Evidence for a rising burden of hepatocellular carcinoma

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After 10 minutes

HCC Lecture layout

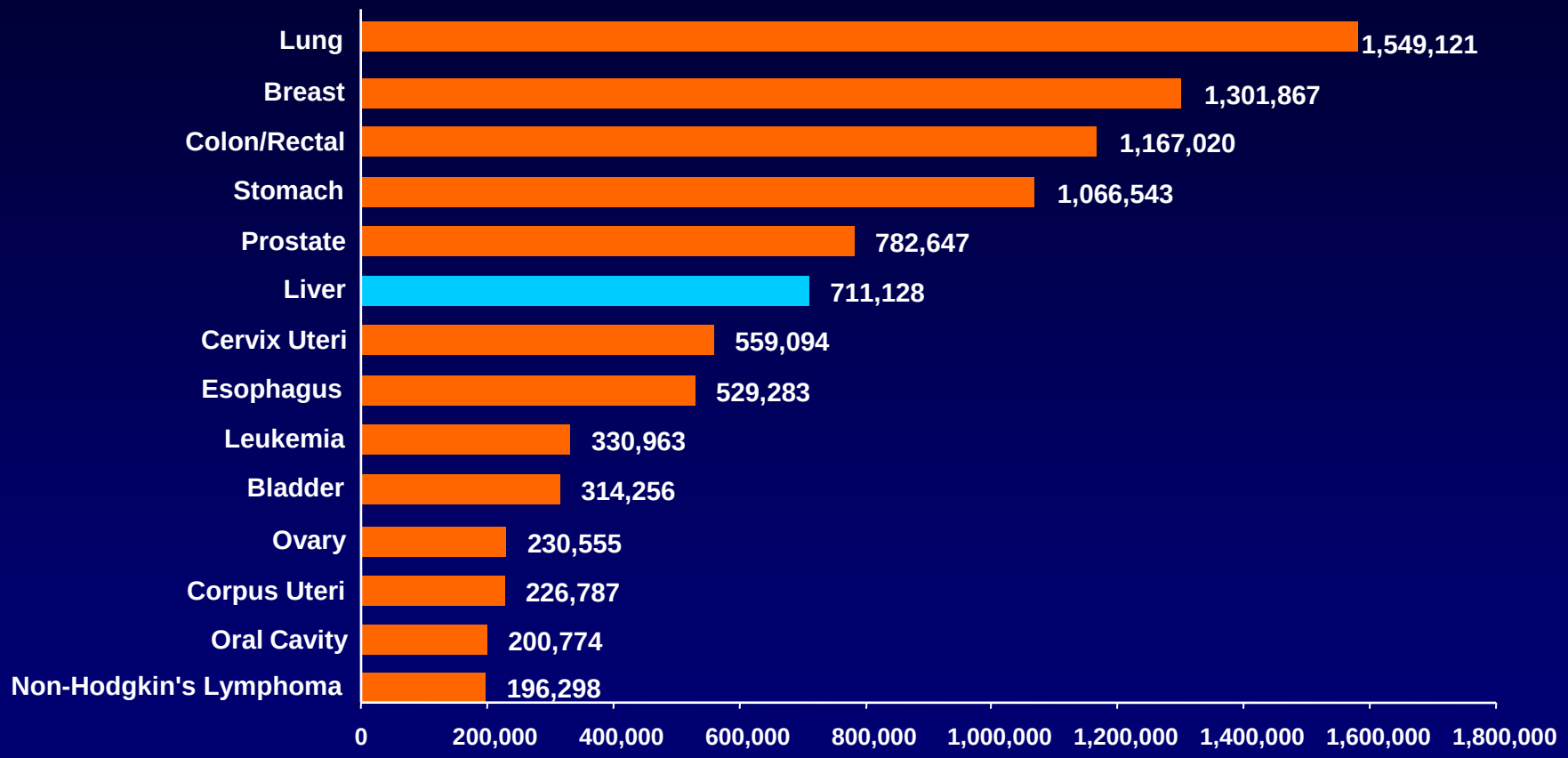
- Epidemiology-general
- Causes:
  - -Viral
  - -non-viral
- HCC Israel
- Prevention

Hepatocellular Carcinoma-facts (1)

- 700,000 cases/yr worldwide
  - 6th among cancers worldwide
- Leading cause of cancer-death Asia/Middle East
- 85% of HCC cases occur in Eastern and South-east Asia and Sub Saharan Africa
- Leading cause of death in cirrhotic patients

Joseph M Llovet and Margarita Sala. *Eur Jo Gastro & Hep.* 2005, (17) 5

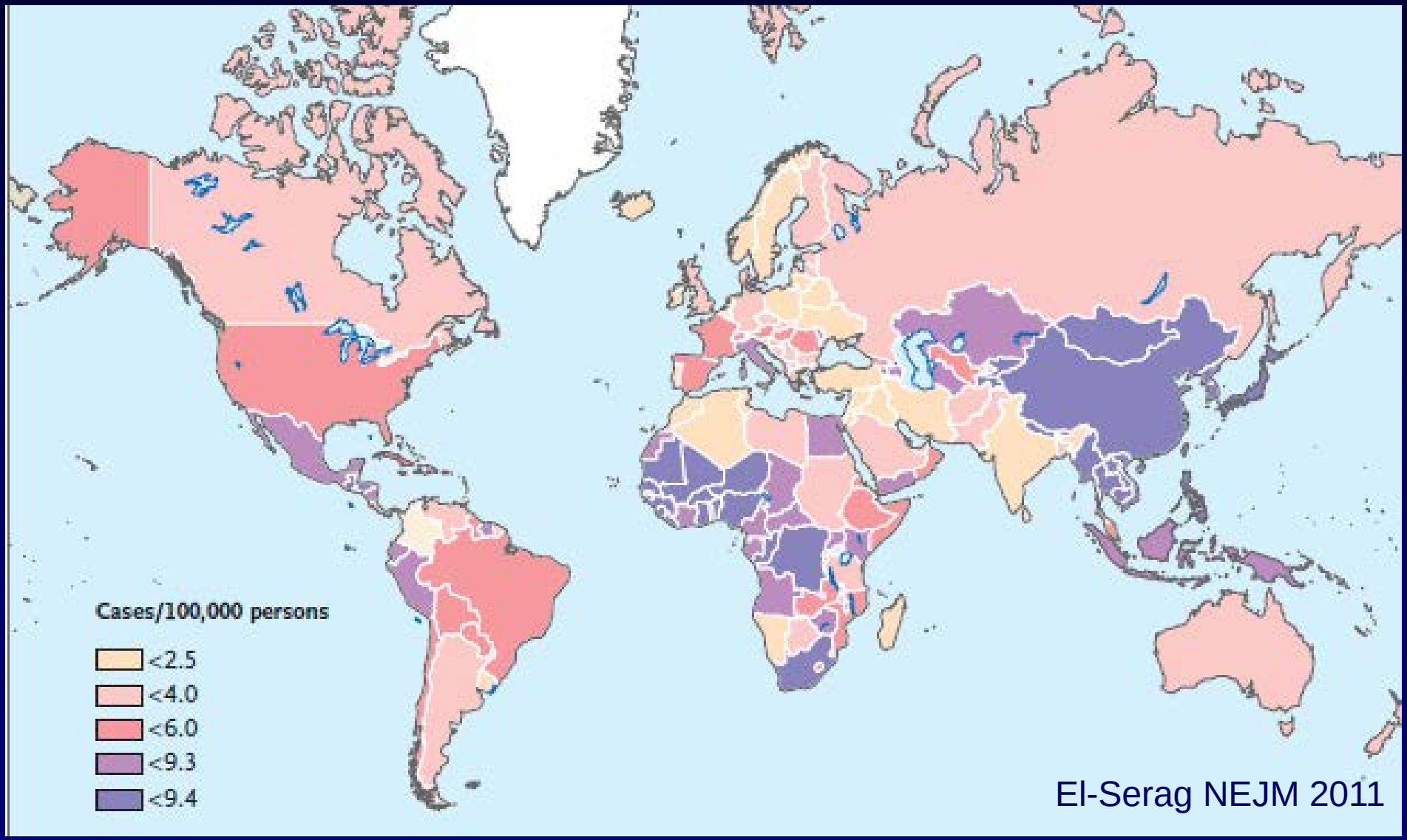
Liver Cancer Incidence: Sixth Most Common Cancer Worldwide[1]



- **HCC is the most common primary liver malignancy in adults[2]**

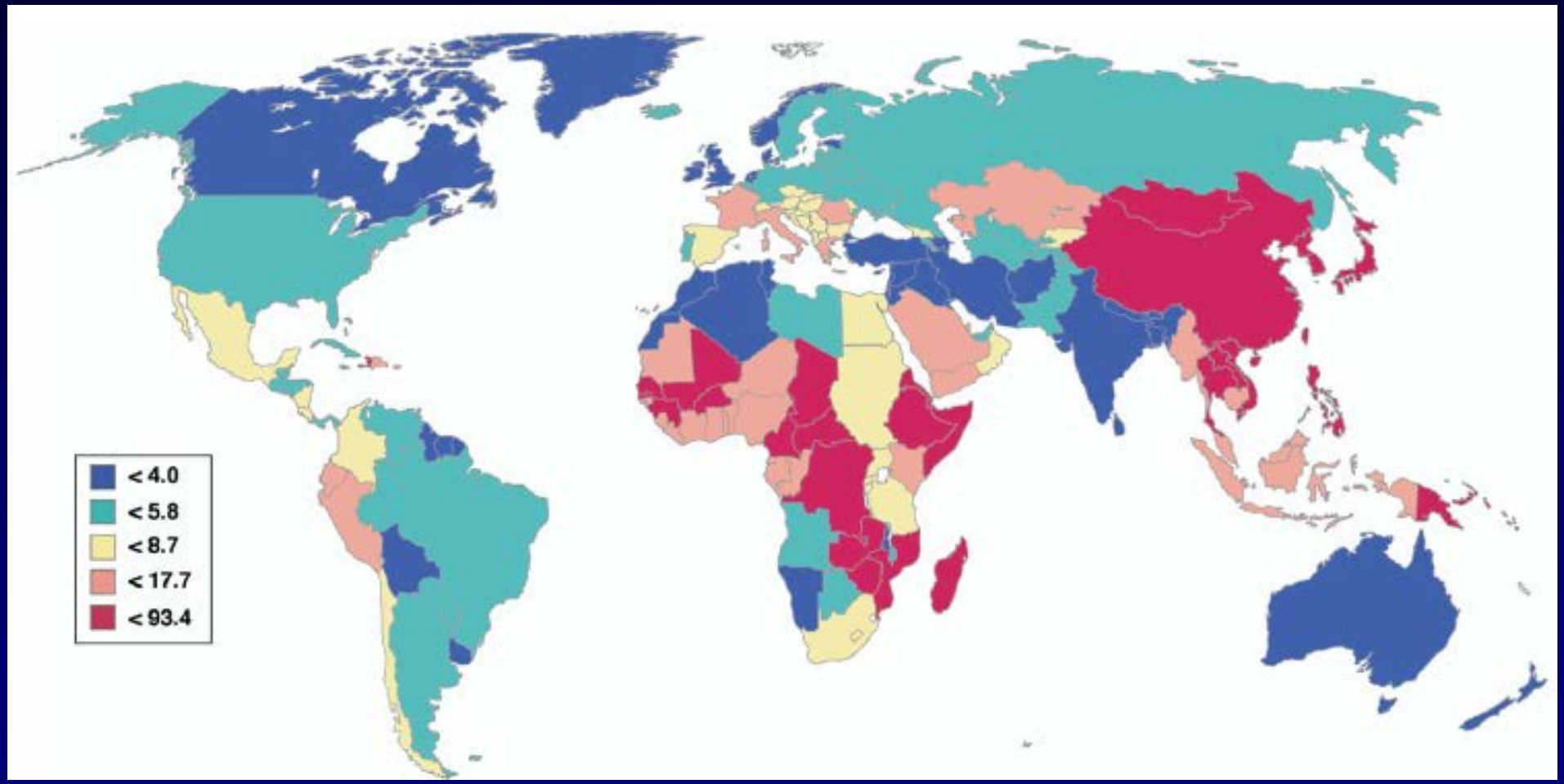
1. Garcia M, et al. American Cancer Society, 2007. www.cancer.org. Accessed March 20, 2008.
2. Perz JF, et al. *J Hepatol*. 2006;45:529-538.

