Metabolic Syndrome and HCC

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MetS and risk of HCC and ICC

- All with HCC and ICC between 1993 and 2005 identified in the Surveillance, Epidemiology, and End Results (SEER)-Medicare database.
- For comparison, a 5% sample of individuals residing in the same regions as the SEER registries of the cases was selected
- 3649 HCC cases, 743 ICC cases, and 195,953 comparison persons

Table 6. Multiple Logistic Regression Analysis Examining the Association Between Metabolic Syndrome and HCC or ICC, Adjusting for Demographic Variables and Major HCC or ICC Risk Factors

	HCC			ICC		
	Adjusted OR†	95% Confidence interval	*P* Value	Adjusted OR‡	95% CI	*P* Value
Metabolic syndrome*	2.13	(1.96-2.31)	<0.0001	1.56	(1.32-1.83)	<0.0001

*Following the 2001 U.S. NCEP-ATP III definition.

†HCC risk factors are adjusted for demographic characteristics and HBV infection, HCV infection, unspecified viral hepatitis, alcoholic liver disease, unspecified cirrhosis, biliary cirrhosis, hemochromatosis, Wilson's disease, and smoking.

‡ICC risk factors are adjusted for biliary cirrhosis, cholangitis, cholelithiasis, choledochal cysts, HBV infection, HCV infection, unspecified viral hepatitis, alcoholic liver disease, nonspecified cirrhosis, inflammatory bowel disease, (Crohn's disease, ulcerative colitis), and smoking.

Welzel T et al; HEPATOLOGY 2011;54:463-471

The NEW ENGLAND JOURNAL of MEDICINE

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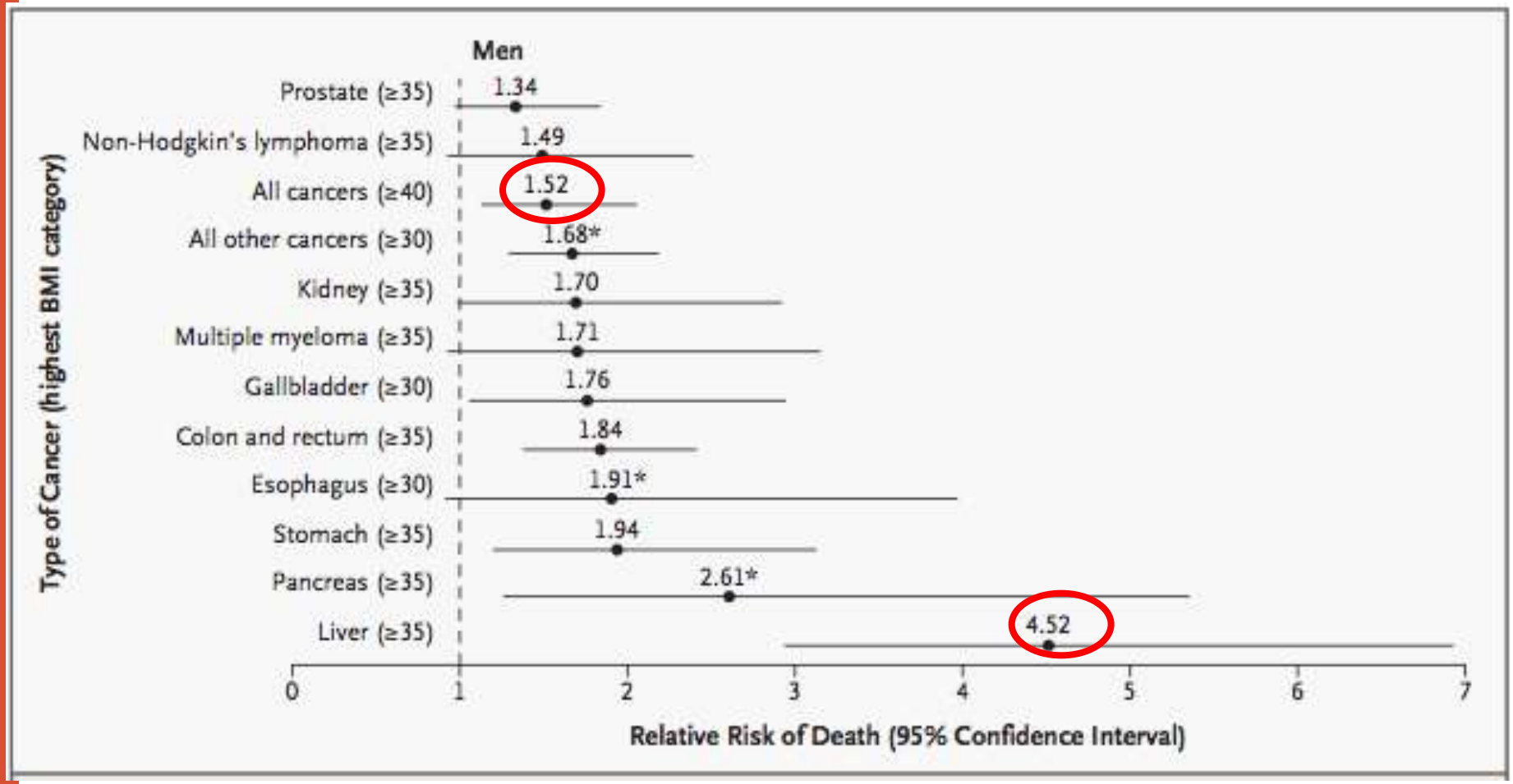
Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults

Eugenia E. Calle, Ph.D., Carmen Rodriguez, M.D., M.P.H., Kimberly Walker-Thurmond, B.A., and Michael J. Thun, M.D.

