



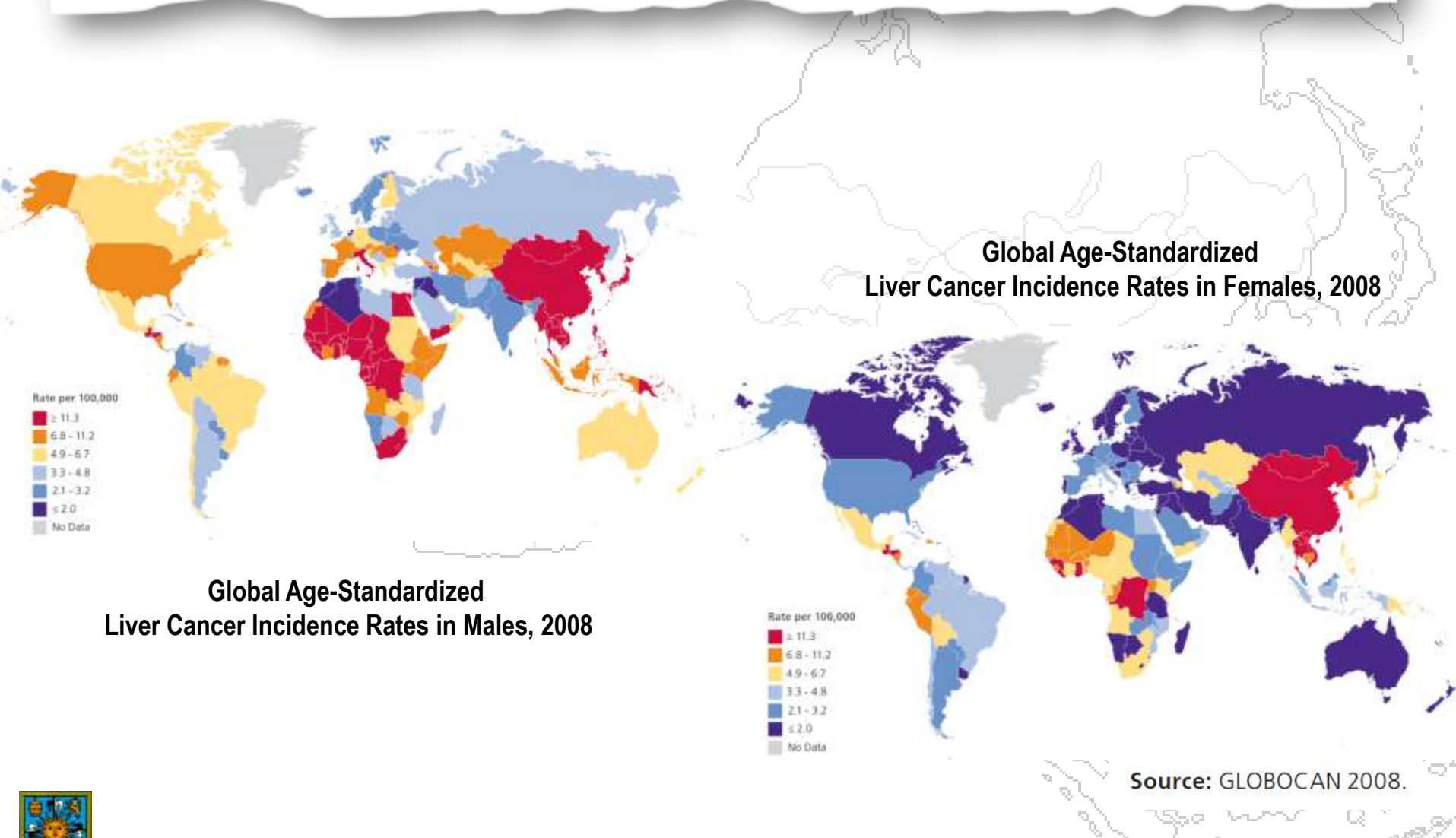
The Epidemiology of Hepatocellular Carcinoma in the Asia Pacific

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University of Santo Tomas
Manila, Philippines



International Variation in Age-Standardized Liver Cancer Incidence Rates in Both Sexes, 2008

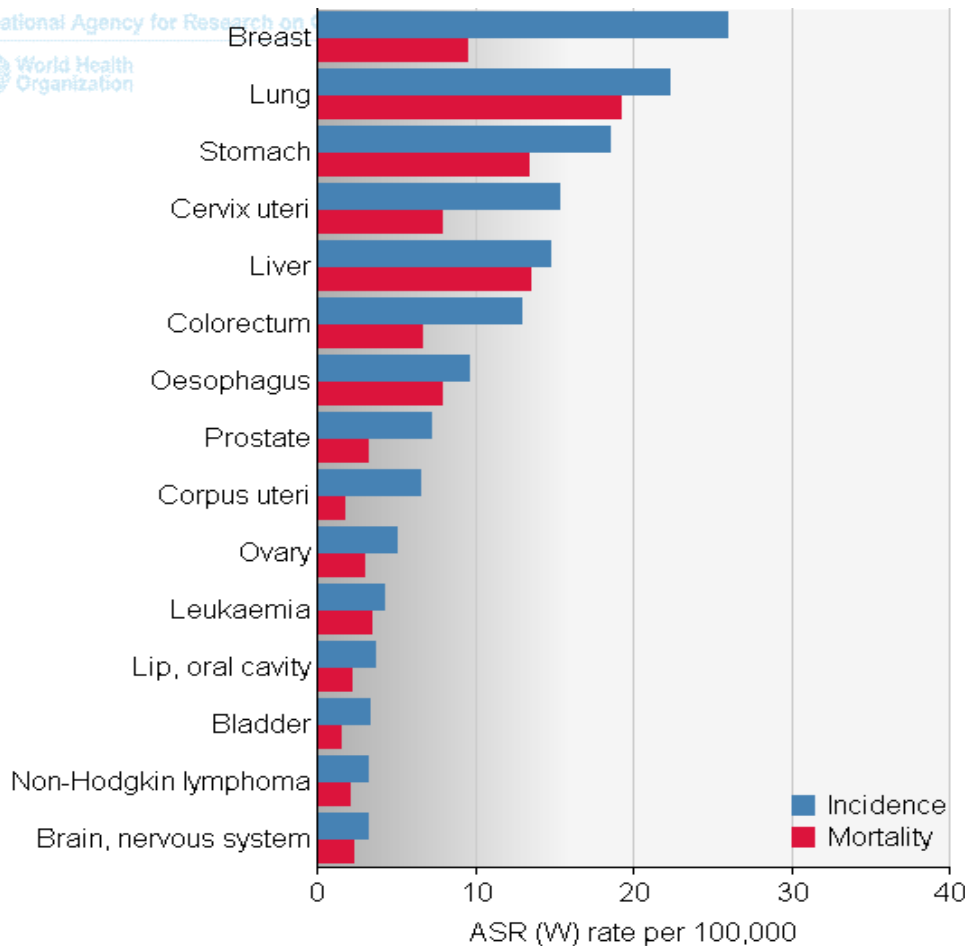


Source: GLOBOCAN 2008.

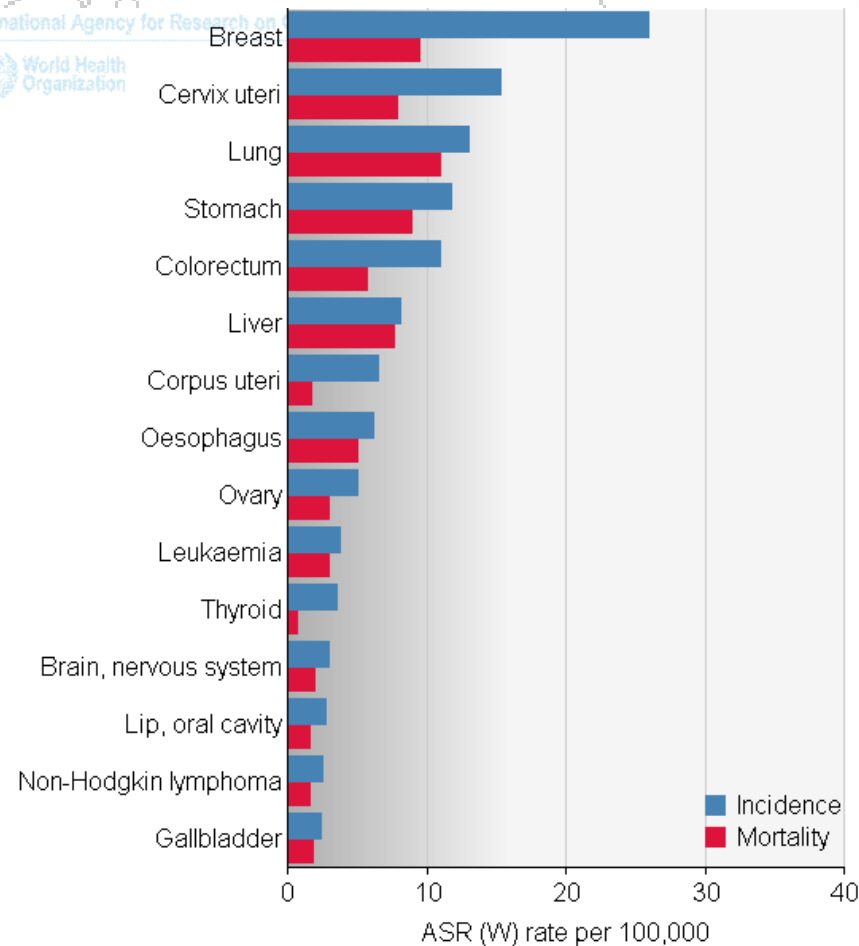


Estimated Age-standardized Incidence and Mortality Rates of HCC for Men and Women (GLOBOCAN 2008)

