Hepatocellular Carcinoma in SSA – Some Info. to Guide the Guidelines

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Basic Demographics of SSA

- The 2nd Largest Continent and home to about 900 million peoples, less than 15% of the world population.
- Most Africans are blacks and live south of the Sahara desert
- Perhaps up to 80% of African live in rural settings where medical facilities are sparse or non-existent altogether
- The population is in a perpetual flux from famine, wars and economic pressures
- Reliable population statistics are hard to come by

Malignant Disease Burden in Africa – An Overview

- 10.1 million new cancer cases were recorded worldwide in the year 2000
- Expected to rise to 15 million by 2020, 27 million by 2030 and 20 million cancer-related deaths
- The brunt of this burden is expected to be borne by the poor countries, especially the countries of sub-Saharan Africa
- Obtaining accurate cancer statistics in Africa has been bedeviled by
  - Lack of population-based cancer registries
  - Non-uniform distribution of health centres and hospitals
  - Lack of diagnostic facilities and expertise

Stewart BW, Kleinhues P (eds) World Cancer Report. Lyon, France: IARC Press; 2003

HCC Worldwide

- HCC constitutes 90 – 95% of all malignant tumours of the liver in the high-incidence settings
- It's 70 – 85% in the low incidence areas
- 6th most common human malignancy and 9.25% of all new cancers in 2008
- M:F Ratio 2.3:1.0
- The Second most common cause of cancer deaths
- Annual fatality rate 0.93, the highest for any human tumour
- The vast majority of new cases are from low resource countries

Ferlay et et Establishment of worldwide burden of cancer in 2008: Globocan 2001. Int. J Cancer 2010 127: 2893 - 917

HCC in Resource-poor Countries

- 626,700 were reported from resource-poor countries; 2/3rds were from men (No 3 Cancer) and 1/3rd from women (No 6 Cancer)
- 2nd leading cause of cancer deaths in men and the 5th in women
- These dismal figures are the tip of an iceberg: up to 85% of HCC may come from resource-poor countries.
- 55% is estimated to be from China alone
- High incidence HCC may be up to 100 times higher than the low-incidence HCC

Ferlay et et Establishment of worldwide burden of cancer in 2008: Globocan 2010. Int. J Cancer 2010 127: 2893 - 917

Age-standardized rates

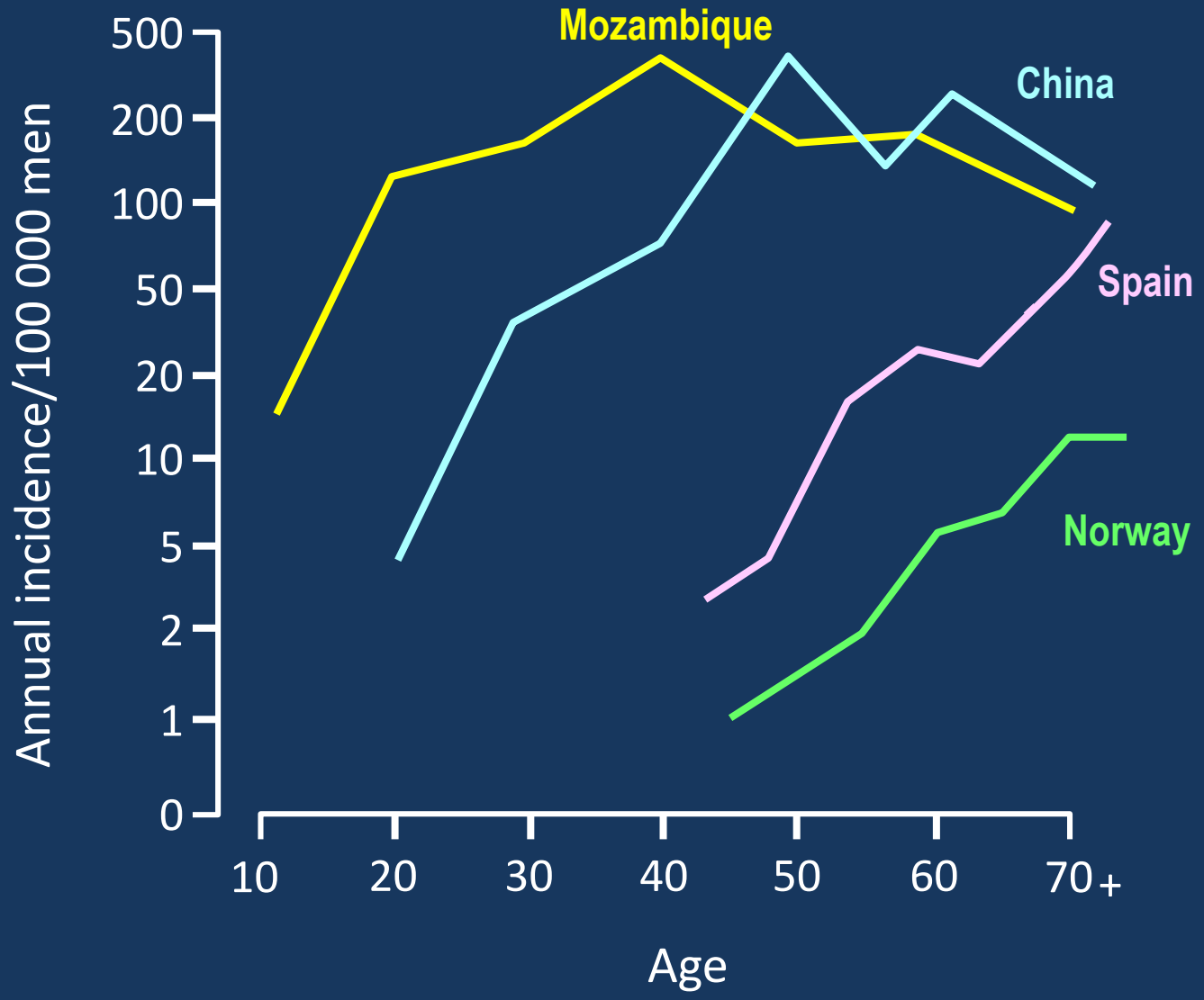
- High incidence = more than 15 cases per 100,000 population
- Low-incidence = Less than 5 per 100,000 person per year
- China has an estimated age-standardized rate of 52.1
- Melanesia 25 per 100,00
- Varies between 20 and 42/ 100,000 persons per year in SSA

