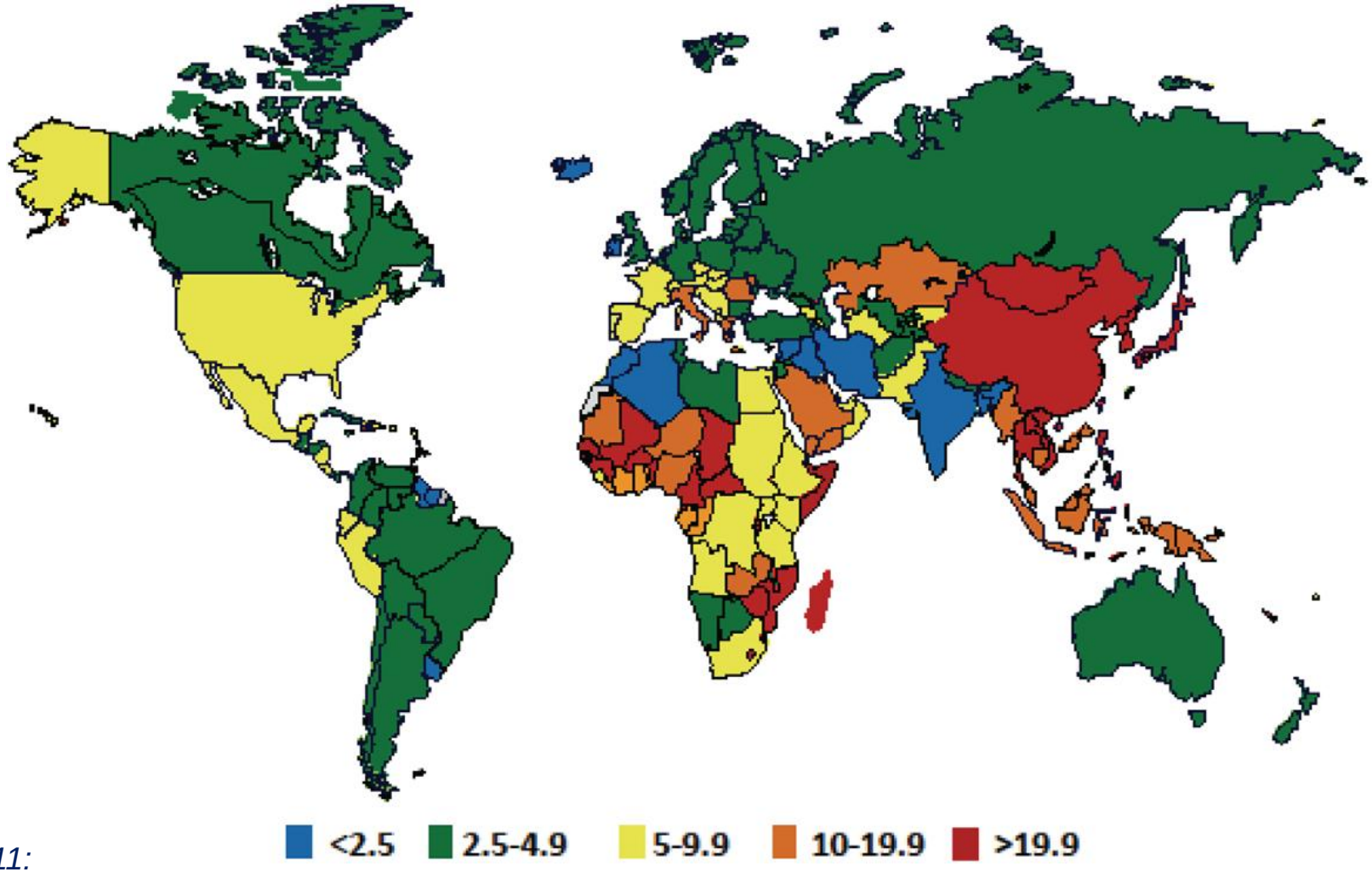
HCV-related HCC

Eli Zuckerman, M.D.
Liver Unit, Carmel Medical Center,
Technion Faculty of Medicine,
Haifa, Israel

Disclosures

- Advisory boards (international): Gilead, Abbvie, Merck, Janssen, BMS
- Consultant: Janssen, Gilead, Merck, Roche, Neopharm, Abbvie, GSK
- Advisory committees or review panels: Merck, Gilead, Janssen, BMS, Abbvie
- Speaker: Merck, Janssen, Roche, Novartis, BMS, Neopharm, GSK, Abbvie, Gilead