Males



Females



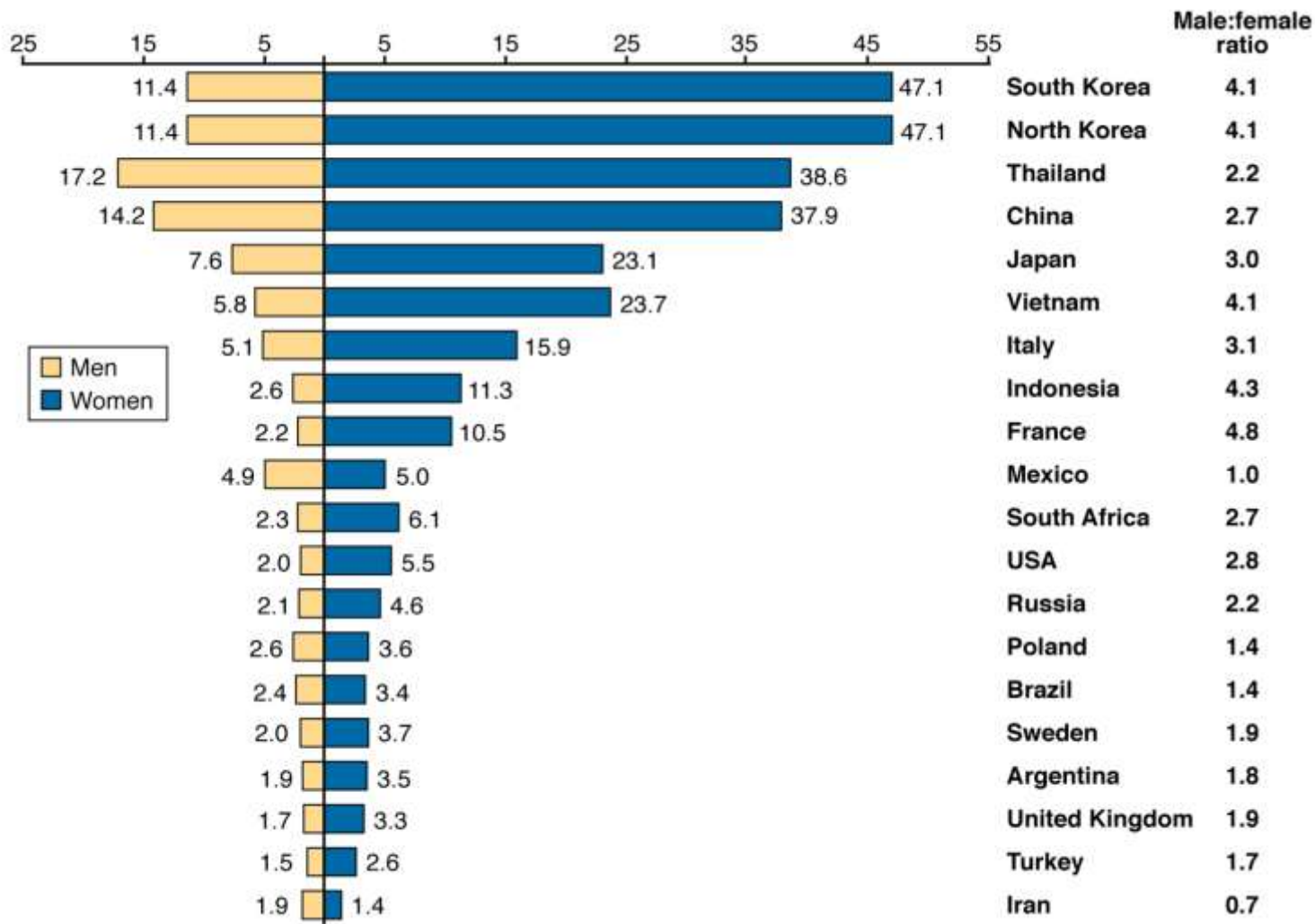
Hepatocellular Carcinoma (HCC)

Incidence and mortality rates of hepatocellular carcinoma according to race/ethnicity and gender, reported in Surveillance Epidemiology and End Results database 2006-2010

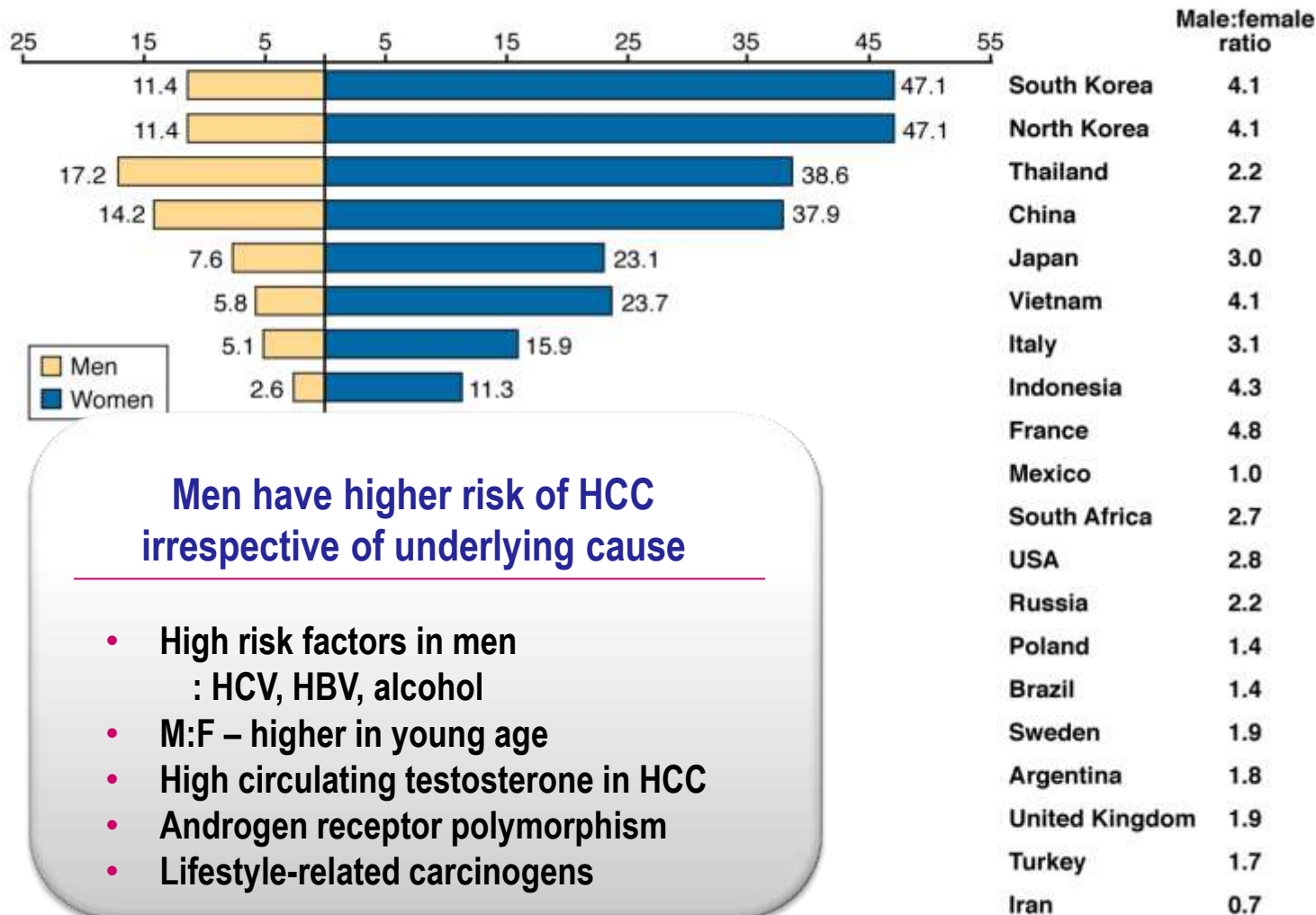
Race/Ethnicity	Incidence rate per 100000		Mortality rate per 100000	
	Male	Female	Male	Female
All races	11.9	4.0	8.3	3.4
Non-Hispanic White	10.4	3.5	7.6	3.2
African American	15.1	4.5	11.8	4.1
Hispanics	18.3	6.9	12.3	5.4
Asian/Pacific Islander	21.4	8.2	14.4	6.0
American Indian/Alaska Native	20.6	7.7	13.2	6.1



Age-standardized Incidence Rates of HCC per 100,000 person years for Men and Women (GLOBOCAN 2002)



Age-standardized Incidence Rates of HCC per 100,000 person years for Men and Women (GLOBOCAN 2002)



Men have higher risk of HCC irrespective of underlying cause

- High risk factors in men : HCV, HBV, alcohol
- M:F – higher in young age
- High circulating testosterone in HCC
- Androgen receptor polymorphism
- Lifestyle-related carcinogens



Number of Immigrants, Estimated HBsAg Prevalence, and Number of Imported Chronic Hepatitis B cases into the US by country of birth, 1974–2008

Birth country	No. immigrants*	(%)	Est HBsAg prevalence (%)**	Chronic hepatitis B cases	(%)
Region (no. countries)**					
Africa (48)	939,183	(3.3)	11.1	104,698	(8.0)
Americas (49)	13,201,197	(46.7)	1.6	207,800	(15.8)
Eastern Mediterranean (24)	1,695,778	(6.0)	5.0	85,565	(6.5)
Europe (58)	3,994,078	(14.1)	2.9	117,335	(8.9)
Southeast Asia (9)	1,847,292	(6.5)	4.0	73,360	(5.6)
Western Pacific (38)	6,604,083	(23.4)	11.0	724,002	(55.2)
TOTAL	28,281,611	(100.0)	4.6	1,312,760	(100.0)
Top 10[‡]					
Philippines	1,765,203	(6.2)	10.0	176,520	(13.4)
China	1,372,025	(4.9)	12.0	164,643	(12.5)
Vietnam	1,200,863	(4.2)	12.0	144,103	(11.0)
Korea	918,505	(3.2)	12.0	110,221	(8.4)
Mexico	5,807,590	(20.5)	1.0	58,076	(4.4)
India	1,323,110	(4.7)	3.0	39,693	(3.0)
Taiwan	313,643	(1.1)	12.0	37,637	(2.9)
Dominican Republic	940,769	(3.3)	4.0	37,631	(2.8)
Haiti	532,968	(1.9)	5.0	26,648	(2.0)
Hong Kong	211,472	(0.75)	12.0	25,377	(1.9)

*From United States Department of Homeland Security, for persons obtaining legal permanent residency in United States (www.dhs.gov/files/statistics/publications/yearbook.shtm).

