



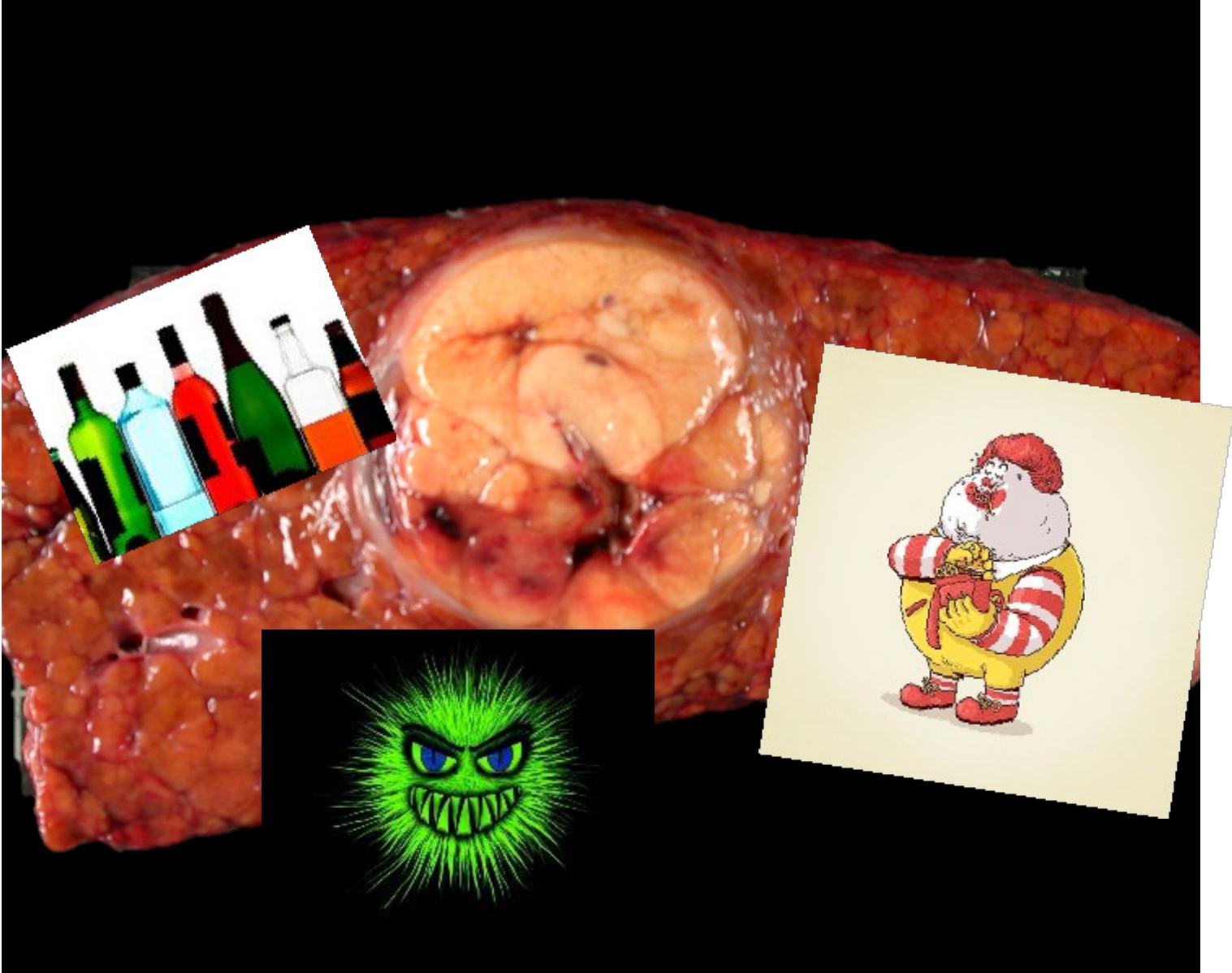
Hepatocellular Carcinoma and Metabolic Syndrome

Valérie Paradis

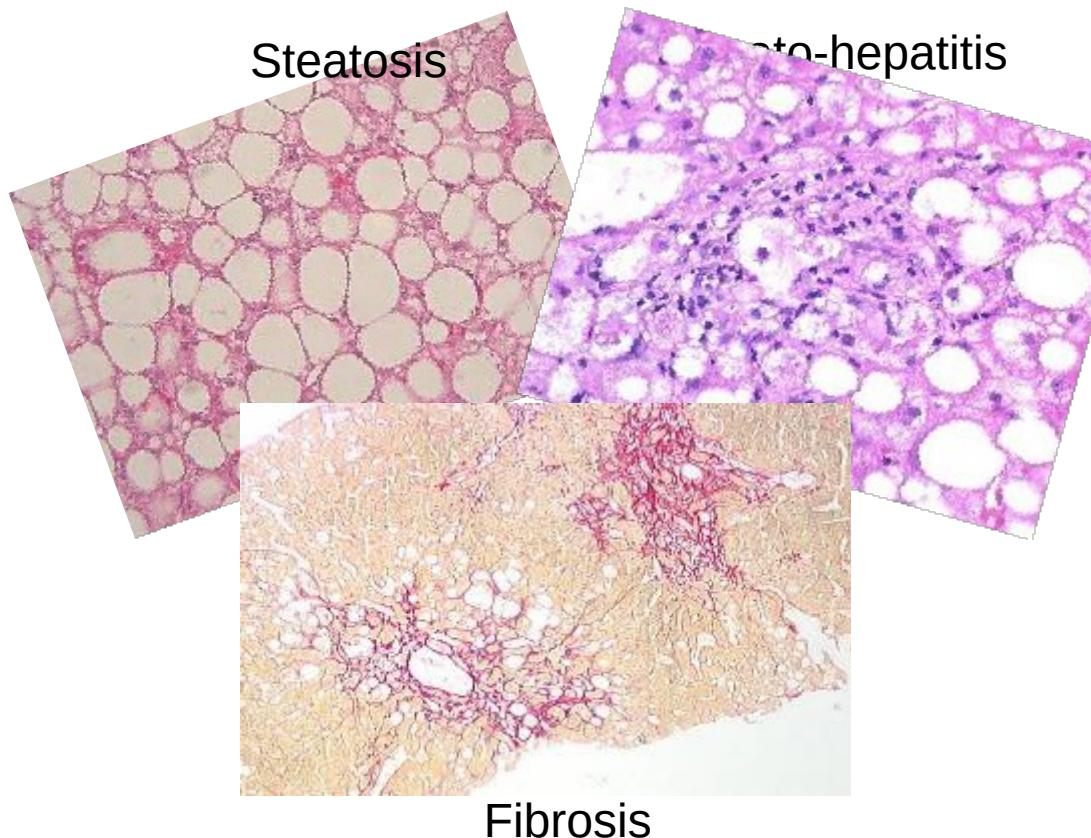
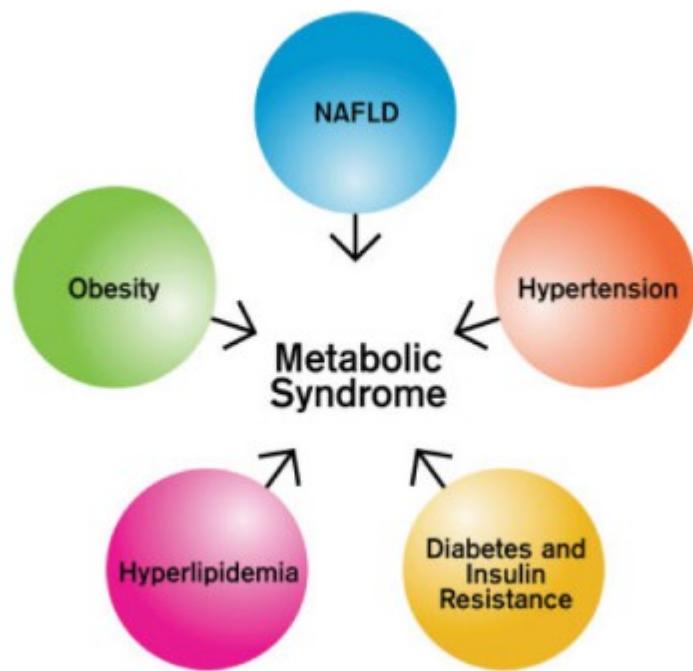
Pathology Dpt, Hôpital Beaujon