Stewart BW, Kleinhues P (eds) World Cancer Report. Lyon, France: IARC Press; 2003

Incidence in SSA

- West Africa 20.9 per 100,000 per year
- East Africa, 29.7 per 100,000 persons per year
- Middle Africa 42.1 per 100,000 persons per year
- Mozambique has a reported incidence of 101 per 100,000 male persons and 34 per 100,000 females
- Mozambique's may be the world's highest figures

Stewart BW, Kleinhues P (eds) World Cancer Report. Lyon, France: IARC Press; 2003


Mozambique
China
Spain
Norway
Annual incidence/100 000 men
500
200
100
50
20
10
5
2
1
0
10
20
30
40
50
60
70+
Age

Evidence from 19 Years of Population-Based Cancer Registration in Gambia(1988–2006)

Table 1. Most common cancers in The Gambia for the period 1998–2006.

	Men			Women		
Site	**Total Number of cases**	**ASR (w) per 100000**	**% of all cancers**	**Total number**	**ASR (w) per 100000**	**% of all cancers**
Oesophagus	17	0,55	0,87	14	0,51	0,76
Stomach	48	1,58	2,45	17	0,59	0,92
Colorectal, Anus	40	1,17	2,04	28	0,93	1,51
Liver	1215	32,84	61,99	512	14,90	27,69
Pancreas	22	0,73	1,12	13	0,51	0,70
Trachea, bronchus and lung	71	2,46	3,62	10	0,39	0,54
Kaposi sarcoma	21	0,51	1,07	9	0,20	0,49
Soft tissues	25	0,60	1,28	32	0,94	1,73
Breast	11	0,35	0,56	215	5,82	11,63
Cervix	-	-	-	545	15,45	29,48
Corpus uteri	-	-	-	31	0,92	1,68
Ovary	-	-	-	36	0,97	1,95
Prostate	95	3,46	4,85	-	-	-
Bladder	29	0,91	1,48	8	0,21	0,43
Thyroid	11	0,25	0,56	36	0,90	1,95
Non-Hodgkin lymphoma	88	1,42	4,49	67	1,29	3,62

Age Distribution

- Mean age of Low-incidence HCC is 65 years
- HCC in SSA affects significantly your age groups
- This could be as low as 34.7 years in rural black men to 51 tears in urban black women
- The mean age for urban southern African black men is 50.9 years
- In Mozambique, Prates et al reported that up to 50% of HCC patients were below the age of 30 years

Bosch FX et al Primary liver cancer: Worldwide incidence and trends. Gastroenterology 2004; 127: 55 – 516
Prates et al. A cancer survey in Lourenco Marques, Portuguese East Africa J. Natl Cancer1965; 35; 729 – 57
Kew MC et al . Some characteristics of Mozambican Shangaans with primary hepatocellular cancer S Afr Med J 1977; 51 306 - 309

Gender Distribution

- HCC affects more men than women worldwide
- In SSA, this is more so – M:F ratios vary from 1.8: 1.0 to 28.0: 1.0 (Mean ratio is 3.5: 1.0)
- Male preponderance is particularly striking in young males in SSA – 8.1:1.0 in patients younger than 30 and 4.2 :1.0 in patients older than 40 years
- The male preponderance reflects an equally high HBsAg seroprevalence among males

Stewart BW, Kleinhues P (eds) World Cancer Report. Lyon, France: IARC Press; 2003
Steiner et al. Comparison of liver cancer and cirrhosis in 9 areas in Transaharan Africa. Acta Unio Internat Cntra Cancrum 1961; 17 798 – 802
Anthony PP. Primary Carcinoma of the liver: A Study of 282 cases in Ugandan Africans. J Pathol 1973; 110: 37 – 48
Kew MC et al. The effect of age on the aetiological role of the HBV in hepatocellular carcinoma in Blacks. Gastroenterology 1988; 94439 - 42