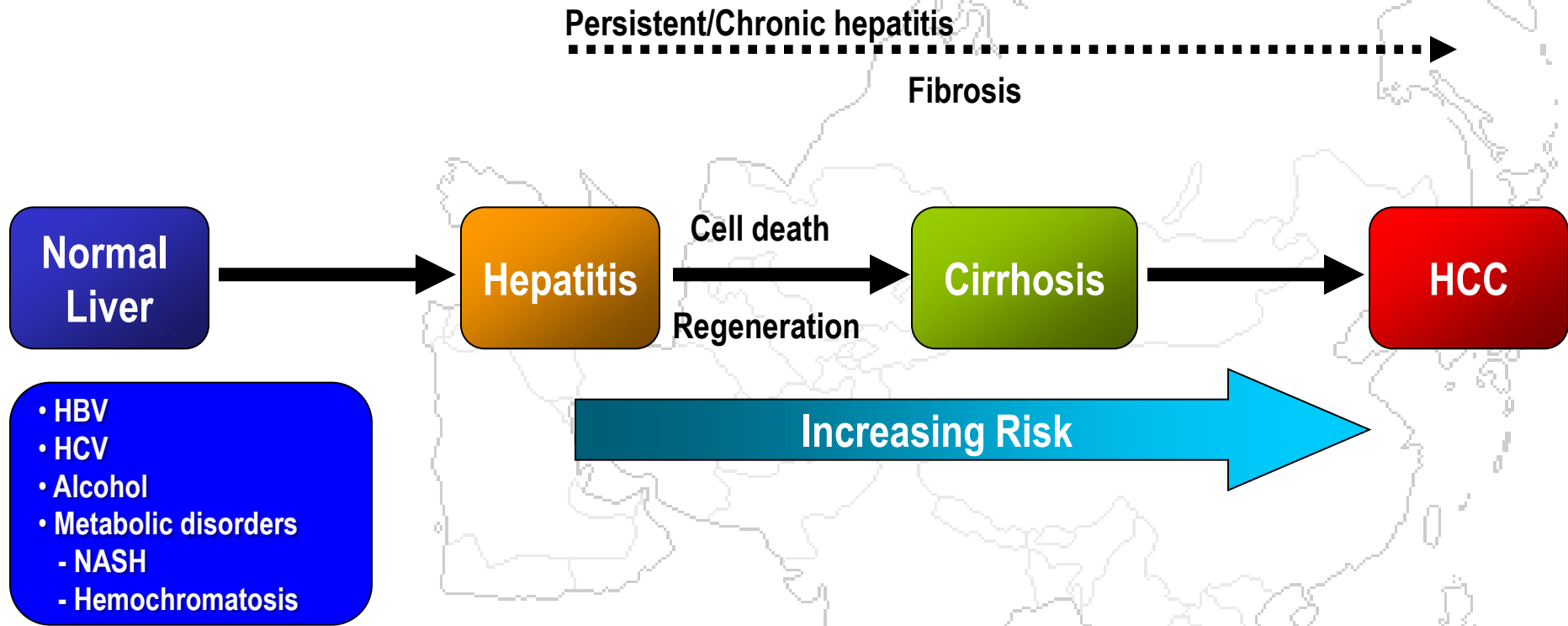
**World Health Organization regions. Estimated HBsAg prevalence by region is the weighted average of estimated prevalence for each country in the region.

‡Top 10 countries by estimated number of imported chronic hepatitis B cases.

doi:10.1371/journal.pone.0027717.t001



Multifactorial Pathogenesis of HCC



HBV = hepatitis B virus; HCV = hepatitis C virus; NASH = nonalcoholic steatohepatitis.

1. Adapted from Rivenbark AG, et al. *Clin Cancer Res.* 2007;13:2309-2312; 2. Marotta F, et al. *Clin Ther.* 2004;155:187-199;
3. Thorgeirsson S, et al. *Nat Genet.* 2002;31:339-346; 4. Wang XW, et al. *Toxicology.* 2002;181-182:43-47;
5. Koike K. *Hepatol Res.* 2005;33:145-150.



Chronic HBV and HCV Infection are the most common causes of HCC in Asia



- Hepatocellular carcinoma (HCC) is the 5th most common cancer, and 3rd most common cause of mortality worldwide^{1,2}
- Globally, ~50% of all HCC cases are attributable to HBV³
- In regions where HBV is endemic (South-Eastern Asia, Sub-Saharan Africa), 70–80% of HCC cases are attributable to HBV³

Etiology of Hepatocellular Carcinoma in the Philippines

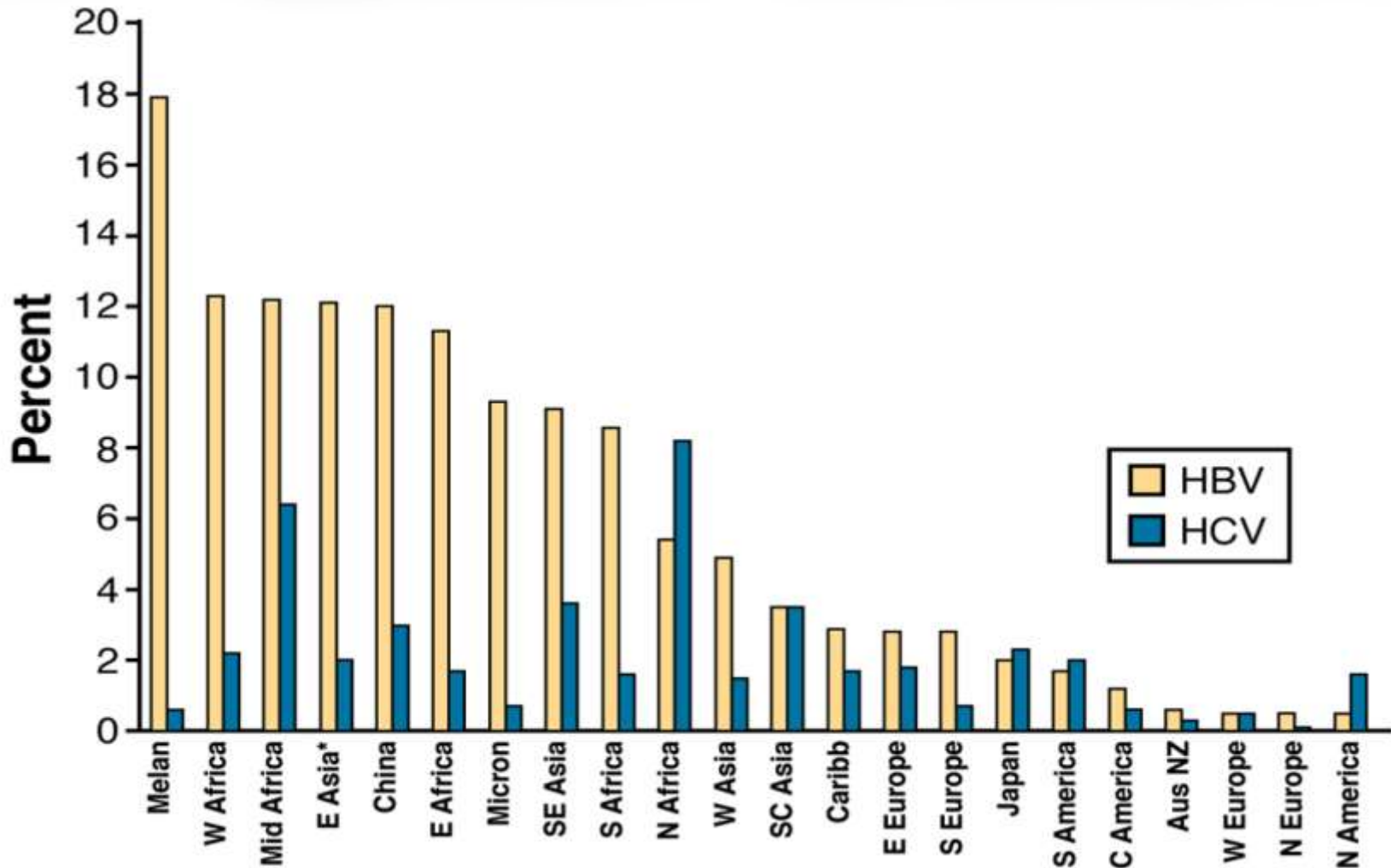
Etiology	Male n (%)	Female n (%)	Total n (%)
HBV	125 (51.4%)	39 (16%)	164 (67.4%)
HCV	5 (2.1%)	3 (1.2%)	8 (3.3%)
ETOH	23 (9.5%)	0	23 (9.5%)
Cryptogenic	32 (13.2%)	16 (6.6%)	48 (19.8%)
Total	185	58	243

1. Tan YJ, et al. *World J Gastroenterol* 2011;17:4853-4857. 2. European Association For The Study Of The Liver. *Hepatology* 2012;57:167-185.

2. 3. Nguyen VT, et al. *J Viral Hepat* 2009;16:453-463. 4. Altekruse SF, et al. *J Clin Oncol* 2009;27:1485-1491.



Prevalence of HBsAg carriers and chronic HCV status in different geographic regions of the World



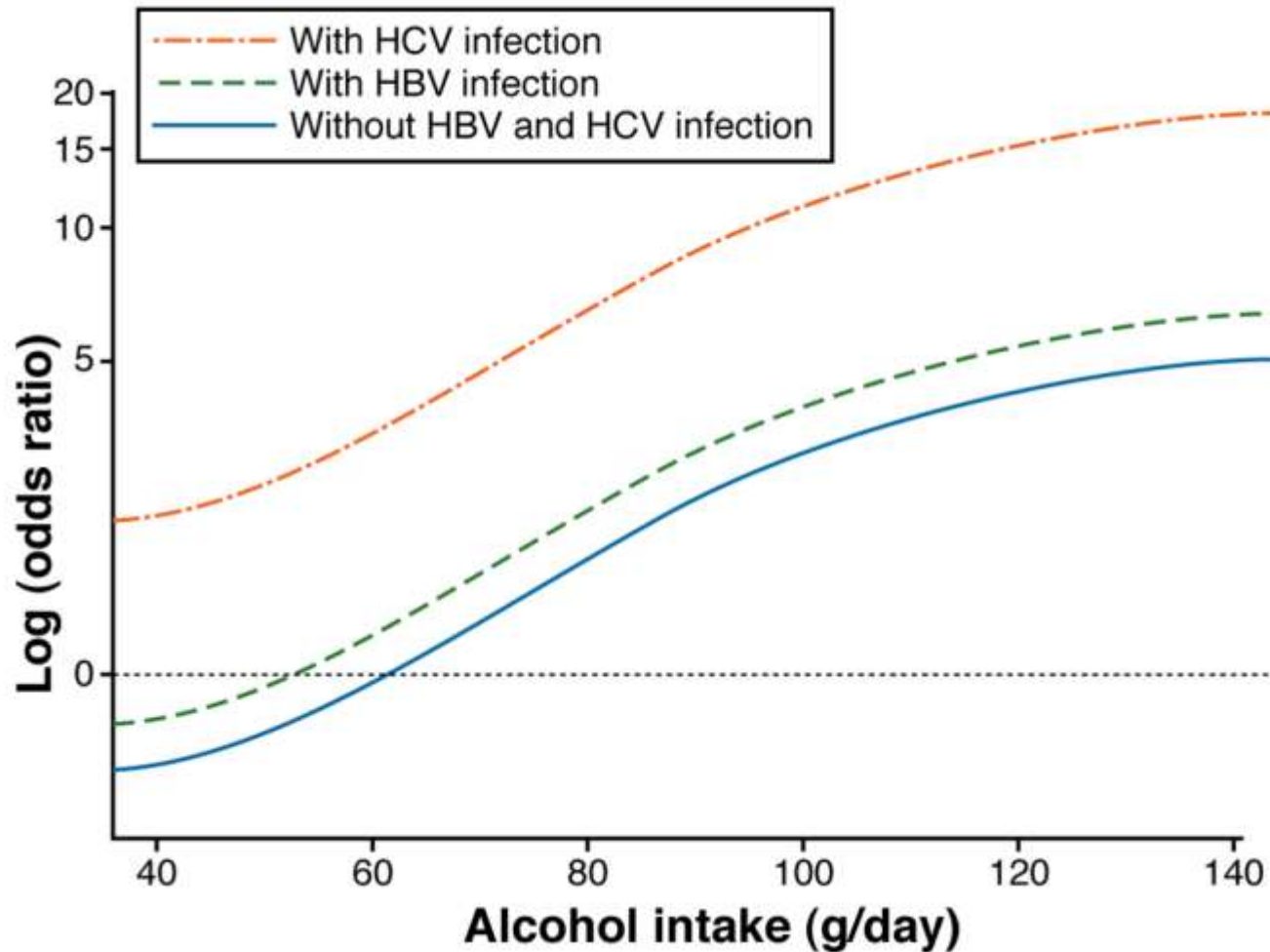
Multiplicative Synergistic Risks for HCC Development among HBV and HCV co-infected Subjects in HBV Endemic Region