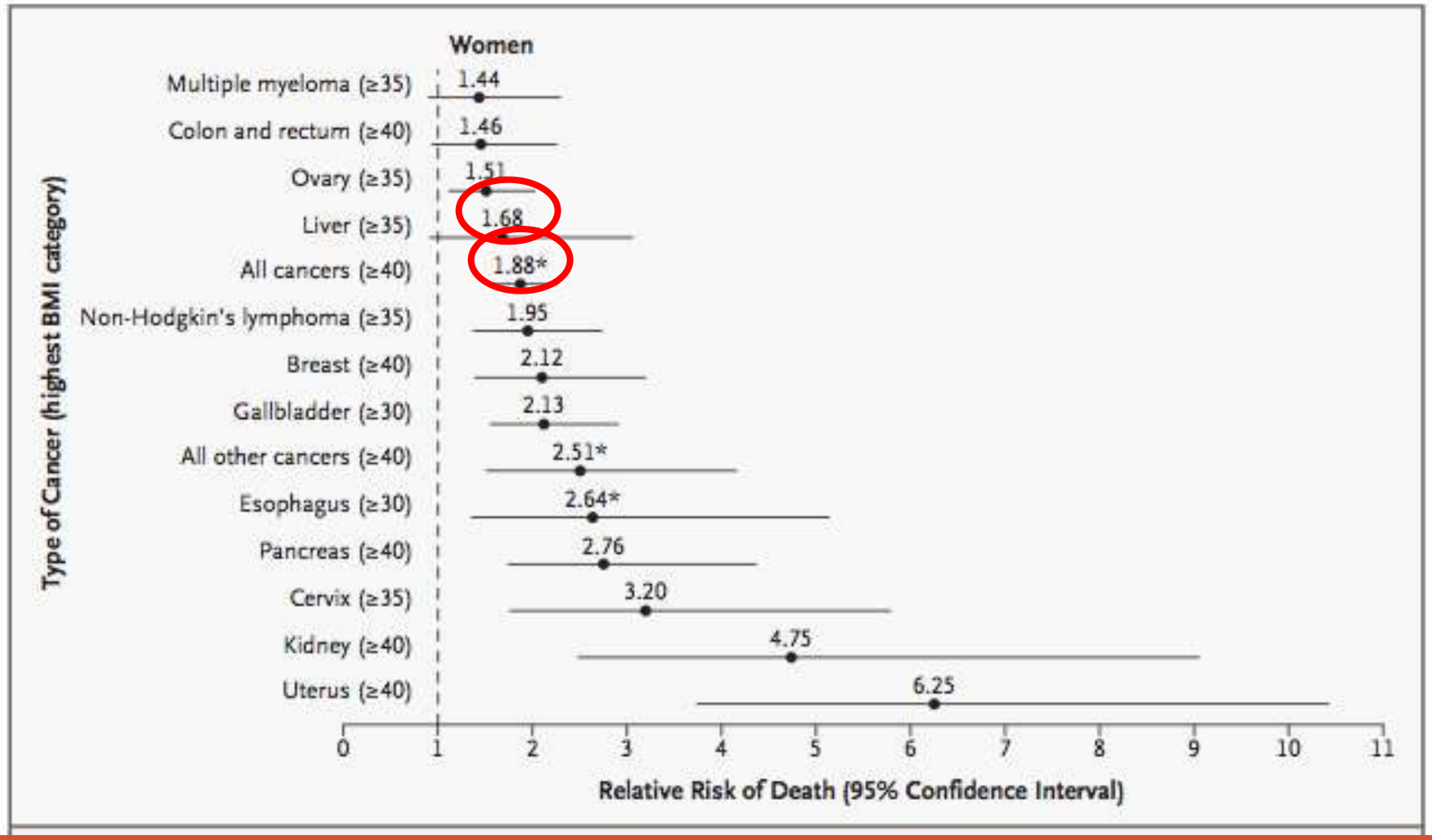
- **900,053 subjects from the American Cancer Society's Cancer Prevention Study II.**
- **Average age at enrollment was 57 years. Baseline weight and height, plus smoking status, race, level of education attained, exercise, dietary information, medications, alcohol intake.**
- **After 16 years of follow up, 32,303 deaths from cancer with detailed information on diagnosis for 98.8%.**

Morbid obesity and death due to cancers



Calle et al NEJM 2003

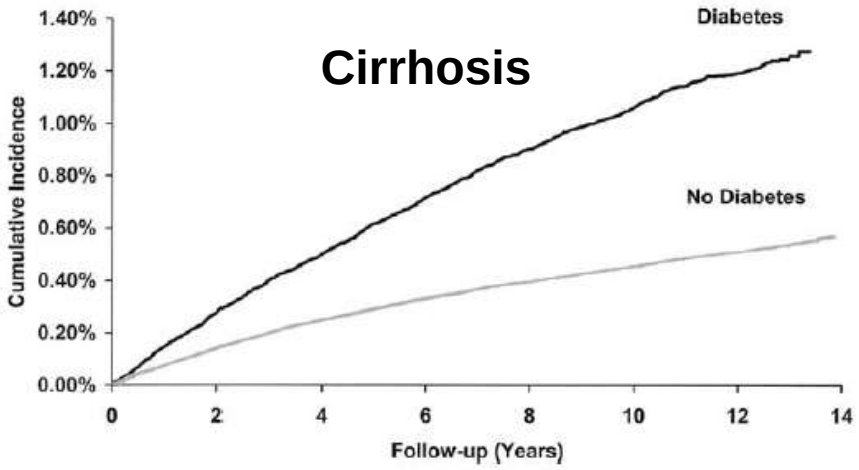
Morbid obesity and death due to cancers

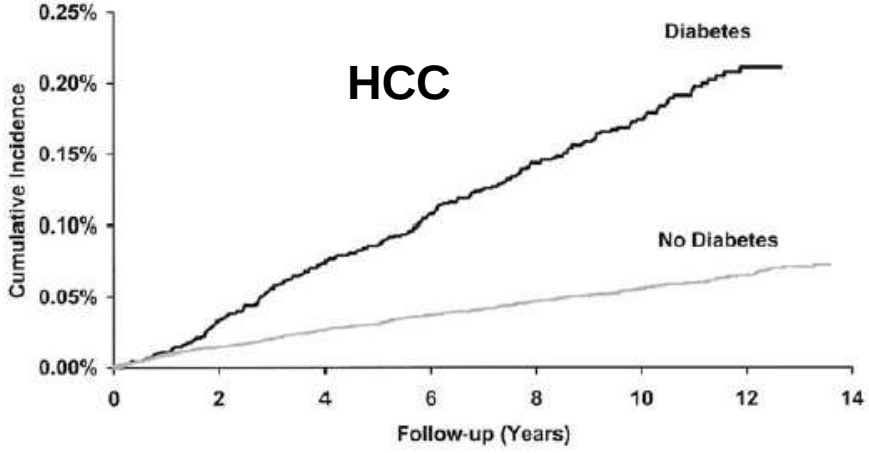


Calle et al NEJM 2003

Diabetes and HCC

- Hospital discharge with diabetes between 1985 and 1990 VA.
- 3 patients without diabetes for every patient with diabetes.
- Excluded patients with concomitant liver disease and followed to 2000
- 173,643 patients with diabetes and 650,620 patients without diabetes. 98% men
- *Diabetes* was associated with an HRR of 1.98 (95% CI: 1.88 to 2.09, *P < 0.0001) of CNLD and an HRR of 2.16 (1.86 to*2.52, *P < 0.0001) of HCC*
- *Diabetes* carried the highest risk among patients with >10 years follow-up.