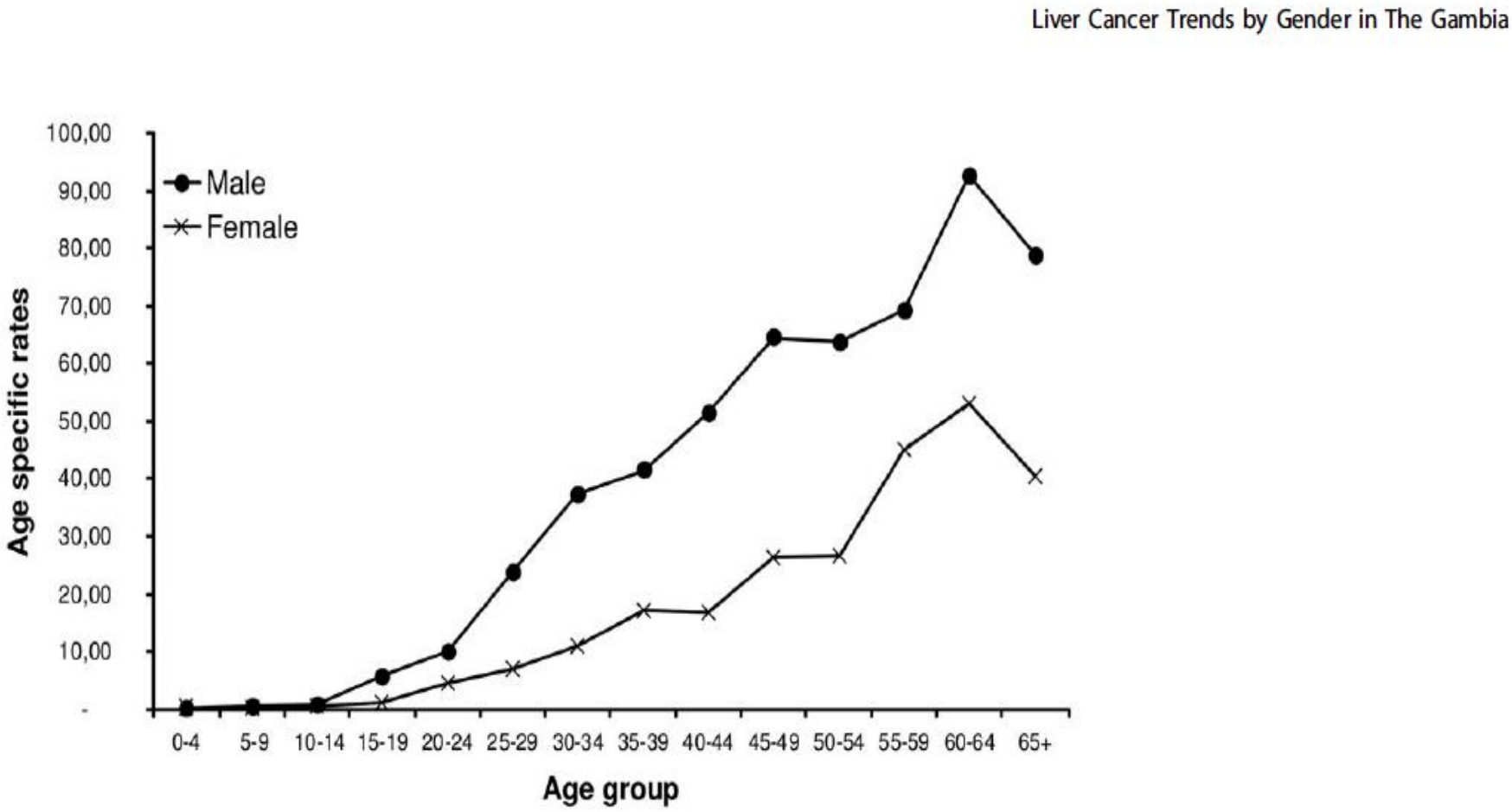


Figure 1. Liver cancer incidence rates per 100000 Gambians by 5-years age groups. Data from the Gambia National Cancer Registry, 1998–2006.

A Non-Uniform Distribution is Strongly Suggestive of a Role for Environmental Factors

- In Mozambique, the incidence is highest in the Eastern region than the others
- There is a disparity in incidences between the low and highlands of Swaziland
- In Uganda, there is a significant differences between the tribes
- In South Africa, HCC incidence is strikingly higher in urban than rural black

Prates et al. A cancer survey in Lourenco Marques, Portuguese East Africa J. Natl Cancer1965; 35; 729 – 57
Peers FG et al Dietary Aflatoxins and human liver cancer: A study in Swaziland. Int J Cancer 1976; 17: 167 – 76
Alpert et al. Primary hepatoma in Uganda: A prospective clinical and epidemiological study of 46 patients. Am J Med 1969 46: 794 – 802
Kew MC et al. Comparison between the polyclonal and 1st and 2nd generation monoclonal radioimmunoassays in the detection of HBsAg in patients HCC Hepatology 1986; 6: 636 - 9

Ethnicity and HCC

- Higher incidence in Fula and Wollof ethnicity
- Increase due to genetic polymorphism in enzymes in AFB1 metabolism
- Higher prevalence between Fula and Mandinka in Gly 399 Allele of *XRCC1* *r*esponsible for genetic repair of DNA aflatoxin adducts

Kirk GD 2005 Cancer Epid Biomarkers Prev 14: 373-379

HCC With and Without Cirrhosis

- Low incidence HCC is associated with Cirrhosis in more than 90% of cases and this figure is higher cohorts of older patients
- In SSA HCC with cirrhosis is significantly less common and not related to age
- 59.7% of patients less than 30 years have HCC with cirrhosis
- Only 63.8% patients who are 50 or older have coexisting cirrhosis

Kew MC Clincal manifestations and paraneoplastic syndromes of hepatocellular carcinoma. In : Okuda and Ishak (eds) Neoplasms of the liver. Tokyo Springer Verlag 1987p199 – 211
Kew MC et al . Some characteristics of Mozambican Shangaans with primary hepatocellular cancer S Afr Med J 1977; 51 306 - 309

HCC In Black Children

- Unlike in low-incidence countries, HCC is common among African Black children but the incidence is lower than in adults
- Patients are usually between 5 and 15 years old
- M:F Ratio 2 – 3: 1.0
- HBV is strongly associated with childhood cases of the disease in SSA rather than the know metabolic causes of the disease in rich countries
- The fibrolamellar HCC is commoner in Black children than adults

Kew MC et al. Hepatitis B virus infection in Black children with hepatocellular carcinoma. J Med Virol. 1982a; 9, 201 – 207
More Sw et al Malignant liver tumours in children: A national audit. World J Surg 2008; 32: 1389 - 95

Why the high incidence in Africa? - I

Three major environmental causes

- Chronic HBV infection
- Dietary exposure to fungal toxin aflatoxin B1
- Chronic HCV infection

Epidemiology of HBV infection in Africa

- ± 65 million chronically infected
- Responsible for ± 255,000 deaths each year
- Chronic carriage more common in males Vs Females (1.5-2.0 : 1.0)
- More common in rural than in urban dwellers