Infection status	No. of subjects	Person-years	No. of HCC	HR ^a (95% CI)
HBsAg(-) / anti-HCV(-)	5744	53,504	16	1.0 (reference)
HBsAg(+) / anti-HCV(-)	335	2,981	15	17.1 (8.4-34.8)
HBsAg(-) / anti-HCV(+)	360	3,731	12	10.4 (4.9-22.1)
HBsAg(+) / anti-HCV(+)	14	133	3	115.0 (32.5-407.3)
				SI and 95% CI: 4.5 (1.3-15.5) ^b

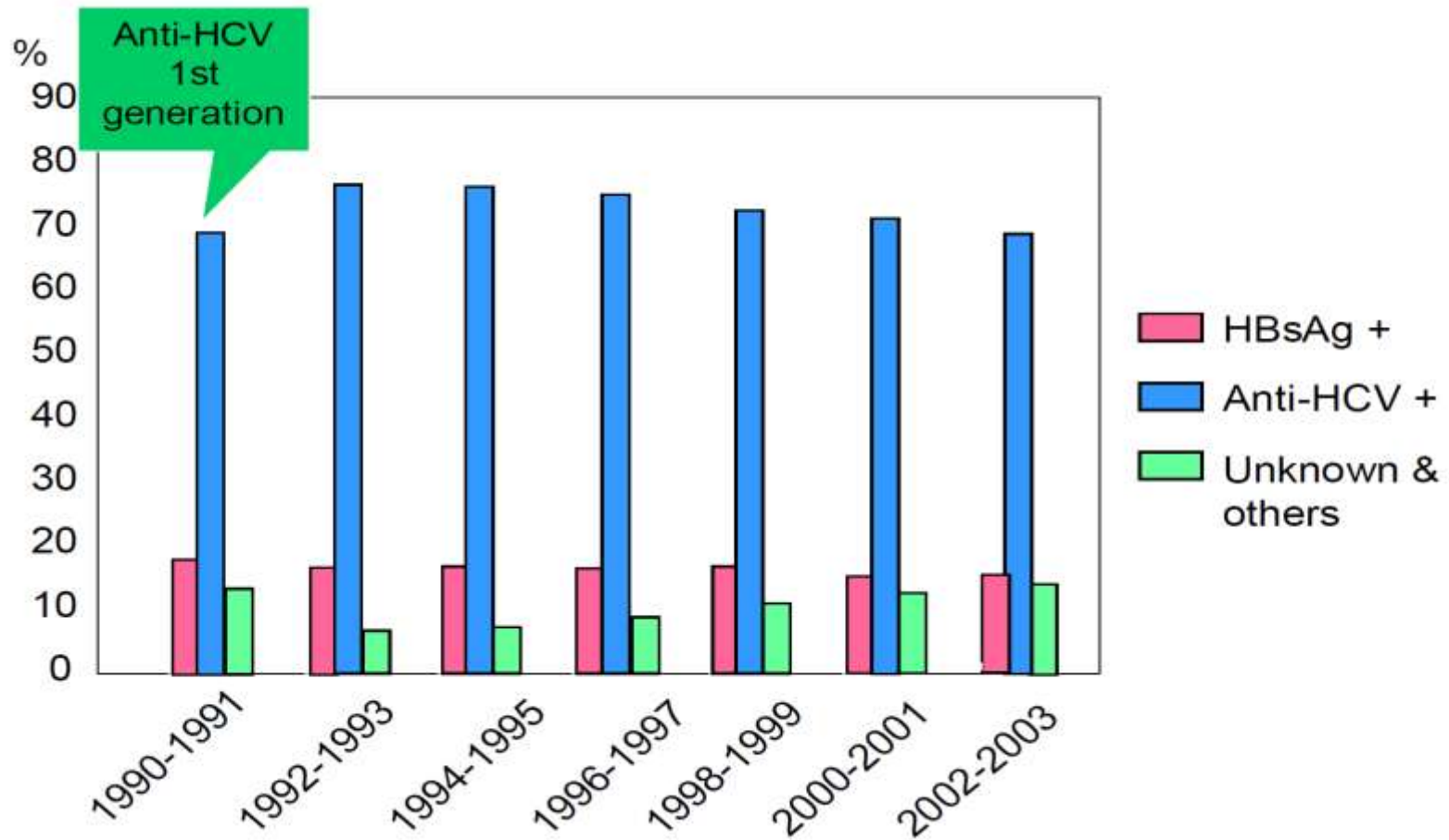
HBsAg, hepatitis B surface antigen; anti-HCV, antibodies against hepatitis C virus. ^aHR: age- and sex-adjusted. ^bSI: synergy index= $(RR_{11}-1)/(RR_{01}+RR_{10}-2)$, in which RR_{11} =relative risk of the joint effect of two risk factors; RR_{01} and RR_{10} =relative risk of each risk factor in the absence of the other. Two hundred and forty-one subjects including 4 HCC cases had no information on HBsAg or anti-HCV, and were excluded from the analysis.



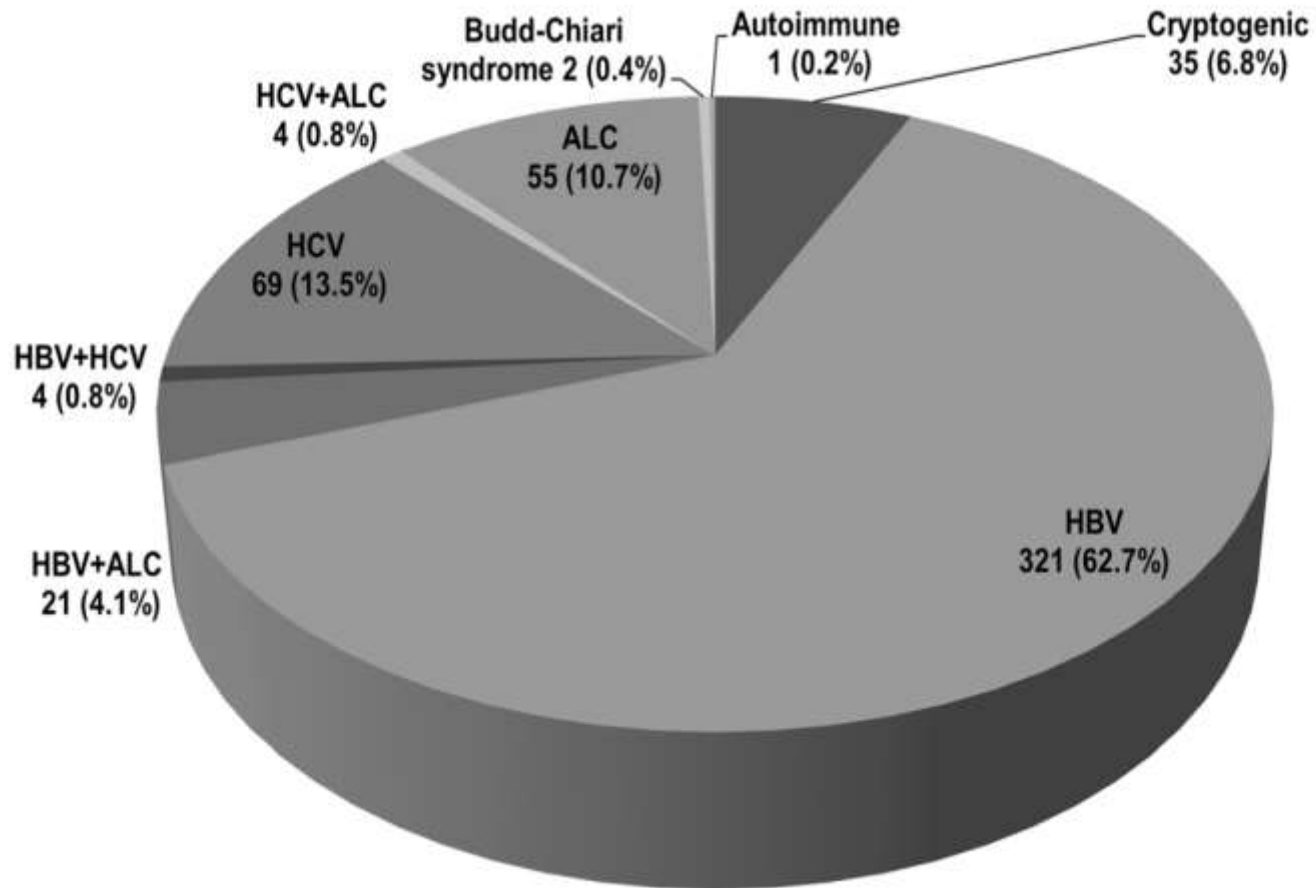
Odds ratio for HCC according to alcohol intake and presence of HBV or HCV Infection