Inserm U1149 CRI, DHU UNITY Paris





Non Alcoholic Fatty Liver Diseases



NAFLD: An Epidemic Disease

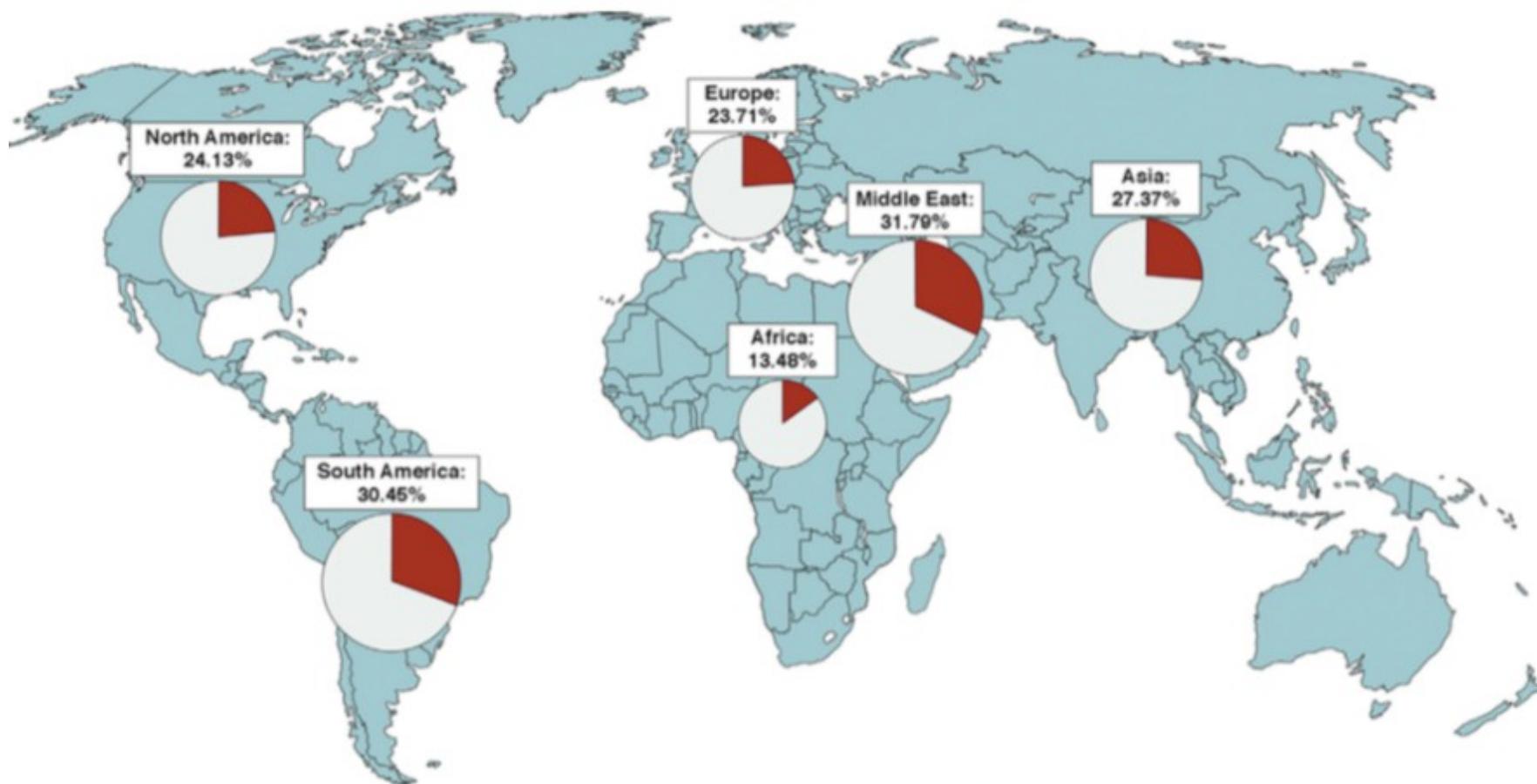


Figure 1. Global prevalence of NAFLD.

From Younossi Z & Henri L Gastro 2016

NAFLD : The Leading Risk Factor of HCC

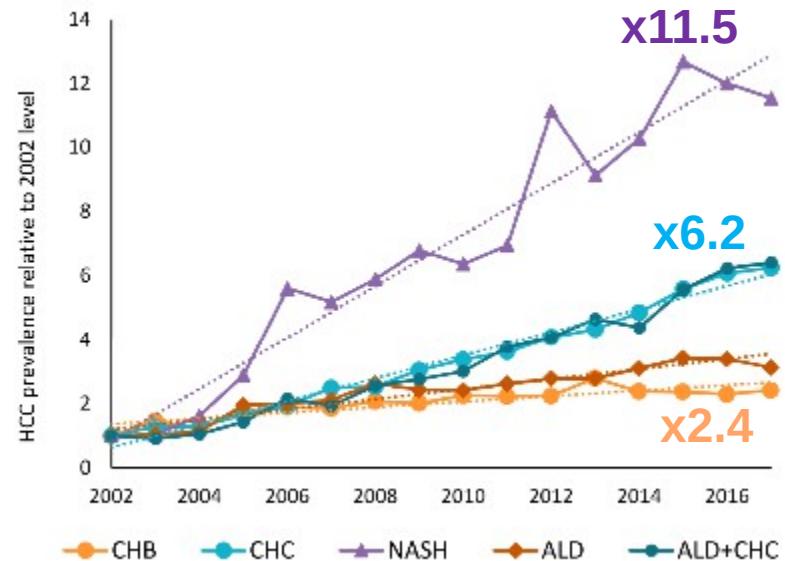
MarketScan
(2002-2008)

Liver disease	HCC n=440	Control n=4406
NAFLD/NASH	58.5 %	3.1 %
Diabetes	35.8 %	20.4 %
HCV	21.9 %	0.4 %
Alcohol	12.2 %	0.2 %
HBV	5.7 %	0.1 %

SEER-Medicare
database
(1993-2005)

1 Sanyal A CMRO
2010

Scientific Registry of Transplant
Recipients (2002-2016)



HCC-related to NAFLD

A multistep process of carcinogenesis

Steatosis

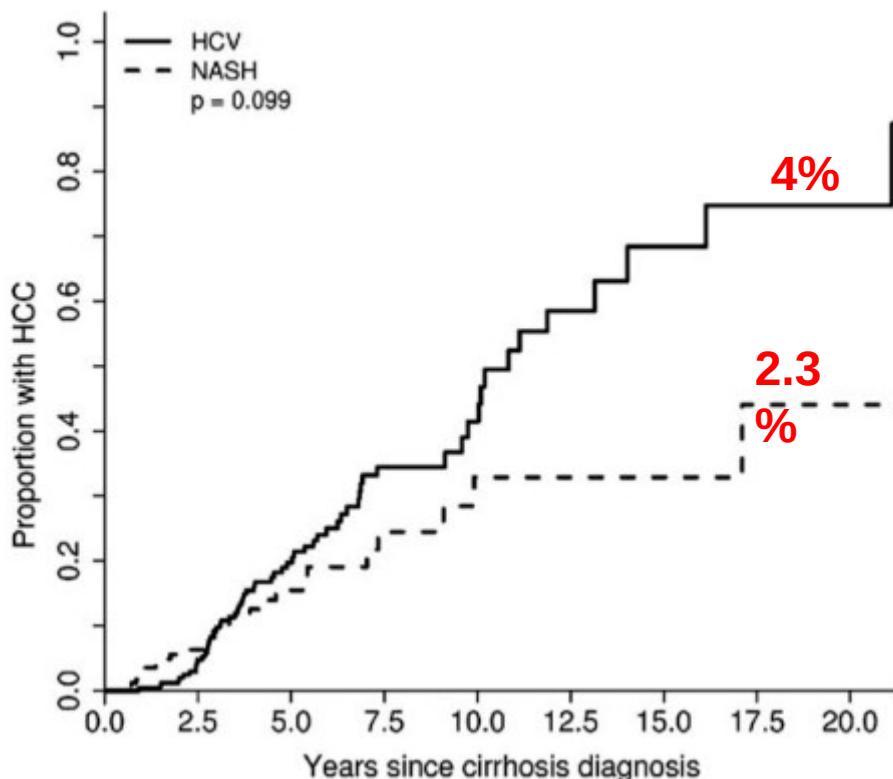
Steato-
hepatitis

Cirrhosis

HCC

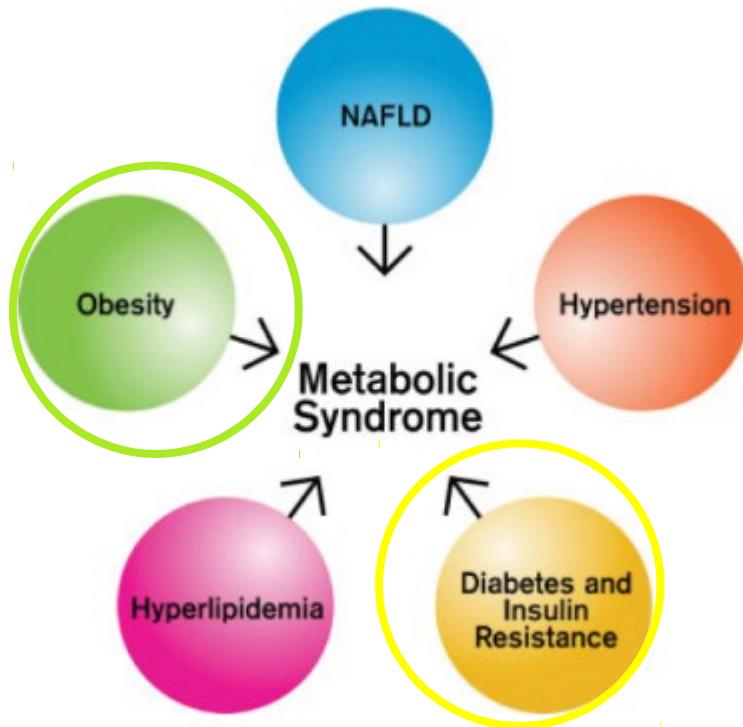
The Incidence and Risk Factors of Hepatocellular Carcinoma in Patients with Nonalcoholic Steatohepatitis

- 315 HCV- & 195 NASH-related cirrhosis (2003-2007)
 - Median follow-up 3.2 y



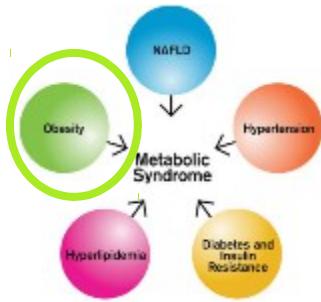
HCC related to MS: Oncogenic Risk factors

