocellular Carcinoma

Incidence	Cirrhotic patients	5-year incidence	15-20%
		1st cause of death	
Prevalence	Child-Pugh's A		5%
	Variceal bleeding		15%
	Spontaneous bacterial peritonitis		20%
	Necropsy		25%
Risk factors	Sex & age		
	Hepatitis C & B, ethanol		
	AFP, portal hypertension, platelet count		
	AgNor, PCNA, cell dysplasia, irregular regeneration		
	Intermediate hepatobiliary cells		

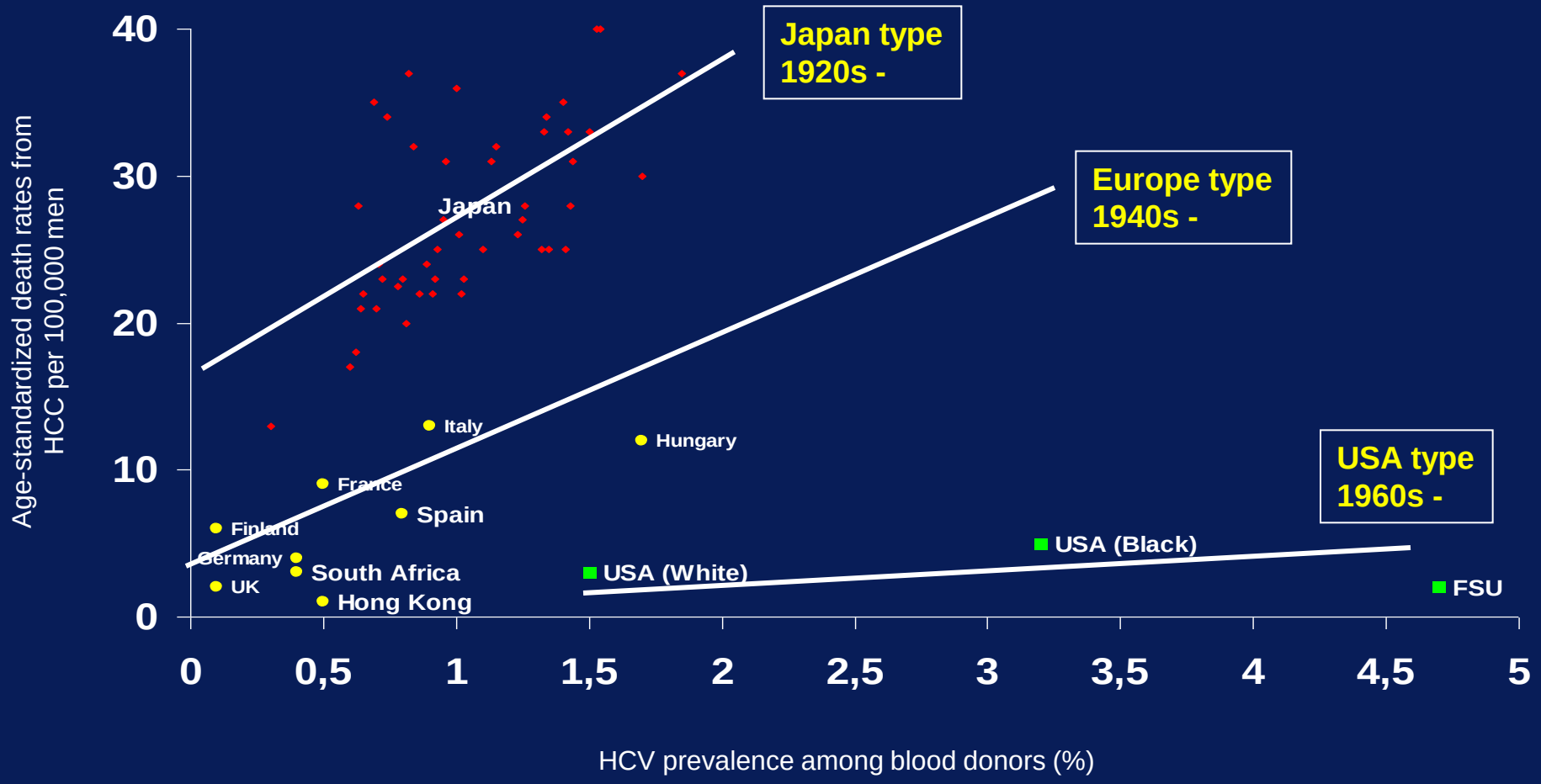
Colombo et al, 2001; Fattovich et al, 1997; Donato et al,2001; Degos et al, 2000; Bruix et al, 2001; Sangiovanni et al 2004
Ziol et al, Gastroenterology 2010