Regional variation in incidence rates of HCC



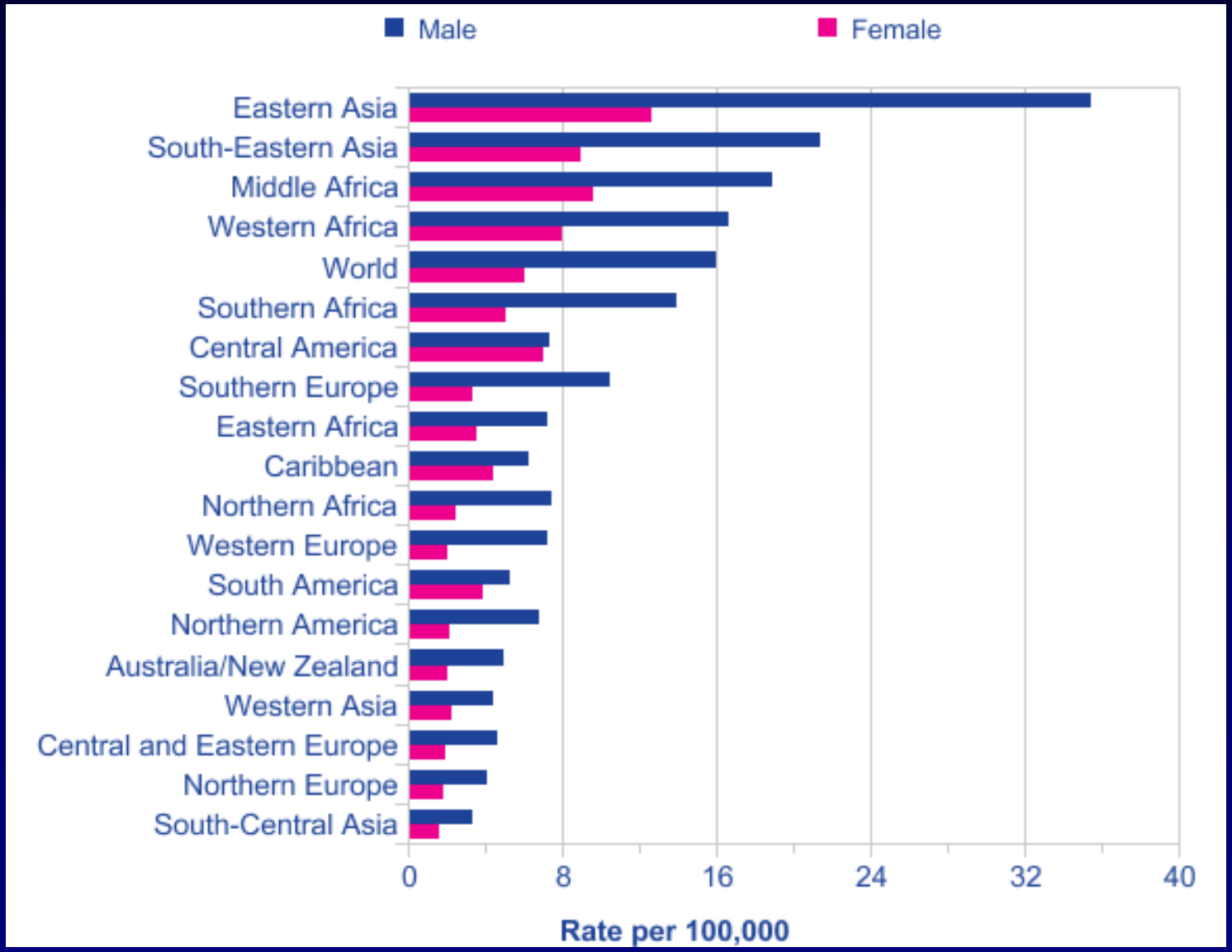
El-Serag NEJM 2011

Regional variations in mortality rates of HCC



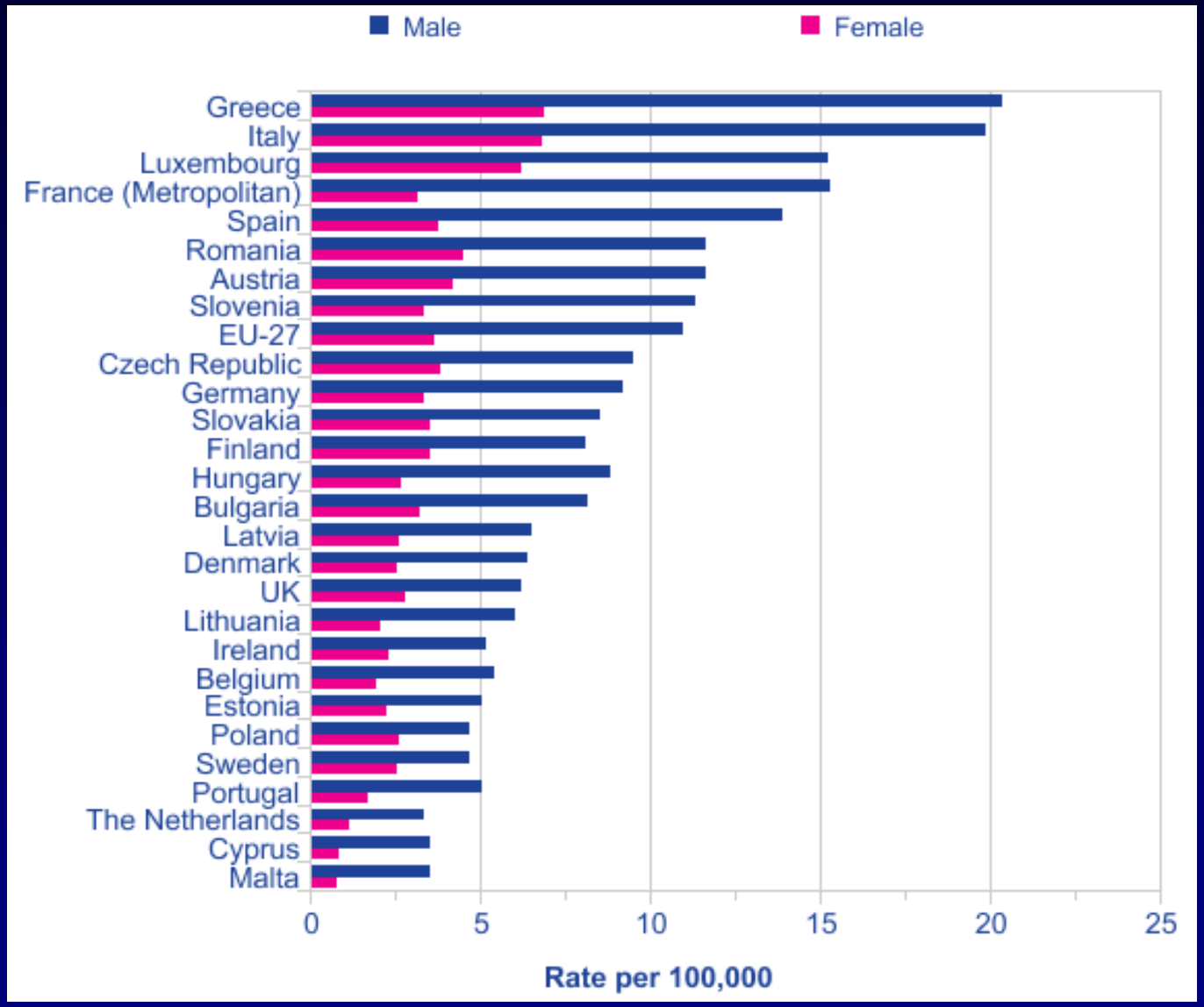
El-Serag H et al, Gastroenterology 2007

HCC standardised incidence rates per 100K population, world regions 2008



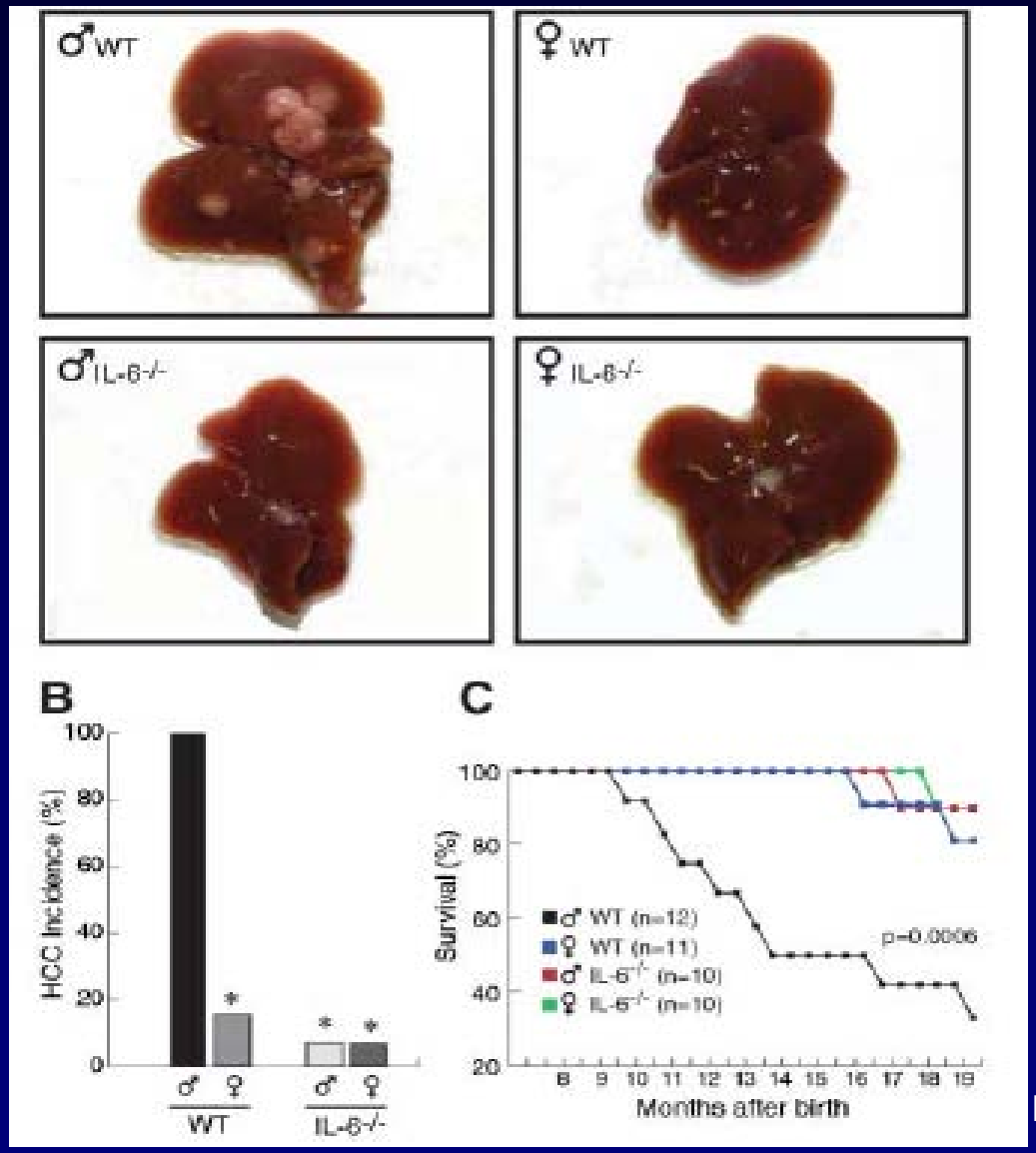
CANCER RESEARCH UK

HCC European standardized incidence rates per 100K, EU-27 countries



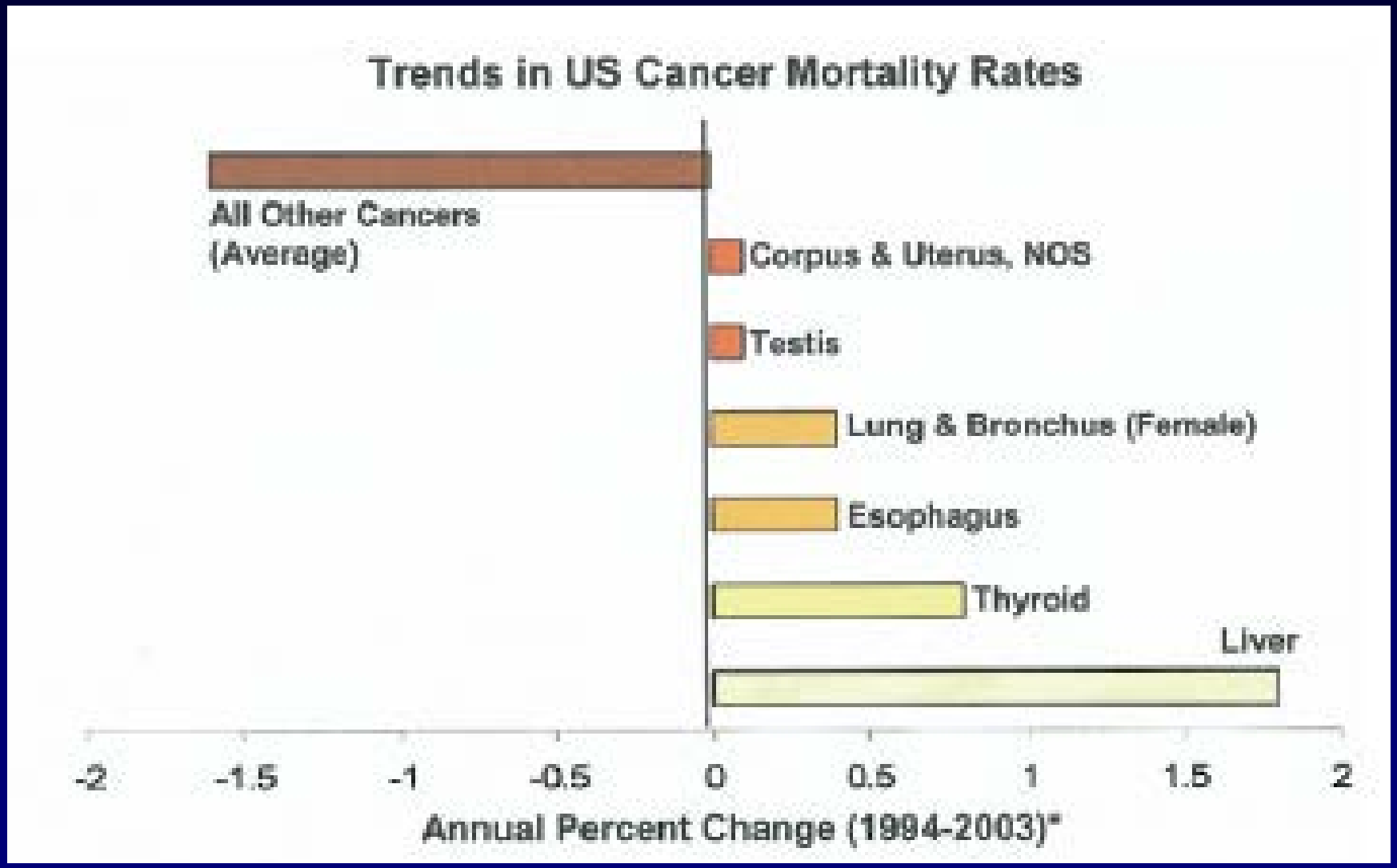
CANCER RESEARCH UK

Role of IL-6 in gender disparity in HCC



Karin M, Science 2007

HCC has the fastest growing death rate in the USA.