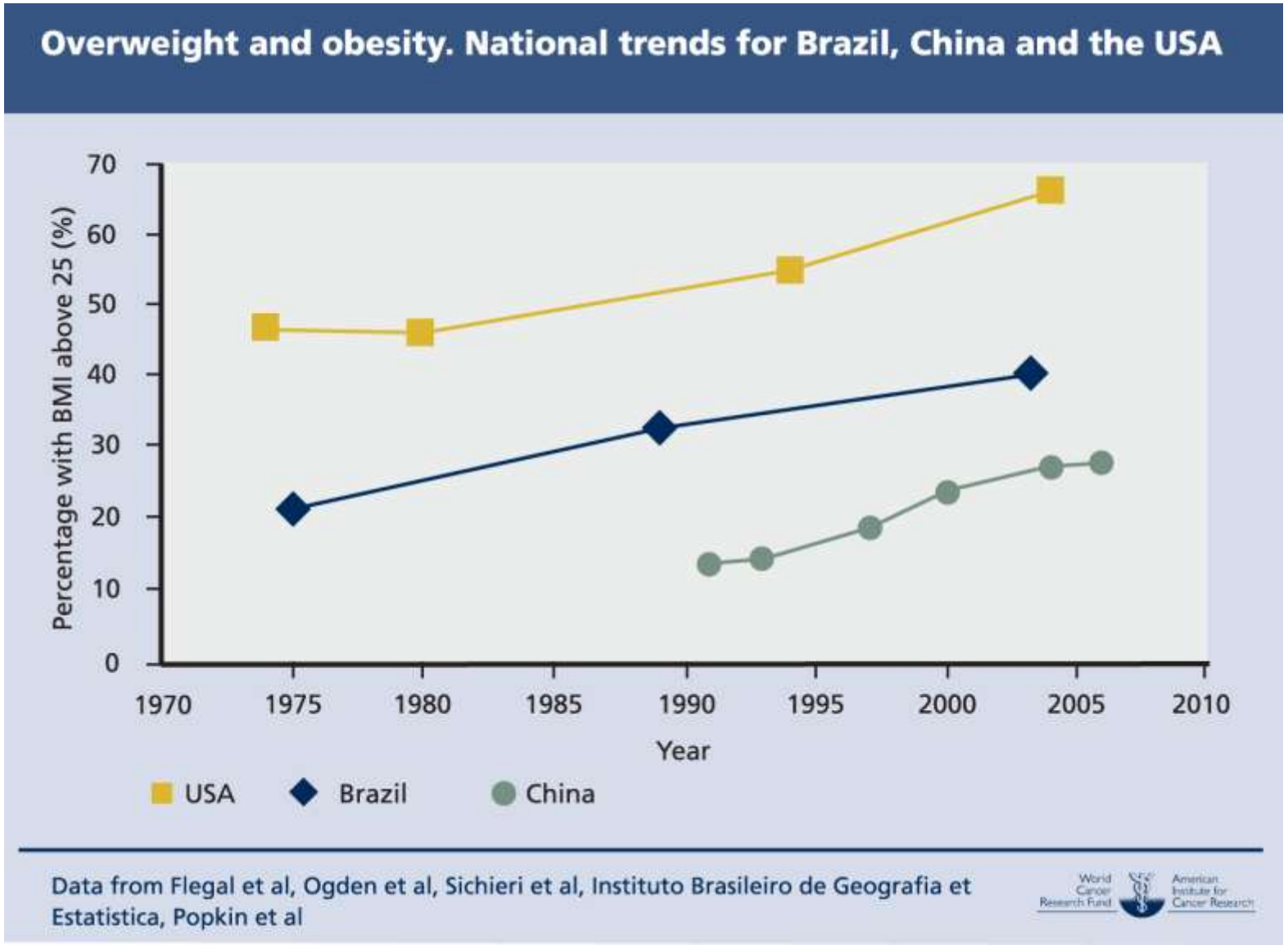




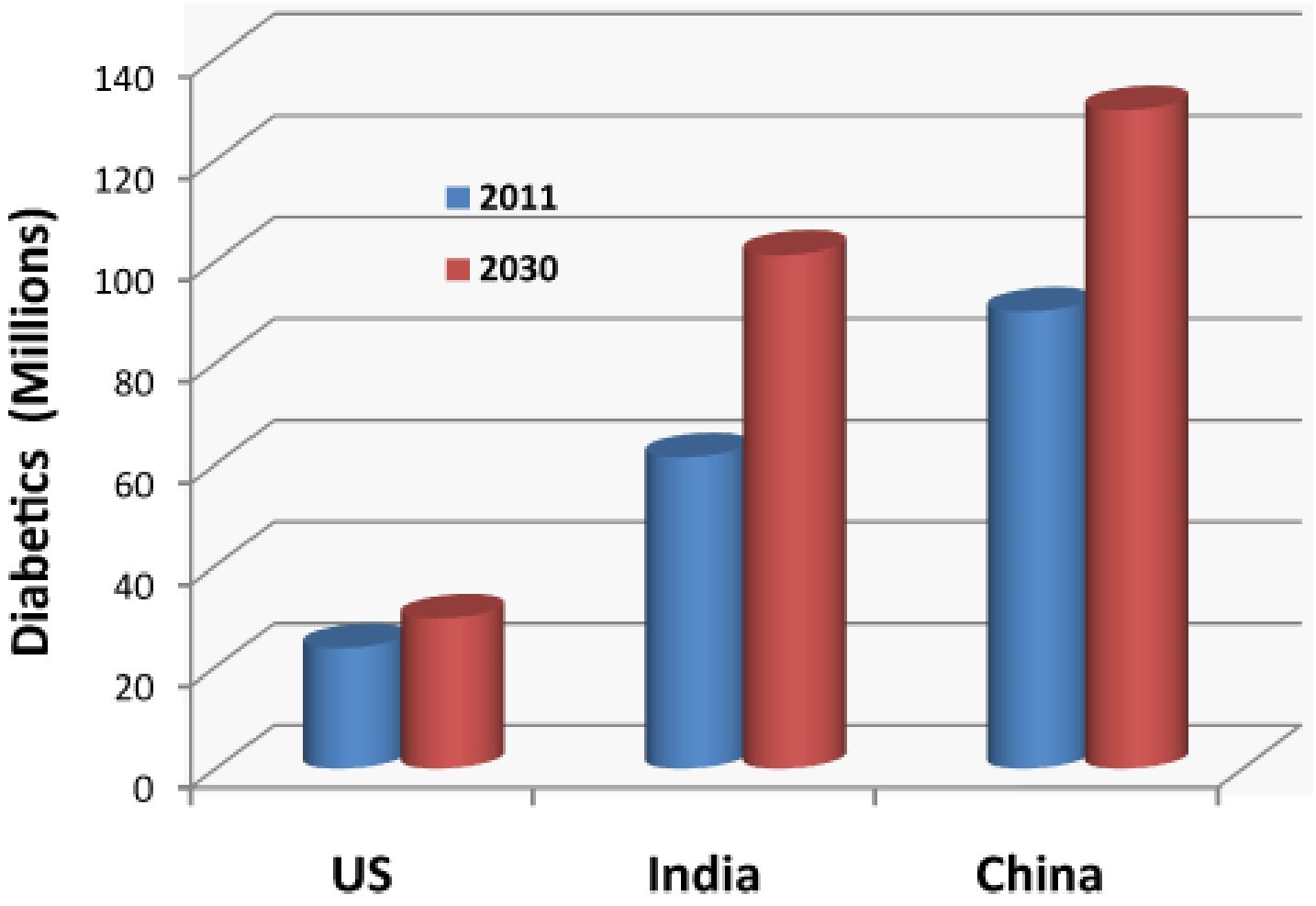
El-Serag et al; GASTROENTEROLOGY 2004;126:460–468