Metabolic Syndrome



Calle EE NEJM 2003

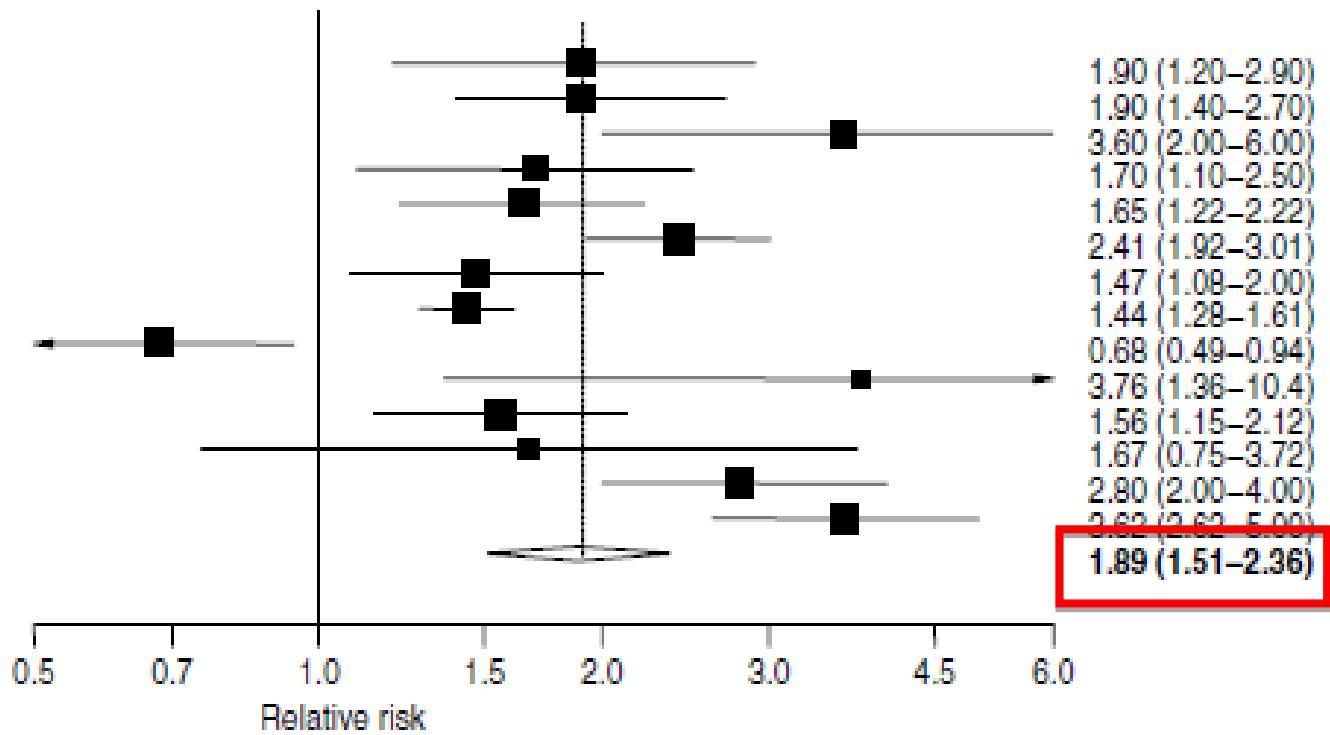


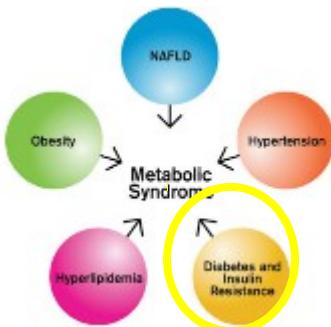


Overweight, obesity and risk of liver cancer: a meta-analysis of cohort studies

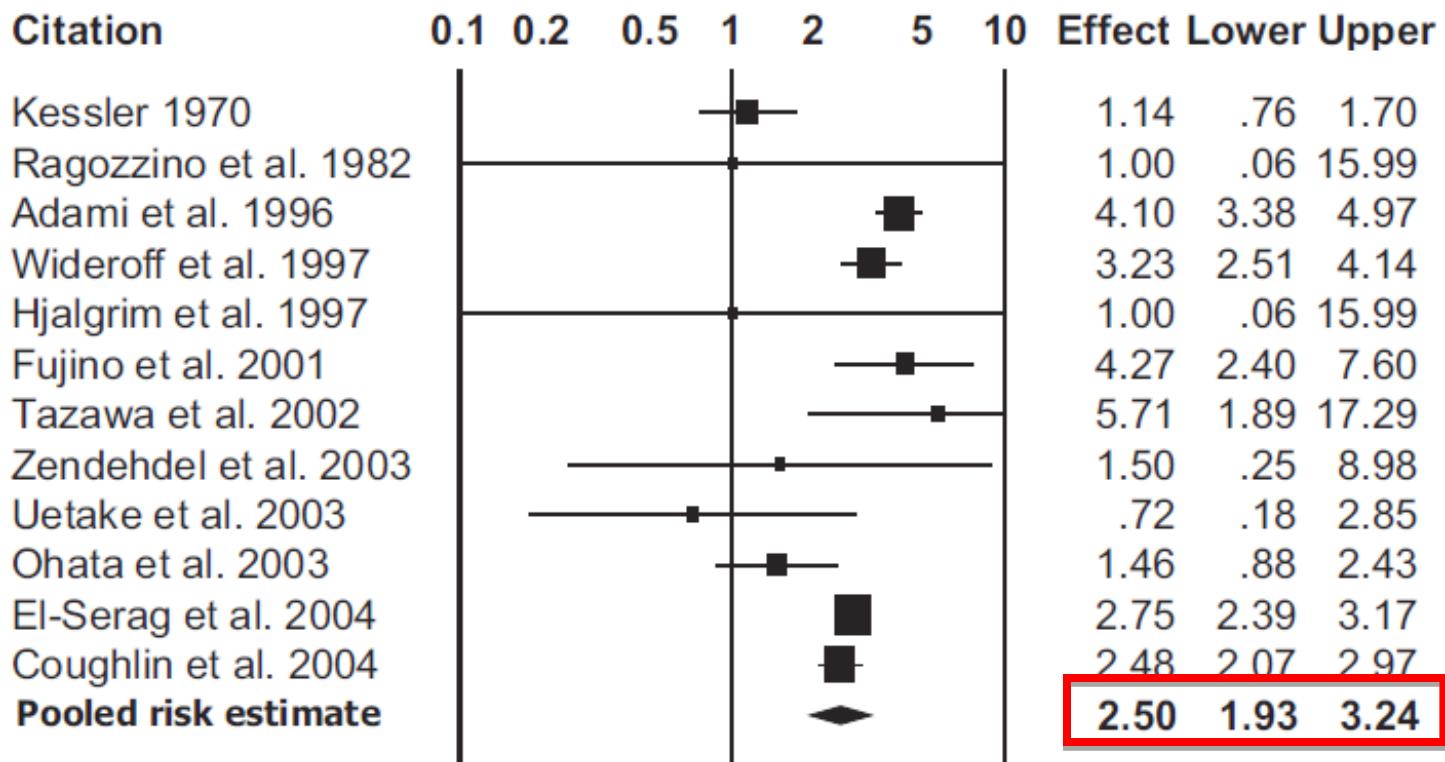
Obesity

Möller <i>et al</i> (1994) (M)	1.90 (1.20–2.90)
Möller <i>et al</i> (1994) (W)	1.90 (1.40–2.70)
Wolk <i>et al</i> (2001) (M)	3.60 (2.00–6.00)
Wolk <i>et al</i> (2001) (W)	1.70 (1.10–2.50)
Nair <i>et al</i> (2002) (M/W)	1.65 (1.22–2.22)
Calle <i>et al</i> (2003) (M)	2.41 (1.92–3.01)
Calle <i>et al</i> (2003) (W)	1.47 (1.08–2.00)
Samanic <i>et al</i> (2004) (M, whites)	1.44 (1.28–1.61)
Samanic <i>et al</i> (2004) (M, blacks)	0.68 (0.49–0.94)
Batty <i>et al</i> (2005) (M)	3.76 (1.96–10.4)
Oh <i>et al</i> (2005) (M)	1.56 (1.15–2.12)
Rapp <i>et al</i> (2005) (M)	1.67 (0.75–3.72)
N'Kontchou <i>et al</i> (2006) (M/W)	2.80 (2.00–4.00)
Samanic <i>et al</i> (2006) (M)	3.82 (2.32–5.00)
Summary estimate	1.89 (1.51–2.36)





The Association Between Diabetes and Hepatocellular Carcinoma: A Systematic Review of Epidemiologic Evidence



Diabetes, Plasma Glucose, and Incidence of Fatty Liver, Cirrhosis, and Liver Cancer: A Prospective Study of 0.5 Million People