Overall incidence of HCC per 100,000

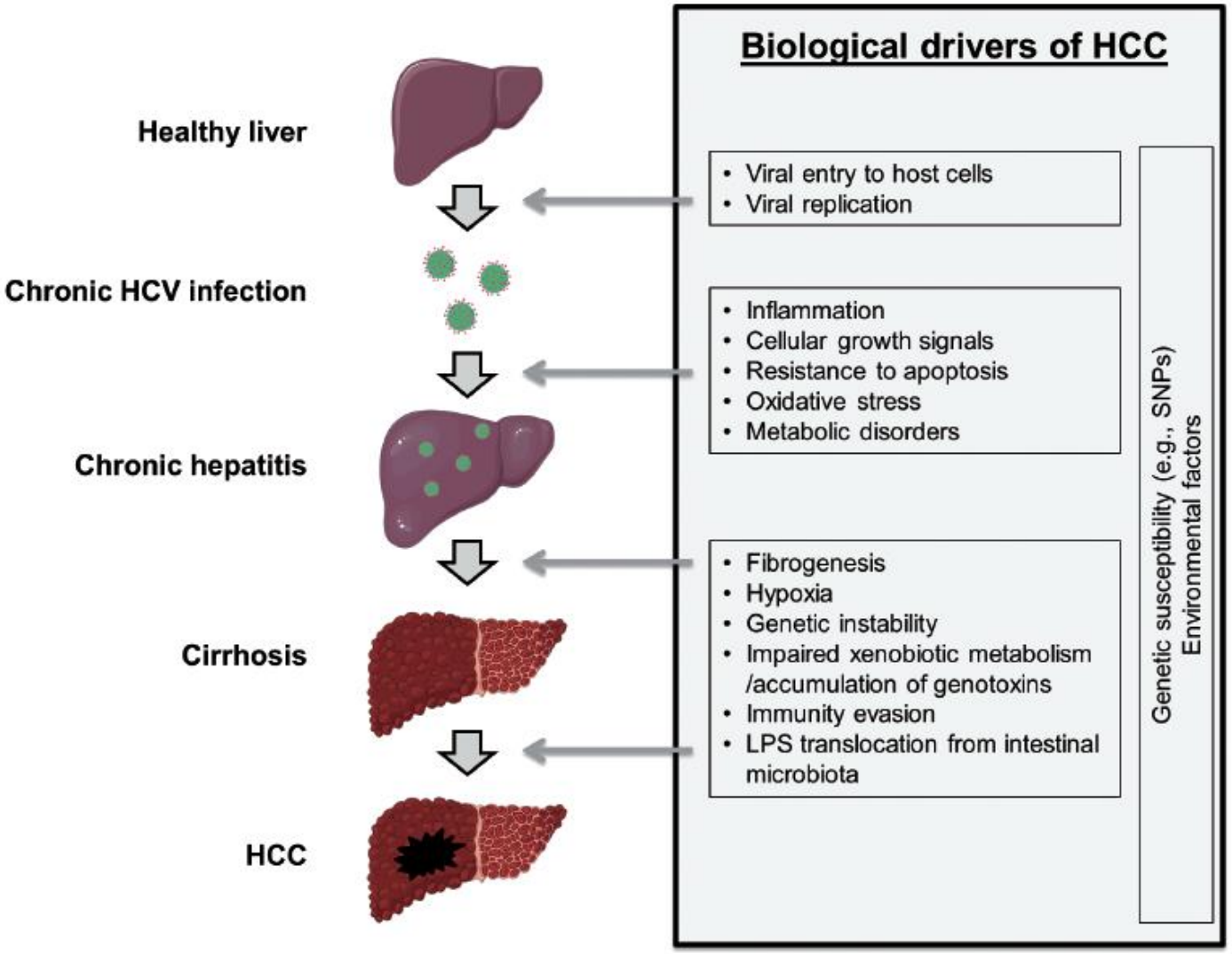


UpToDate 2011:
High incidence ≥15 cases/100,000
Intermediate incidence 4-14 cases/100,000
Low incidence ≤3 cases/100,000

What is it so special in HCV-related HCC?