Is the substrate for NAFLD-HCC increasing in Asia Pacific

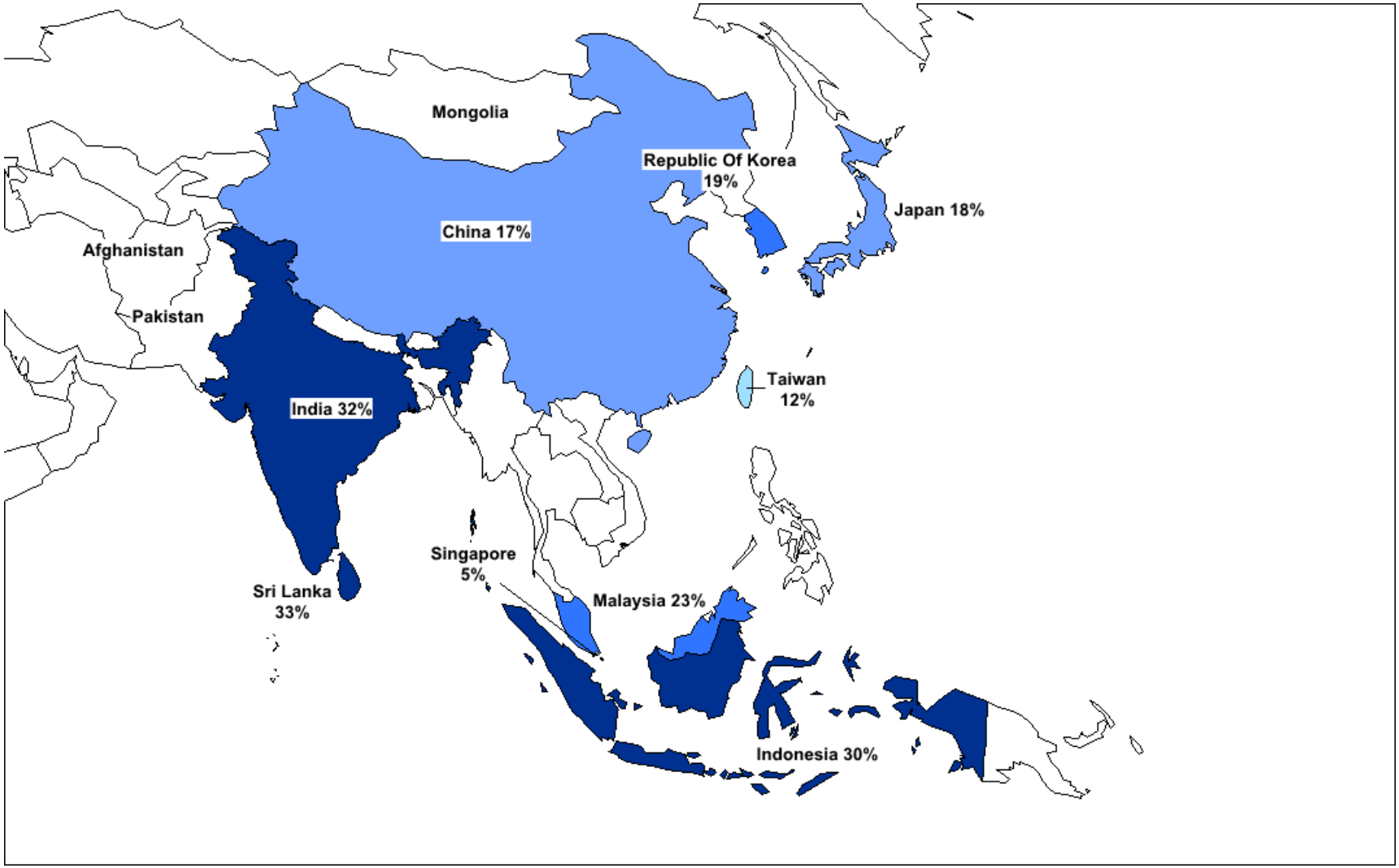
National obesity trends



T2DM trends


Diabetics (Millions)
140
120
100
80
60
40
20
0
2011
2030
US
India
China

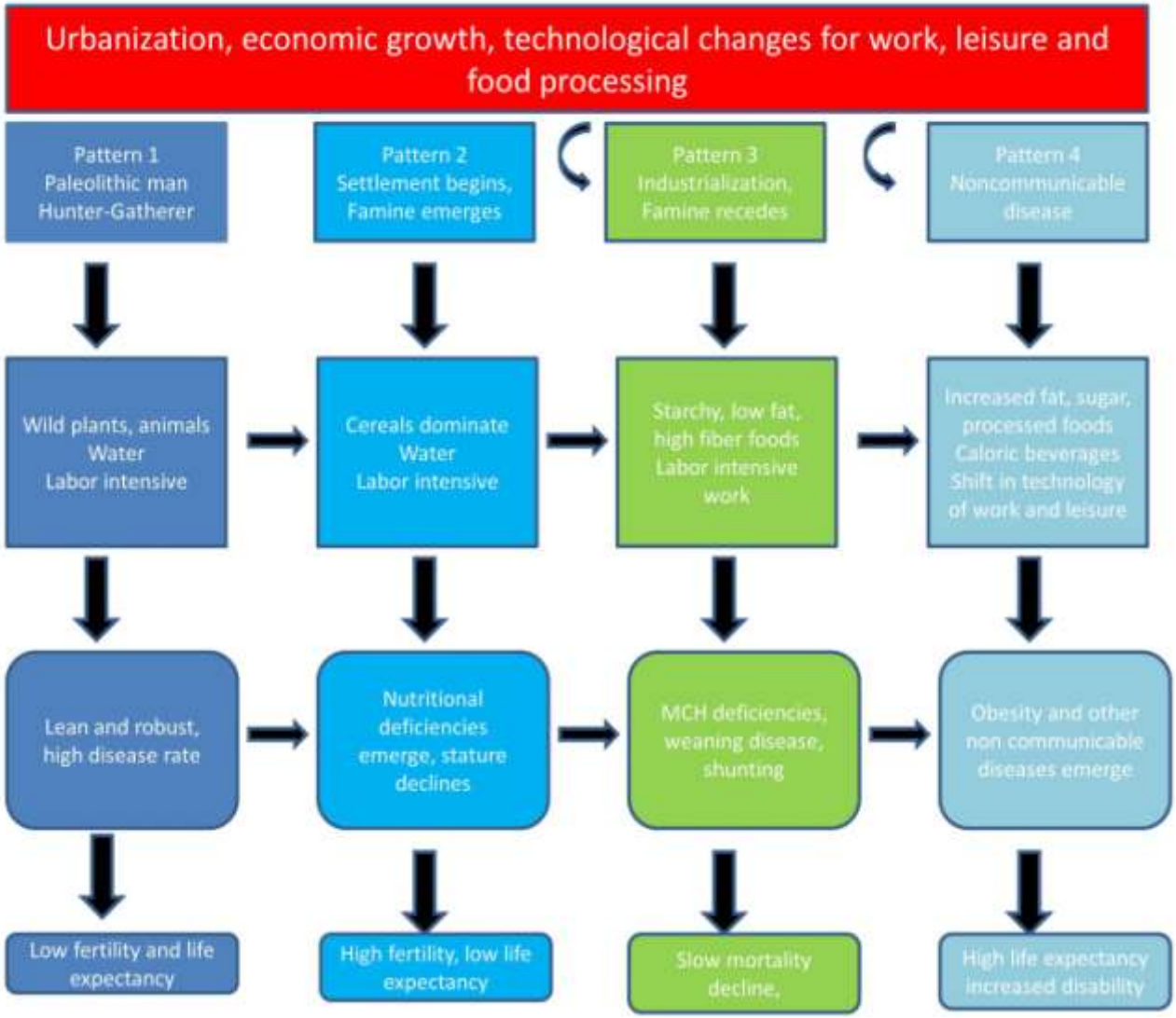
NAFLD Prevalence in A-P



Mahady S et al, JCEH

Substrate for NAFLD-HCC is increasing in Asia Pacific: Why?

Stages of the nutrition transition



Mahady S et al adapted from Popkin BM, et al, Int J Ob & Rel Metab Disord 2004;28 Suppl 3:S2-9

Does MetS contribute to viral HCC

Cirrhosis and MetS, DM

Table 4 Multivariate logistic regression analysis on factors associated with possible and probable cirrhosis

N=1466, CHB

Parameter	Possible cirrhosis LSM>8.4		Probable cirrhosis LSM>13.4	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Male gender	1.8 (1.4 to 2.4)	<0.001	1.6 (1.1 to 2.4)	0.02
Age>40 years	1.8 (1.4 to 2.4)	<0.001	2.1 (1.3 to 3.1)	0.001
Obesity (BMI≥25 kg/m^2)	1.4 (1.1 to 1.9)	0.02	1.3 (0.9 to 2.0)	0.14
Metabolic syndrome	1.6 (1.1 to 2.4)	0.008	1.7 (1.1 to 2.6)	0.03
Albumin<40 g/l	4.2 (2.7 to 6.4)	<0.001	3.3 (2.1 to 5.2)	<0.001
Bilirubin>15 μmol/l	1.2 (0.9 to 1.5)	0.22	1.3 (0.9 to 1.8)	0.17
AP>ULN	2.4 (1.6 to 3.4)	<0.001	2.9 (2.0 to 4.4)	<0.001
ALT>ULN	2.8 (2.2 to 3.7)	<0.001	2.9 (2.0 to 4.1)	<0.001
HBV DNA>2 $\log_{10}$ copies/ml	1.1 (0.7 to 1.6)	0.65	0.9 (0.6 to 1.7)	0.91

AP, alkaline phosphatase; ALT, alanine aminotransferase; BMI, body mass index; CI, confidence interval; HBV, hepatitis B virus; OR, odds ratio; ULN, upper limit of normal.

CHC

	Patients with Ishak Fibrosis Score 6 (n = 303)	
	Hazard Ratio (95% CI)	*P* Value
Age (years)	1.07 (1.02–1.12)	0.007
Male gender	2.91 (1.03–8.26)	0.044
Diabetes mellitus	3.28 (1.35–7.97)	0.009
Platelet count	0.57 (0.12–2.73)	0.48
Bilirubin	1.26 (0.47–3.37)	0.64
Albumin	0.07 (0.00–9.66)	0.28
Body mass index	0.93 (0.81–1.07)	0.30

G L-H Wong, Gut 2009;58:111–117; Veldt et al HEPATOLOGY 2008;47:1856-1862

NASH as a cofactor in HCC

- 23,820 residents in Taiwan; followed 14 y.