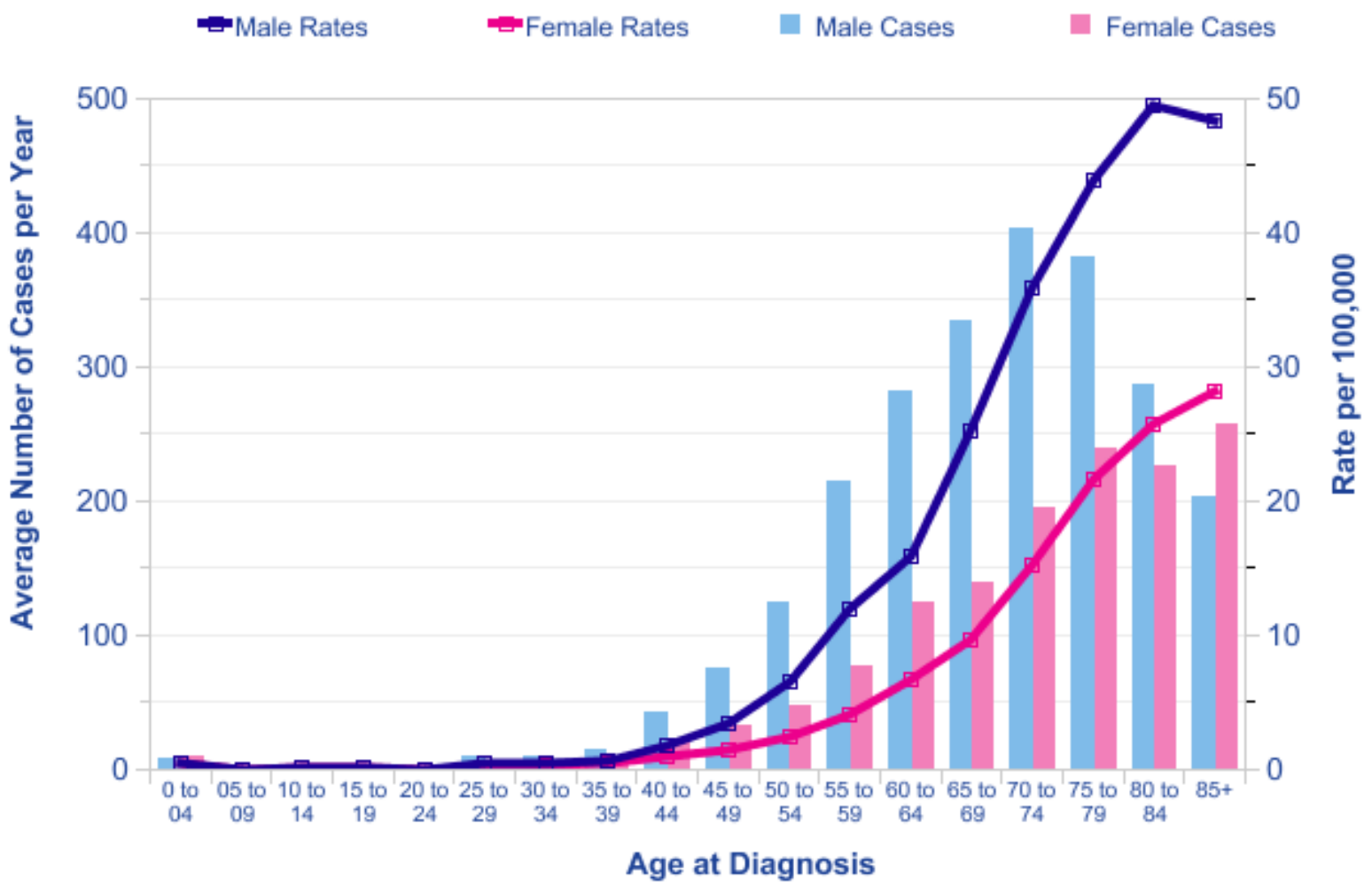


El-Serag H et al, Gastroenterology 2007

Hepatocellular Carcinoma-facts (2)

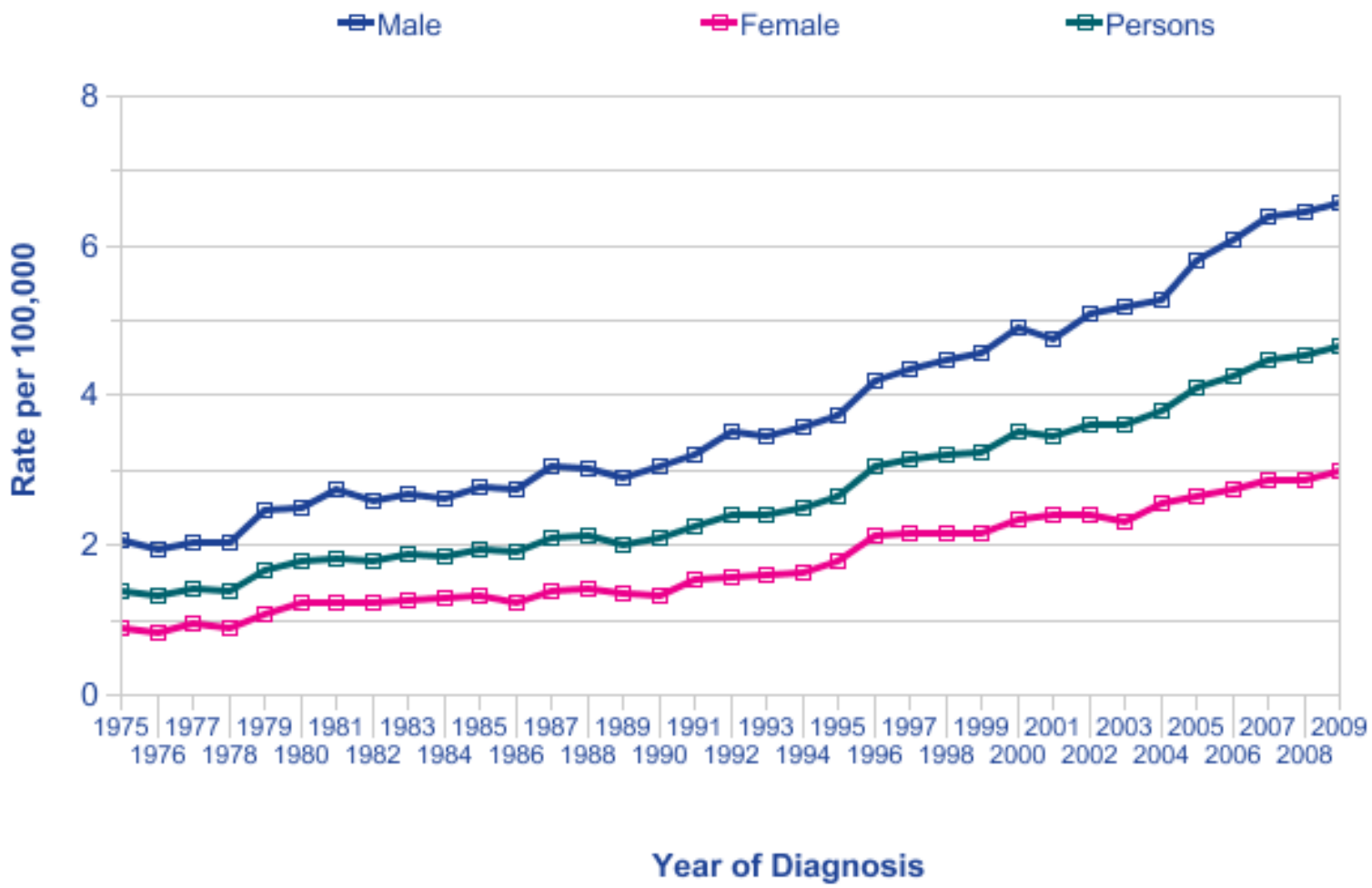
- 1985-2009 incidence has increased 3-fold
  - Estimation of new cases: 21,370
  - Estimation of deaths: 17,000
- Incidence increasing in United States and Europe

HCC number of new Cases per year and Incidence Rates per 100K (UK)



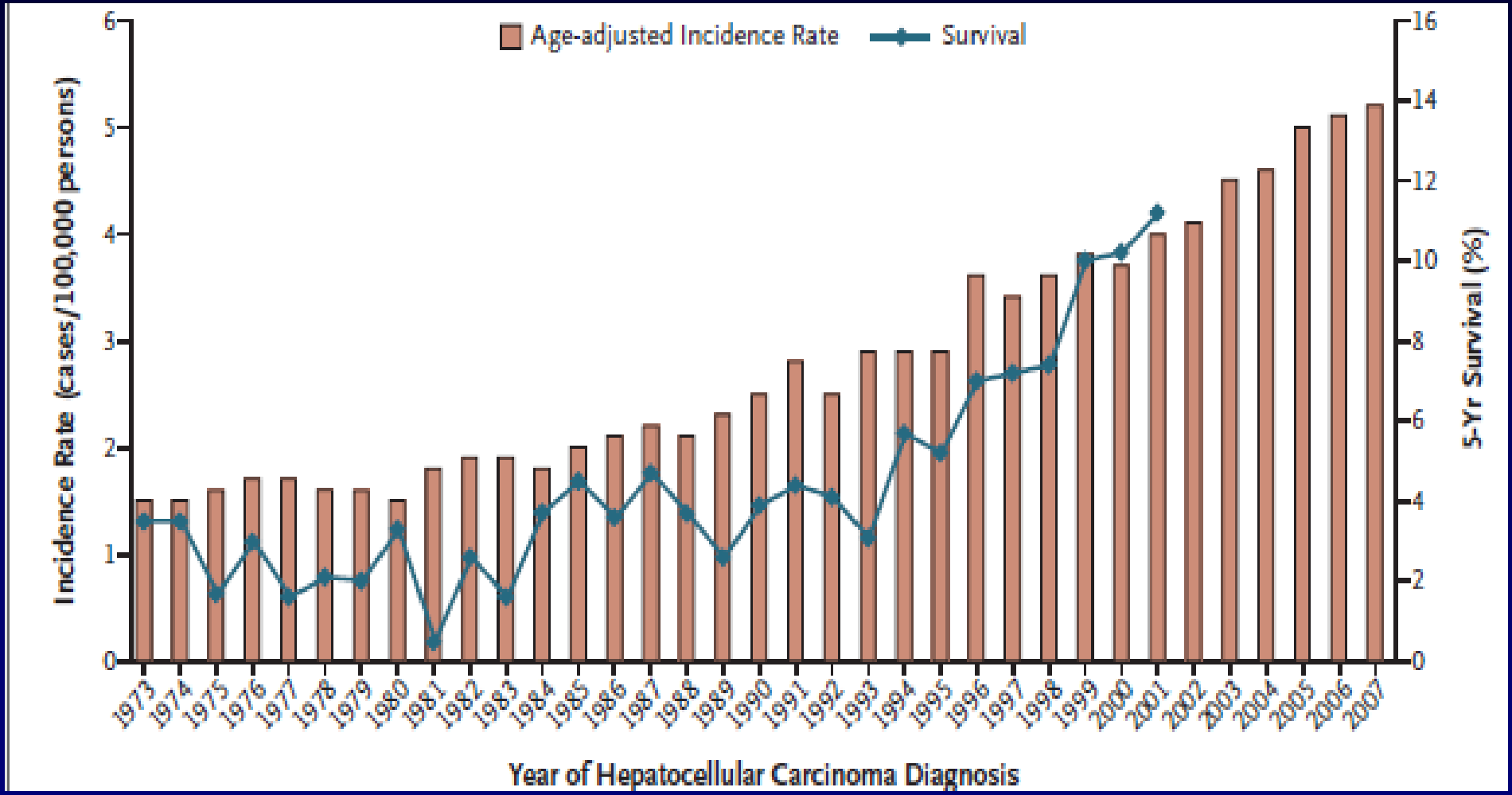
CANCER RESEARCH UK

HCC European incidence rates per 100K by Sex, (UK) 1975-2009



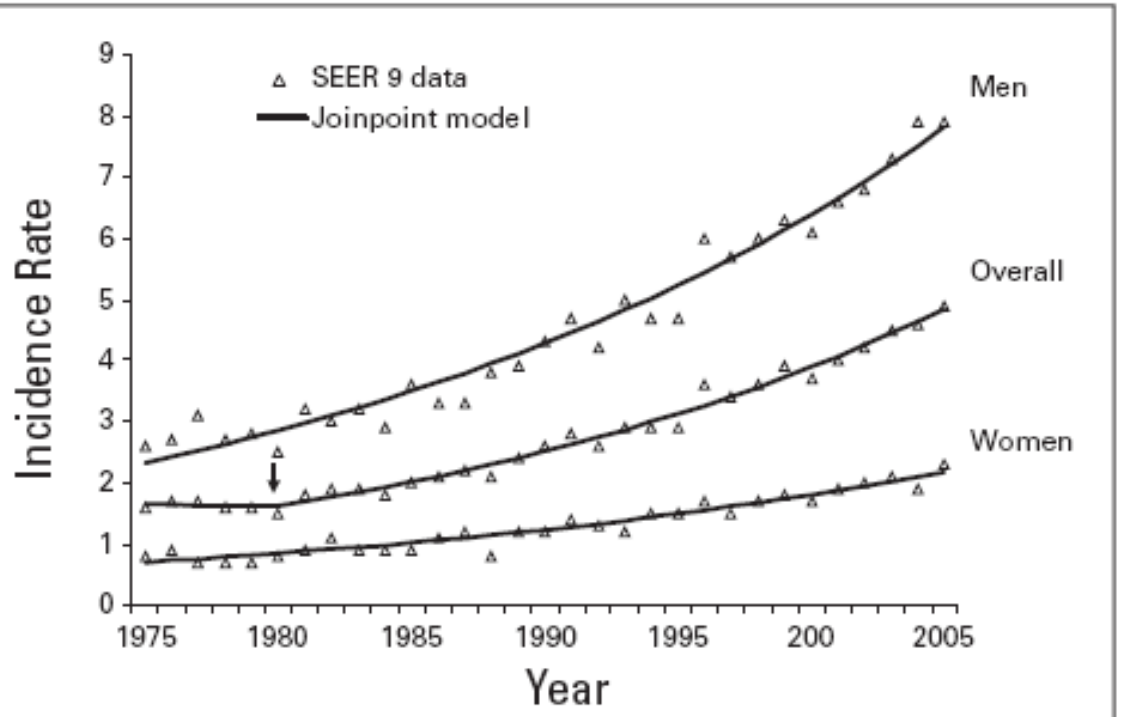
CANCER RESEARCH UK

Incidence and 5-Year Survival Rates for Patients with HCC in the USA, 1973–2007.