(Epidemiology and clinical aspect)

Natural History and Biological Drivers of HCV-Related HCC



Clin Mol Hepatology 2015

5-Year Cumulative Incidence of HCC in Patients With Cirrhosis*

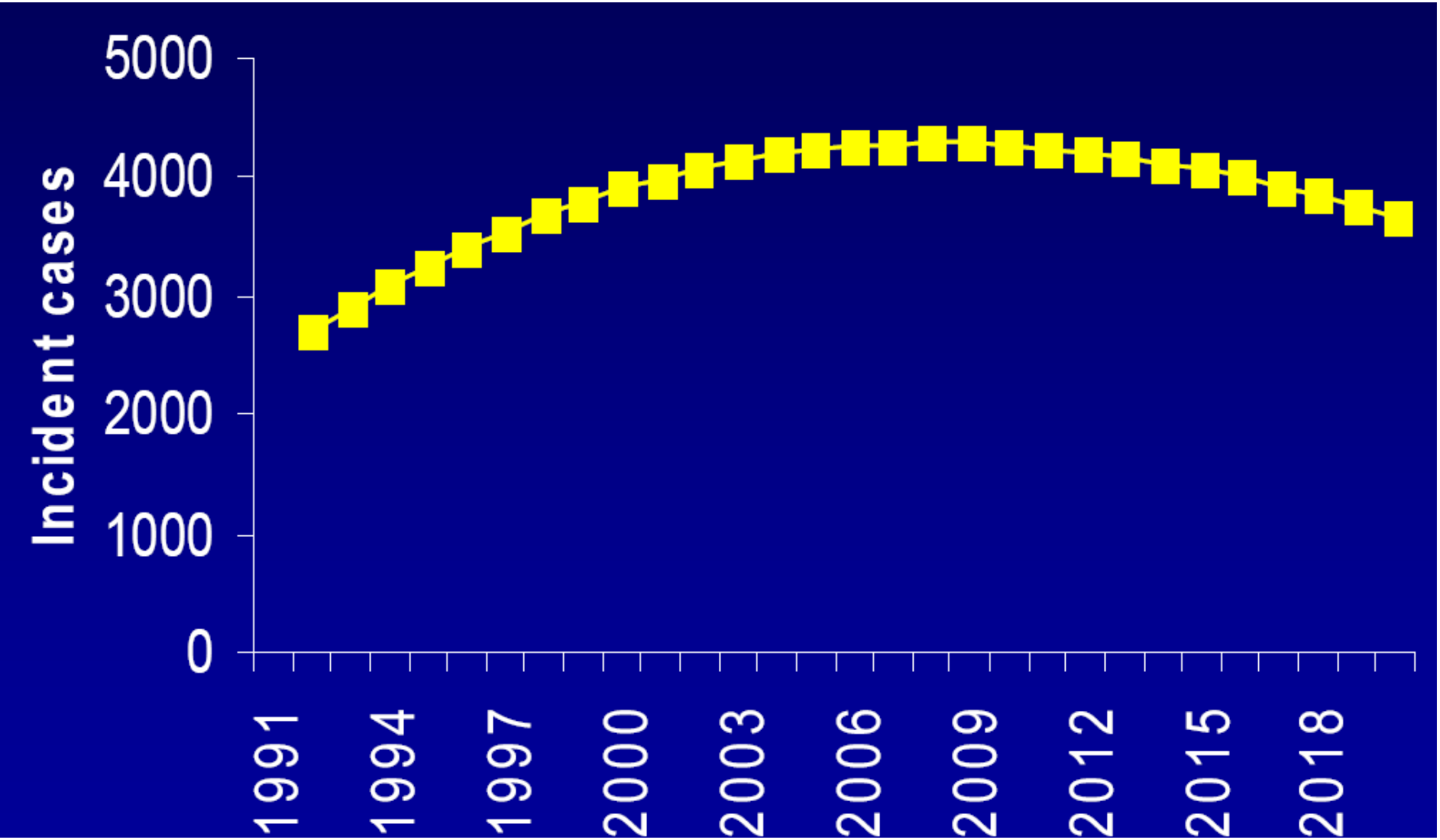
Etiology of Cirrhosis	5-Year Cumulative Incidence of HCC
Hepatitis C virus	
Japan	30%
Europe and US	17%
Hepatitis B virus	
Taiwan and Singapore	15%
Europe	10%
Hereditary hematochromatosis	21%
Alcoholic cirrhosis†	8%
Primary biliary cirrhosis†	4%

*Retrospective analysis of combined data from published studies.

†In the absence of HCV and HBV viral markers.

Fattovich G, et al. *Gastroenterology.* 2004;127:S35-S50.

Projected future incidence in HCC from HCV



HCV-related HCC

Phylogenetic studies of HCV show that HCV began to infect:

- Japan 1920s
- Southern Europe 1940s
- North America 1960s and 1970s

HCV+ serology in patients with HCC:

- Japan 80-90%
- Italy 44-66%
- US 30-50%

Incidence of HCC in Japan is X3 than Italy and X 6 than US

NIH public access, Gastroenterology 2012

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.