- BMI >30 kg/m2 associated with 4-fold risk of HCC (RRa, 4.13; 95% CI, 1.38 –12.4) among HCV+; and 2-fold risk (RRa, 2.36; 95% CI, 0.91– 6.17) without HBV and HCV infections, after controlling for other metabolic components, but not in HBsAg positive (RRa, 1.36; 95% CI, 0.64 –2.89).
- DM associated with HCC, with risk in those with HCV (RRa, 3.52; 95% CI, 1.29 –9.24) and in HBV (RRa, 2.27; 95% CI, 1.10–4.66).
- >100-fold increased risk in HBV or HCV carriers with both obesity and diabetes

Chen et al; GASTROENTEROLOGY 2008;135:111–121

NASH as a cofactor in HCC

Serum hepatitis markers status	BMI (kg/m^2)		RR (95% CI)
HBsAg negative/anti-HCV negative[a]	<30		1.00
HBsAg negative/anti-HCV negative	≥30		2.50 (0.99–6.32)
HBsAg positive/anti-HCV negative	<30		19.9 (14.3–27.6)
HBsAg positive/anti-HCV negative	≥30		22.0 (10.3–46.9)
HBsAg negative/anti-HCV positive	<30		15.7 (10.4–23.8)
HBsAg negative/anti-HCV positive	≥30		34.5 (13.5–87.6)
HBsAg negative/anti-HCV negative[b]		Diabetes (no)	1.00
HBsAg negative/anti-HCV negative		Diabetes (yes)	3.49 (1.08–11.3)
HBsAg positive/anti-HCV negative		Diabetes (no)	18.7 (13.6–25.9)
HBsAg positive/anti-HCV negative		Diabetes (yes)	43.5 (20.5–92.3)
HBsAg negative/anti-HCV positive		Diabetes (no)	15.0 (9.95–22.5)
HBsAg negative/anti-HCV positive		Diabetes (yes)	60.3 (23.6–153.6)
HBsAg negative/anti-HCV negative[c]	<30	Diabetes (no)	1.00
HBsAg negative/anti-HCV negative	≥30	Diabetes (no)	2.81 (1.11–7.12)
HBsAg negative/anti-HCV negative	<30	Diabetes (yes)	4.39 (1.35–14.3)
HBsAg negative/anti-HCV negative	≥30	Diabetes (yes)	[d]
HBsAg positive/anti-HCV negative	<30	Diabetes (no)	20.6 (14.7–29.0)
HBsAg positive/anti-HCV negative	≥30	Diabetes (no)	20.4 (9.13–45.6)
HBsAg positive/anti-HCV negative	<30	Diabetes (yes)	43.0 (19.3–96.1)
HBsAg positive/anti-HCV negative	≥30	Diabetes (yes)	264.7 (35.2–1993)
HBsAg negative/anti-HCV positive	<30	Diabetes (no)	15.7 (10.2–24.1)
HBsAg negative/anti-HCV positive	≥30	Diabetes (no)	33.6 (12.0–94.2)
HBsAg negative/anti-HCV positive	<30	Diabetes (yes)	63.6 (22.6–179)
HBsAg negative/anti-HCV positive	≥30	Diabetes (yes)	134.5 (17.5–1035)