El-Serag H et al, Gastroenterology 2007

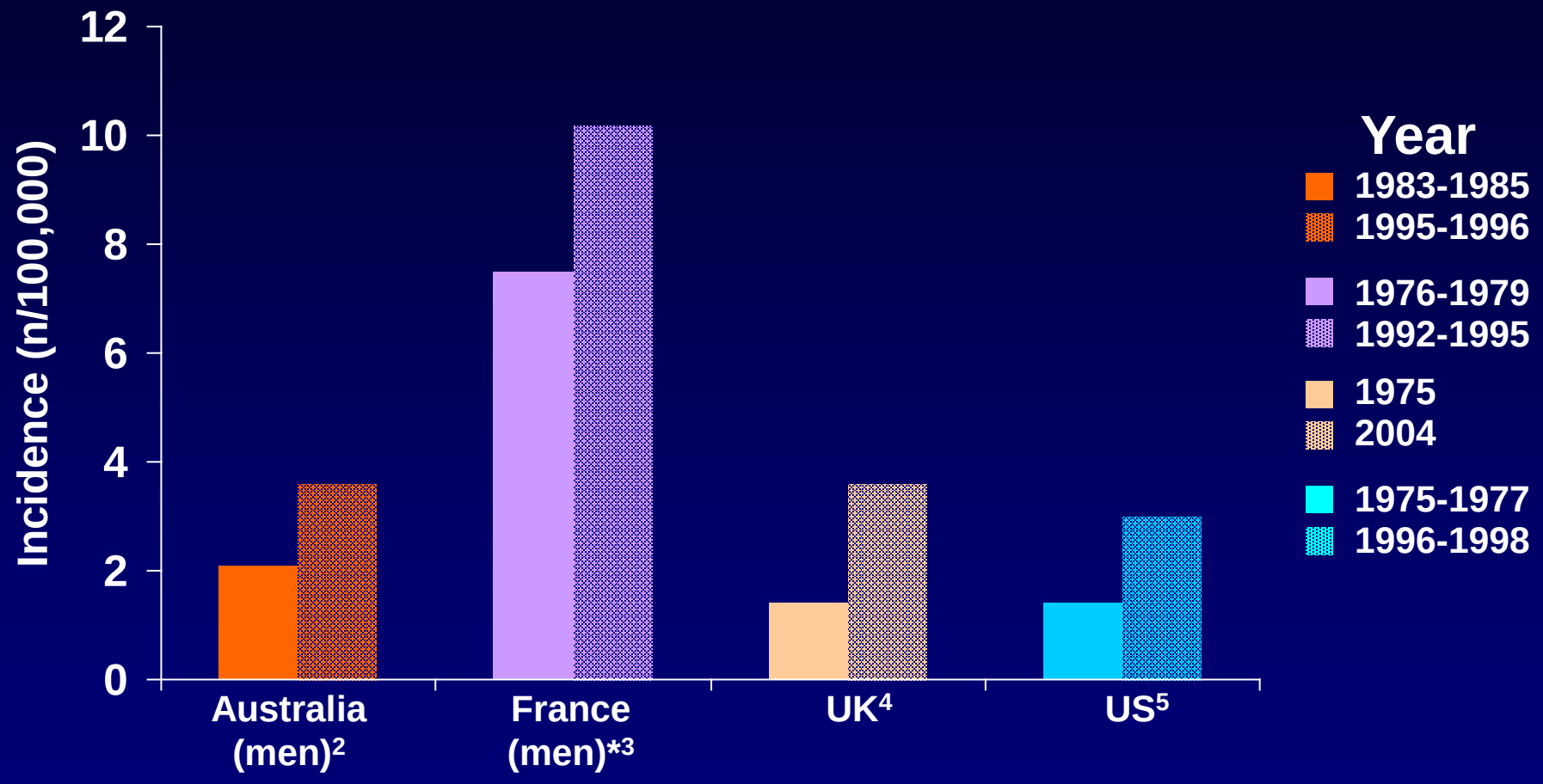
HCC incidence tripled over the last three decades in the USA



	Joinpoint		Incidence		Annual Percent	
Sex	Segments	Years	Start	End	Change (APC)	Comments
Men	1	1975-2005	2.6	7.9	4.1*	
Overall	2	1975-1980	1.6	1.5	-.04	Jointpoint at arrow
		1975-2005	1.5	4.9	4.5*	(1980)
Women	1	1980-2005	0.8	2.3	3.8*	

Altekruse, JCO 2009

Incidence of HCC Is Increasing[1]



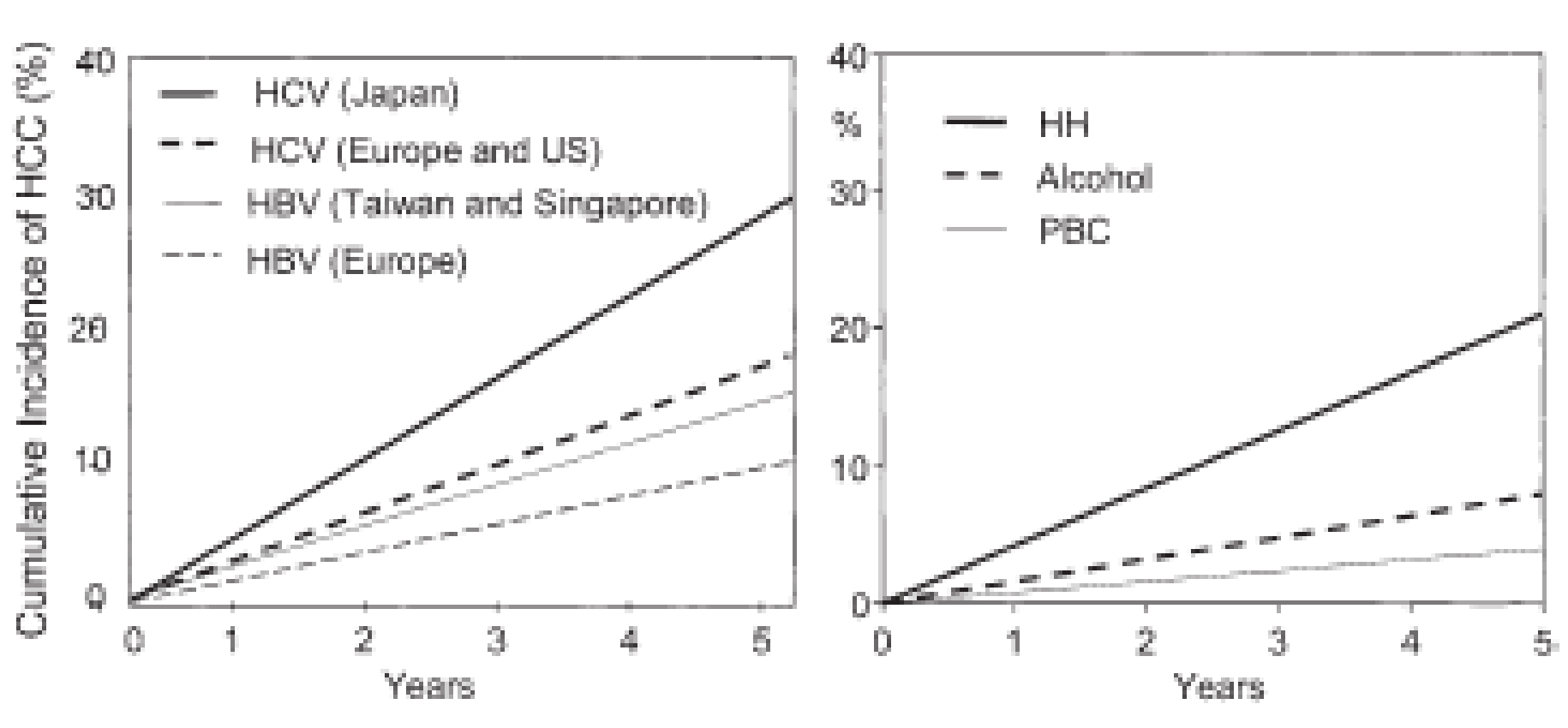
*Primary liver cancer. UK=United Kingdom; US=United States.

1. El-Serag HB, et al. *Gastroenterology*. 2007;132:2557–2576. 2.Law MG, et al. *Med J Aus.* 2000;173:403-405. 3. Benhamiche A-M, et al. *J Hepatol*. 1998;29:802-806. 4. http://info.cancerresearchuk.org/cancerstats/types/liver/incidence/?a=5441. Accessed August 2008. 5. El-Serag HB, et al. *Ann Intern Med*. 2003;139:817-823.

Hepatocellular Carcinoma-facts (3)

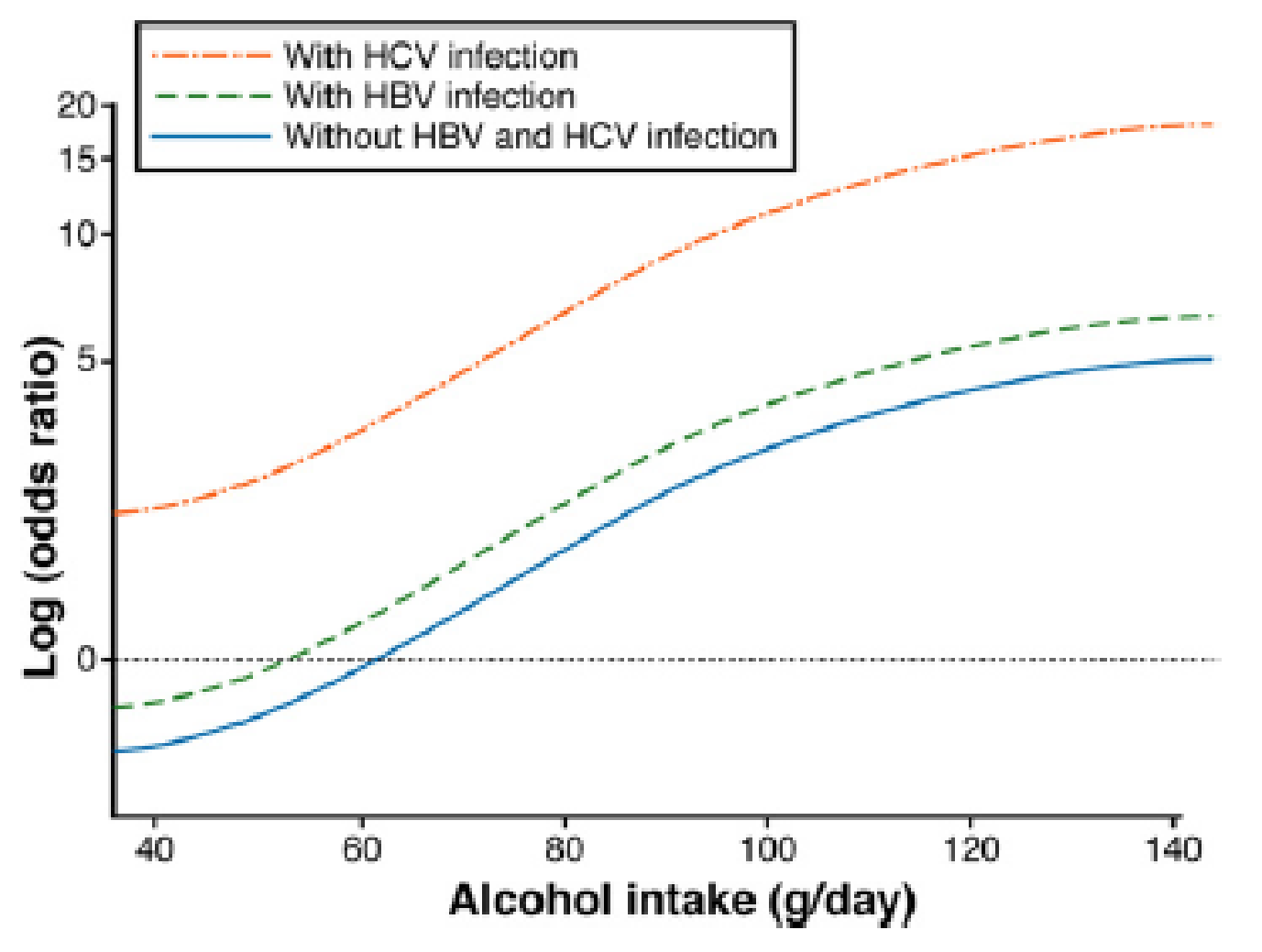
- Most patients with HCC in have liver cirrhosis
- Hepatitis B virus is the most frequent underlying cause world wide
- In the US, HCV-related HCC is the most prevalent (50-70% of cases)
- Other risk factors include alcohol use, NAFLD , inherited liver disease, hemochromatosis