Hepatitis B Surface Antigenaemia among Adult Nigerians with Clinical Features of Liver Diseases

Liver disease	HBsAg sero-positivity	
	Yes number (%)	No number (%)
Hepatitis	17 (23.9)	27 (39.1)
Liver cirrhosis	28 (39.5)	34 (49.3)
Hepatocellular carcinoma	26 (36.6)	8 (11.6)
Total	71 (100.0)	69 (100.0)

PATHOGENESIS OF HEPATITIS B VIRUS-INDUCED HEPATOCELLULAR CARCINOMA

HBV DNA does not contain an oncogene

- HBV DNA integration occurs in almost all patients with HBV-induced HCC

Cis-activation of cellular genes

1. Integration into or close to a gene disrupts the gene or interferes with its function
2. Changes in flanking sequences

- deletions, translocations, duplications

Trans-activation of cellular genes

Mediated through signal transduction pathways

Two HBV proteins have *trans*-activating capability:

- x protein
- preS/S protein when 3' truncated during integration

HEPATITIS B VIRUS INFECTION IN SOUTH AFRICAN BLACKS WITH HEPATOCELLULAR CARCINOMA

HBsAg: 69.5%

occult HBV 22.5%

Total HBV positivity ± 92%

Consequences of early hepatitis B virus infection

Infected in 1st year of life: 90% become chronic

Infected in 5th year of life: 50% become chronic

Infected in adulthood: < 10% become chronic

27- 40% DEVELOP H.C.C

RELATIVE RISK OF H.C.C: > 100

PATHOGENESIS OF HEPATITIS B VIRUS-INDUCED HEPATOCELLULAR CARCINOMA

Unrestrained proliferation of hepatocytes

and

Series of genetic and epigenetic changes

- Dividing cells susceptible to viral integration
- Accelerated hepatocyte turnover rate allows less time for DNA repair before cell divides again, 'fixing' abnormal DNA in daughter cells

Why the high incidence of HCC in Africa? II

Lesser risk factors

- Alcohol
- Metabolic conditions associated with obesity and/or T2DM
- Dietary iron overload

Relative of importance of each risk factor vary widely as a function of geography and local prevalence of chronic viral hepatitis

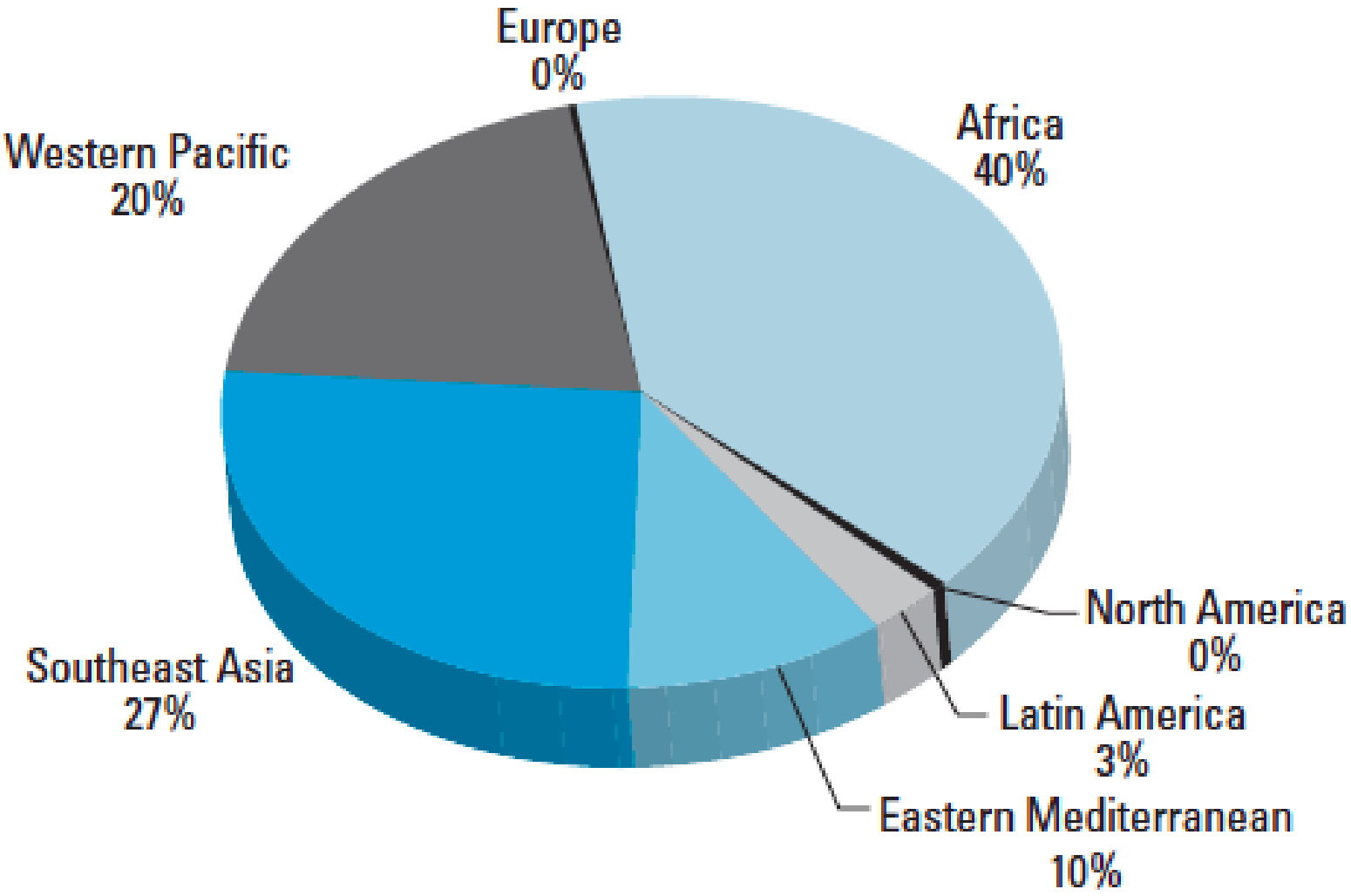
Dietary exposure to fungal toxin aflatoxin B1