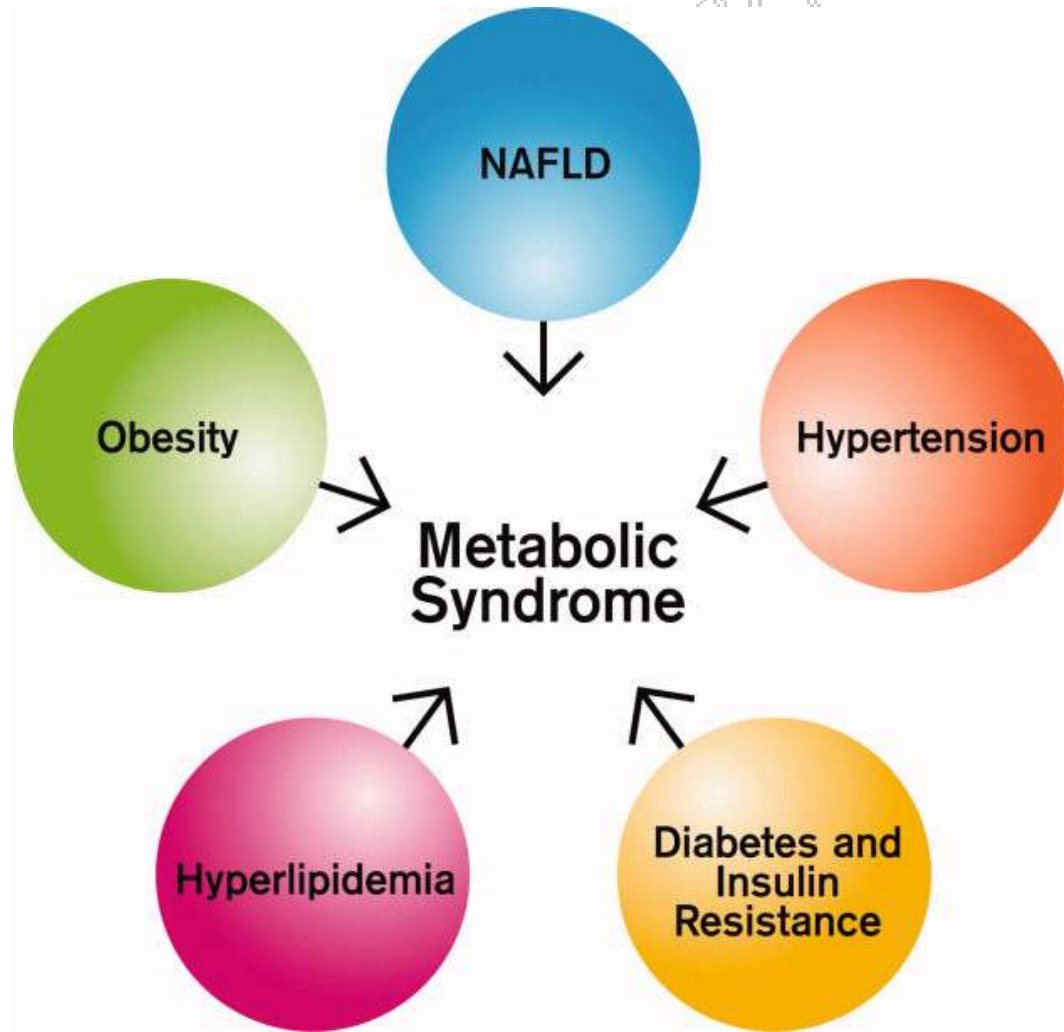
Changes in the Etiology of Primary Liver Cancer in Japan: 1990 - 2003



Prevalence of Cryptogenic Hepatocellular Carcinoma in South Korea



Metabolic Syndrome (MetS): the New Epidemic!

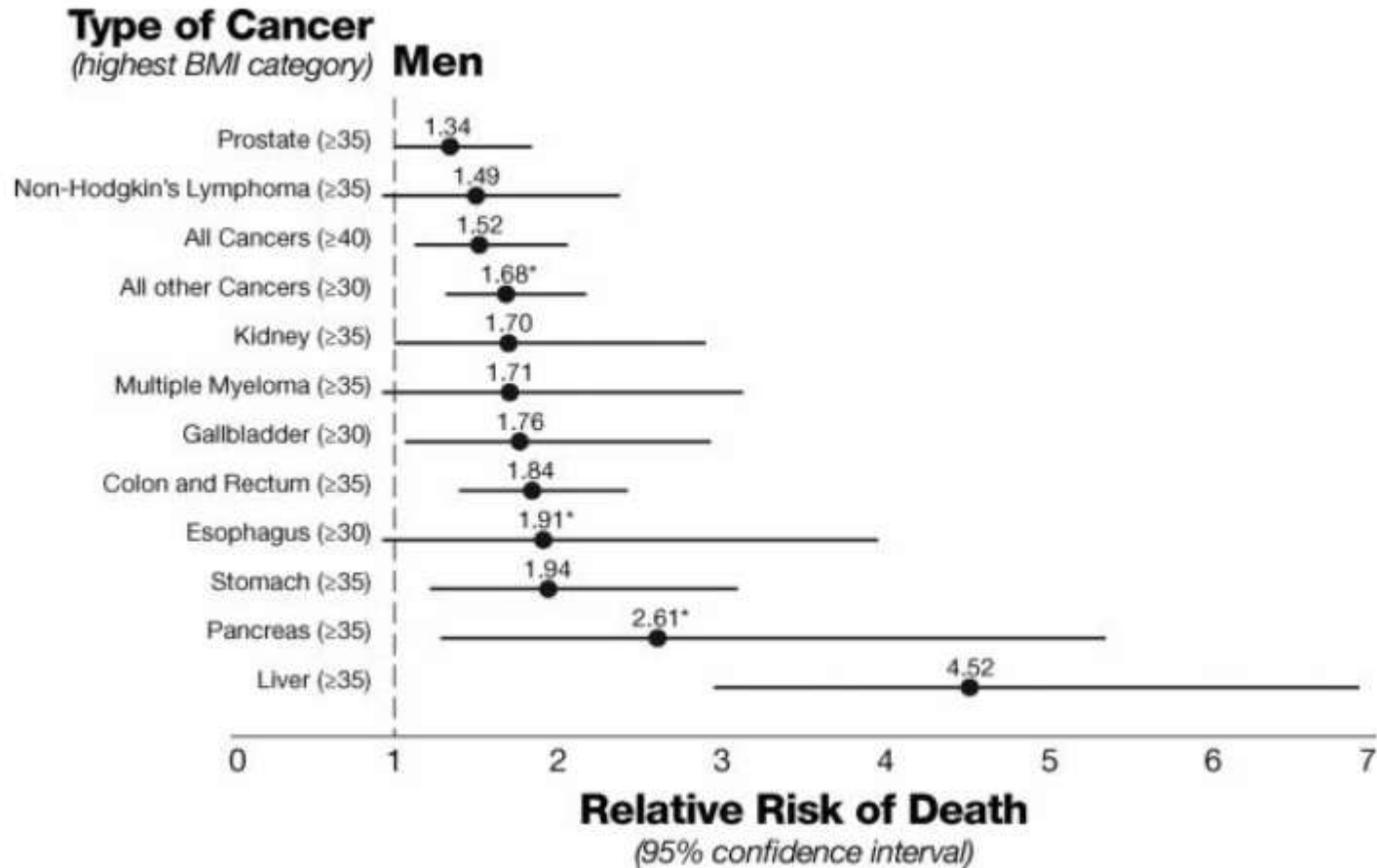


Association of the Different Components of the Metabolic Syndrome and the Development of Hepatocellular Carcinoma

Author	Type of Study	Risk Parameter	Obesity	DM	Hyperlipidemia	HTN
Larsson <i>et al</i> ^[35]	Meta analysis	RR	1.85			
Calle <i>et al</i> ^[37]	Prospective	RR	4.52 (Male) 1.68 (Female)			
Welzel <i>et al</i> ^[40]	Retrospective	OR	1.93	2.9	1.35	2.2
Borena <i>et al</i> ^[25]	Prospective	RR	1.39	2.13	0.85	2.08
Turati <i>et al</i> ^[48]	Retrospective	OR	1.97	4.33		
Davila <i>et al</i> ^[42]	Retrospective	OR		2.87		
Lagiou <i>et al</i> ^[43]	Prospective	RR		4.5 (Male) 1.86 (Female)		
El-Serag <i>et al</i> ^[46]	Prospective	RR		2		
Tomimaru <i>et al</i> ^[55]	Prospective	RR		82.2 (with cirrhosis)		



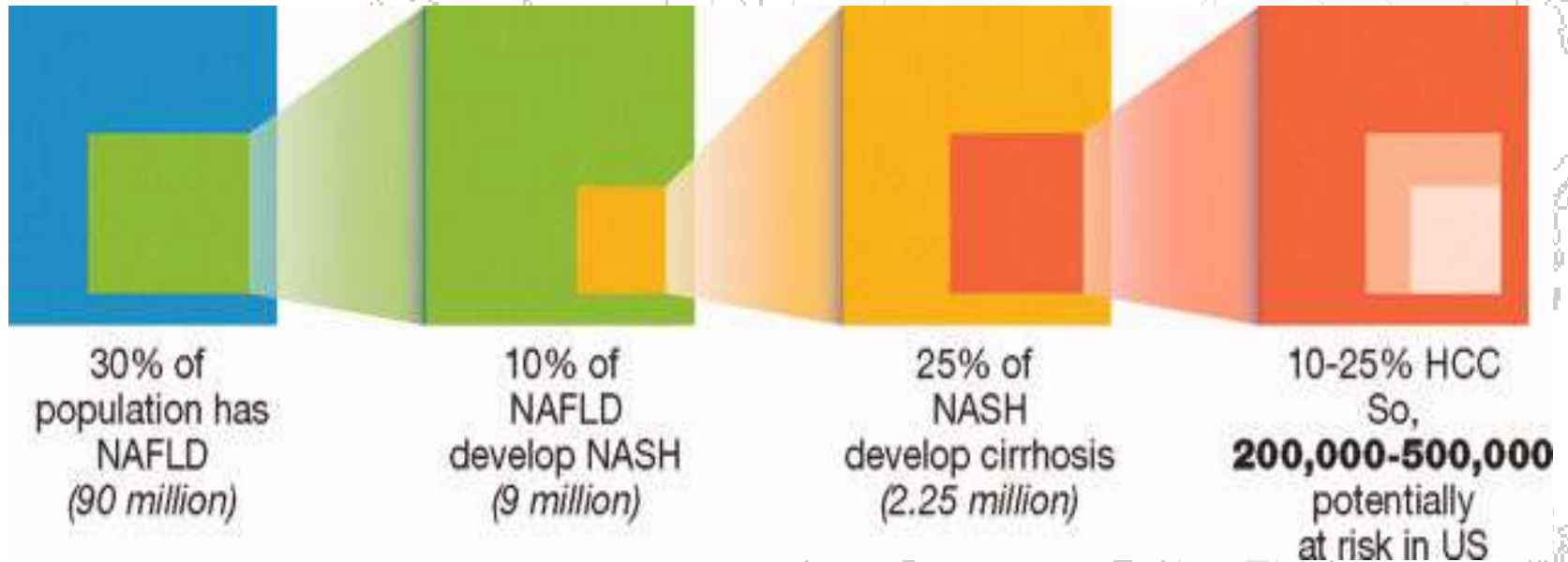
Metabolic Syndrome and Hepatocellular Carcinoma: Two Growing Epidemics with a Potential Link