HCC May Also Develop in Non Cirrhotic Patients with Chronic Viral Hepatitis

HBV, Reveal [1]	164 incident HCCs diagnosed during 11.4 yr of follow-up 41,779 person-years of follow-up 33 (20%) without cirrhosis
HCV, HALT C [2]	48 incident HCC diagnosed during 4.6 yr of follow-up 8 (17%) with S_2-S_4
NAFLD/NASH [3]	65 case reports in patients with 0-2 fibrosis stage by Metavir or Ishak

[1]Chen et al JAMA 2006;295:65-73; [2]Lok et al Gastroenterology 2009;136:138-148; Marion-Audibert Liver International in press

Molecular Tracing of the Global HCV Epidemic Predicts Regional Patterns of HCC Mortality



Tanaka Y et al Gastroenterology 2006;130:703-714

Measures adopted for preventing HCC

Primary prevention	Measures designed to inhibit tumor occurrence
Secondary prevention	Measures designed to inhibit tumor progression to a more aggressive stage (screening/surveillance)
Tertiary prevention	Measures designed to minimize impact of established tumors on life expectancy and quality of life

National Cancer Institute. 2006.

Why are current studies in patients with viral hepatitis inadequate to evaluate anti-HCC activity of IFN?

- Studies were originally designed to assess antiviral activity of IFN using surrogate endpoints and, therefore, were underpowered to capture enough hard endpoints of the natural history of viral hepatitis
- To maximize sensitivity, enrolment was skewed toward patients with less advanced liver disease, who had better predicted compliance to IFN, but less risk of developing HCC in the short term
- Studies were hardly comparable with each other due to lack of patient stratification by risk predictors such as sex, duration and severity of liver disease, alcohol, obesity, and diabetes

Does IFN prevent HCC in chronic hepatitis C patients?

Study	Design	Patients	HCC per year		
			SVR, %	NR, %	Controls, %
Imai, 1998	R	419 IFN (144 Co.)	0.45	6.40	6.10
Yoshida, 1999	R	2,400 IFN (490 Co.)	0.40	4.00	3.20
Tanaka, 2000	R	594 IFN (144 Co.)	0.35	2.10	2.34
Ikeda, 1999	P	1,191 IFN (452 Co.)	0.14	1.75	1.24

Imai Y, et al. Ann Intern Med. 1998;129:94-9.; Yoshida H, et al. Ann Intern Med. 1999;131:174-81. Tanaka H, et al. Int J Cancer. 2000;87:741-9. Ikeda K, et al. Hepatology. 1999;29:1124-30.

Antiviral therapy for HCV-cirrhosis: association with reduced HCC development and improved survival

Tokyo-Chiba: prospective study of 74 cirrhotics who declined treatment and 271 treated with IFN for 26–88 week

Cause of Death	Interferon-Treated Patients (n = 271)			Untreated Patients (n = 74)
	All	Patients with SVR (n = 64)	Patients with Non-SVR (n = 207)	
Patients who died	45	1	44	24
Liver-related deaths				
Overall, *n (%)*	32 (71)	0 (0)	32 (73)	19 (79)
Hepatocellular carcinoma, *n*	25	0	25	11
Liver failure, *n*	6	0	6	8
GI bleeding, *n*	1	0	1	0
Deaths unrelated to liver disease				
Overall, *n (%)*	13 (29)	1 (100)	12 (27)	5 (21)

Shiratori Y, et al. Ann Intern Med. 2005; 142:105-14.