HCV-related HCC

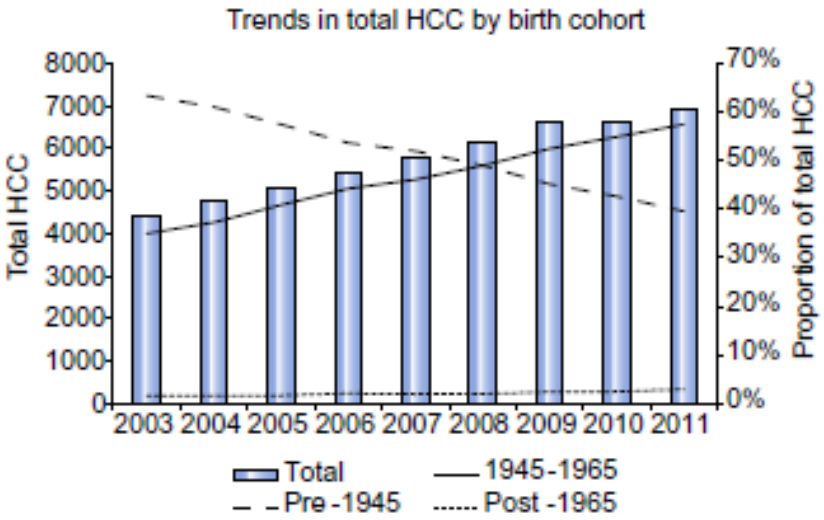
The “baby boomers:

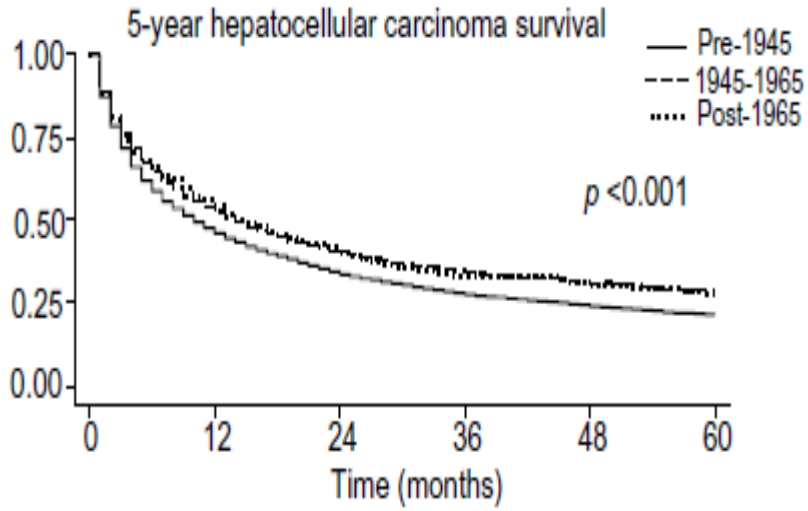
- **Americans born between 1945 and 1965**
- **Represent 27% of the population of US**
- **Account for 75% of HCV infection in the US**
- **As cohort ages : cirrhosis and HCC become more prevalent**

HCV-related HCC

SEER: HCC 2003-11: 50,723 cases with HCC

BB HCC vs. pre-1945 and post-1965





- BB HCC prevalence increased **by 64%** (2003 to 2011)
- BB HCC accounts for **57.4%** of all HCC cases in the US
- BB HCC : earlier stage of HCC at diagnosis
- BB HCC: better 5y survival (vs. pre-1945)
-

Yan M. et at, J Hepatology 2016, 64:326-32

HCV-related HCC in non-cirrhotics

HALT-C study

- Cumulative 5 years incidence of HCC in CHC: higher in patients with cirrhosis vs. bridging fibrosis (7% vs. 4.1%, **p= 0.08**)

Dig Liver Dis 2015 *(Beaujon H, Clichy)*

- 162 pts with HCC (2000-2011)
- 137 F3-4 vs. 25 F0-2
- 16% of HCC occurred patients without advanced fibrosis
- Patients with advanced fibrosis and HCC

  older (65 vs 62)

  more steatosis (43% vs 20%)

Lok A, et al, Gatroenterology 2009, Kutal et al, Dig Liver Dis 2015

HCV-related HCC in non-cirrhotics

Dig Liver Dis 2015 *(Beaujon H, Clichy)*

Predictors for HCC in patients without advanced fibrosis

- Presence of HBcAb (p=0.044)
- Duration of HCV infection (0.003)

Patients without advanced fibrosis did not have more DM or steatosis

Kutal et al, Dig Liver Dis 2015

HCV-related HCC

Risk Factors for HCC in CHC

- HBV co-infection (odds ratio 165 vs. 17 in HCV alone)
- Alcohol (RR 2.33 in pooled M-A data , 15,000 patients)
- Metabolic syndrome
- Host genetic factors (only case-control studies)
- TNF-α polymorphism (TNF-α 308, odds ration 1.88 in Asians)
- Age (age distribution has shifted with the largest proportion in 45-60 y/o)
- Genotype 3