Incidence of HCC in patients with cirrhosis according to etiology



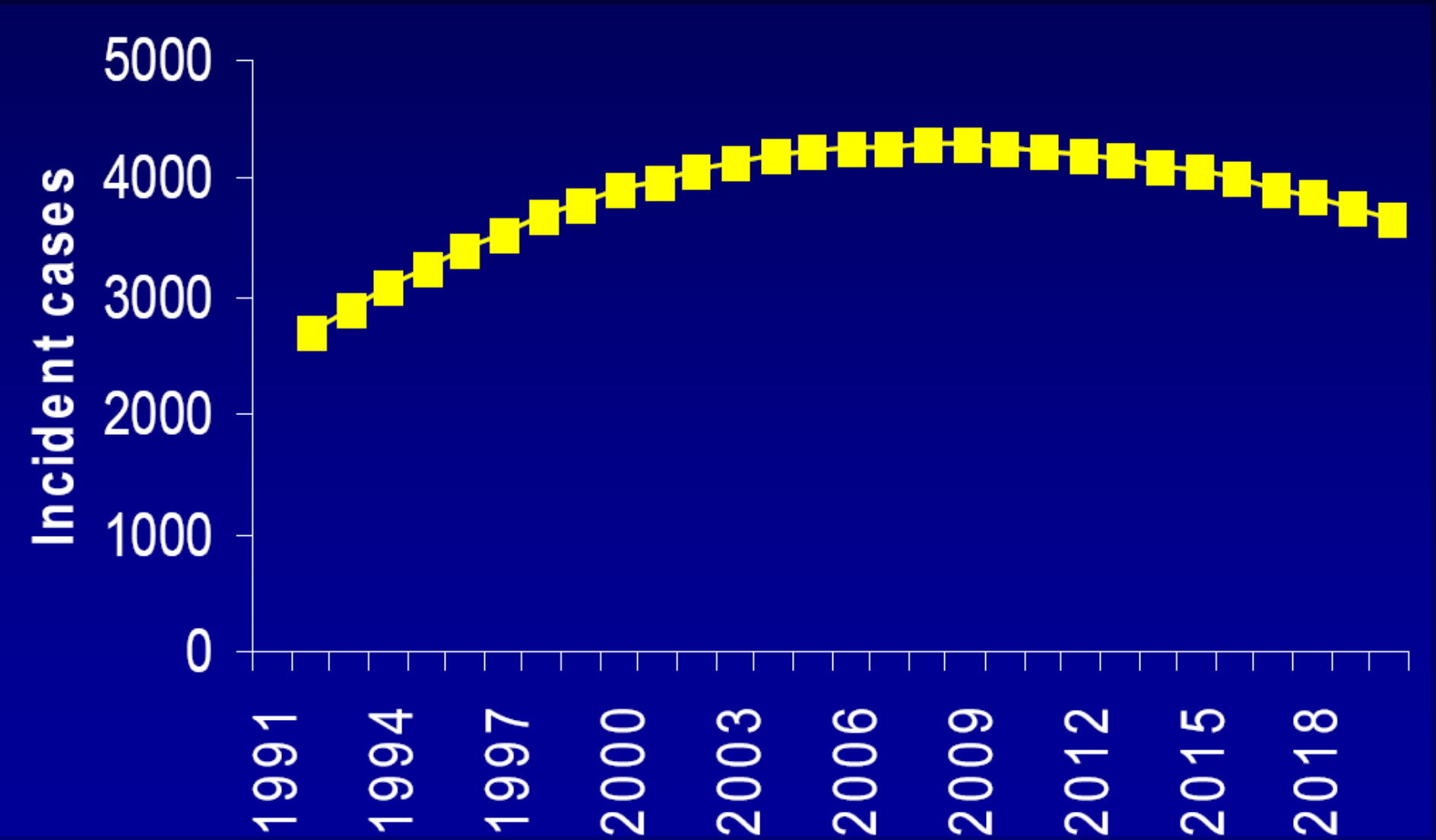
Fattovich G, Gastroenterology 2004

Viruses enhance the carcinogenic effect of alcohol

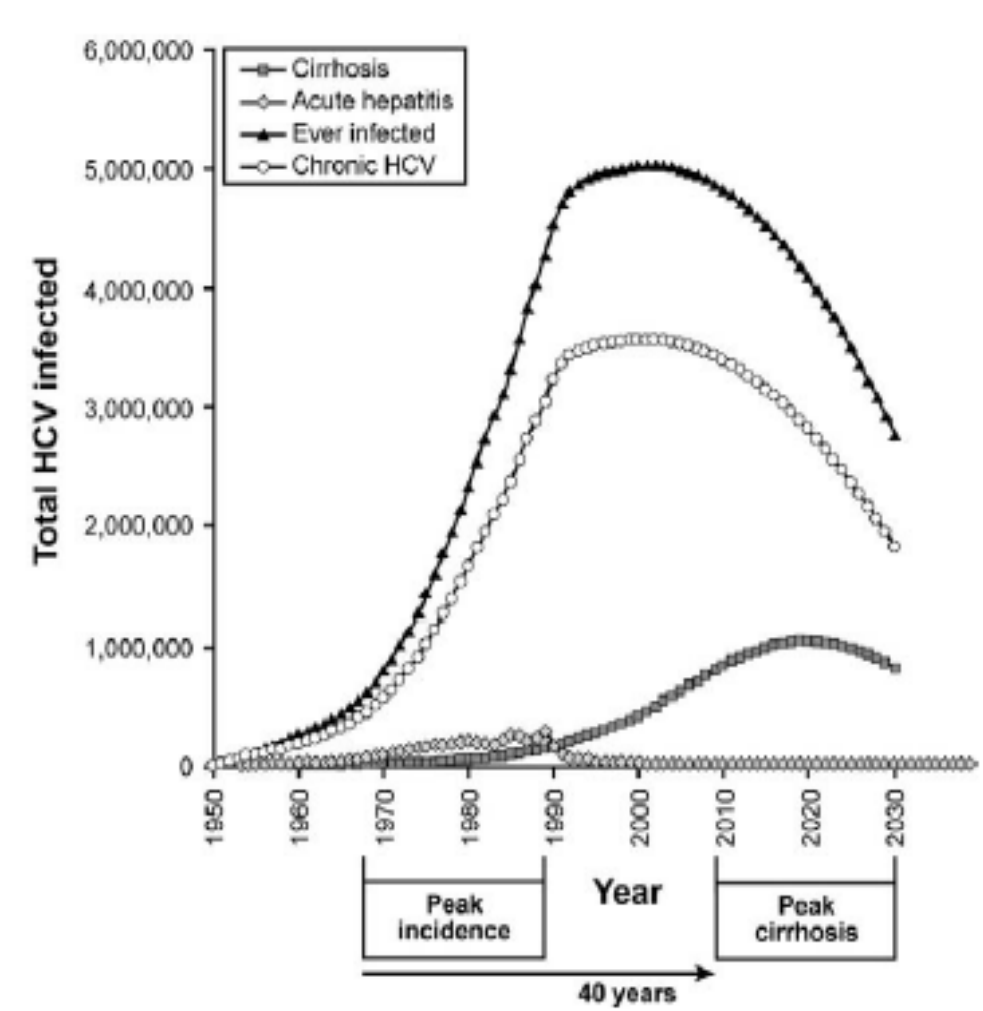


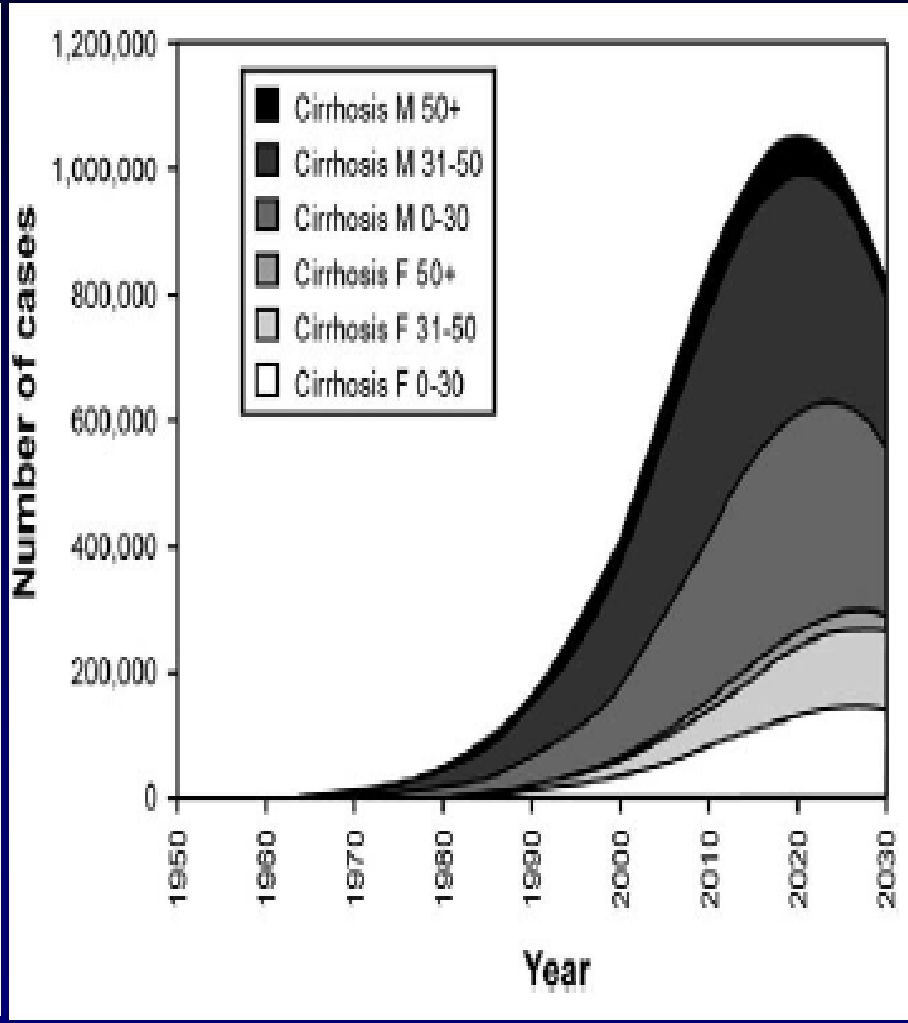
El-Serag H et al, Gastroenterology 2011

Projected future incidence in HCC from HCV



Aging HCV population and the risk of HCC





Davis GL, Gastroenterology 2010

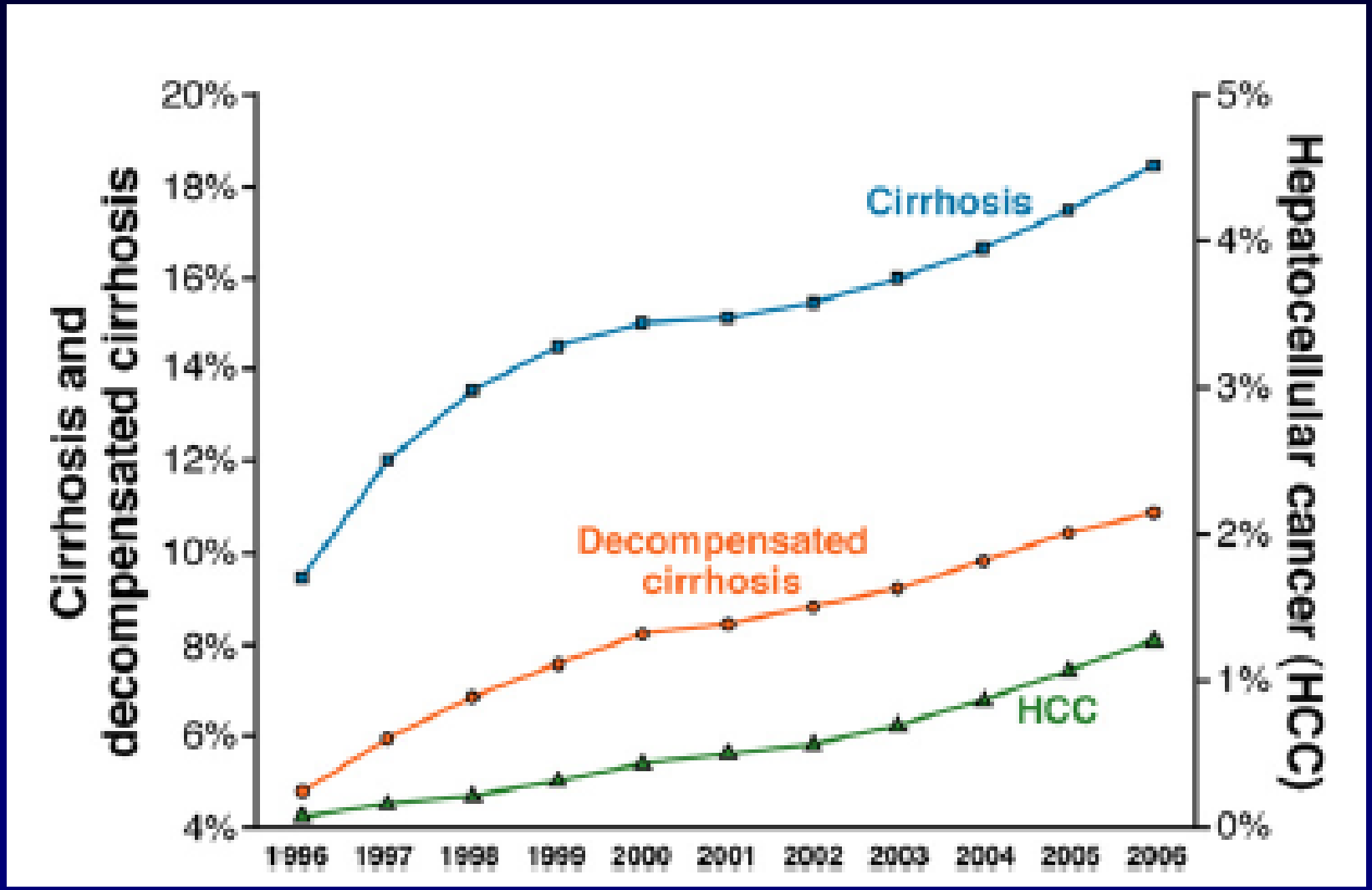
Why is the incidence rising?