SVR to IFN-α is associated with improved outcome in HCV-related cirrhosis: a retrospective study in Italy

Strata	No. of patients	Person-years	No. of events	Rate/100 person-years (95% CI)	Rate ratio (95% CI)
Liver-related complications					
Non-SVR	759	5,703	107	1.88 (1.54–2.27)	Not applicable
SVR	124	1,061	0	0 (0–0.35)	
HCC					
Non-SVR	759	5,805	122	2.10 (1.75–2.51)	3.12 (1.42–6.86)
SVR	124	1,055	7	0.66 (0.27–1.87)	
Liver-related mortality					
Non-SVR	728	5,781	83	1.44 (0.14–1.78)	7.59 (1.84–31.29)
SVR	120	1,019	2	0.19 (0.02–0.71)	
Non liver-related mortality					
Non-SVR	759	6,004	31	0.52 (0.35–0.73)	1.28 (0.44–3.68)
SVR	124	1,077	4	0.37 (0.1–0.96)	

Bruno S, et al. Hepatology. 2007;45:579-87.

Effect of Aging on Risk for Hepatocellular Carcinoma in Chronic Hepatitis C Virus Infection

Annual incidence of HCC after IFN treatment

Factors	Total	< 65 years	≥ 65 years
Fibrosis stage			
F0/F1	0.2%	0.1%	0.9%
F2	0.8%	0.6%	1.7%
F3	2.5%	1.8%	4.6%
F4	4.6%	4.4%	5.1%
Total	1.1%	0.8%	2.4%
Virological response			
SVR	0.4%	0.2%	1.3%
Non-SVR	1.4%	1.0%	2.9%

Asahina et al, Hepatology 2010;52:518-527

Does maintenance therapy with peg-IFN prevent HCC? The HALT-C study

Study outline: Pegasys 90 mcg x week for 3.5 years

Non-responders to combo therapy: 622 S_{3-4} + 428 S_{5-6}

Outcomes	Treated, % (n = 517)	Controls, % (n = 533)	p value
Decompensation	6.6	4.6	ns
HCC	2.8	3.2	ns
Increased stage	28.2	31.9	ns
Death	6.6	4.6	ns
Any outcome	34.1	33.8	ns

Di Bisceglie A, et al. N Engl J Med. 2008;359:2429-41.

Is HCC prevented by antiviral therapy? The position of the international liver societies

AASLD PG (HCC)[1]	HBV: continue to offer surveillance even after therapy-induced remission of inflammation or seroconversion HCV: SVR not a reason to withold HCC surveillance
JSH (HCC)[2]	No recommendation
AASLD PG (HCV)[3]	SVR cirrhotics should continue HCC surveillance. Maintenance therapy not recommended for F3/F4 patients with a previous therapeutic failure
EASL CPG (HBV)[4]	Needs to be established

1. Bruix J, Sherman M. Hepatology. 2005;42:1208-36. 2. Makuuchi M, et al. Hepatol Res. 2008;38:37-51.;22:607-10.
3. Ghany MG, et al. Hepatology. 2009;49:1335-74. 4. EASL. J Hepatol. 2009;50:227-42.