Relationship of Obesity, MetS, NAFLD, NASH, and HCC

The New Menace of the 21st Century

Body Mass Index and Nonalcoholic Fatty Liver Disease

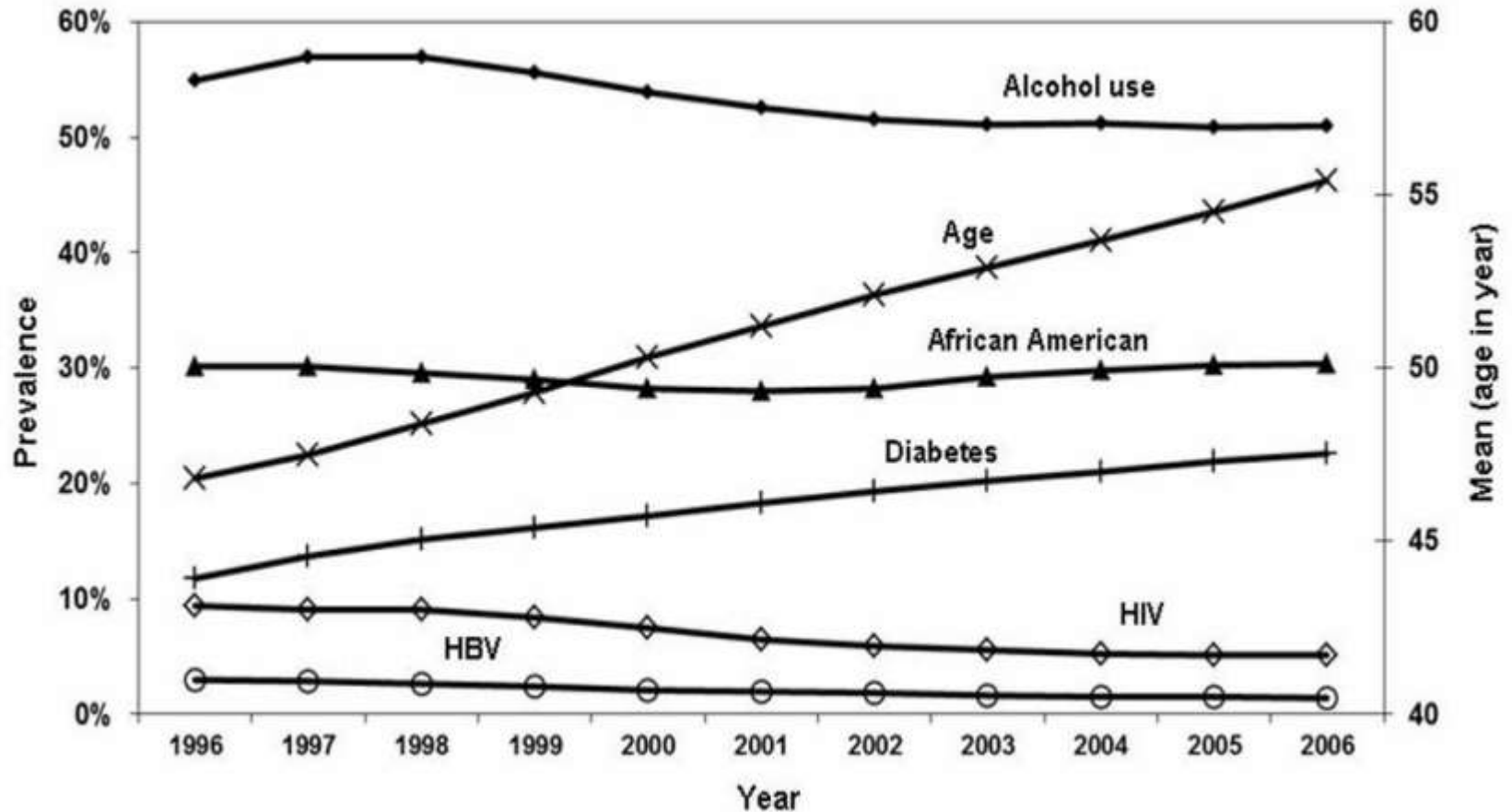


The basis for the American description of a new epidemic of cirrhosis and HCC!

Williams R. *Hepatology* 2006;44:521-526



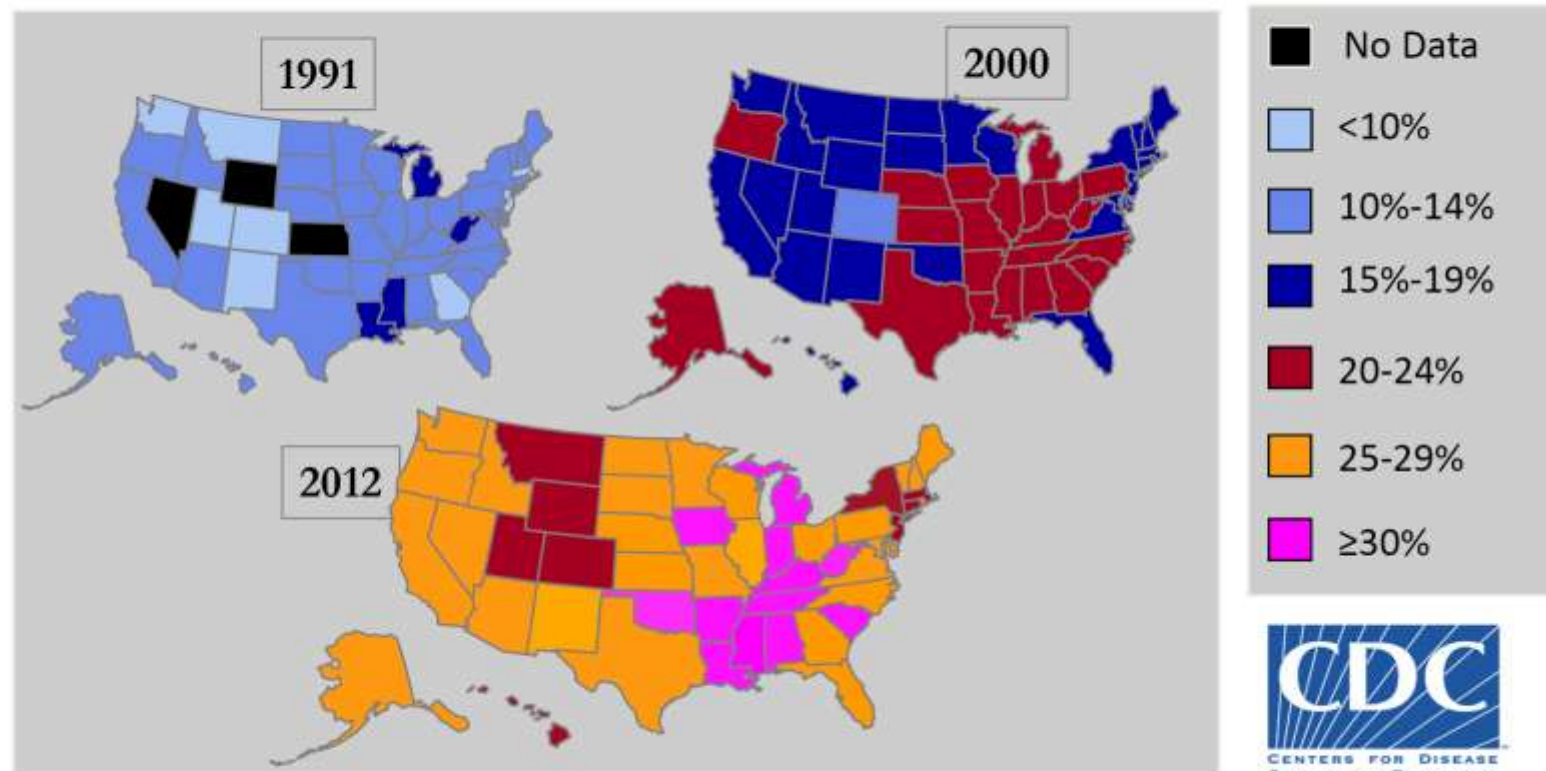
Changes in the Demographics and Clinical Characteristics of HCC in the USA: 1996-2006



Is the Obesity Epidemic in the US also happening in Asia Pacific?

The real bottom line

% of population that is obese (BMI >30, or ~ 30 lbs overweight for 5'4" woman) by state



CDC website, Mokdad AH. JAMA 1999;282:16,
2001;286:10, 2003;289:1



Prevalence of Adult Obesity in Asia versus the USA

	Survey year (ref)	Prevalence of overweight adults (%)*	Prevalence of obese adults (%)
USA	2007-2008 [7]	34.0	30.2
India	1998-1999 [8]	10.0	2.2
Malaysia	1996-1997 [9]	16.6	4.4
Philippines	1998 [10]	16.9	3.3
Taiwan	1993-1996 [11]	21.1	4.0
Japan	2001 [10]	23.0	3.0
Singapore	1998 [12]	24.4	6.0
China	1999-2000 [4]	25.0	4.0
Hong Kong	1996-1997 [13]	25.1	3.8
Korea	2001 [14]	27.4	3.2
Thailand	1998 [15]	28.3	6.8



Global Estimates:
OVERWIEGHT -1.6 billion
OBESE -0.4 billion

World Health Organization, 2005

Yoon KH et al. *Lancet* 2006;368(9548):1681-1688



Diabetes in Asia

Epidemiology, Risk Factors, and Pathophysiology

Country	Diabetes		Impaired Glucose Tolerance	
	2007	2025	2007	2025
India	40 850	69 882	35 906	56 228
China	39 809	59 270	64 323	79 058
Japan	6 978	7 171	12 891	12 704
Bangladesh	3 848	7 416	6 819	10 647
Korea	3 074	4 163	3 224	4 240
Thailand	3 162	4 660	1 896	2 399
Philippines	3 055	5 572	4 410	7 582
Indonesia	2 887	5 129	14 144	20 597
Malaysia	1 530	2 743	2 915	4 442
Vietnam	1 294	2 500	1 175	1 902
Subtotal ^b				
Western Pacific	66 993	99 401	111 898	142 693
Southeast Asia	46 543	80 341	45 169	70 525
Grand total Asia ^b	113 536	179 742	157 067	213 218

^aSource: International Diabetes Federation.² All values are in thousands.