NIH public access, Gastroenterology 2012

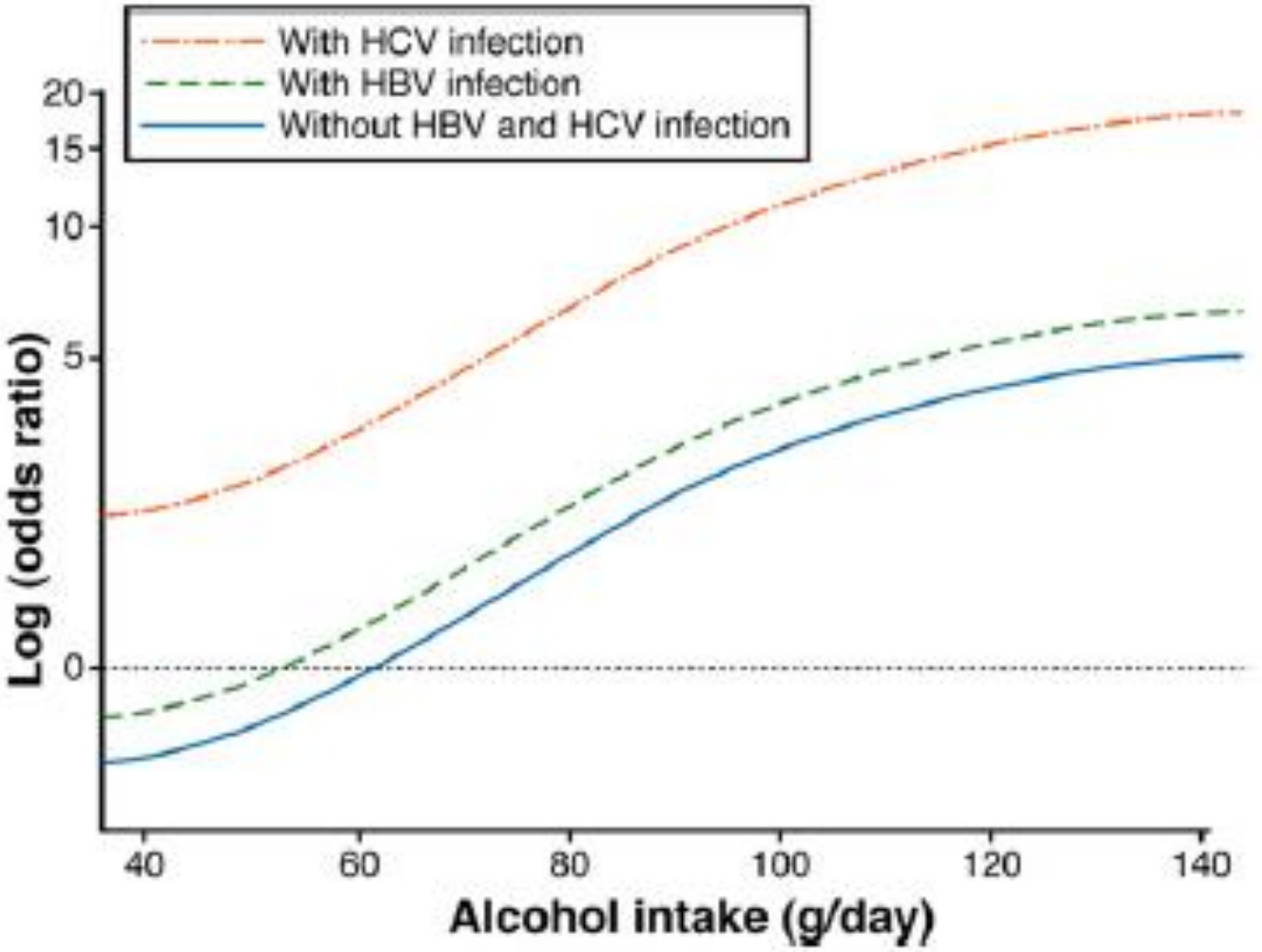
HCV-related HCC

HCC and Genotype 3

- Increased progression to advanced fibrosis/cirrhosis
- A retrospective cohort study (353 G3 patients with HCC) develop more HCC (vs. non-G3): 44% vs. 26%
- Larger cohort studies showed that G3 had higher risk of developing cirrhosis and HCC than G1