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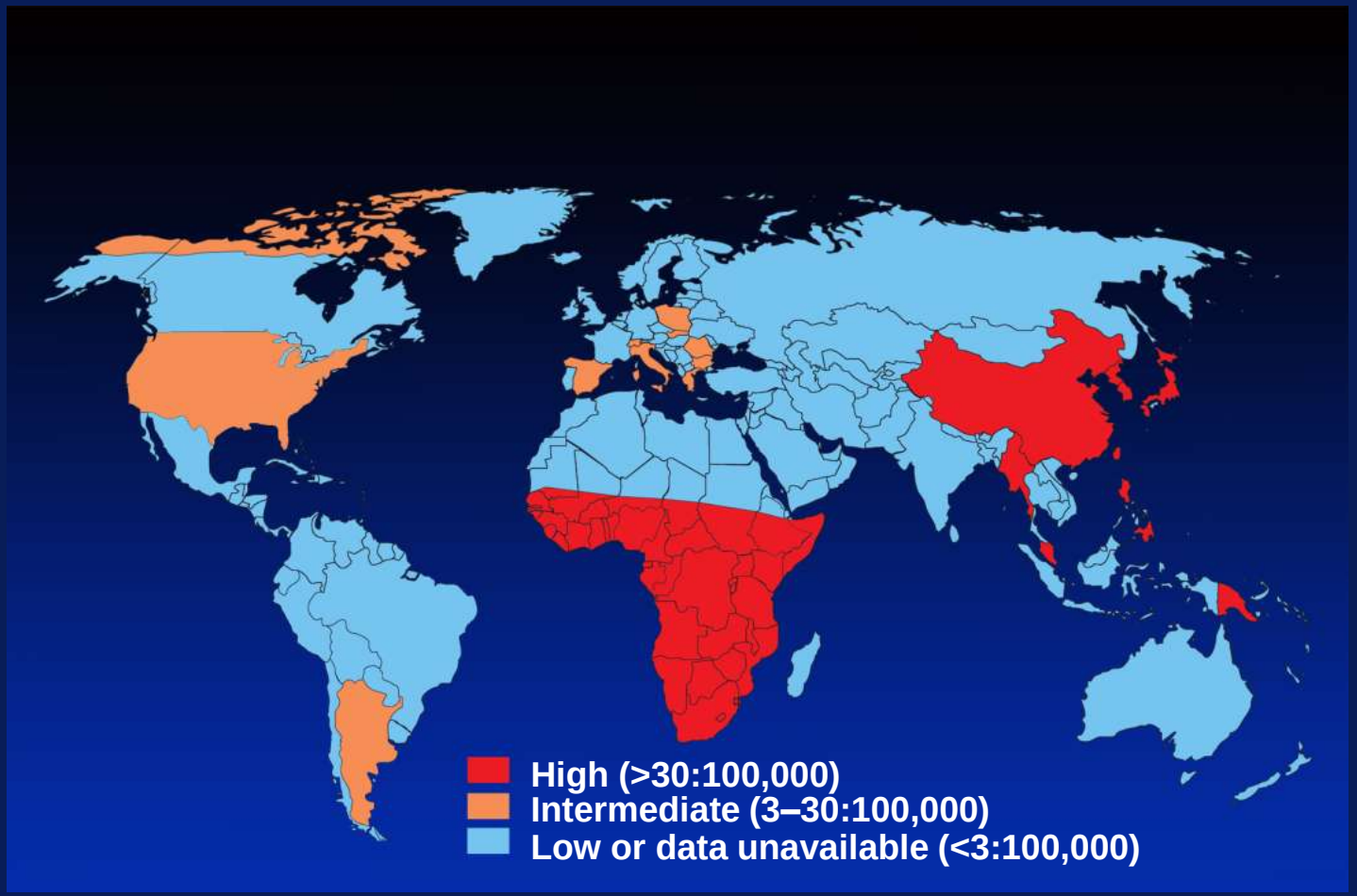
Total	1.1%	0.8%	2.4%
Degree of liver steatosis			
< 10%	0.5%	0.2%	1.4%
≥ 10%	2.0%	1.8%	3.0%
Virological response			
SVR	0.4%	0.2%	1.3%
Non-SVR	1.4%	1.0%	2.9%

Asahina et al, Hepatology 2010;52:518-527

Worldwide Distribution of Hepatocellular Carcinoma



Ferlay, et al, Globocan 2000, Lyon IARC Press 2001; El-Serag HB, Gastroenterology 2007;132:2557–76

The Magnitude of the Association Between Metabolic Syndrome and Clinical Outcomes

Outcome	No. pts	Population	OR (95% C.I.)
[1]HCC	3,649	USA	2.13 (1.96-2.31)
[1]ICC	743	USA	1.56 (1.32-1.83)
[2]CVD	172,573	Europe & USA	2.18 (1.63-2.93)
[2]Death	172,573	Europe & USA	1.60 (1.37-1.92)

[1]Welzel et al, submitted; [2]Gami et al, J Am College Cardiol, 2007;49:403-414

Why Is HCC Incidence Rising in USA and Europe?