- 5.8 % of participants had diabetes at baseline

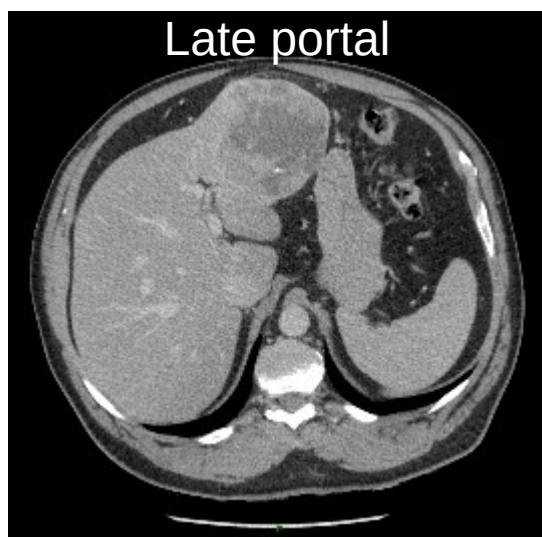
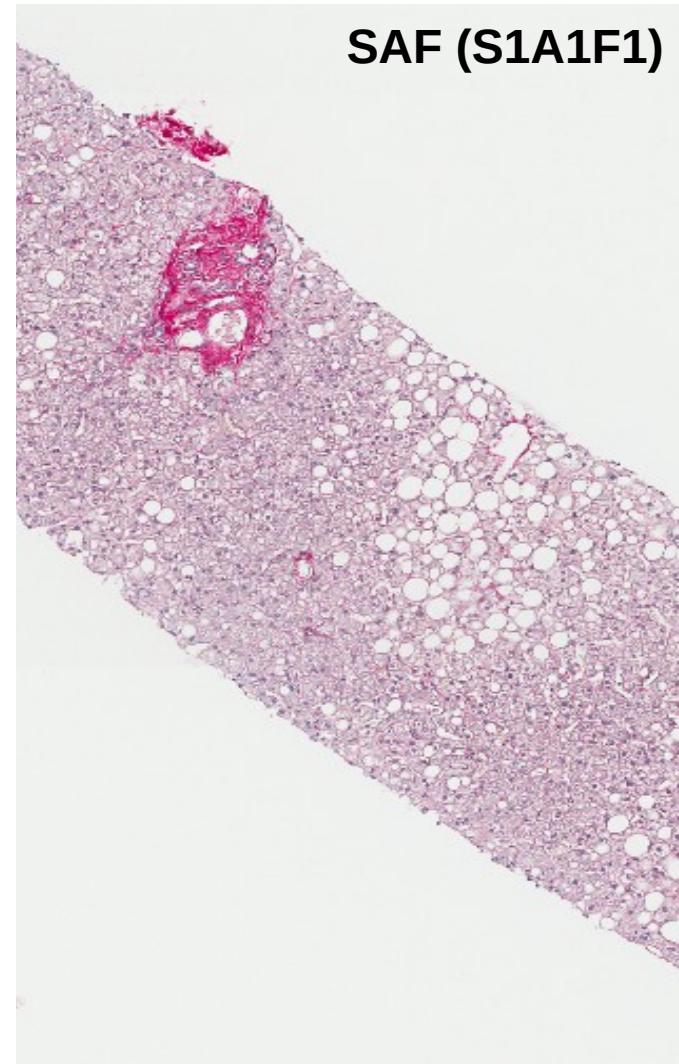
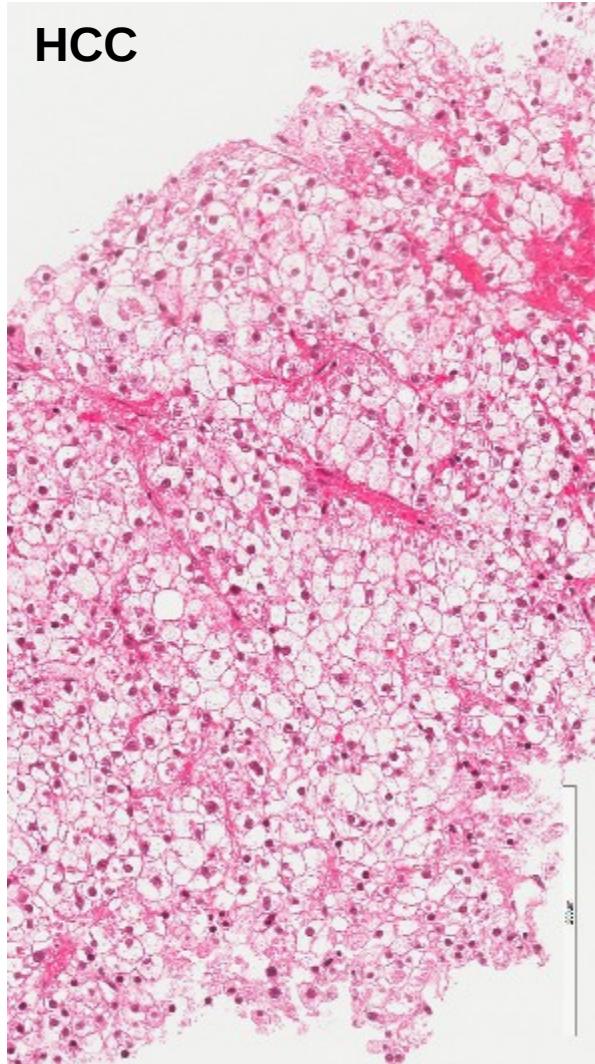
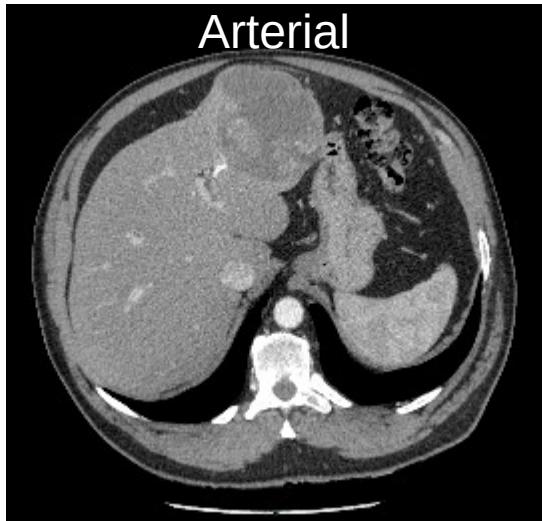
TABLE 2. Adjusted HRs for Liver Cancer and Chronic Liver Diseases by Diabetes Status

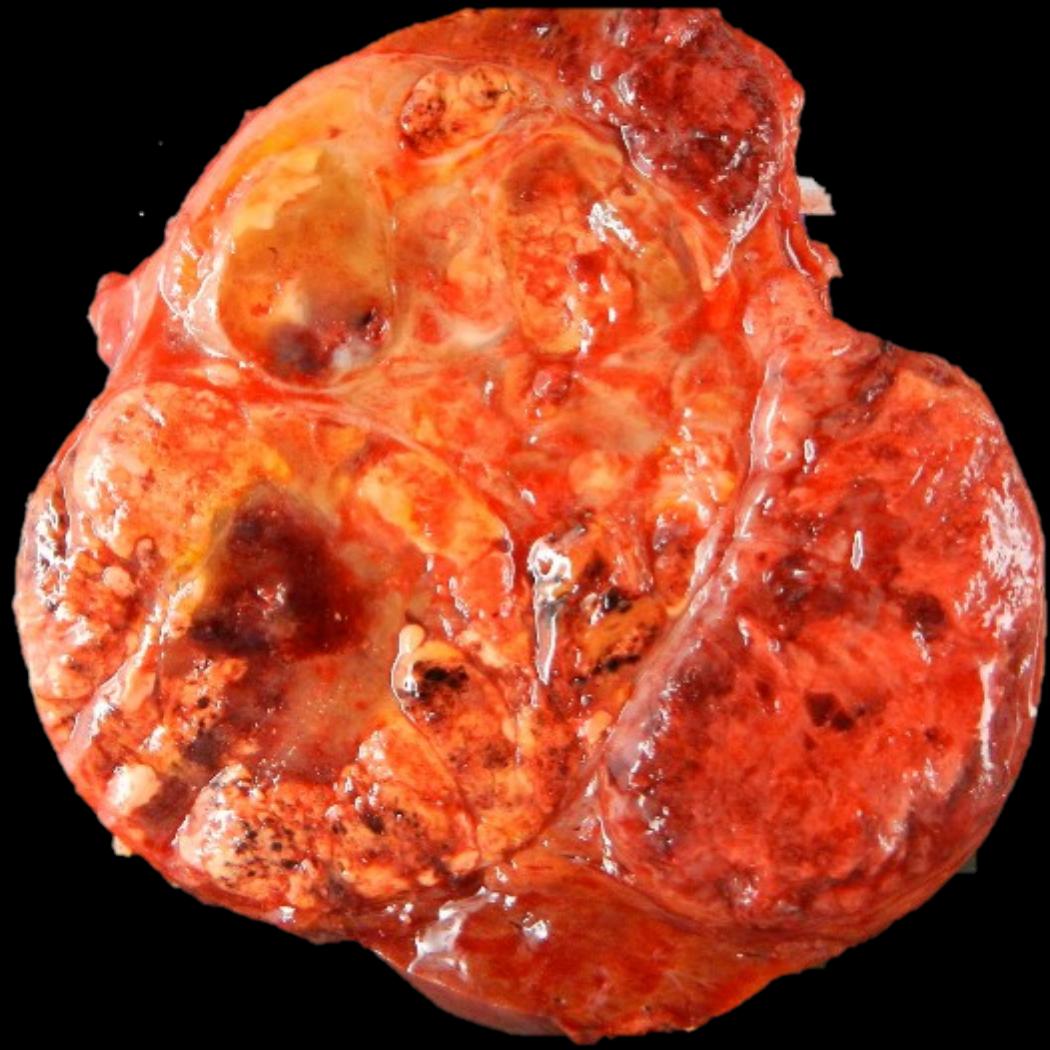
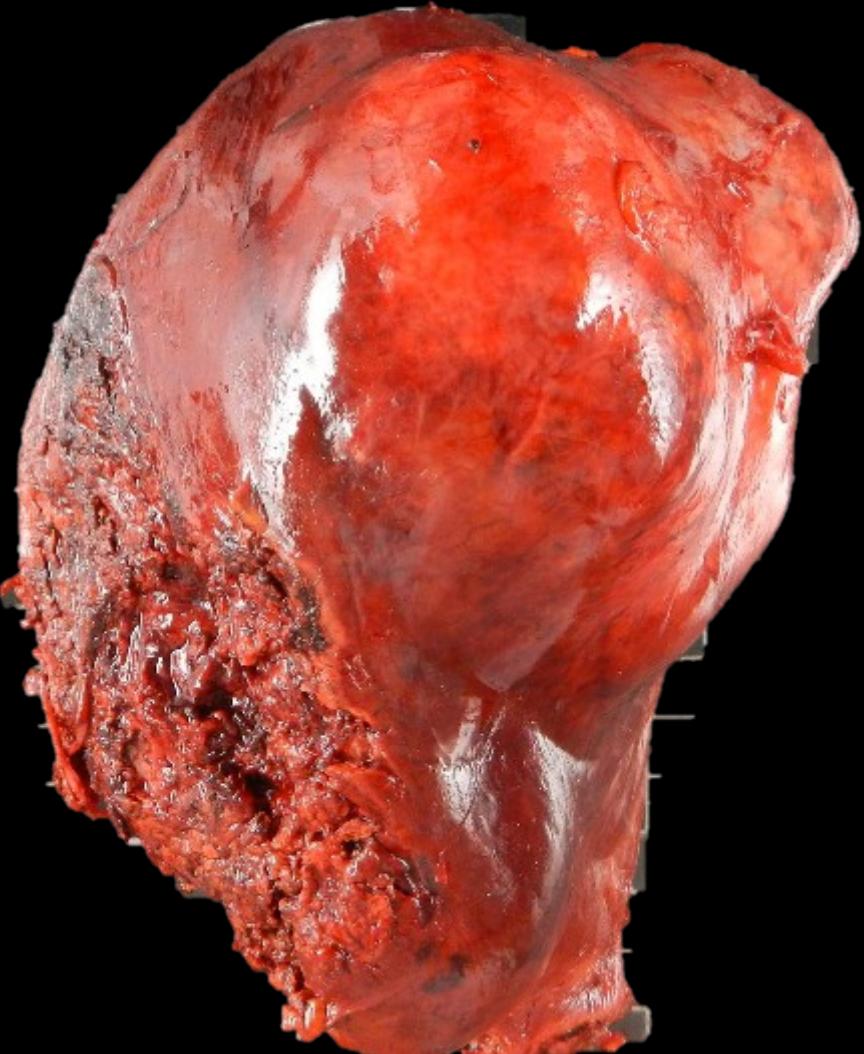
	No. Events	Rate, per 100,000	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Liver cancer				
No diabetes	2,313	487.6	Reference	Reference
Diabetes	255	862.1	1.49 (1.30-1.70)	1.52 (1.33-1.74)
Cirrhosis				
No diabetes	1,858	397.4	Reference	Reference
Diabetes	224	756.4	1.81 (1.57-2.09)	1.83 (1.59-2.12)