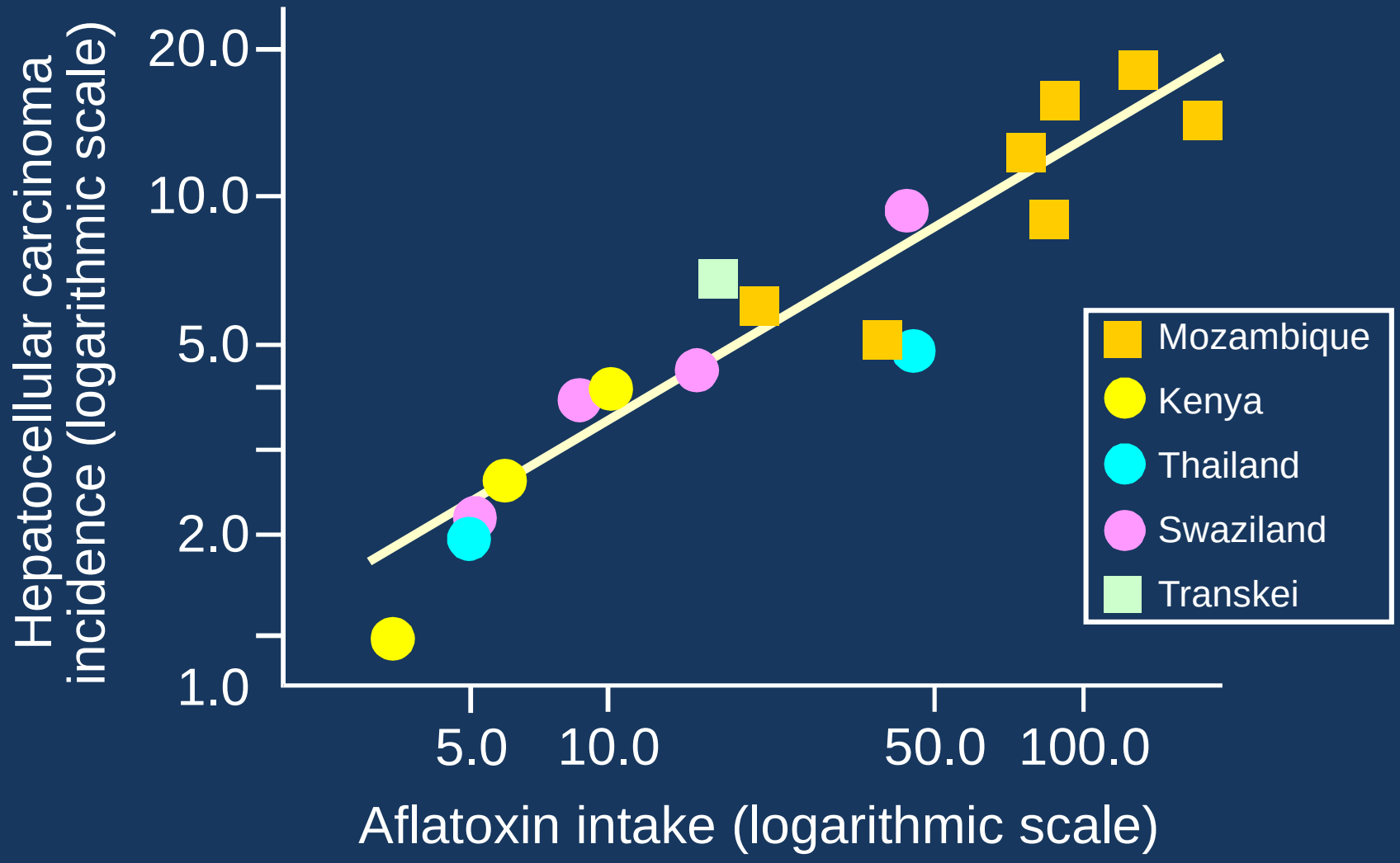
- Difuranocoumarin derivatives of Aspergillus flavus and A. parasiticus
- Contaminate crops, particularly maize, ground nuts and fermented soy beans, in tropical and subtropical countries
- Associated with warm, humid climates
- Contamination occurs both during growth of the crops and as a result of their improper storage.

- Sub-Saharan Africa and the Asia-Pacific region have high levels of exposure to the fungal toxin.
- Aflatoxin B1 (AFB1) is the aflatoxin most often found in contaminated human foodstuffs and is the most potent hepatocarcinogen
- **Strong statistical association between dietary ingestion of aflatoxin B_1 and the development of HCC**

Wild CP *Carcinogenesis* 2010; **31**: 71-82

Distribution of HCC cases attributable to aflatoxin in different regions of the world.