Increasing prevalence of patients with cirrhosis

Rising incidence of cirrhosis

- **HCV (main reason)**
- **HBV**
- **Other (NAFLD/insulin resistance)**

Improved survival of patients with cirrhosis

El-Serag HB, Gastroenterology 2004

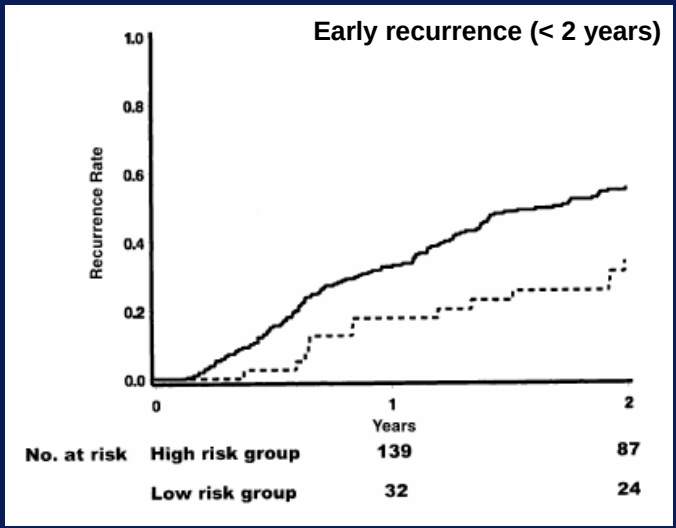
Levels of evidence according to study design

Grade	Definition
I	Randomized controlled trials
II-1	Controlled trials without randomization
II-2	Cohort or case-control analytic studies
II-3	Multiple time series, dramatic uncontrolled experiments
III	Opinion of respected authorities, descriptive epidemiology

META-ANALYSIS

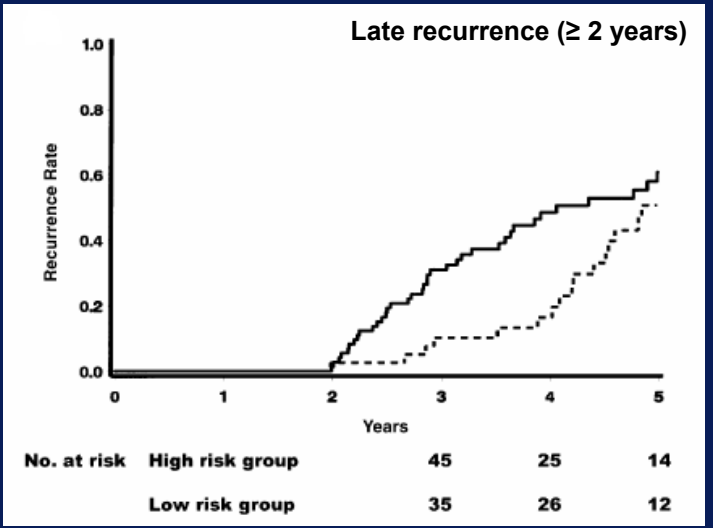
Risk factors contributing to early- and late-phase intrahepatic recurrence of HCC after hepatectomy

- University of Tokyo and Shiushu. Database: 1990–1998. 249 patients with ≤ 5 cm HCC resected
- Surveillance with AFP, DCP, US, and CT scan. 184 (74%) with recurrence, April 2001



Predictors of recurrence:

- Microscopic vascular invasion
- Serum AFP value ≥ 32 ng/mL
- Non anatomical resection



Predictors of recurrence:

- Grade of hepatitis activity
- Tumor nodule multiplicity
- Gross tumor classification

Imamura H, et al. J Hepatol. 2003;38:200-7.