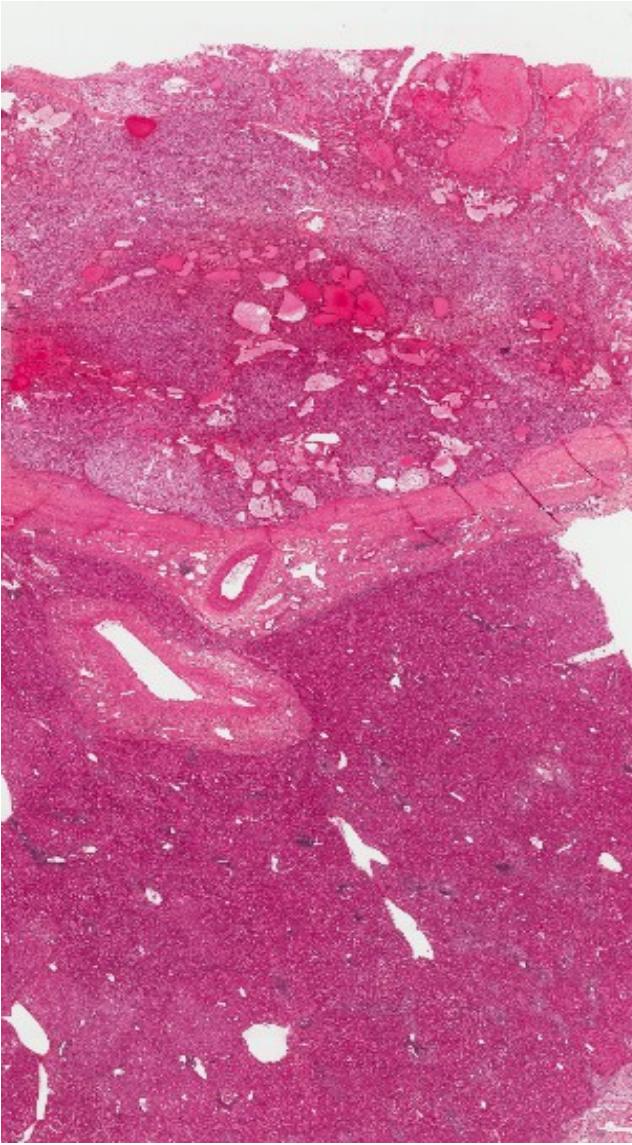
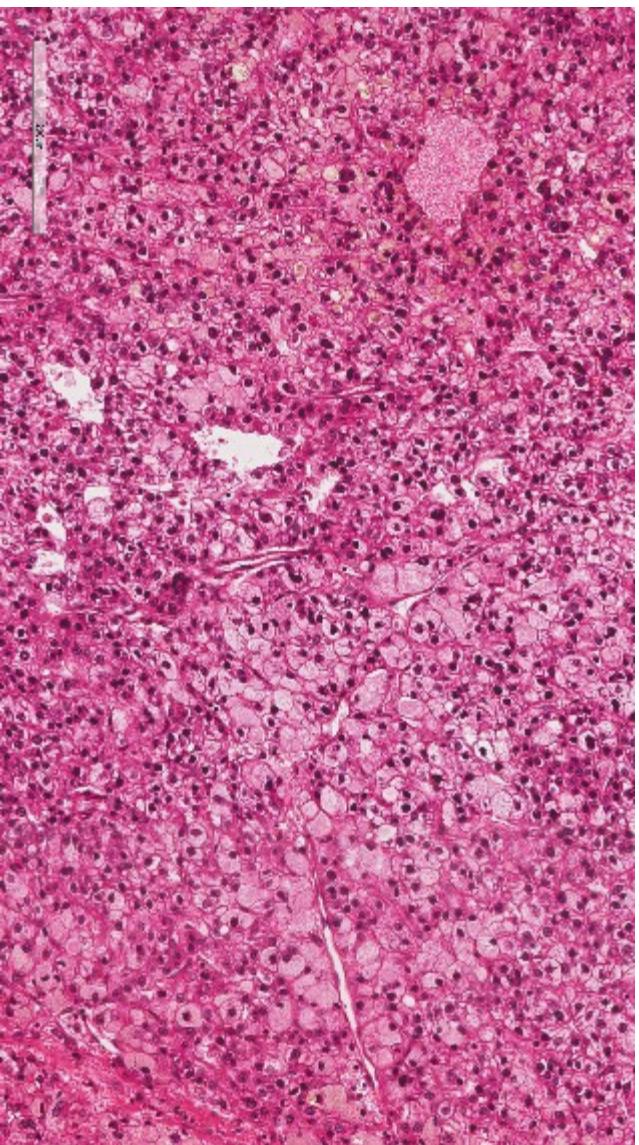
Plasma glucose levels positively correlated with liver disease

HCC related to MS: Specific features

61 year-old ♂, BMI 33, HT, Dyslip.







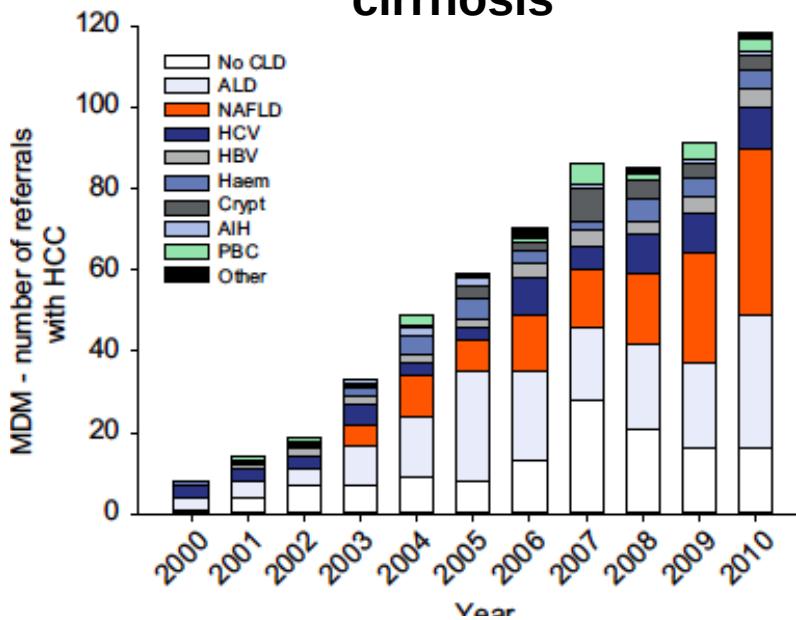
Hepatocellular Carcinomas in Patients With Metabolic Syndrome Often Develop Without Significant Liver Fibrosis: A Pathological Analysis

Surgical series

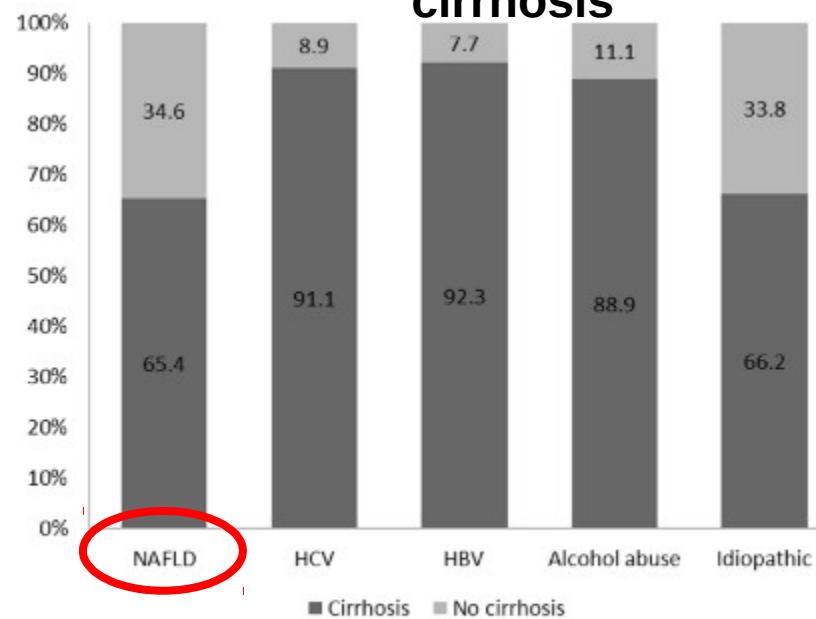
	MS Group (n = 31)	CLD Group (n = 81)	
Liver fibrosis			
F0-F2	20 (65.5%)	21 (26%)	p<0.001
F3-F4	11 (35.5%)	60 (74%)	
Steatosis			
0 (<5%)	6 (19%)	47 (58%)	p<0.001
1 (5%-33%)	12 (39%)	29 (36%)	
2 (33%-66%)	11 (35.5%)	3(4%)	
3 (>66%)	2 (6.5%)	2(2%)	