Hepatocellular carcinoma incidence (logarithmic scale)
20.0
10.0
5.0
2.0
1.0
5.0
10.0
50.0
100.0
Aflatoxin intake (logarithmic scale)
Mozambique
Kenya
Thailand
Swaziland
Transkei

Biotransformation of AFB1

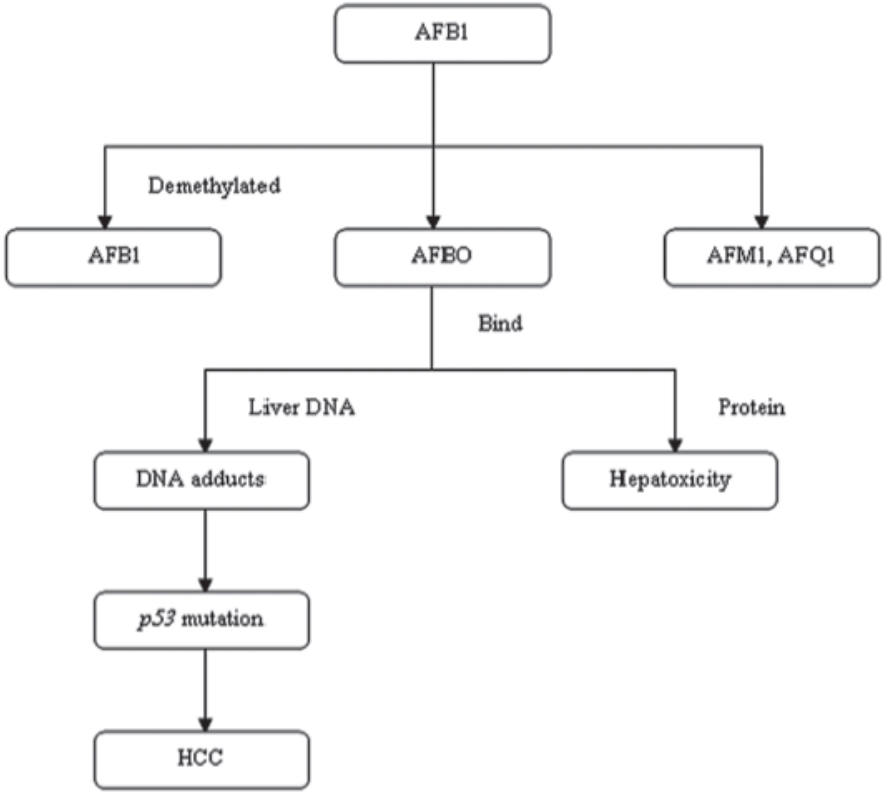
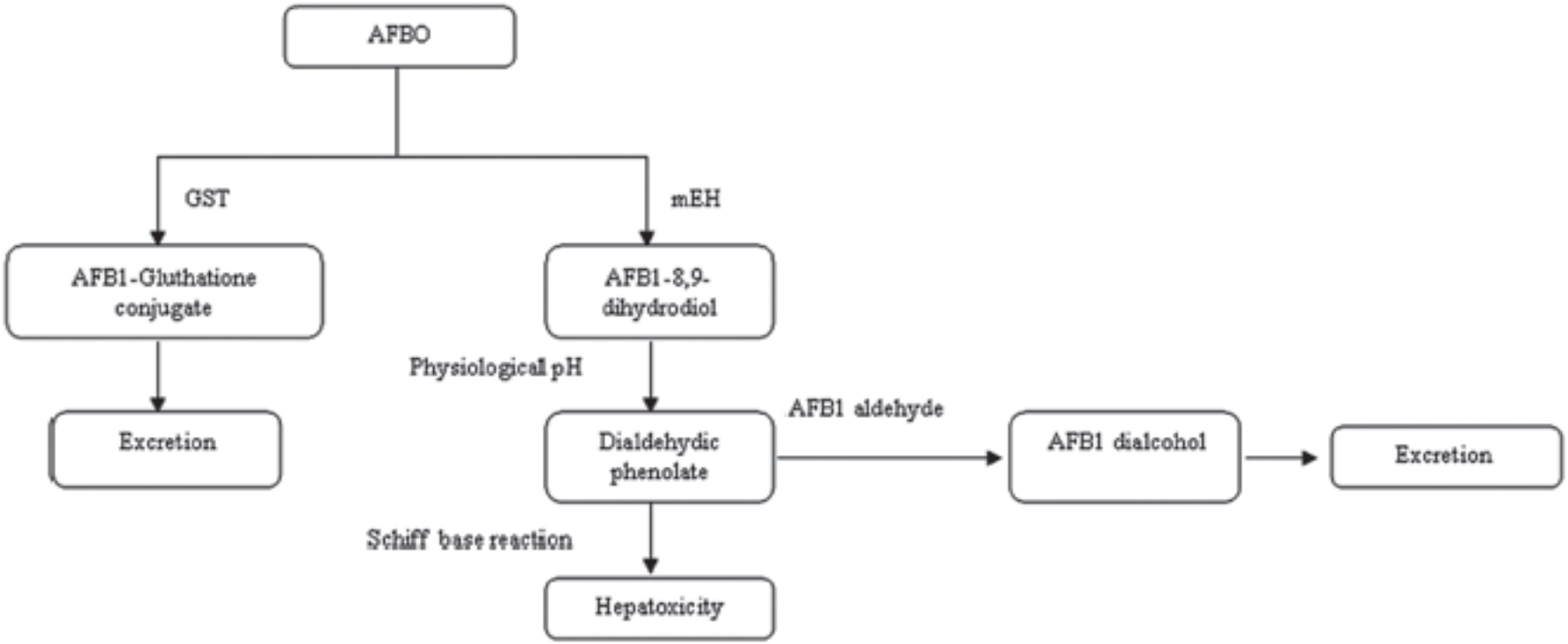


Figure 2. Biotransformation of AFB1, which comprises CYP450-mediated reactions resulting in a highly nucleophilic genotoxic reactive intermediate (AFBO), hydroxylation (to AFM1 and AFQ1) or demethylation (to AFP1). When AFBO binds to liver cell DNA, it causes mutation of *p53* that may lead to HCC. AFBO is also capable of causing aflatoxicosis when it binds to protein amino acids. AFB1, aflatoxin B1; AFBO, AFB1-8, 9 epoxide.