Chan JCN *et al*: JAMA 2009;301(20):2129-2140



Metabolic Syndrome [MetS]: Recent Prevalence in East and Southeast Asian populations

Prevalence of the MetS by NCEP ATP III definition and adopted Asian Definition

Population (reference)	Prevalence by ATP III	Prevalence by Asian
South Korea (30)	M: 5.2%; F: 14.4%	M: 9.8%; F: 12.4%
South Korea (31)	M: 16%; F: 10.7%	M: 29%; F: 16%
China (16)	All: 10.1%	All: 26.3%
Singapore (14)	M: 13.1%; F: 11%	M: 20.9%; F: 15.5%
Taiwan (18)	M: 11.2%; F: 18.6%	M: 23.8%; F: 17.7%
Hong Kong (19)	M: 15.3%; F: 18.8%	M: 20.2%; F: 23.6%
Philippines (32)	M: 14.3%; F: 14.1%	M: 18.6%; F: 19.9%

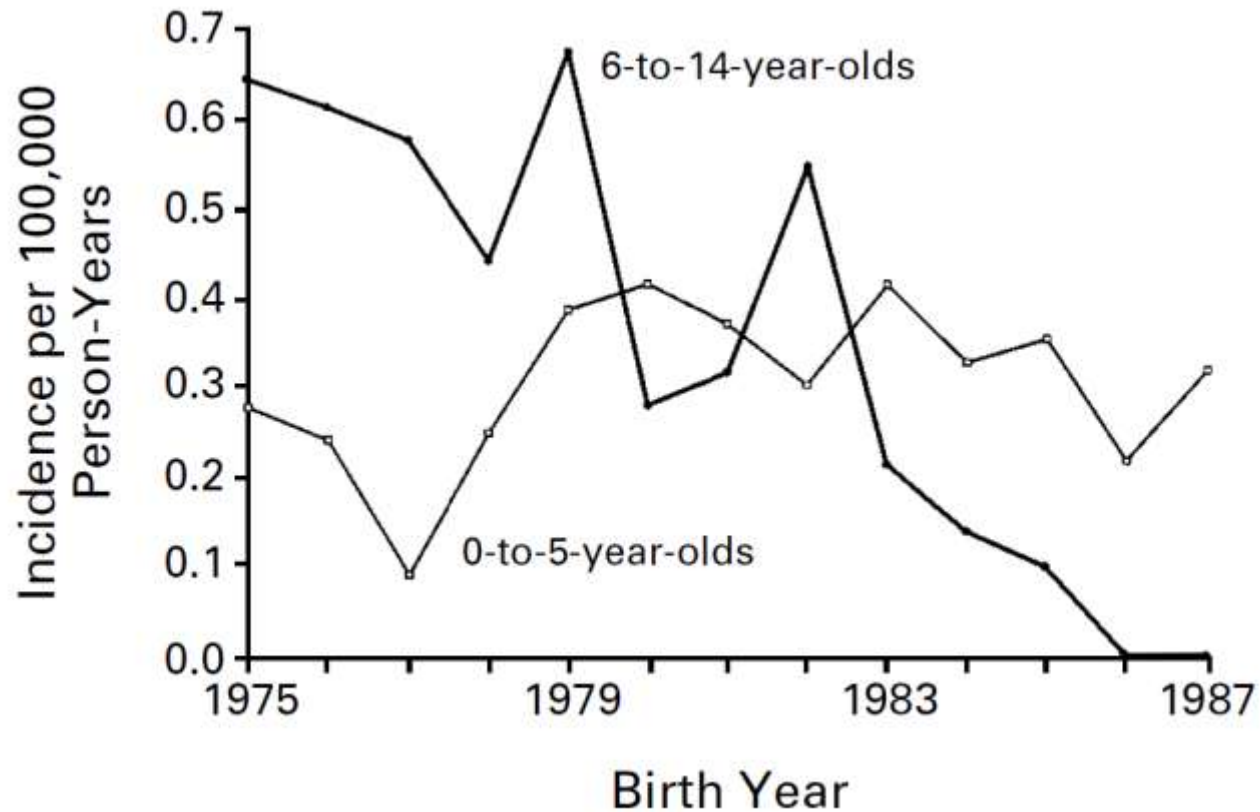


Total Infection-Attributable Cancers Worldwide: 2002

Agent	Cancer	Number of cases	% of all cancers
H. pylori	Stomach	592,000	5.5
	Lymphoma	11,500	
HPV	Cervix	492,800	5.2
	Ano-genital	53,880	
	Mouth, pharynx	14,500	
HBV and HCV	Liver	535,000	4.9
EBV	Nasopharynx	78,100	1.0
	Hodgkin lymphoma	28,600	
	Burkitt lymphoma	6,700	
	Kaposi sarcoma	66,200	
HIV/HHV-8	Non-Hodgkin lymphoma	36,100	0.9
Schistosomes	Bladder	10,600	0.1
HTLV-I	ATL	3,300	0.03
Liver flukes	Liver	2,500	0.02
Total		1,932,800	17.8



Comparison of the Incidence of Liver Cancer in Taiwanese Children 6 to 14 and 0 to 5 years of age, according to Birth Cohort



Chang MH et al. *N Engl J Med* 1997;336:1855-9



Impact of setting a time-bound goal for hepatitis B control in the WHO Western Pacific Region on political commitment and national policy

Increased political commitment:

- In 2005, China recognized hepatitis B as one of four priority communicable diseases, along with HIV/AIDS, schistosomiasis and tuberculosis.
- China issued a national hepatitis B control plan in 2006 and adopted the more ambitious target of reducing the HBsAg seroprevalence to less than 1% among 5-year-old children by 2010.
- The Governments of China and Viet Nam started fully financing hepatitis B vaccines after the end of GAVI Alliance support in 2006 and 2007, respectively.
- In 2006, the Philippines made a commitment to provide 100% funding for hepatitis B vaccination for the first time.

**Hepatitis B control by 2012 in the WHO Western Pacific Region:
rationale and implications**

Manju Rani,^a Baoping Yang^a & Richard Nestil^a



Recent Hep B surveys conducted in WPR

Country	Year	Purpose	Ages (years)	Sample size	HB prevalence
Am Samoa ^a	2011	Guide program + Verification	6-7	562	0.2
Brunei Dar ^a	2011	Guide program + Verification	8-9	4000	<<1.0
Vietnam ^a	2011	Guide program	3-4 5-7	3426 1738	1.6 2.1
Laos ^a	2011	Guide program	5-9	1008	1.5
Cambodia ^a	2011	Guide program	4-5	Urban=1196 Rural=596 Remote=637	0.3 ^b 1.4 3.4

PNG completing survey February 2013;

Philippines has just completed survey at end of October 2013; results awaited!

a PRELIMINARY DATA

b <2% nat'l prevalence based on 37%, 58%, 6% urban, rural, remote population distribution

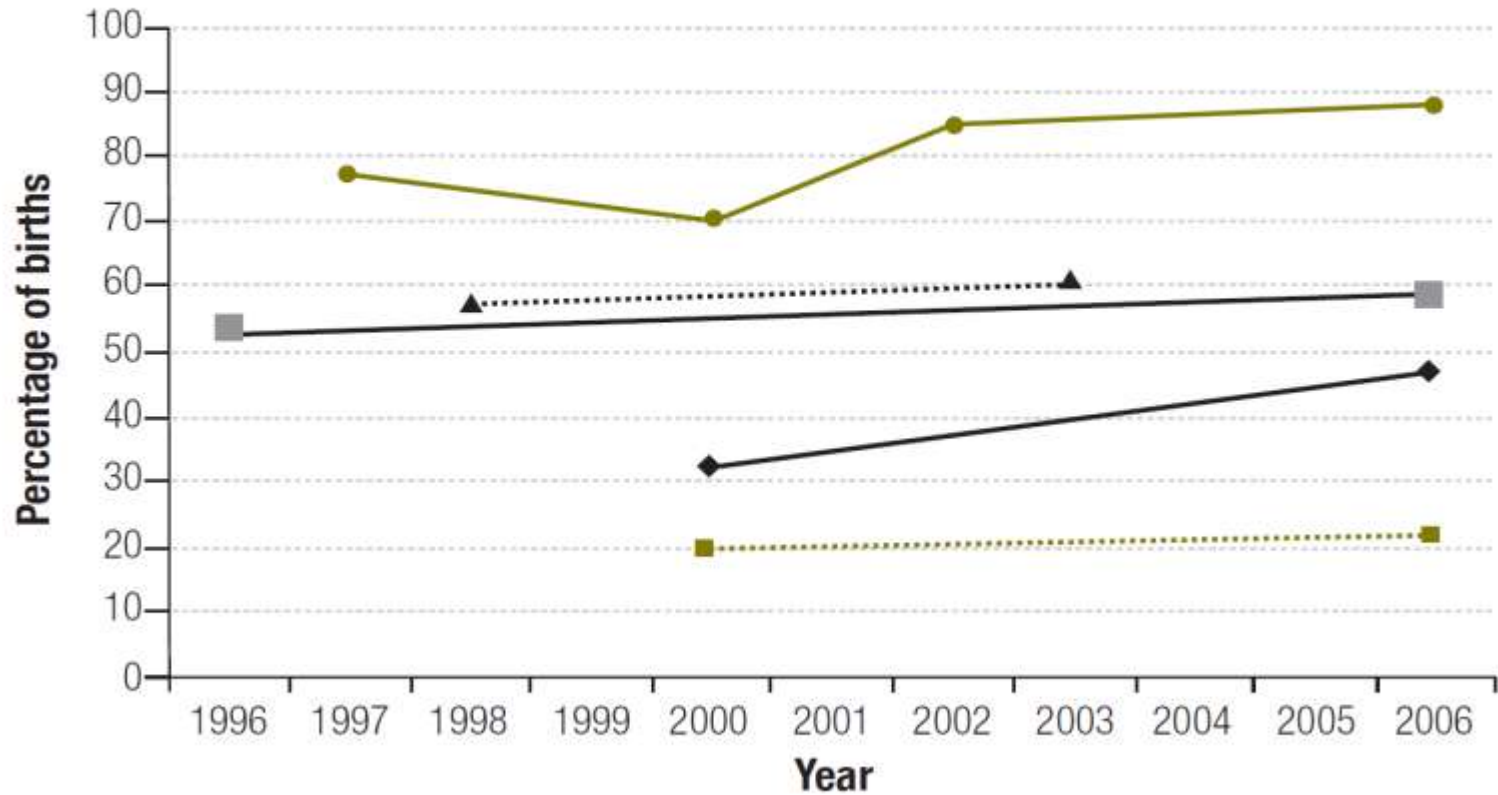


Challenges in the Hepatitis B Immunization Programs in the Asia Pacific



Hepatitis B control in the WHO Western Pacific Region

Percentage of births with skilled attendants present in WHO Western Pacific Region countries between 1996 and 2006



◆ Cambodia ■ Lao People's Democratic Republic ■ Papua New Guinea ▲ Philippines ● Viet Nam