- 632 Patients with HCC [2000-2010]
- **34.8% CHC/NAFLD, 23% without cirrhosis**



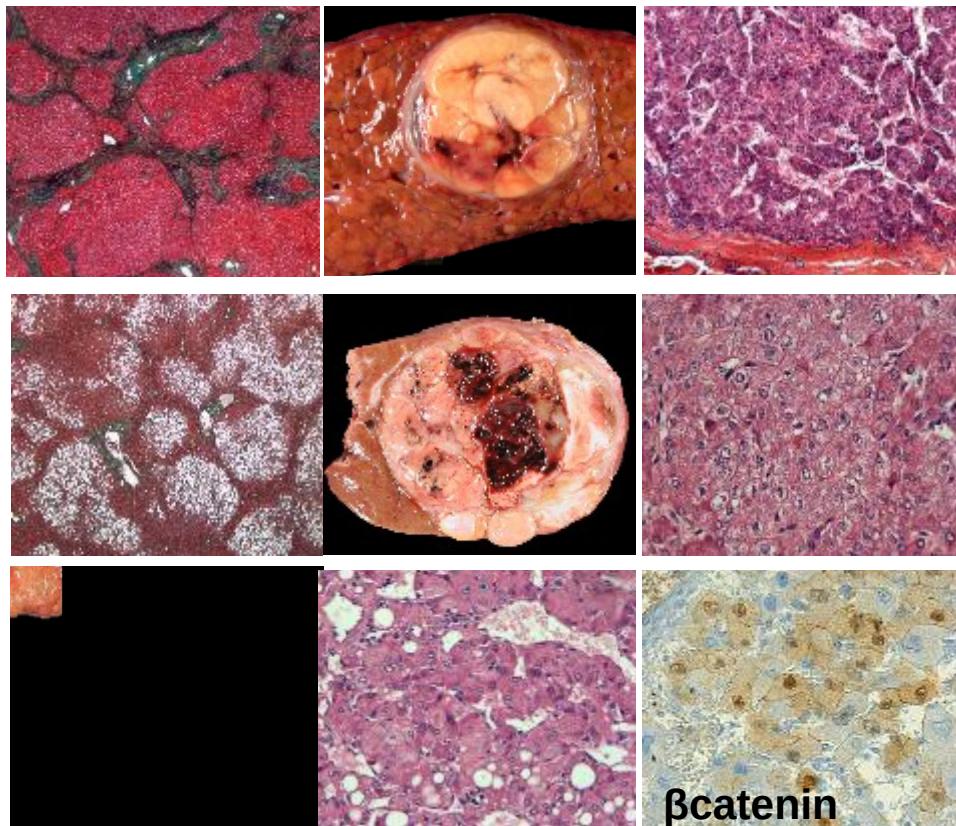
- 1500 US veterans with HCC [2005-2010]
 - 80.1% of patients with cirrhosis
- **HCC/NASH or MS : risk x 5 HCC without cirrhosis**



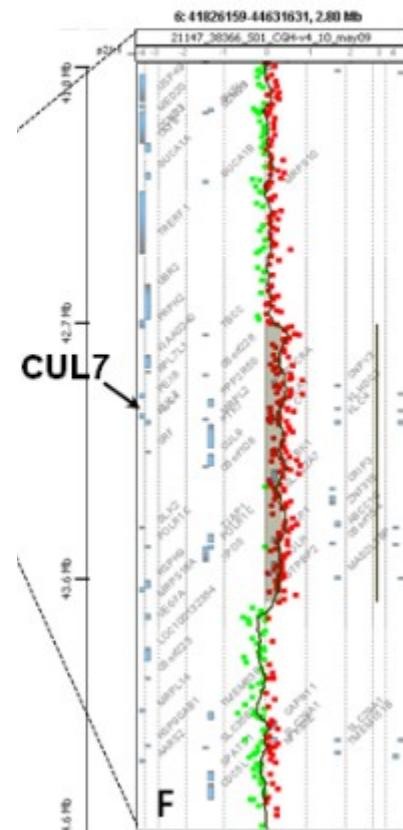
Hepatocellular Carcinomas in Patients With Metabolic Syndrome Often Develop Without Significant Liver Fibrosis: A Pathological Analysis

3 Morphological Patterns

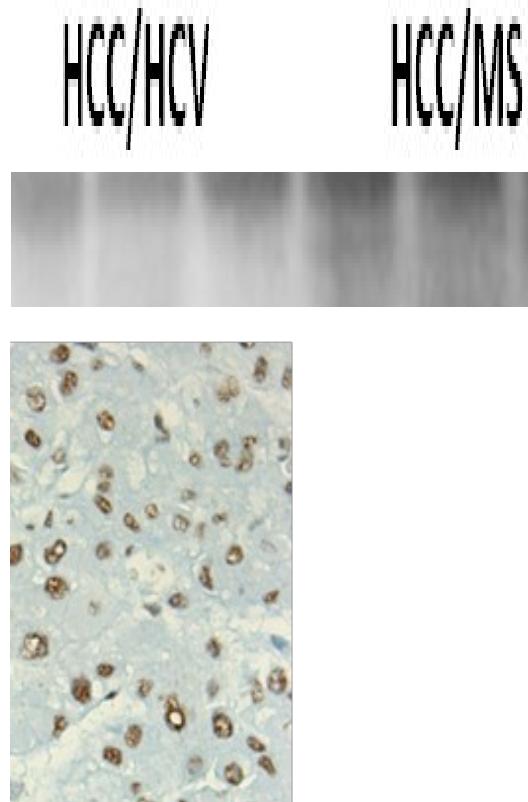
	M:	(n)
Tumor size (cm)	8.8	
Bilobar	7 (
Number of tumors	1 (
Capsule	23	
Macroscopic vascular invasion	6 (
Differentiation		
Well	20	
Moderate	11	
Poor	0 (
Microscopic vascular invasion	14	
Satellite nodules	11	



Cullin7: a new gene involved in liver carcinogenesis related to metabolic syndrome