Chemoprevention of HCC recurrence after curative resection and ablation in patients with chronic hepatitis C: RCTs

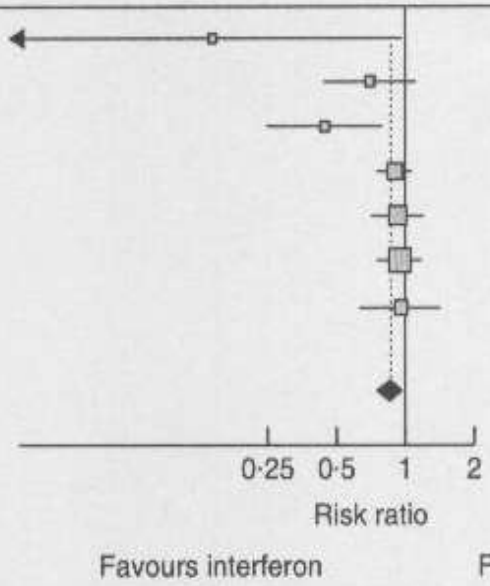
Study	Selection	Control	Treated	Treatment	Recurrence	5-year survival
Ikeda 2000 (R+A) *(Tokyo, J)*	TNM I/II	10	10	IFNβ x 36 mo.	70% vs. 10%*	n.a.
Kubo 2001 (R) *(Osaka, J)*	TNM I/II	15	15	IFNα x 24 mo.	80% vs. 33%*	n.a.
Shiratori 2003 (A) *(Tokyo, J)*	TNM I/II	25	49	IFNα x 12 mo.	92% vs. 80%	48% vs. 68%
Mazzaferro 2006 (R) *(Milan, I)*	TNM I/II	74	76	IFNα x 12 mo.	68% vs. 63%	52% vs. 64%
Muto 1996 (R+A) *(Gifu, J)*	Okuda I/II	45	44	Retinoids x 12 mo.	49% vs. 27%*	n.a.
Kakizaki 2007 (R+A) *(Gunma, J)*	TNM I/III	30	30	Vitamin K_2	90% vs. 61%*	66% vs. 78%**

* Statistically significant differences;
** 3-year survival.

Ikeda K, et al. Hepatology. 2000;32:228-32. Kubo S, et al. Ann Intern Med. 2001;134:963-7. Shiratori Y, et al. Ann Intern Med. 2003;138:299-306. Mazzaferro V, et al. Hepatology. 2006;44:1543-54. Muto Y, et al. N Engl J Med. 1996;334:1561-67. Kakizaki S, et al. J Gastroenterol Hepatol. 2007;22:518-22.

Systematic review and meta-analysis of IFN after curative treatment of HCC in patients with viral hepatitis

Reference	Recurrence rate: Interferon	Recurrence rate: Placebo	Risk ratio	Weight (%)
Ikeda *et al.*[14]	1 of 10	7 of 10	0·14 (0·02, 0·96)	3·4
Kubo *et al.*[15]	9 of 15	13 of 15	0·69 (0·44, 1·09)	6·4
Lin *et al.*[17]	8 of 20	9 of 10	0·44 (0·25, 0·79)	5·9
Shiratori *et al.*[16]	40 of 49	23 of 25	0·89 (0·74, 1·06)	15·0
Mazzaferro *et al.*[23]	44 of 76	47 of 74	0·91 (0·70, 1·18)	23·5
Sun *et al.*[22]	67 of 118	71 of 118	0·94 (0·76, 1·17)	35·0
Lo *et al.*[24]	21 of 40	22 of 40	0·95 (0·64, 1·43)	10·8
Overall	190 of 328	192 of 292	0·86 (0·76, 0·97), I^2 = 44%	



Breitenstein S, et al. Br J Surg. 2009;96:975-81.

Summary

- HCC prevalence continues to increase in many parts of world
- Cirrhosis (e.g. alcohol abuse or hepatitis B or C infection) is the dominant risk factor for HCC
- In patients with hepatitis C cirrhosis, antiviral therapy resulting in SVR is associated with a small reduction in risk
- Following curative resection/ablation in patients with chronic hepatitis C infection, interferon therapy is associated with a small reduction in recurrent HCC