Detoxification pathway of AFBO



Proc. Natl. Acad. Sci. USA
Vol. 92, pp. 2384–2387, March 1995
Genetics

Susceptibility to hepatocellular carcinoma is associated with genetic variation in the enzymatic detoxification of aflatoxin B_1

KATHERINE A. MCGLYNN*†, ELIZABETH A. ROSVOLD*, EDWARD D. LUSTBADER*, YING HU*, MARGIE L. CLAPPER*, TIANLUN ZHOU*, CHRISTOPHER P. WILD‡, XIAO-LING XIA§, AGNES BAFFOE-BONNIE*, DAVID OFORI-ADJEI¶, GONG-CHAO CHEN‖, W. THOMAS LONDON*, FU-MIN SHEN**, AND KENNETH H. BUETOW*

Individuals with mutant genotypes at epoxide hydroxylase and glutathione transferase M1 may be at greater risk of developing AFB1 adducts, p53 mutations, and HCC when exposed to AFB1.

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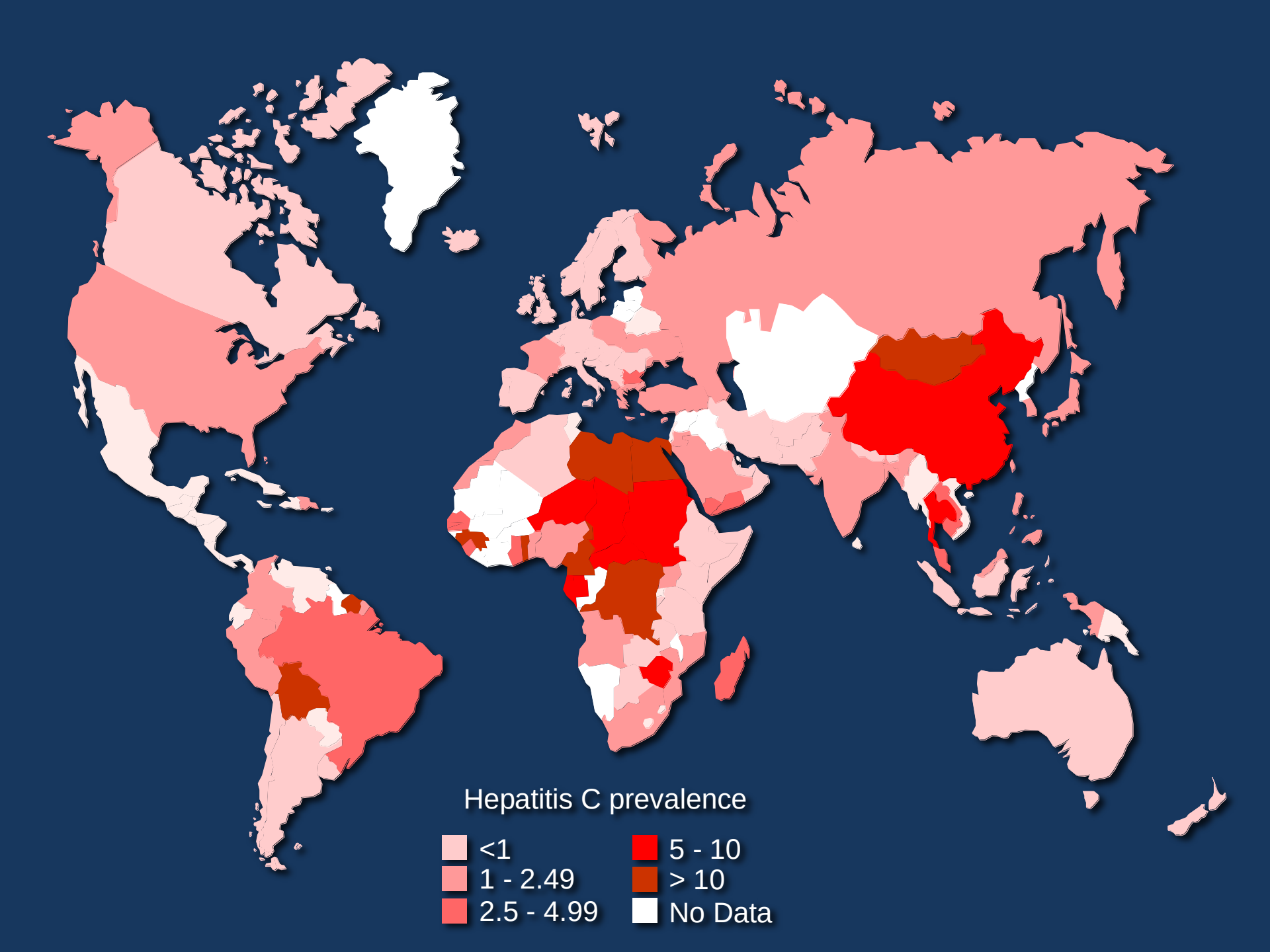
Chronic hepatitis C

- Chronic hepatitis C virus (HCV) and HCV-induced HCC are significantly less common in developing than in developed countries
- Except Somalia where chronic HCV infection is as common as chronic HBV infection(3)

Bile K, Aden C, Norder H, Magnius L, Lindberg G, Nilsson Z. Important role of hepatitis C virus infection as a cause of chronic liver disease in Somalia. *Scand J Dig Dis* 1993; **25**: 559-564


Hepatitis C prevalence
<1
1 - 2.49
2.5 - 4.99
5 - 10
> 10
No Data

PATHOGENESIS OF HCV-INDUCED HEPATOCELLULAR CARCINOMA

Unrestrained proliferation of hepatocytes

and

Series of genetic and epigenetic changes

HCV core and NS5a proteins:

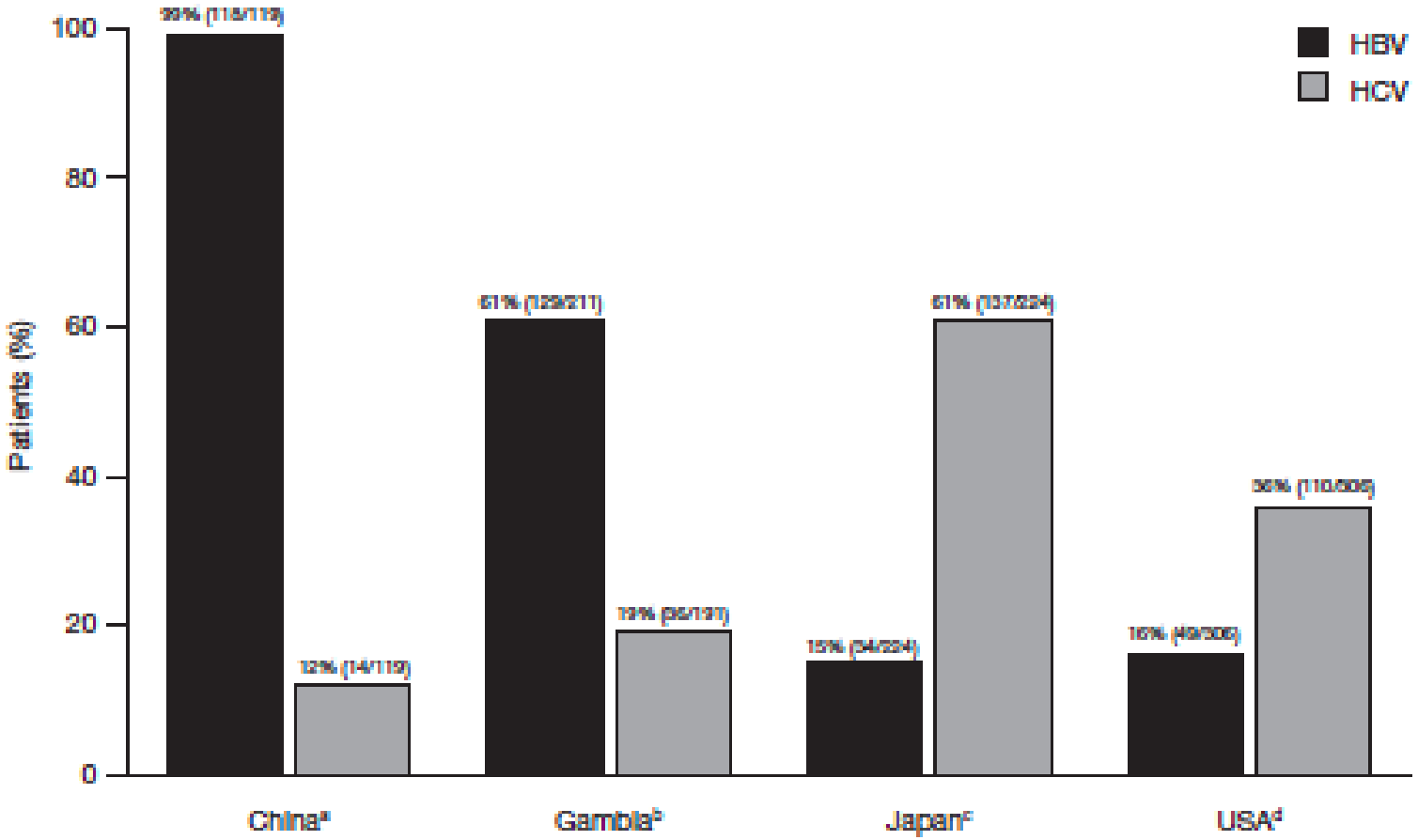
- generate reactive oxygen species
- Repress transcription of p21
- Induces mutations in p53
- Abolishes catalytic activity of PKR (antiviral, antiproliferative induced by IFN)

INTERACTION BETWEEN HEPATITIS B AND C VIRUSES IN HEPATOCARCINOGENESIS IN SOUTHERN AFRICAN BLACKS

RELATIVE RISK FOR H.C.C:

HBV INFECTION ALONE:	23.3 (9.2 - 51.8)
HCV INFECTION ALONE:	6.6 (2.7 - 15.7)
HBV AND HCV CO-INFECTION:	82.5 (8.9 - 761.8)

Variation in prevalence of chronic infection with HBV and HCV in patients HCC



Alan Venook The oncologist 2010 15:5-13

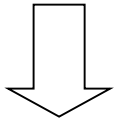
AFRICAN DIETARY IRON OVERLOAD AS A CAUSE OF HEPATOCELLULAR CARCINOMA

- Gordeuk et al (1996): R.R. 23.5 (95% C.L. 2.1- 225) of HCC in those subjects with the highest levels of hepatic iron accumulation, after allowing for confounding effect of cirrhosis

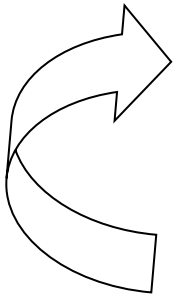
- Moyo et al (1998): R.R. 3.1 (95% C.L. 1.05 - 9.4) of HCC after allowing for the confounding effects of cirrhosis

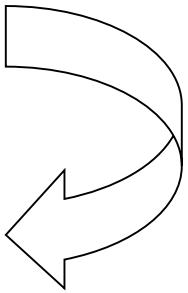
- Mandishona et al (1998): R.R. of 10.6 (95% C.L. 1.5 – 76.8) , after allowing for confounding effects of chronic HBV and HCV infection and aflatoxin B_1 exposure, but not cirrhosis

Free hepatic iron

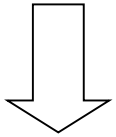


ROS and oxidative damage





Chronic necroinflammatory hepatic disease (cirrhosis; portal fibrosis)



HEPATOCELLULAR CARCINOMA

Thank you