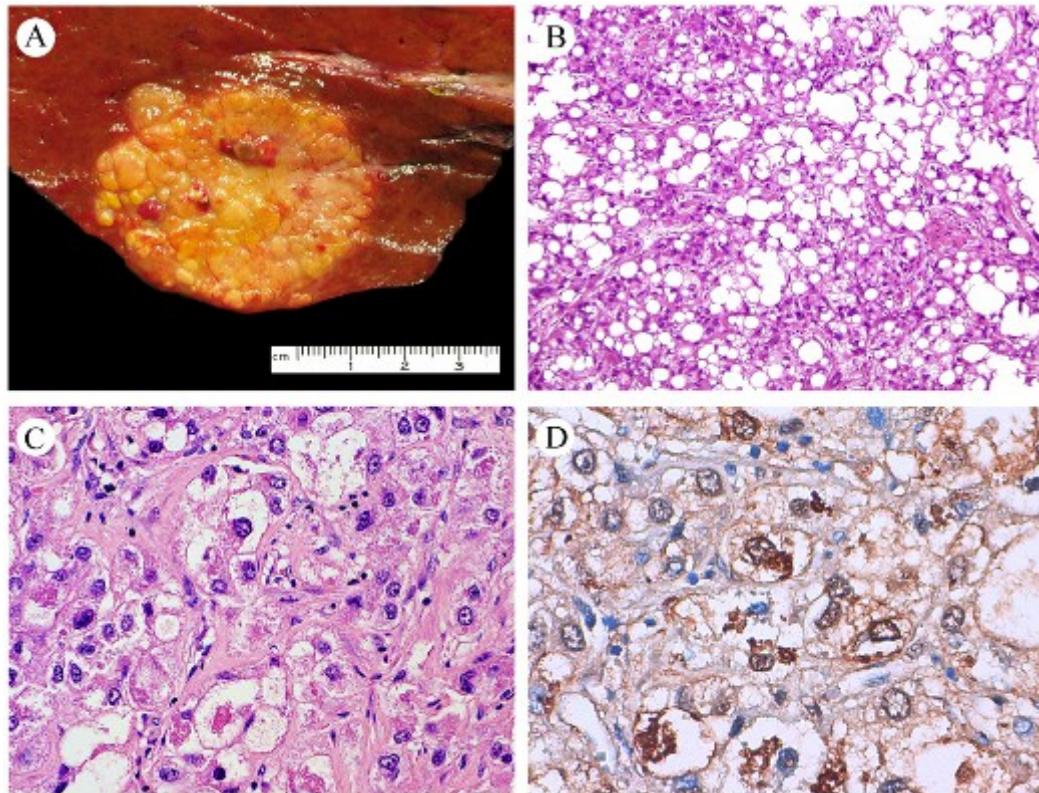


6p21.1 amplification



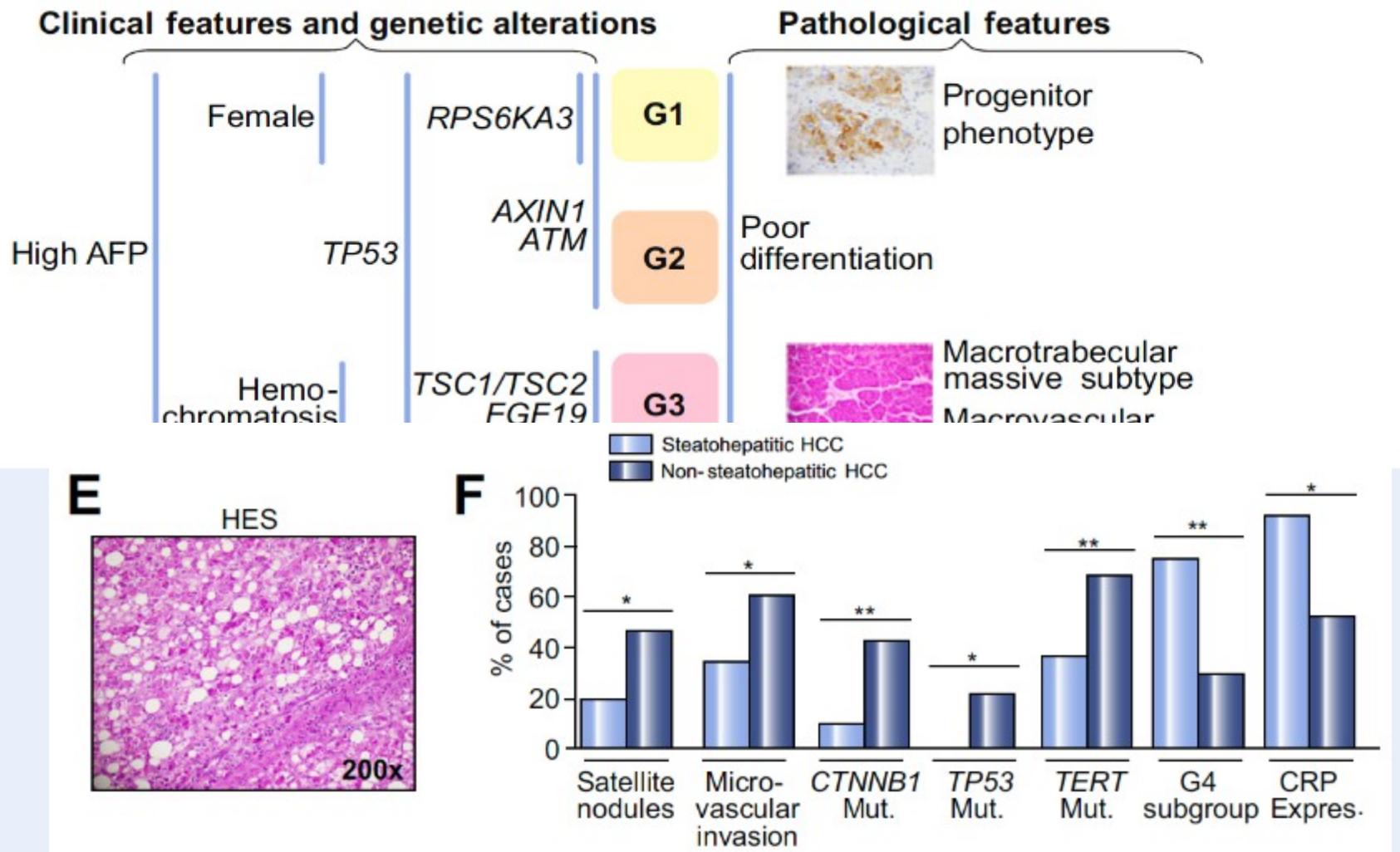
Cullin7 expression in HCC/MS

The steatohepatitic variant of hepatocellular carcinoma and its association with underlying steatohepatitis



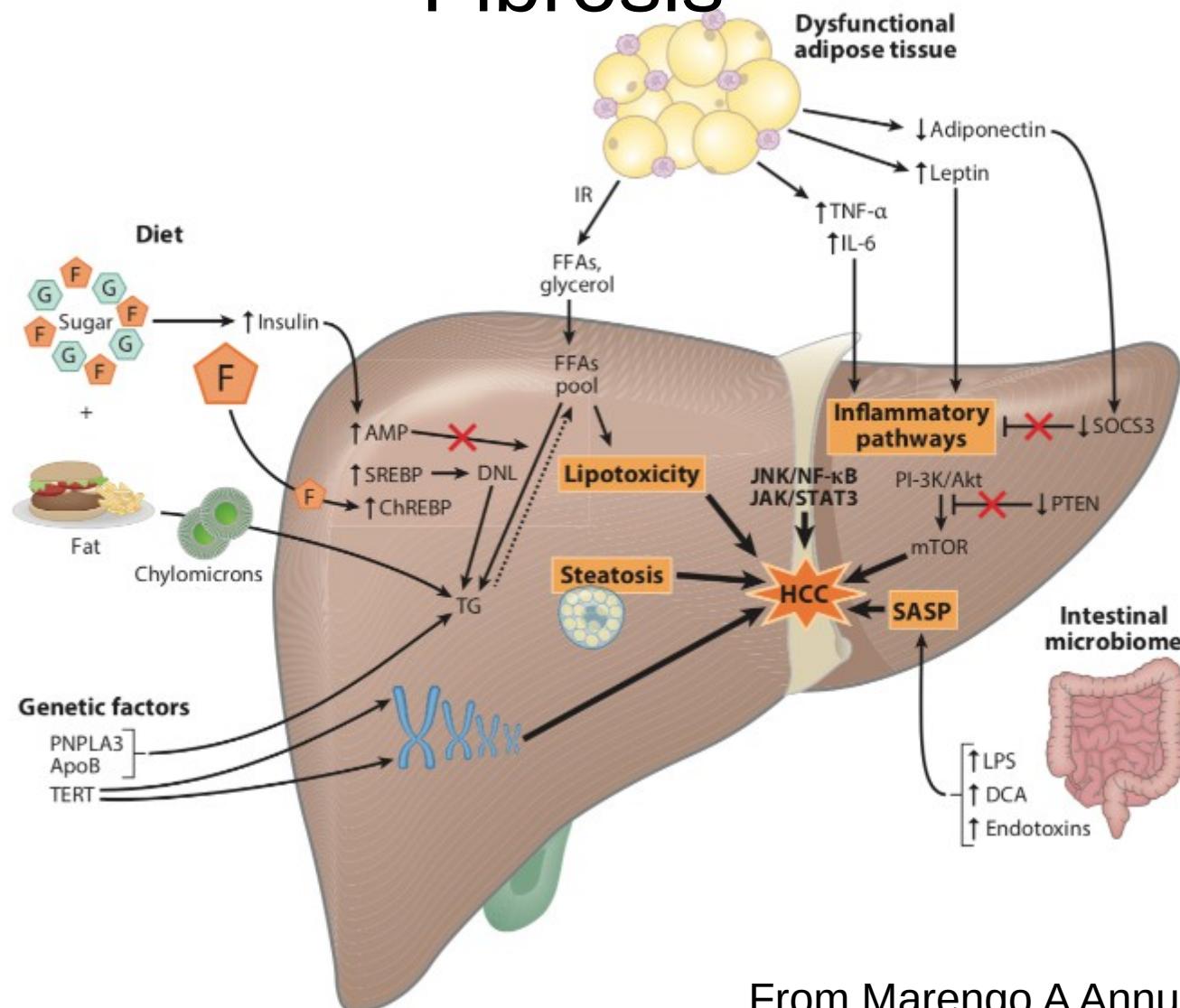
- 1/3 of patients with MS
- NASH in the background liver
 - No ≠ in prognosis

Histological subtypes of hepatocellular carcinoma are related to gene mutations and molecular tumour classification[☆]



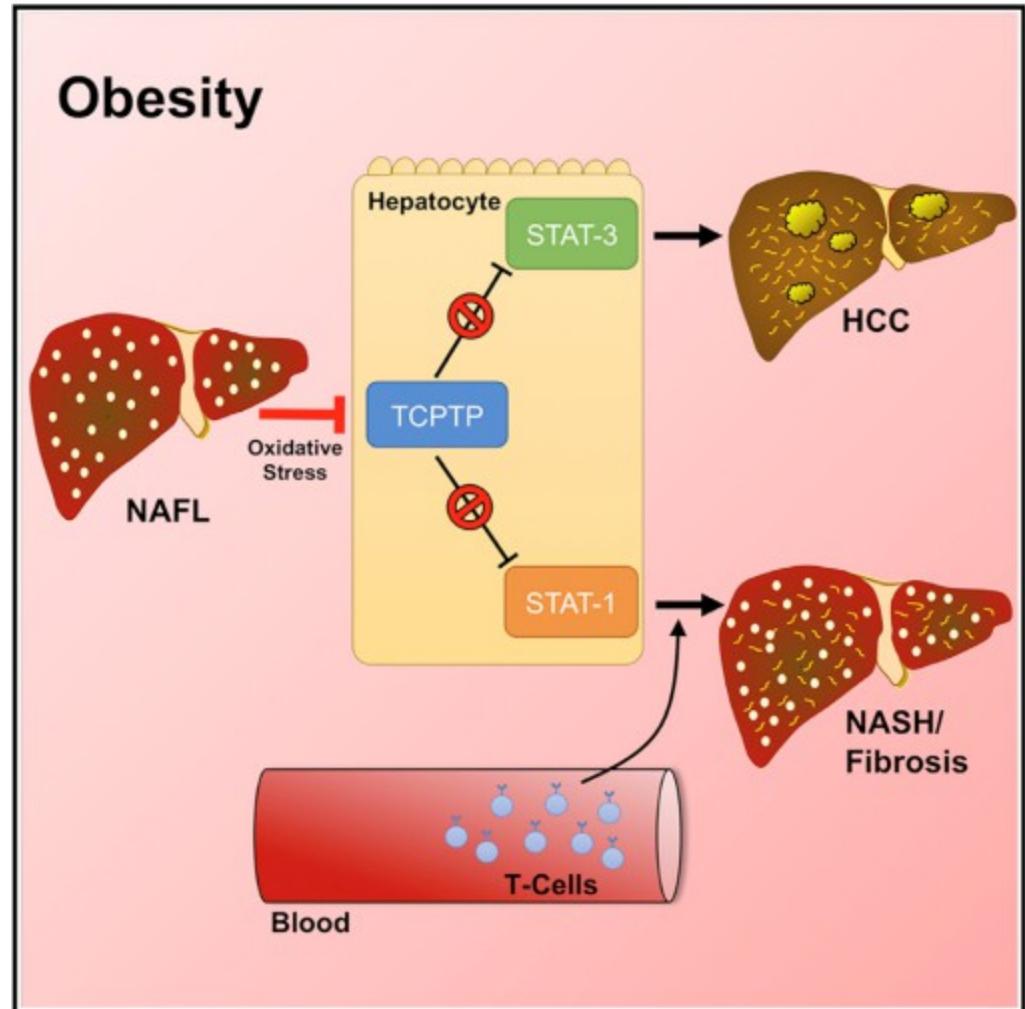
HCC related to MS: Specific Molecular mechanisms