Chen et al; GASTROENTEROLOGY 2008;135:111–121

Clinical features of NASH-HCC

Clin Features: NASH related HCC

Characteristic	Total (n = 87)	Male (n = 54)	Female (n = 33)
Age (*y*)	72 (69–75)	72 (69–75)	72 (68–75)
BMI (kg/m^2)	26.0 (23.8–28.3)	26.0 (23.8–28.8)	26.2 (23.9–27.7)
Obesity	54 (62%)	35 (65%)	19 (58%)
Diabetes	51 (59%)	31 (57%)	20 (61%)
Dyslipidemia	24 (28%)	13 (24%)	11 (33%)
Hypertension	47 (54%)	22 (41%)	25 (76%)
Fibrosis stage[d]			
1	10 (11%)	10 (18%)	0 (0%)
2	15 (17%)	10 (18%)	5 (15%)
3	18 (21%)	13 (25%)	5 (15%)
4	44 (51%)	21 (39%)	23 (70%)

Yasui et al CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2011;9:428–433

Pathology of metS HCC

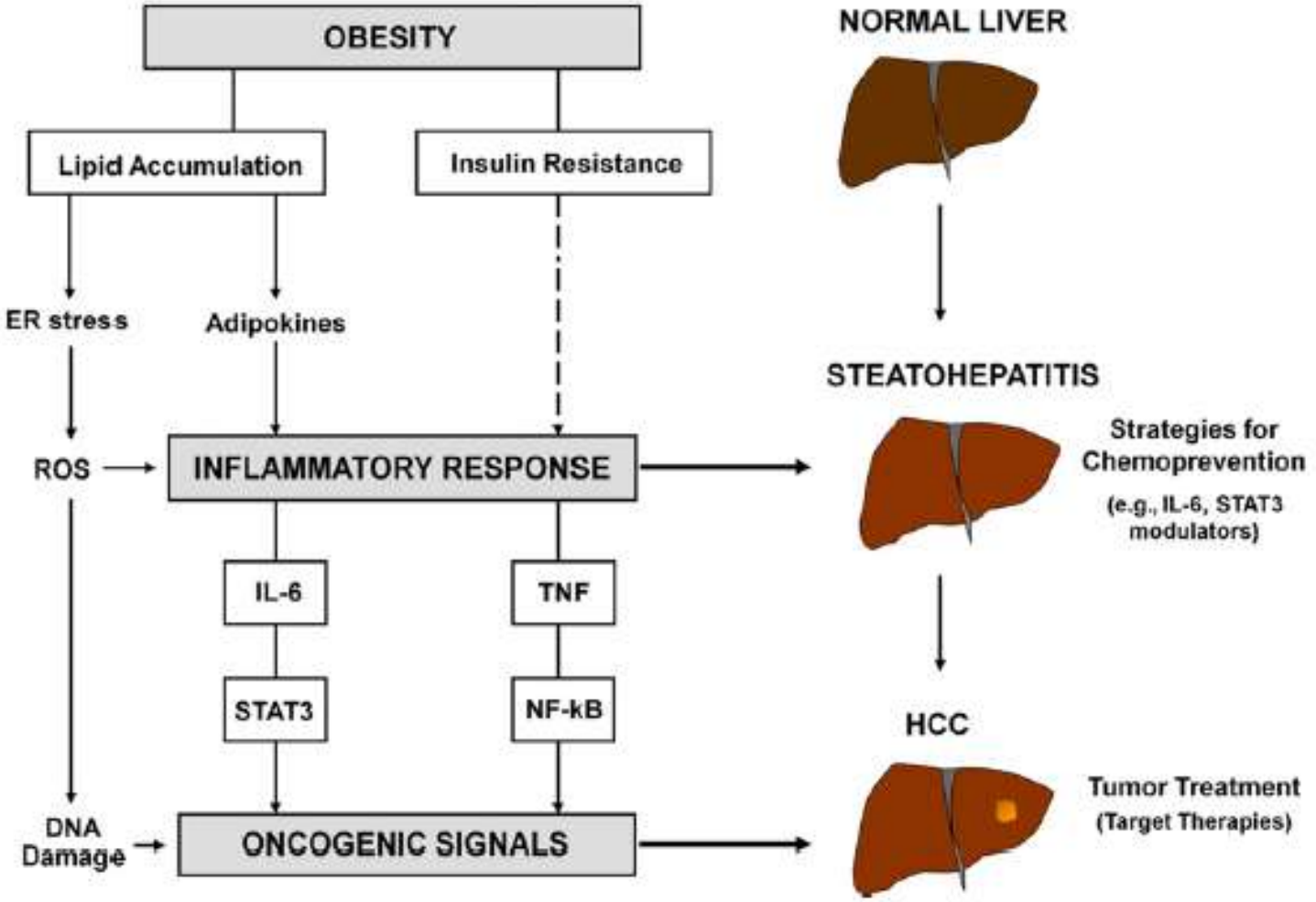
	MS Group (n = 31)	CLD Group (n = 81)	CG Group (n = 16)	*P* (MS Versus CLD)
Differentiation				
Well	20 (64.5%)	23 (28%)	8 (50%)	
Moderate	11 (35.5%)	47 (58%)	7 (44%)	
Poor	0 (0)	11 (14%)	1 (6%)	<0.001
Liver fibrosis				
F0-F2	20 (65.5%)	21 (26%)	12 (75%)	
F3-F4	11 (35.5%)	60 (74%)	4 (25%)	<0.001

- MetS HCC developed in older patients mean age (67 +/-7 versus 59 +/- 14 years, *P < 0.01)*
- 5/31 developed in pre-existing liver cell adenoma, with three showing histological features of telangiectatic adenoma

Paradis et al, HEPATOLOGY 2009;49:851-859

Pathogenesis

Obesity, Inflammatory Signaling, and HCC



Toffanin S et al; Cancer Cell 17, February 17, 2010

Inflammation

- Obesity and the metabolic syndrome are associated with a pro-inflammatory state:

  Elevated CRP, ferritin, IL-6 and TNF

- Inflammation is recognised to be a driver of tumour growth, supplying growth factors, proangiogenic factors and matrix remodelling enzymes that promote invasion.
- The generation of reactive oxygen species is an additional effect leading to chromosomal damage.

➢ *Sustaining proliferative signaling, activating invasion and resisting cell death*

Insulin- IGF1 axis

- Hyperinsulinemia:
  - Has pro-mitotic and anti-apoptotic activity
  - Has been shown to promote aberrant crypt foci in the colon
  - Promotes growth of colon cancer cells in vitro

- Human colorectal adenocarcinomas express IR at high levels
- IGF-1 has stronger pro-mitotic and anti-apoptotic activity than insulin
- Some studies have shown positive associations with circulating IGF-1 levels and colorectal cancer incidence.

➢ *Sustaining proliferative signaling and resisting cell death*

From: Gunter et al (2008) Cancer Res

Adiponectin

- The most abundant fat derived hormone
- Levels are inversely related to body mass ie. Obesity is associated with low adiponectin
- Adiponectin:

  Has anti-inflammatory properties

  Has been shown to reduce proliferation of various cancer cells in vitro including liver tumour cells, colorectal cancer cells

  Low levels in humans are associated with increased risks of endometrial cancer, breast cancer and colorectal cancer.