WJG 2016, J Viral Hepatitis 2011, Hepatology 2014

Viruses enhance the carcinogenic effect of alcohol



El-Serag H et al, Gastroenterology 2011

Coffee lowers the risk for HCC

Meta-analysis 2007 Hepatology

- 10 studies, 2260 cases of HCC

  (6 case-control Southern Europe and Japan, and 4 cohort studies from Japan)

- RR of HCC in coffee drinkers: 0.54 (CC) and 0.64 (cohort)
- Increase of 1 cup of coffee per day: RR of HCC 0.75

Bravi F, Hepatology 2007)

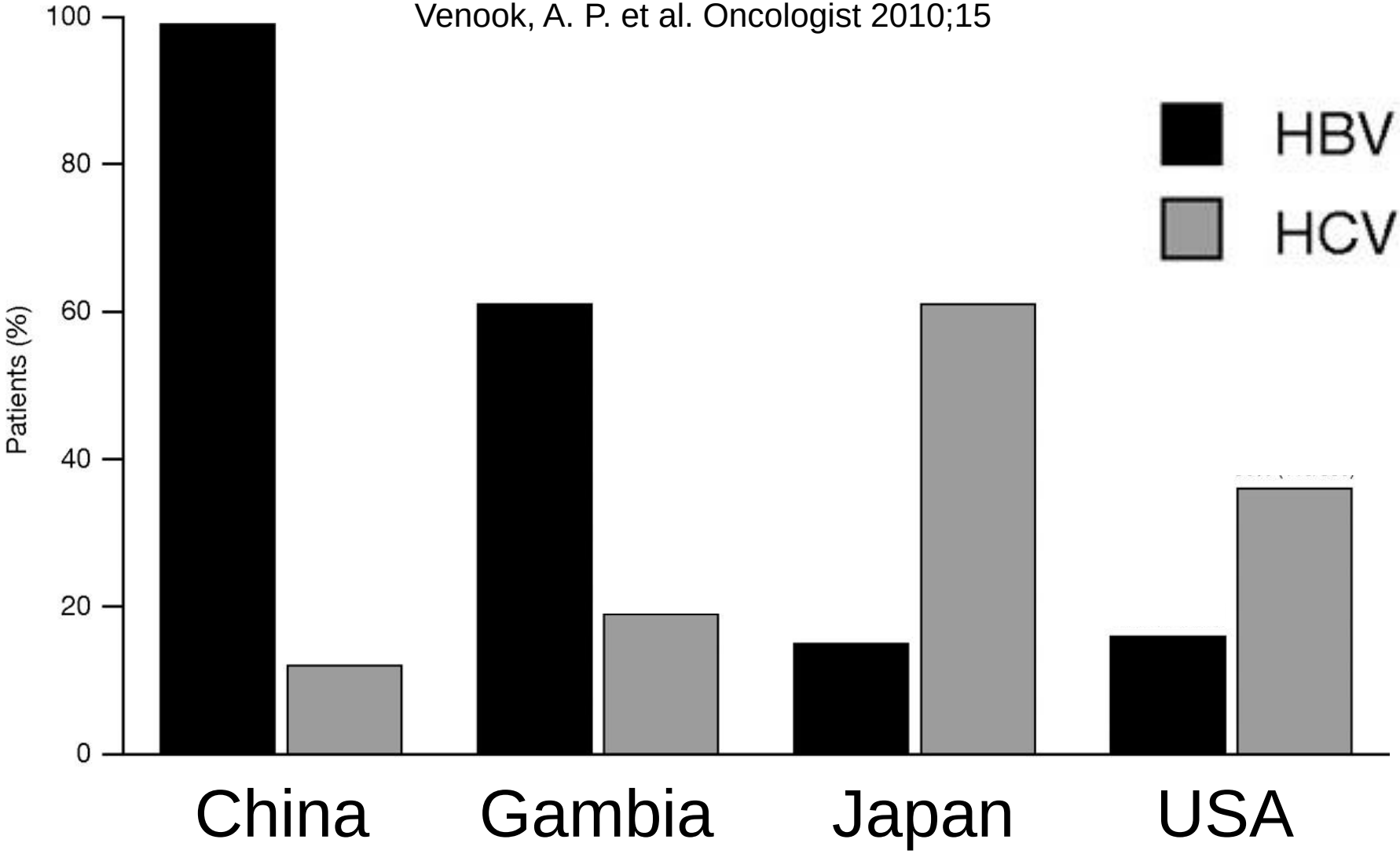
HCV-related HCC

Is HCV-related HCC different from HBV-related HCC?