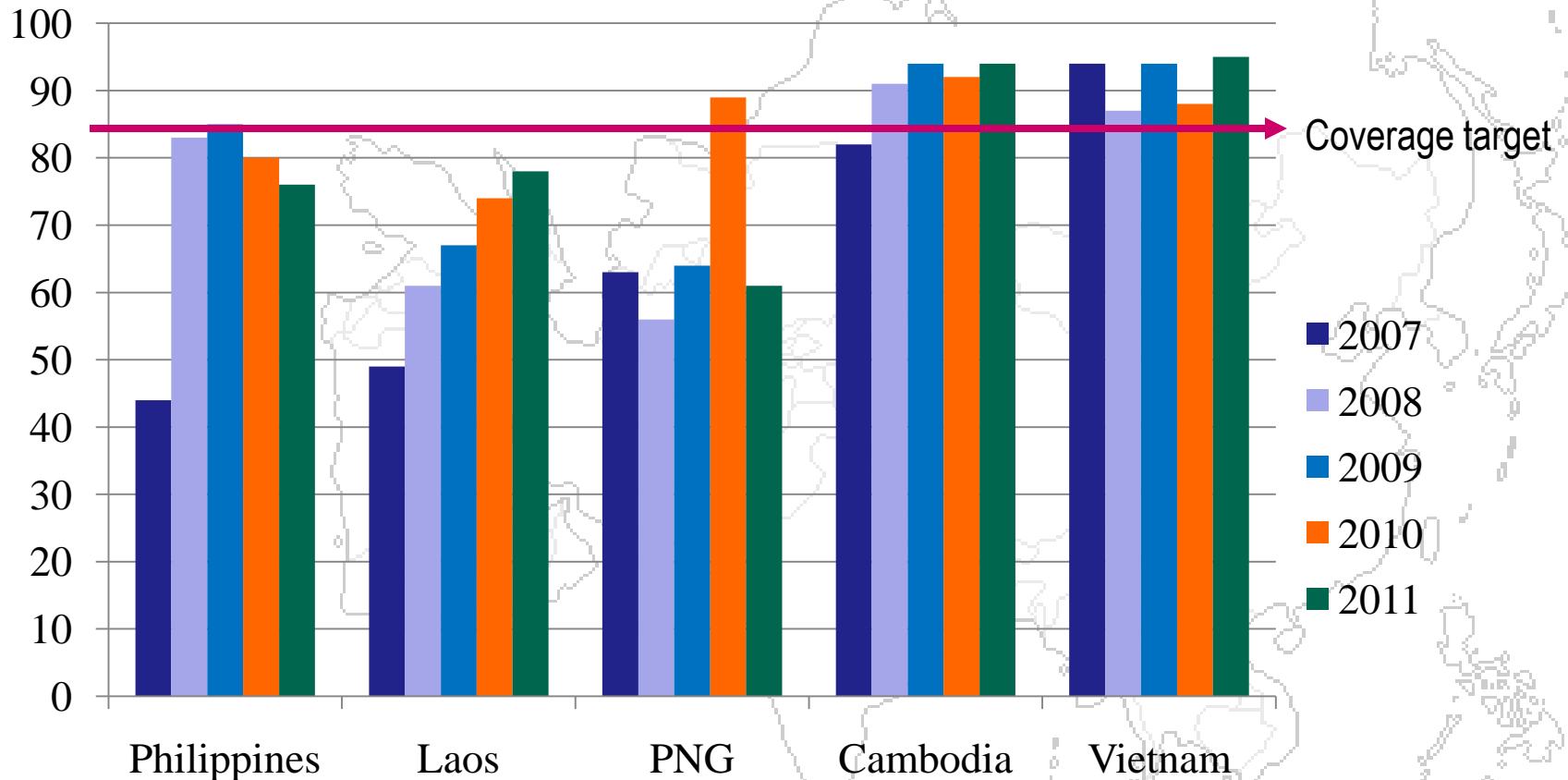
(<http://www.measuredhs.com>) and United Nations Children's Fund Multiple Indicator Cluster Surveys (<http://www.childinfo.org/mics.html>)



HepB₃ Coverage in Priority Countries*

2007 - 2011

*Priority Pacific Island countries (PICs) include: Kiribati, Samoa, Solomon Is, Vanuatu.



In the Philippines, if HepB and DTP vaccination were given simultaneously, 10% more infants could have received all HepB doses.

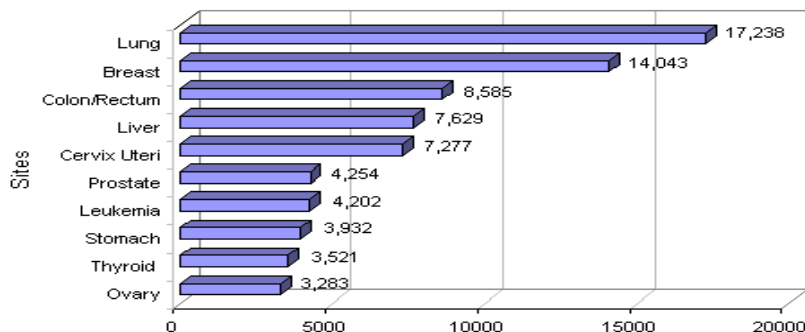
Wallace AS et al. *J Public Health Policy* 2012 Aug;33(3):368-81



Estimated Ten Leading Cancer Sites in the Philippines in 1997, 2005, 2010 Both Sexes

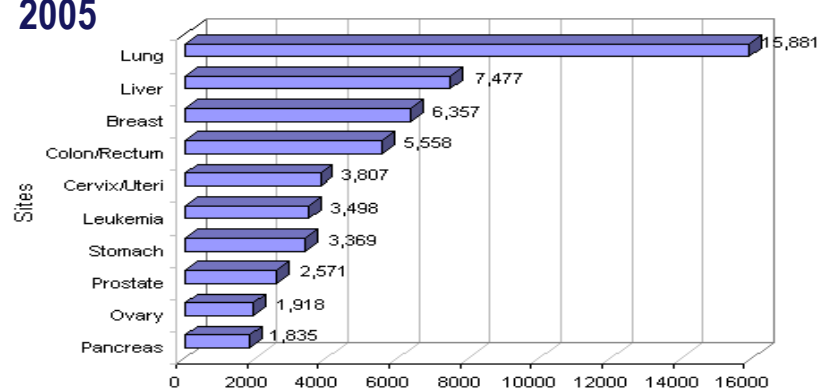
1997

Number of Cases

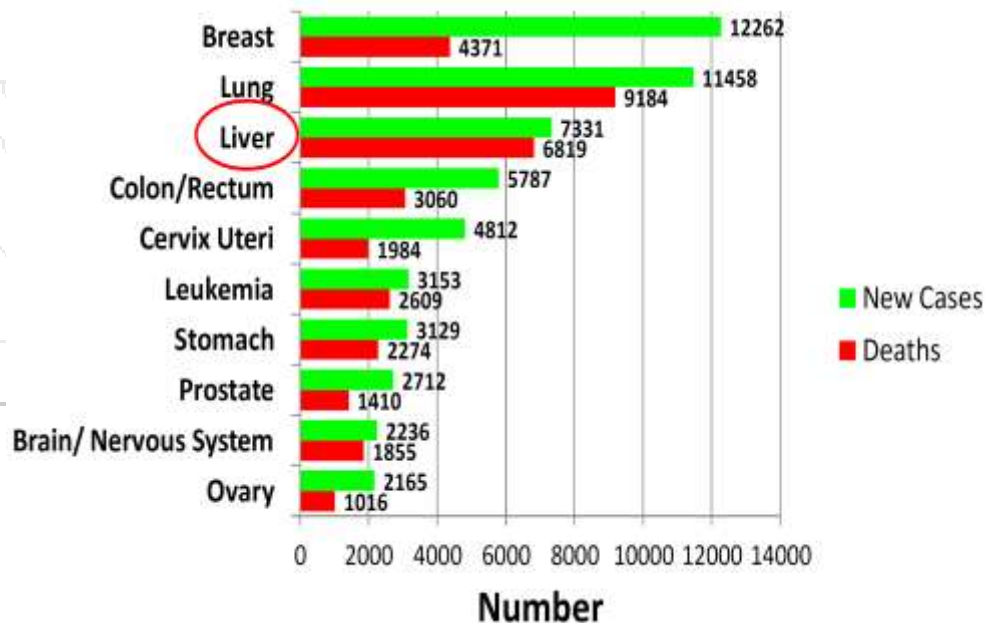


2005

Number of Cases



2010



Laudico et al; Phil Cancer Facts and Estimates 1997, 2005, 2010






Why Immunization is Worth All the Effort

- Immunity against HBV thus far has made an important impact on health; an estimated 225,000 chronic infections and 38,000 HBV-related deaths will be prevented in the 2011 birth cohort alone
- Increasing vaccination coverage to the target levels will prevent an additional 39,000 chronic infections and almost 7,000 deaths in each birth cohort

Henessey K, *World Health Organization*, 2013



Surveillance for HCC as Recommended by AASLD, APASL and EASL/EORTC

Strategy	 AASLD 2010	 APASL 2010	 EASL 2012
Target Population	Cirrhosis, HBV, NAFLD	Viral cirrhosis	Cirrhosis, HBV, HCV F3
Screening modality	Abdominal US	Abdominal US + AFP	Abdominal US
Optional CT/MRI	No	Yes	No
Additional markers DCP/AFP-L3	No	Yes	No
Screening intervals, (months)	6	6	6
Radiological Diagnosis	CT, MRI >1 cm	CE-US, CT-MRI, any size	CT, MRI >1 cm



Geographical distribution of countries with a critical shortage of health service providers, i.e., doctors, nurses and midwives (WHO 2008)

■ Countries with critical shortage

■ Countries without critical shortage



In Asia, access to health care varies among countries within the region, and despite recent economic gains made by developing countries many patients are still unable to receive adequate services.



APASL Recommendations: 2010

Opportunities for Asia

- ★ Chronic and heavy alcohol intake, high body mass index (BMI >25) and diabetes mellitus leading to liver disease increases the risk for HCC (2b)
- ★ Universal hepatitis B vaccination should be implemented in the countries where HBV infection is endemic or hyperendemic (2a, A)
- ★ The control of transfusion-related, iatrogenic, and illicit drug use-related viral transmission is of paramount importance (2a, A).
- ★ Efficient screening for HCV infection would find patients who require treatment (2b, B)
- ★ Prevention of HCC by elimination of aflatoxin contamination is advised (2a, B)
- ★ Prevention of HCC in patients with nonalcoholic steatohepatitis (NASH) is primarily through lifestyle modification with diet and exercise (2, B)



SUMMARY

- ★ **The incidence of hepatocellular carcinoma (HCC) in Eastern and Southeast Asia is the highest in the World and is a common cause of cancer-related mortality in the region**
- ★ **Most HCCs are associated with chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. Currently, HBV infection can be prevented by effective vaccines and promising curative treatments for HCV infection are already available**
- ★ **The changing demographics and the emergence of new risk factors, e.g., MetS, NAFLD, etc may play important roles in the future epidemiology of HCC in the Asia Pacific**
- ★ **Major gains have been achieved in the prevention and treatment of HCC within the region, however, these gains vary among the AP countries**