Increasing prevalence of patients with cirrhosis

- Rising incidence of cirrhosis
  - HCV (main reason)
  - HBV
  - Other
- Improved survival of patients with cirrhosis

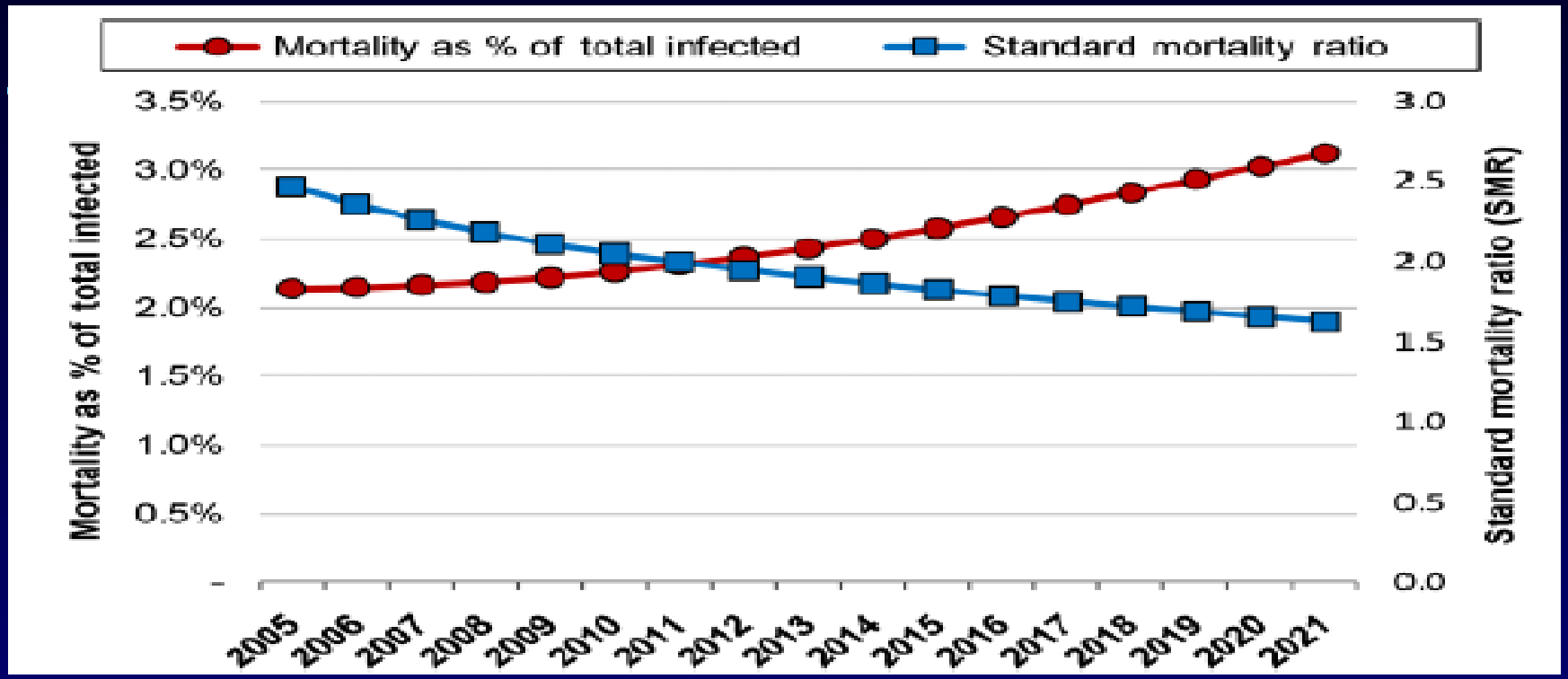
El-Serag HB, Gastroenterology 2004

Incidence of cirrhosis is increasing



El-Serag HB, Gastroenterology 2012

Predicted HCV burden



- USA HCV-infected population in estimated to decline from 3.15 million in 2005 to 2.47 million in 2021
- Disease burden will increase as population ages.
- Mortality rate will increase from 2.1 to 3.1%.
- Diagnosed population was 50% of the total infections, less than 2% of the total infections will be treated.

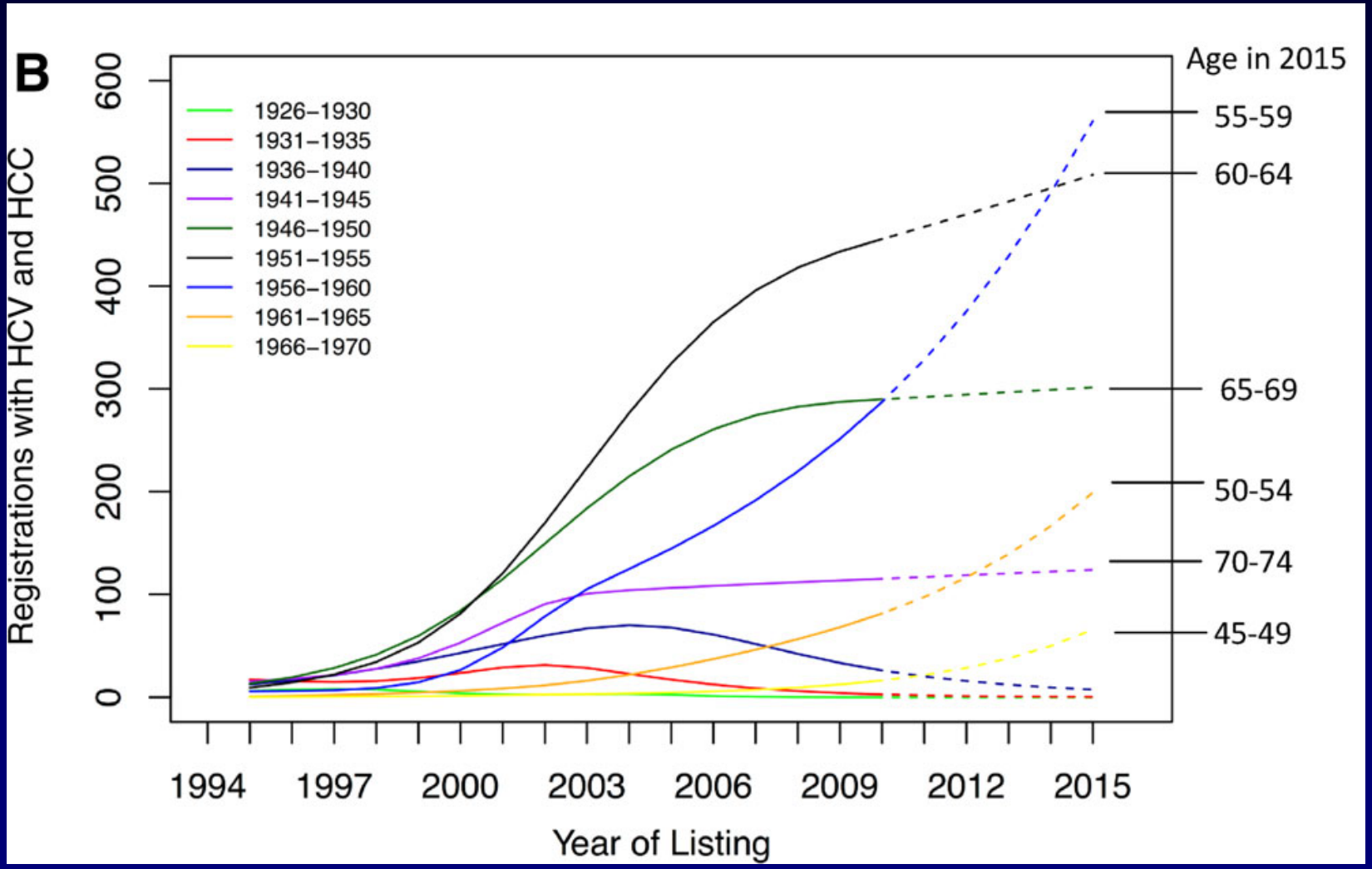
Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Recommendations and Reports / Vol. 61 / No. 4
August 17, 2012

Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965

Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born during 1945–1965*

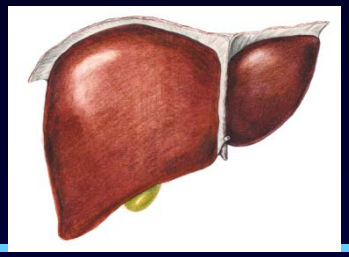
- Adults born during 1945–1965 should receive one-time testing for HCV without prior ascertainment of HCV risk.
- All persons with identified HCV infection should receive a brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment services for HCV infection and related conditions.