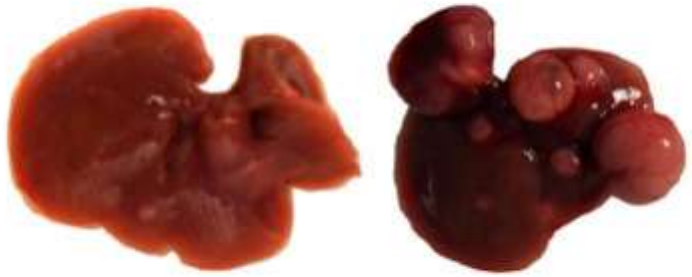
Animal models of HCC in NAFLD

- **HCC induced in wild type (WT) and adiponectin knockout (ADN KO) mice using the carcinogen diethylnitrosamine (DEN)**

- **Liver and tumour tissue was fixed for histology and snap frozen for gene and protein expression.**
- **Tumour volume was estimated by measuring the surface diameter and calculating :**

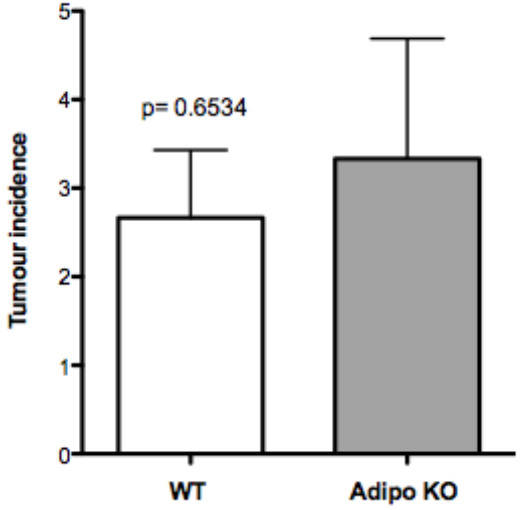
$$\text{Vol} = 4/3\ \pi r^3$$

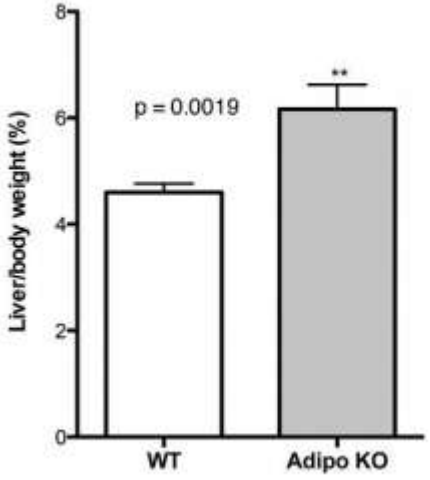
Adiponectin KO mice have bigger tumours

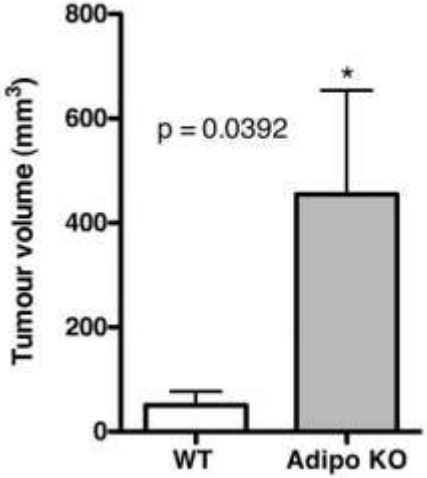


9 month old wild type male liver

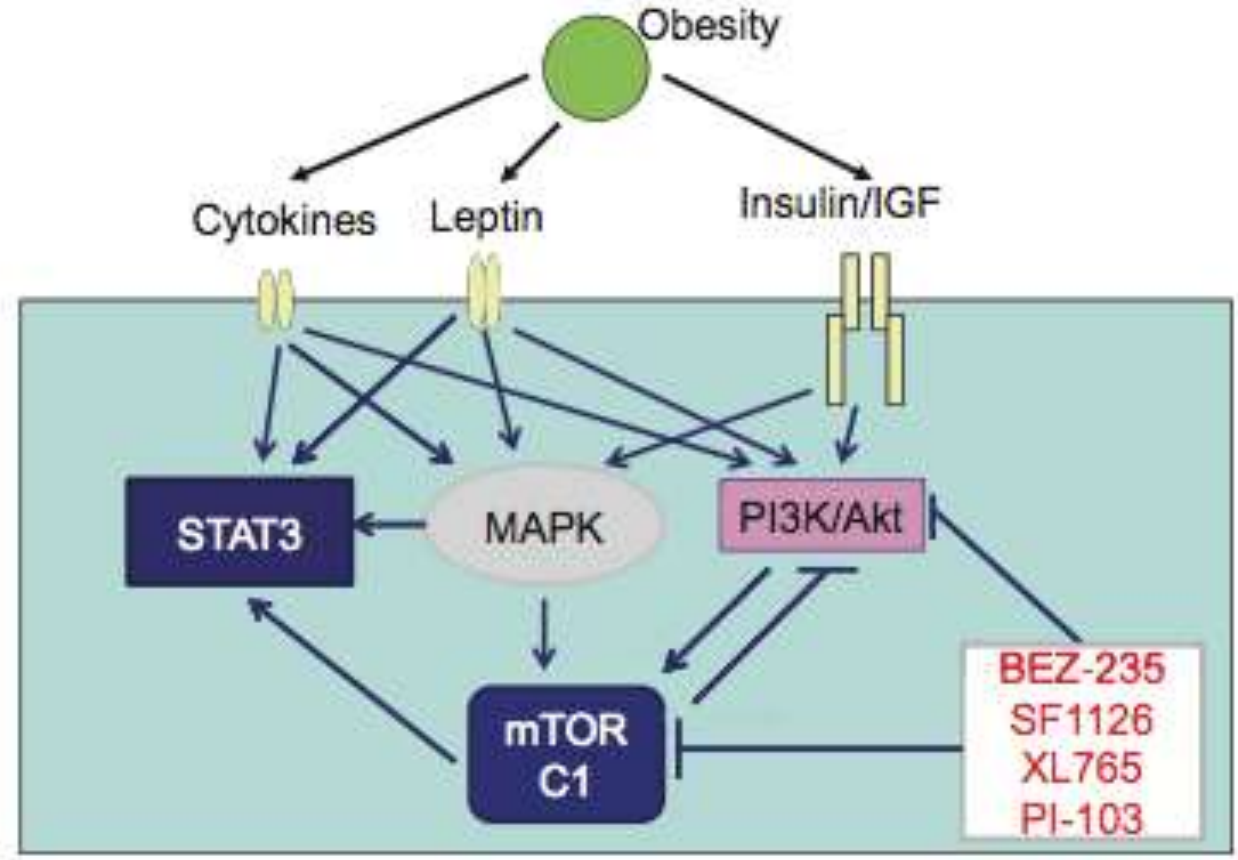
9 month old adiponectin KO male liver





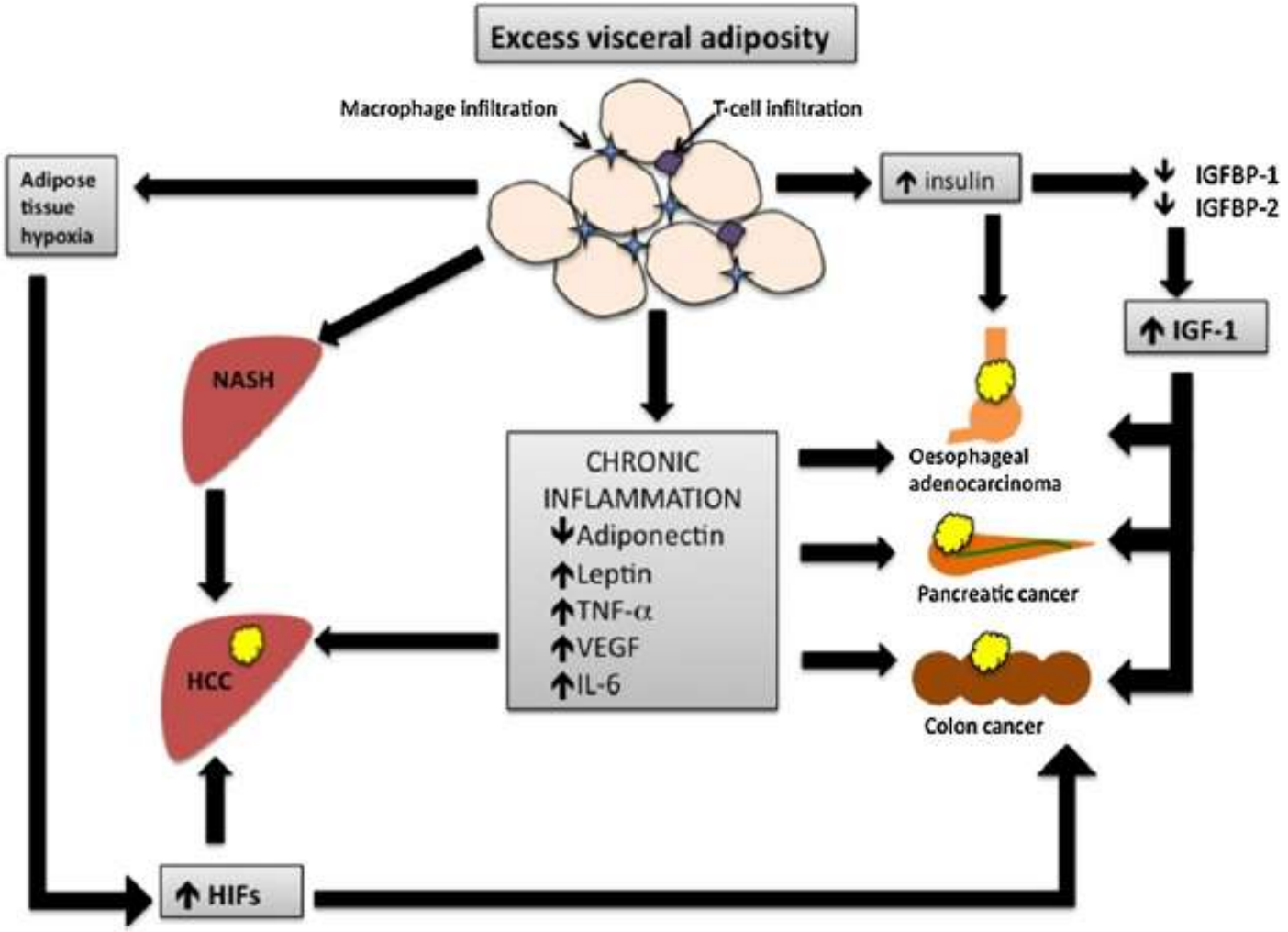


PI3K-Akt-mTOR pathway



From: Chen, J (2011) Obesity Reviews

VAT and cancer



R. Vongsuvanh et al; Cancer Letters 330 (2013) 1–10

VAT and cancer

First author and year of publication (Ref.)	Study design	Cases/ controls (*n*)	Modality of VF assessment	Covariates adjusted for	Effect estimates
HCC risk					
Schlesinger et al. [50]	Cohort	177/ 359,525	WC, WHR, waist–height ratio (WHtR)	Education, smoking, alcohol, height, physical activity, consumption of fruit and vegetables, consumption of meats, BMI	WC 5 cm increment: RR = 1.29, 95% CI = 1.13–1.47 WHR 0.1 unit increment: RR = 1.45, 95% CI = 1.16–1.83 WHtR 0.1 unit increment: RR = 2.31, 95% CI = 1.67–3.19
HCC outcomes					
Ohki et al. [51]	Cross-sectional	62	CT	Age, gender, diabetes, dyslipidemia	Risk of HCC recurrence with 10 cm^2 increment VF area: OR = 1.08, 95% CI = 1.01–1.17