Related to NAFLD, rather than to Fibrosis

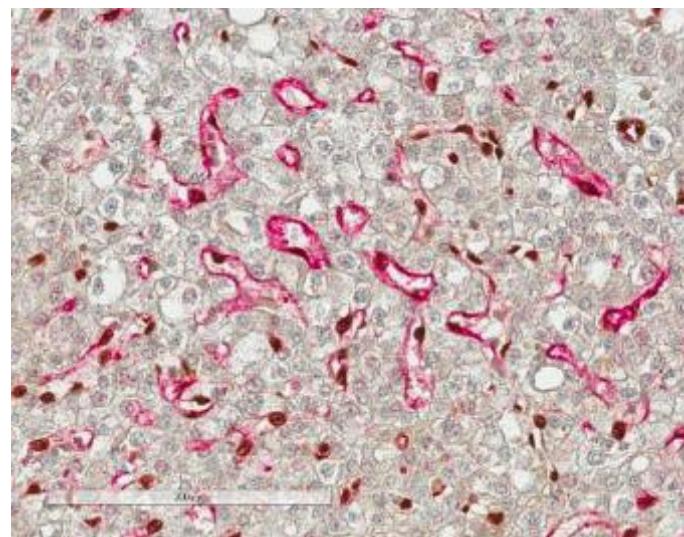
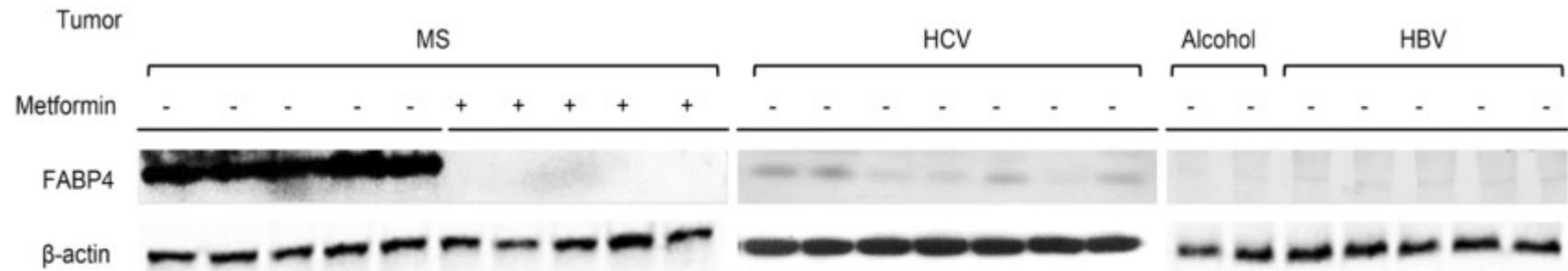


Obesity Drives STAT-1-Dependent NASH and STAT-3-Dependent HCC

- In obesity, NASH, fibrosis and HCC can be dissociated
- Obesity increases STAT-1 and STAT-3 signaling
- Attenuating the enhanced STAT-1 signaling prevented T cell recruitment, NASH & fibrosis, without affecting HCC
- Correcting STAT-3 signaling prevented HCC without affecting NASH & fibrosis

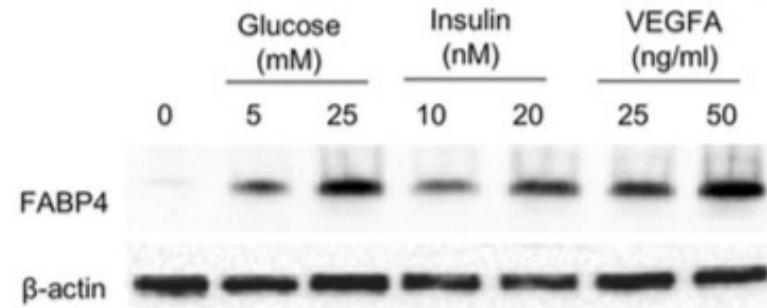


Endothelial fatty liver binding protein 4: a new targetable mediator in hepatocellular carcinoma related to metabolic syndrome



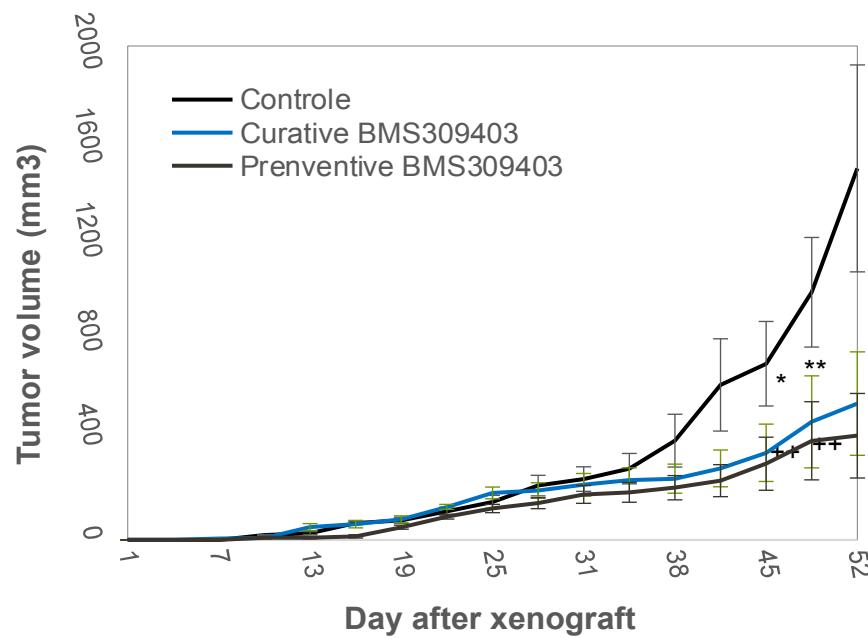
HCC/MS (Erg/FABP4)

Liver Sinusoidal Endothelial Cells

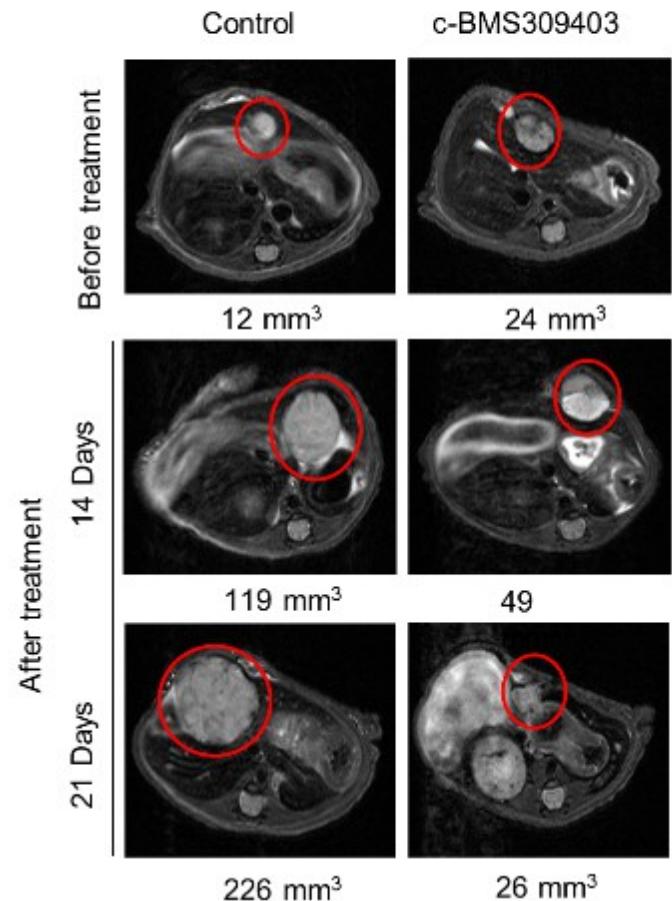


FABP4: A potential therapeutic target ?

Heterotopic xenograft HFD model



Orthotopic xenograft HFD model



Conclusions

- Metabolic Syndrome: A risk factor for NAFLD
 - ↗ prevalence worldwide, **the leading risk factor for HCC**
 - **Diabetes and obesity** are independant factors for HCC
 - Cofactors are frequent (Alcohol/**BASH**)
- HCC related to NAFLD
 - **A new model of liver carcinogenesis**
 - HCC without underlying cirrhosis (up to 35%)
 - Specific molecular mechanisms involving genetics, microbiota, adipokines, ..
 - Issues remain to be solved (specific screening programs & treatment)



Inserm U 1149, CRI

- « From inflammation to cancer in digestive diseases » V Paradis
 - A Couvelard, N Guedj, J Cros, V Rebours, N Poté, A Beaufrère
 - F Cauchy, L de Mestier (Doc)
 - S Paisley, S Frendi (M2)
 - S Laouirem, J Le Faouder, M Albuquerque (IE)

Beaujon hospital

- Pathology (V Paradis)
- Radiology (V Vilgrain)
- Hepatology (F Durand)
- Liver surgery (O Soubrane)
- UNITY (D Vallès)



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LES
GROS

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INTÉRIEURE
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