Expected rise in HCV-HCC Tx candidates according to birth cohort



Biggins SW Liver Trans 2012

What are the settings for NAFLD



obesity

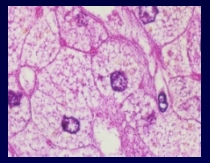
50%

steatosis

metabolic disorders

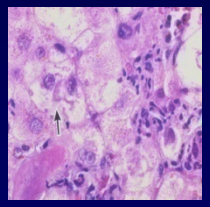
T2DM

CVD, malignancy



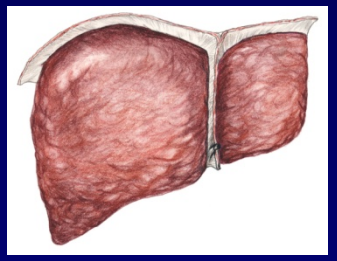
33%

steatohepatitis



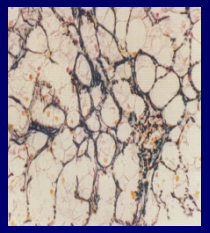
50%

fibrosis



15%~30%

cirrhosis



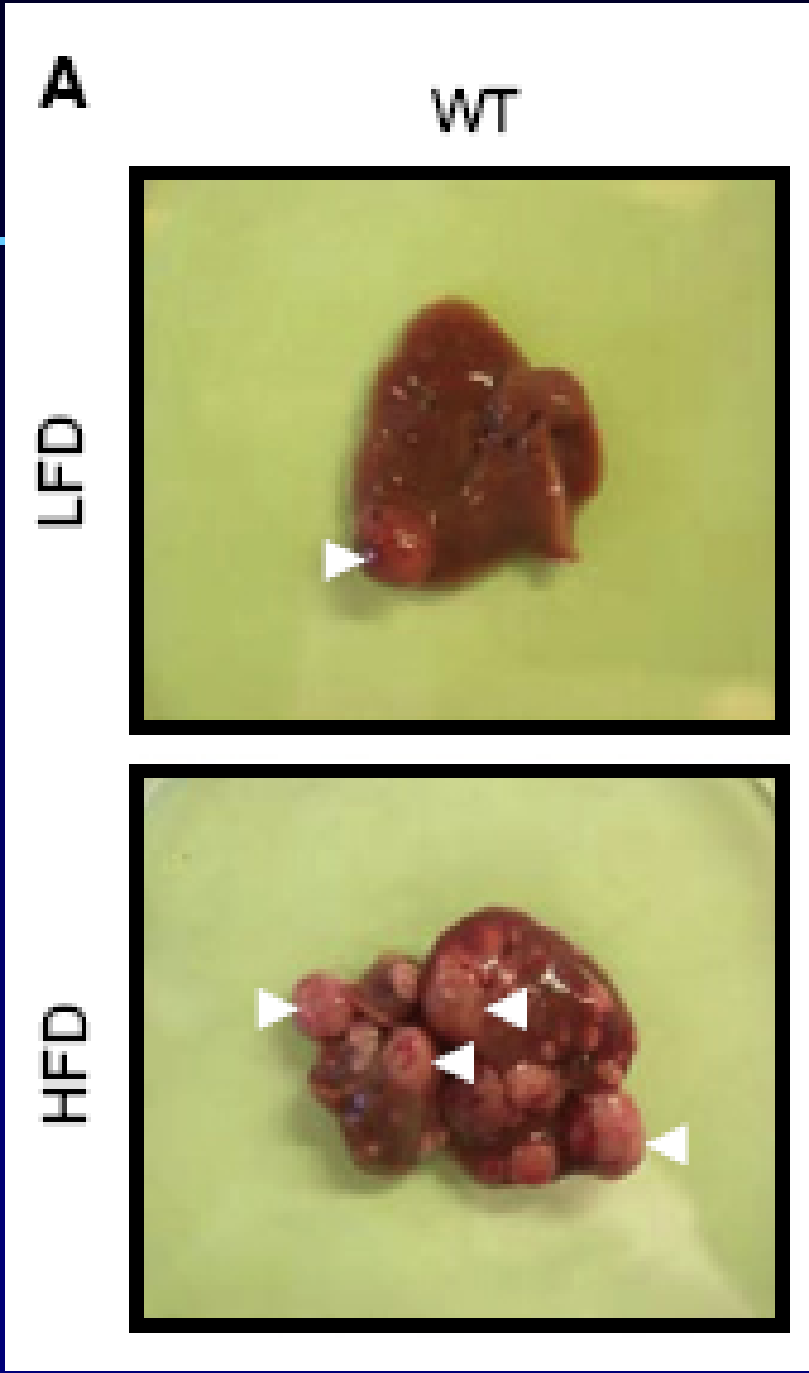
30%~40%

liver-related morbidity and mortality

Patrick L. Altern Med Rev, 2002, 7:276-291

Obesity kills-

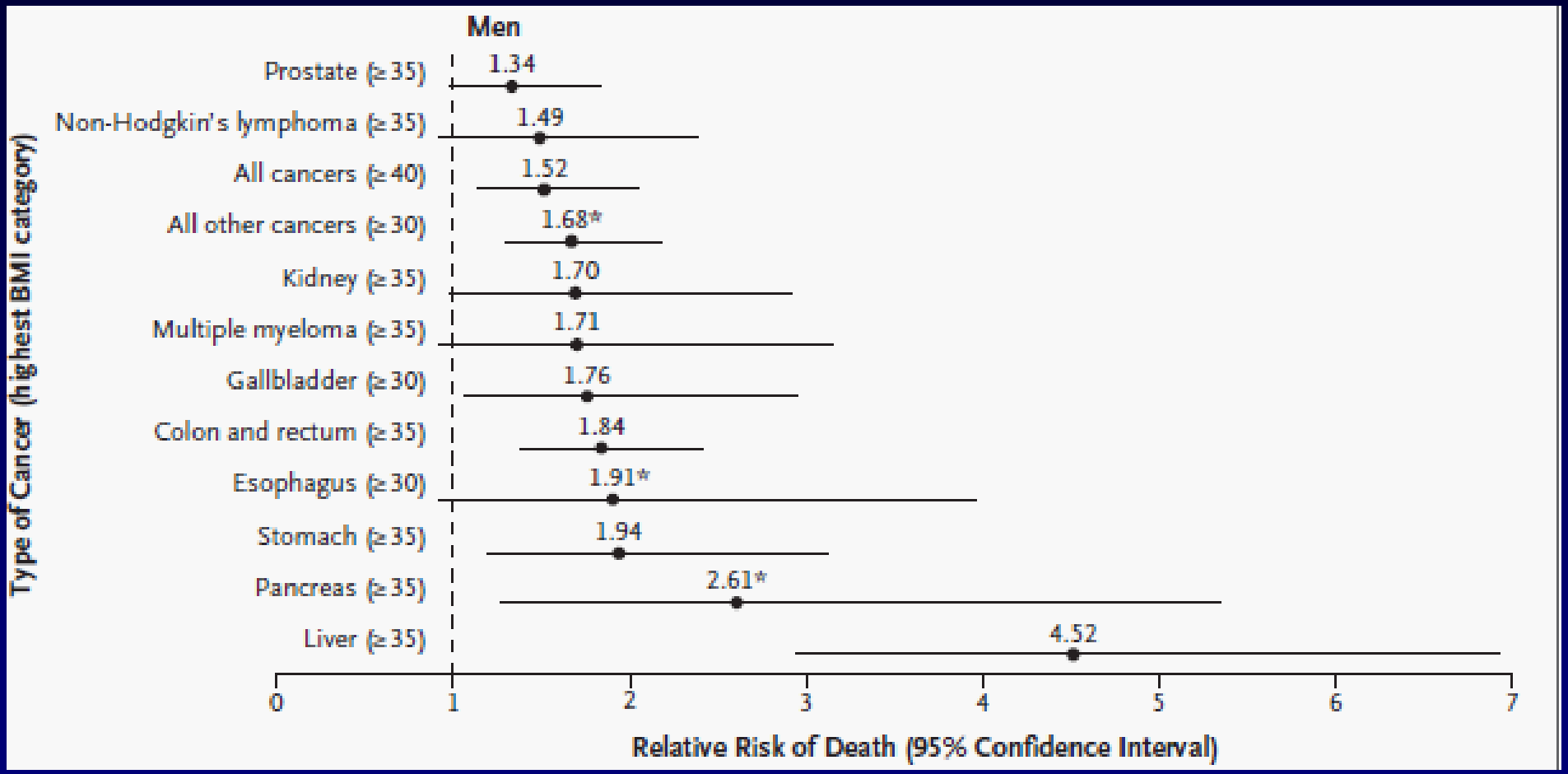
Hepatocellular carcinomas in High Fat Diet (HFD) fed mice



Park EJ et al Cell 2010, Starlet BQ Hepatology 2010

Diabetes, MS, NAFLD and HCC

Obesity increases risk of cancer



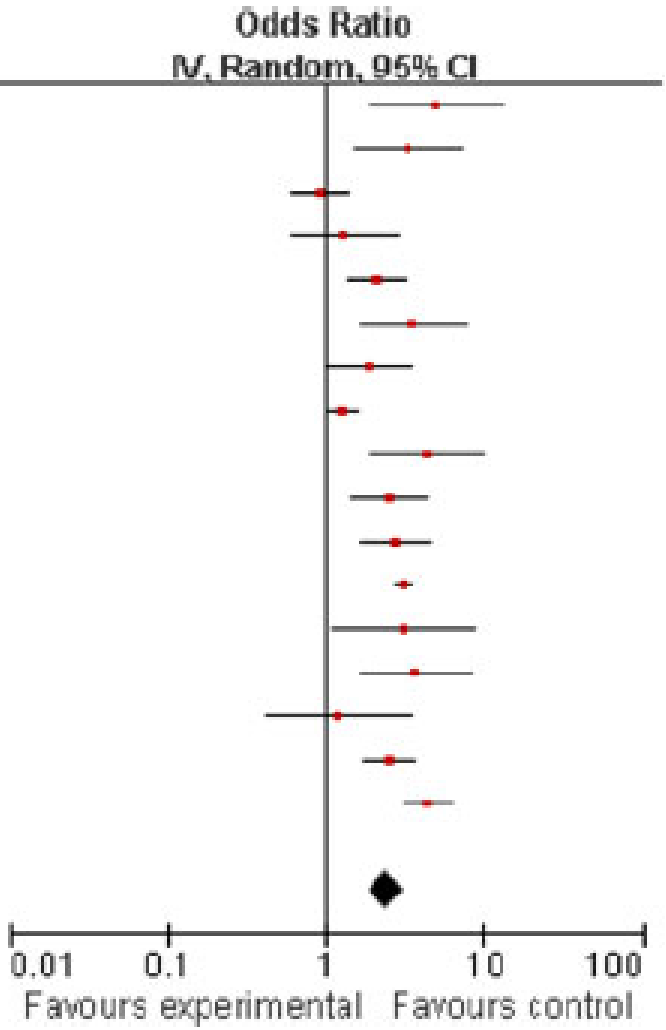
Calle EE et al NEJM 2003

Risk estimates for the association between diabetes and risk of HCC

Study or Subgroup	Weight	Odds Ratio IV, Random, 95% CI
Lawson et al. 1986	3.9%	4.88 [1.83, 13.00]
Yu et al. 1991	4.9%	3.30 [1.51, 7.23]
Fukuda et al. 1993	7.1%	0.92 [0.60, 1.41]
Hadziyannis et al. 1995	5.0%	1.30 [0.60, 2.79]
La Vecchia et al. 1997	7.2%	2.10 [1.39, 3.17]
Shibata et al. 1998	4.9%	3.54 [1.63, 7.67]
Lagiou et al. 2000	5.8%	1.86 [0.99, 3.50]
El-Serag et al. 2001	8.2%	1.27 [1.02, 1.58]
Hassan et al. 2002	4.7%	4.30 [1.88, 9.82]
Matsuo et al. 2003	6.3%	2.51 [1.46, 4.32]
Yuan et al. 2004	6.6%	2.70 [1.65, 4.43]
Davila et al. 2005	8.6%	3.08 [2.74, 3.46]
Rousseau et al. 2006	3.7%	3.10 [1.10, 8.77]
Polesel et al. 2009	4.8%	3.70 [1.66, 8.22]
Tung et al. 2010	3.6%	1.20 [0.42, 3.45]
Donadon et al. 2010	7.3%	2.50 [1.70, 3.68]
Hassan et al. 2010	7.4%	4.40 [3.04, 6.38]
Total (95% CI)	**100.0%**	**2.40 [1.85, 3.11]**

Heterogeneity: Tau² = 0.20; Chi² = 92.29, df = 16 (P < 0.00001); I² = 83%

Test for overall effect: Z = 6.59 (P < 0.00001)



Wang P et al Diabetes Metab Res Rev 2012

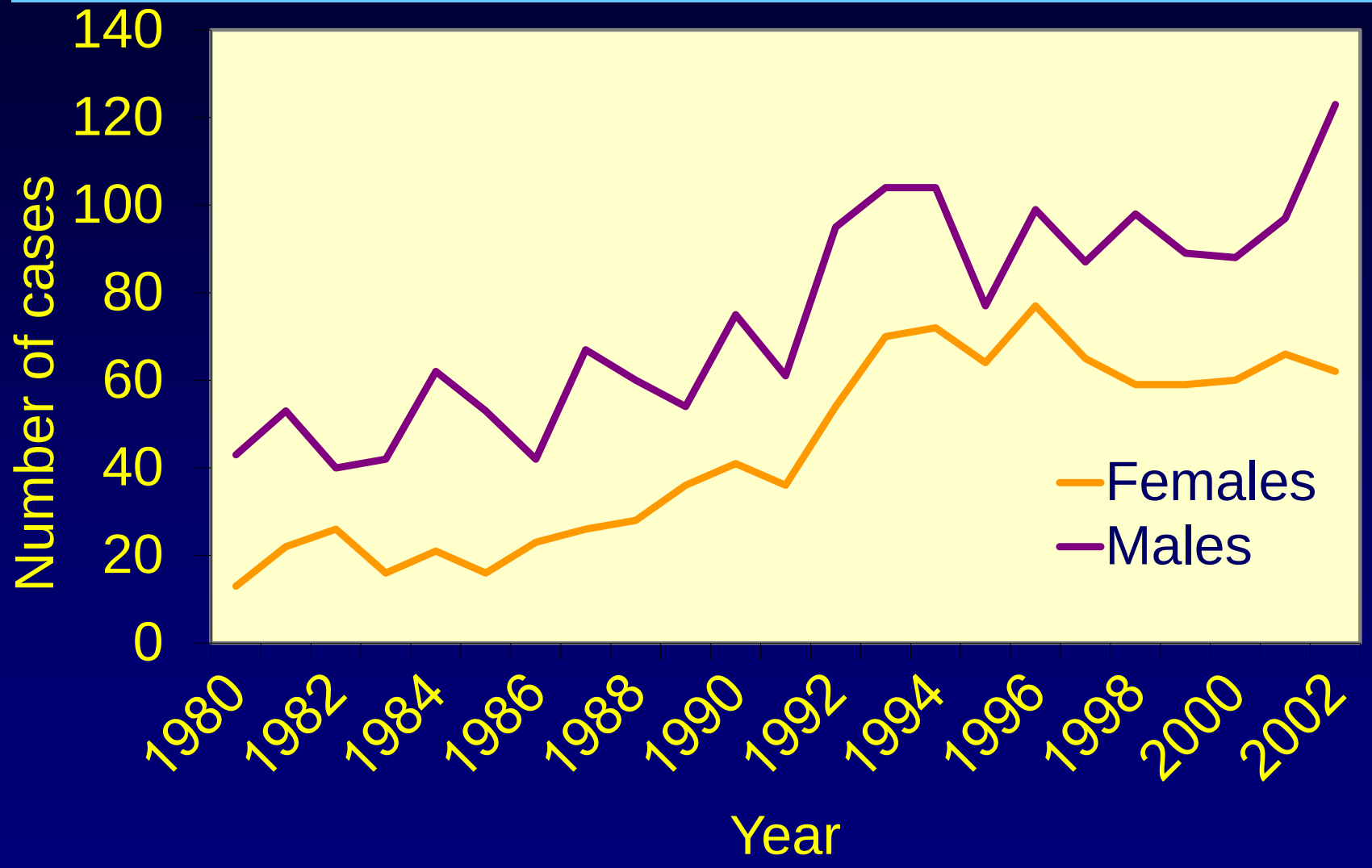
Association Between NAFLD and Risk for HCC: Systematic Review

- 17 cohort studies, 18 case-control and cross-sectional studies, and 26 case series.
- NAFLD/NASH without cirrhosis cases had a minimal risk for HCC (cumulative HCC mortality 0%–3% for periods up to 20 y).
- NASH and cirrhosis (cumulative incidence ranging from 2.4%-12.8%).
- There is an association between NAFLD/NASH and increased risk of HCC, limited to individuals with cirrhosis.

White D et al, CGH 2012

HCC In Israel

Reported annual incidence of HCC in Israel



Hadassha-TLVMC-HCC database

- Database for HCC patients shared by two liver units in Israel since 6/ 2011
  - Newly diagnosed HCC (6/2011 to 9/2012 (15 months))
  - Each center individually manage it's own cohort
  - The diagnosis of HCC is according with the EASL criteria.

Results-Etiology 80 HCC Patients

Basic Characteristics	80 HCC patients (%)
Age	67.6±11
Sex (male)	65(81)
HCV	42 (52)
NASH	20(25)
HBV	11(13.7)
Alc comorbidity	10(12)
Alc alone	3(3.7)
Crypto	4(5)
CPS A/B/C	65/13/2
CLIP 0/1/2+	34/27/19
BCLC A/B/C/D	19/23/36/2

Results- Etiology

- **Etiology of HCC**
  - HCV 52%,
  - **<u>NASH 25%</u>**
  - Alcohol (alone +comorbidity) 16%
  - HBV 13.5%
  - Cryptogenic 4.9%.

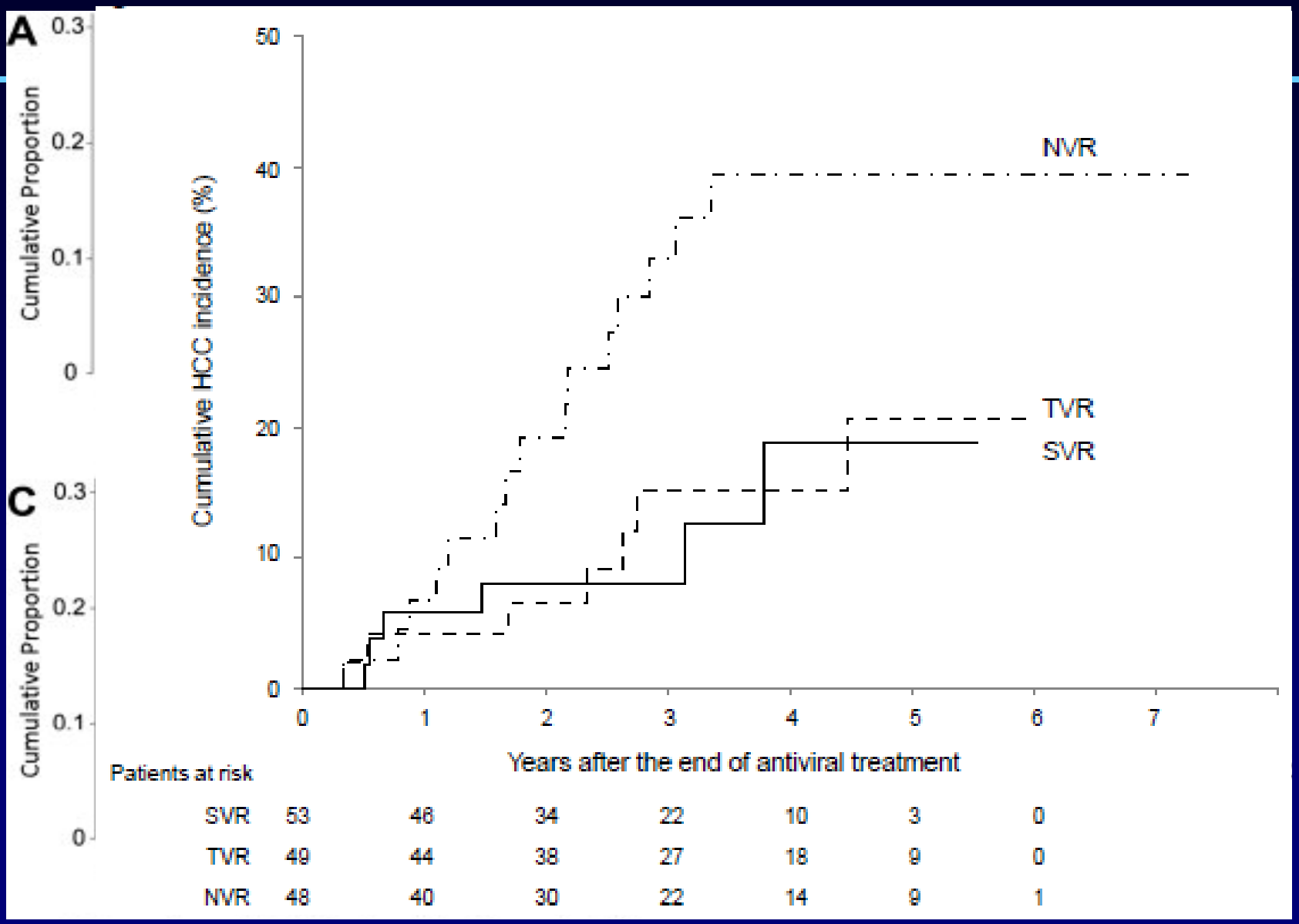
- **Fatty liver is becoming the second risk factor for HCC in Israel**
  - NASH: cryptogenic cirrhosis with metabolic syndrome , while viral, alcohol and all other etiology are ruled out.