R. Vongsuvanh et al; Cancer Letters 330 (2013) 1–10

Metformin and HCC risk

97 430 HCC patients and 194 860 age-, gender- and physician visit date-matched controls

Diabetic patients (N=47 820)	ORs (95% CI)	p Value
Metformin use (each incremental year)	0.93 (0.91 to 0.94)	<0.0001
Age (each incremental year)	1.00 (1.00 to 1.00)	0.8437
Gender (male vs female)	1.03 (0.99 to 1.08)	0.1629
Hepatitis B	13.81 (12.61 to 15.13)	<0.0001
Hepatitis C	17.07 (15.57 to 18.71)	<0.0001
Liver cirrhosis	4.29 (3.61 to 5.10)	<0.0001
End stage renal failure	0.83 (0.77 to 0.89)	<0.0001
DM duration (each incremental year)	0.96 (0.95 to 0.96)	<0.0001
DM control (each incremental visit per year)	1.02 (1.02 to 1.03)	<0.0001
Other OHA agents use (each incremental year)	1.02 (1.01 to 1.04)	0.0052
Thiazolidinediones use (each incremental year)	0.91 (0.87 to 0.95)	<0.0001
Insulin use (each incremental year)	1.13 (1.10 to 1.16)	<0.0001

DM, diabetes mellitus; OHA, oral hypoglycaemic agent.

Gut 2013;62:606–615. doi:10.1136/gutjnl-2011-3017

MetS and HCC

- Poor data across the region with variations in quality
- HBV-HCC will dramatically decline with vaccination
- HCV-HCC will begin to decline with newer therapies once treatment is affordable
- Diabesity will become a major cause of HCC
- Diabesity will be an important co-factor for viral hepatitis associated HCC
- Outcomes highly variable depending on country


Thank you !

Acknowledgements