(Clinical aspects)

Variations of HBV & HCV Prevalence in HCC: developing or developed countries

Venook, A. P. et al. Oncologist 2010;15



HCV-related HCC

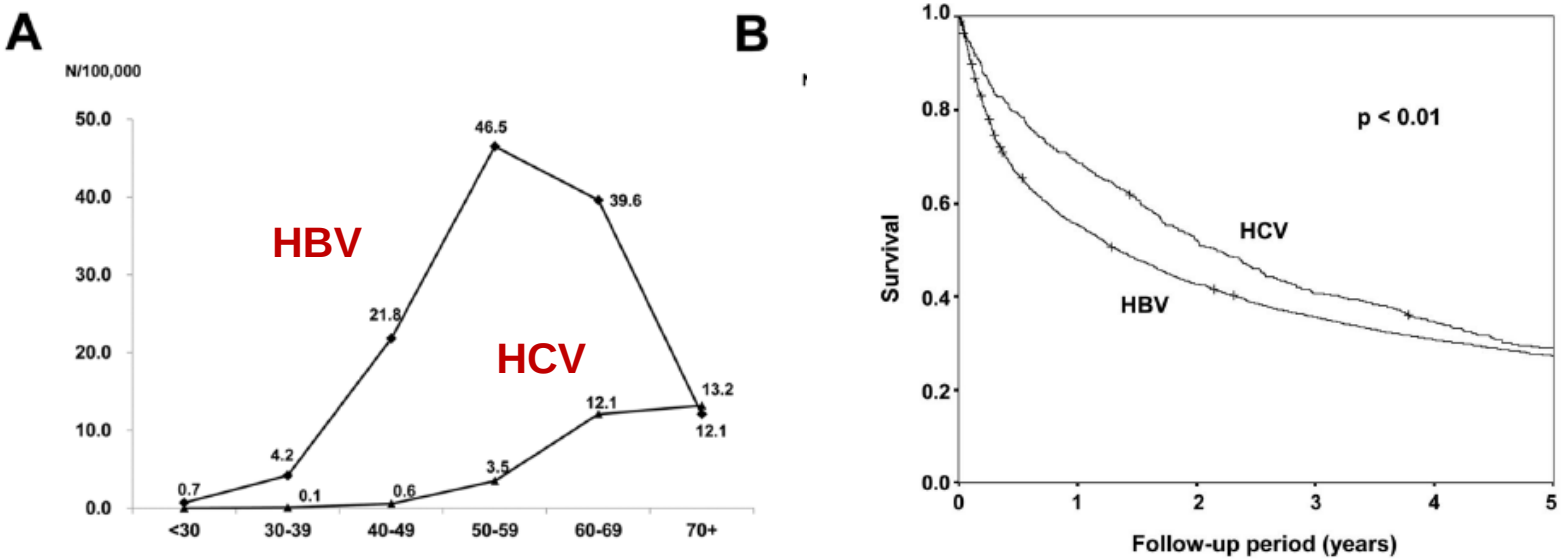
HCV- vs. HBV-related HCC

- 31,521 new HCC cases 2003-5 (Korea): 4630 randomly studied (2785 HBV , 447 HCV)
- Incidence /100,000: HBV 20.8 vs. HCV 4.9
- HBV-related HCC: more large tumors (≥ 5 cm) and PV invasion
- HCV-related HCC: multiple tumors

WJG 2016, J Viral Hepatitis 2011, Hepatology 2014

HCV-related HCC

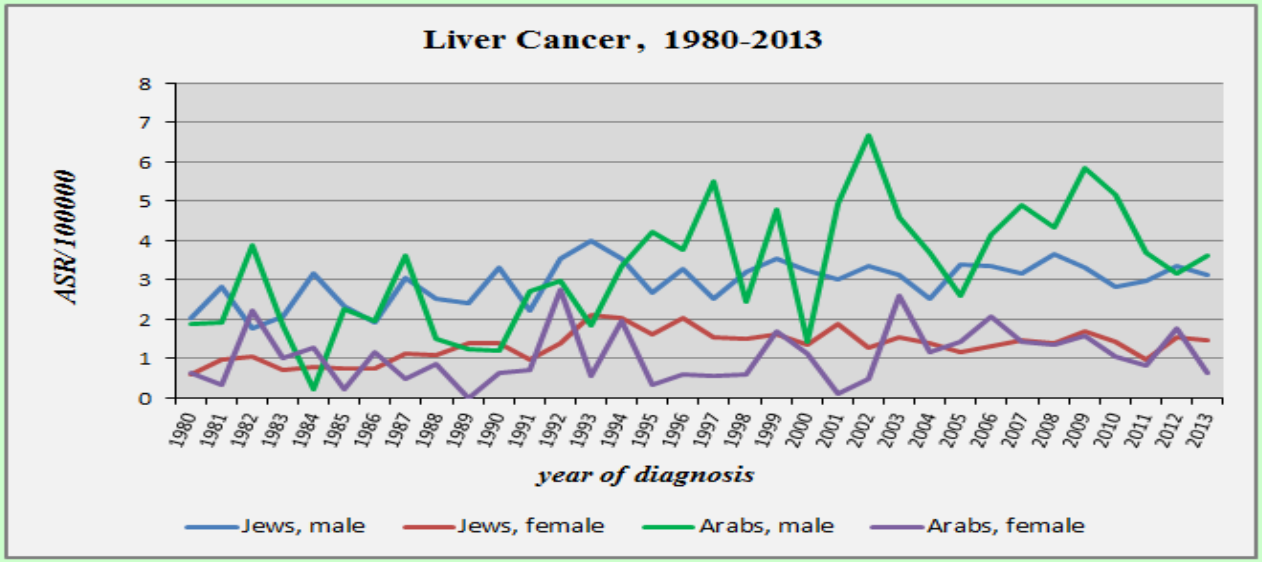
Clinical manifestations and outcome of HCV- vs. HBV-related HCC