Results – Treatment

Treatments	80 HCC patients (%)
TACE	39(48.8)
Resection	14(17.5)
OLT	7(8.7)
RFA	11(13.5)
NEXAVAR	17(21)
SIRT	3(3.7)
No Treatment	8(9.9)

Prevention

Effect of SVR on HCC develpoment



Morgan TR et al, Hepatology 2011

Ogawa H et al, J Hep 2012

Eradication of HCV and the development of HCC

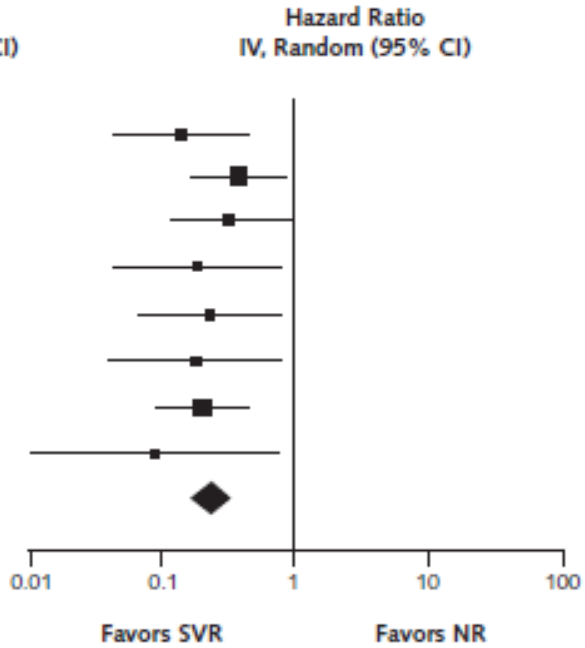
Figure 1. Forest plot of adjusted hazard effects in persons at all stages of fibrosis.

Figure 2. Forest plot of adjusted hazard effects in persons with advanced liver disease.

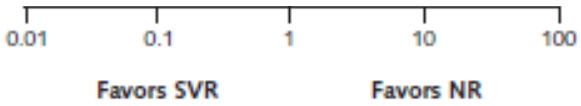
Study, Year (Reference)	log(Hazard Ratio)	SE	Total SVR	Total NR	Weight, %	Hazard Ratio IV, Random (95% CI)
Braks et al, 2007 (37)	–1.966	0.601	37	76	11.2	0.14 (0.04–0.45)
Bruno et al, 2007 (38)	–0.954	0.425	124	759	22.4	0.39 (0.17–0.89)
Cardoso et al, 2010 (40)	–1.120	0.514	103	204	15.3	0.33 (0.12–0.89)
Hasegawa et al, 2007 (64)	–1.690	0.755	48	57	7.1	0.18 (0.04–0.81)
Hung et al, 2006 (65)	–1.468	0.622	73	59	10.4	0.23 (0.07–0.78)
Morgan et al, 2010 (52)	–1.721	0.764	140	309	6.9	0.18 (0.04–0.80)
van der Meer et al, 2012 (63)	–1.592	0.416	192	338	23.4	0.20 (0.09–0.46)
Velosa et al, 2011 (60)	–2.433	1.108	39	91	3.3	0.09 (0.01–0.77)
Total			756	1893	100.0	0.23 (0.16–0.35)

Heterogeneity: tau-square = 0.00; chi-square = 3.64; $P = 0.82$; $I^2 = 0\%$

Test for overall effect: $Z = 7.21$; $P < 0.001$

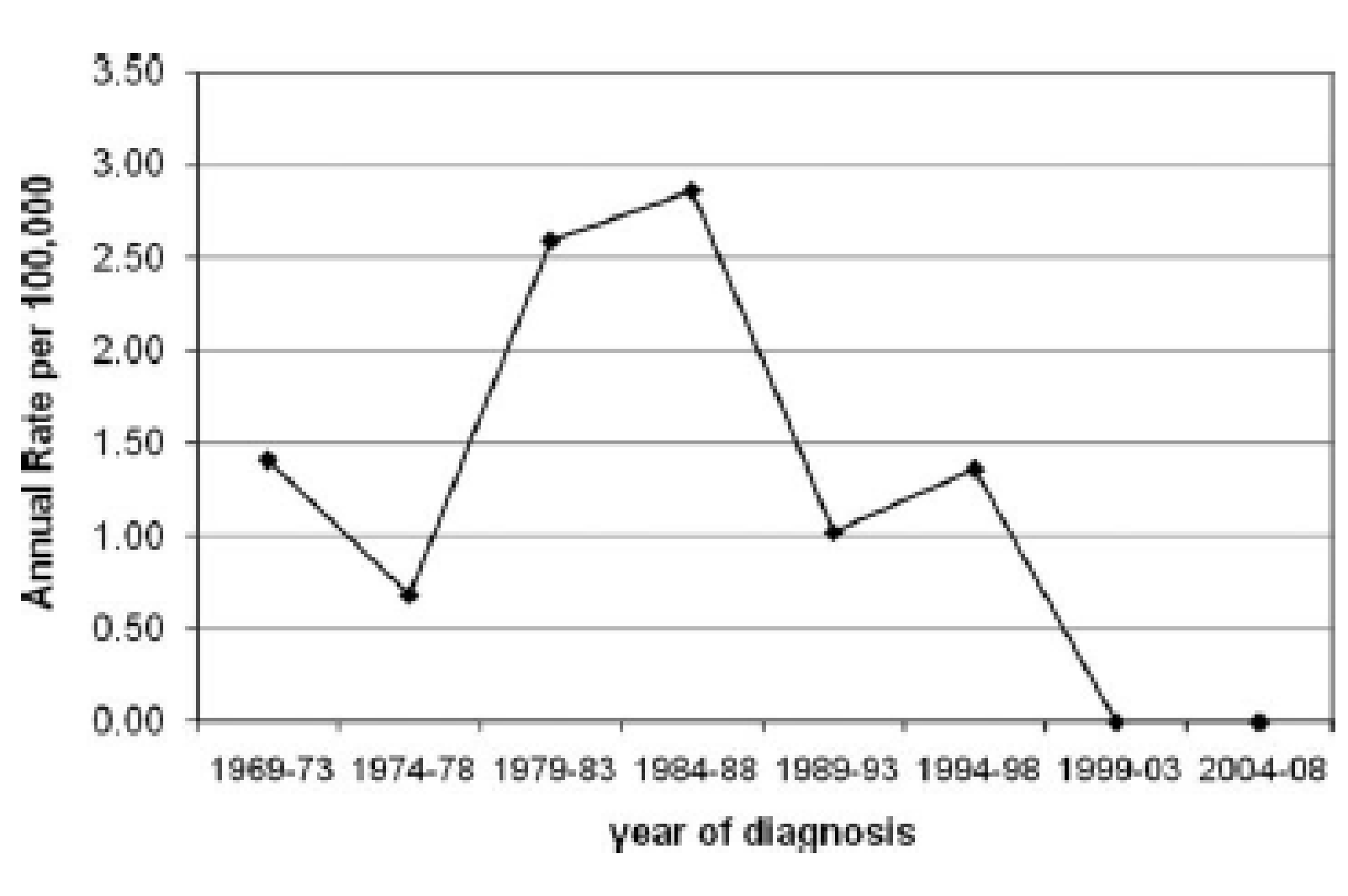


Test for overall effect: $Z = 10.80$; $P < 0.001$



Morgan RL, Ann Int Med 2013

Effect of HBV vaccination on annual incidence of HCC in Alaska

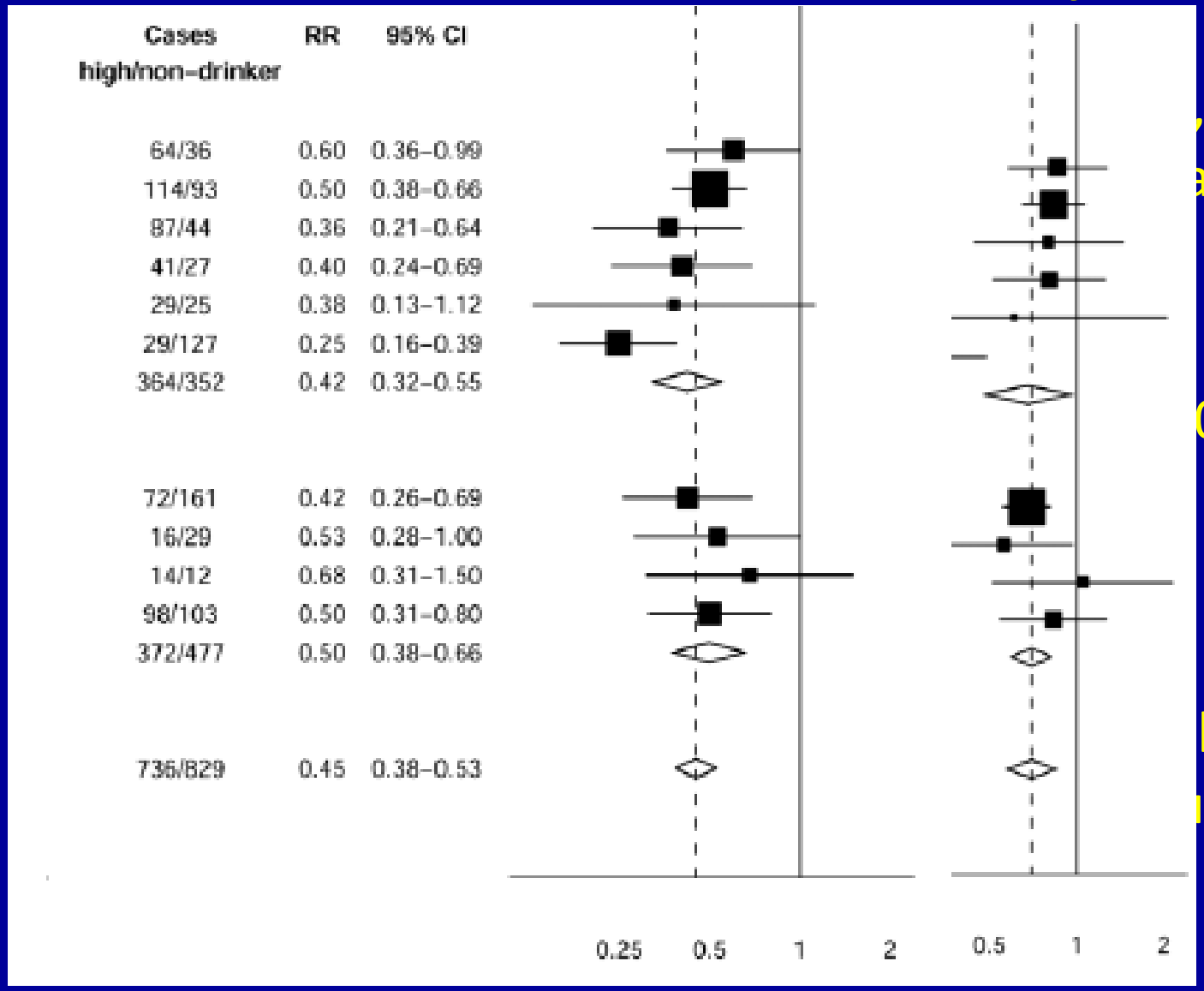


McMahon BJ et al, Hepatology 2011

Primary Prevention of HCC

- Vaccinate to HBV!
- Treat HCV with effective treatment
- Suppress HBV
- Abstain from alcohol?
- Weight loss?

Coffee Drinking and Hepatocellular Carcinoma Risk: A Meta-Analysis



, 6 case– control
and 4 cohort

0.49-0.72). RR
(95% CI 0.57-
0.38-0.53).

he inverse
ugh inference on

Bravi F Hepatology 2007

Conclusion

- Burden of HCC is increasing
- Common risk factors are cirrhosis from any cause (main reasons HCV, HBV, NASH)
- Primary prevention is paramount
- Data about incidence of epidemiology of HCC in Israel is lacking

Recipe

IRISH (HOT) 2 SERVINGS

- **2 cups strong coffee**
  2 tablespoons orange juice
  2 teaspoons lemon juice
  whipped cream
  Mix coffee, orange juice and lemon juice
- **Pour into Irish whiskey glass**
- **Top with whipped cream**

Tel-Aviv Sourasky Medical Center

Thank You For Your Attention