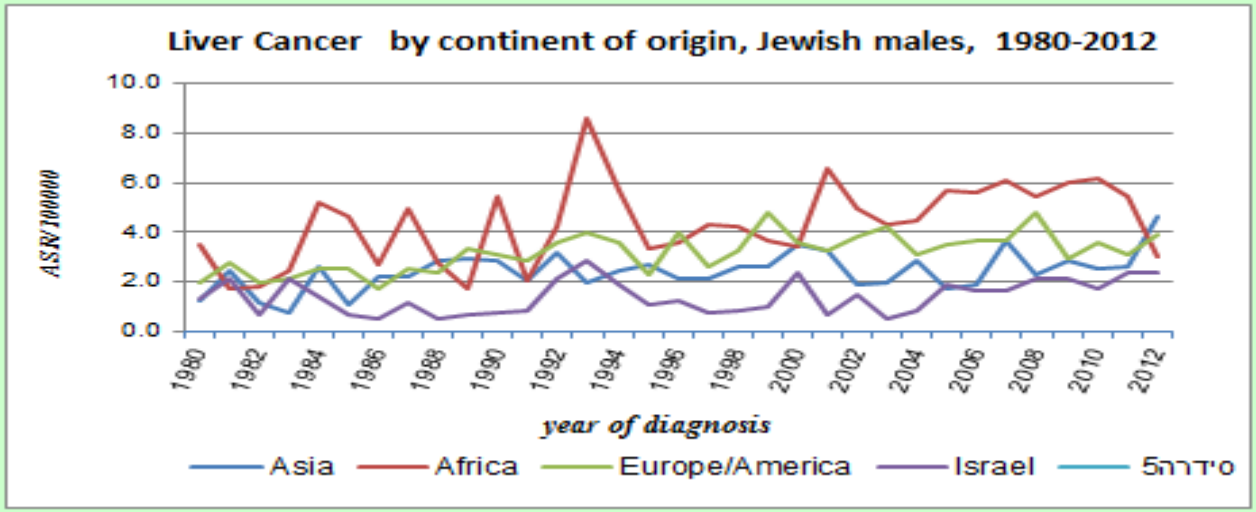


- HCV-related HCC: older than HBV (70+ vs. 50-59)
- Multiple tumors, smaller tumors, less outside Milan's
- Less vascular (PV) invasion

PLoS one 2014

Liver Cancer in Israel





MOH, update 1.16

Hadassah-Ichilov database (6.11-9.12)
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

HCC-Carmel Medical Center 2010-2.2016 (n=133)

Clinical characteristics	HCC patients 133, (%)
Age	66.5
HCV	112 (84)
NASH	12 (9)
HBV	4 (3)
ALD	2 (1.5)
GSD	2 (1.5)
BCS	1 (<1)
Liver transplantation	12 (9)
Resection	16 (12)
TACE/SIRT/RFA	83 (62)
Symptomatic treatment	22 (16.5)
Elevated AFP (40-118,000)	51 (40)

HCV-related HCC

Conclusions

- HCV is the leading etiology of HCC in the US, Europe and Japan
- Risk factors for CHC-HCC include DM, obesity, steatosis/NASH, alcohol, old age ,genotype 3, elevated AFP
- In 80-90% HCC occurs in patients with cirrhosis but may appears in patients without advanced cirrhosis (F0-2).
- Predictors for HCC in non-cirrhotics include HBcAb +, prolonged duration of HCV infection and other parameters
- Bio- or genetic markers may assist in prediction the risk for HCC in patients with chronic HCV infection

Thank You