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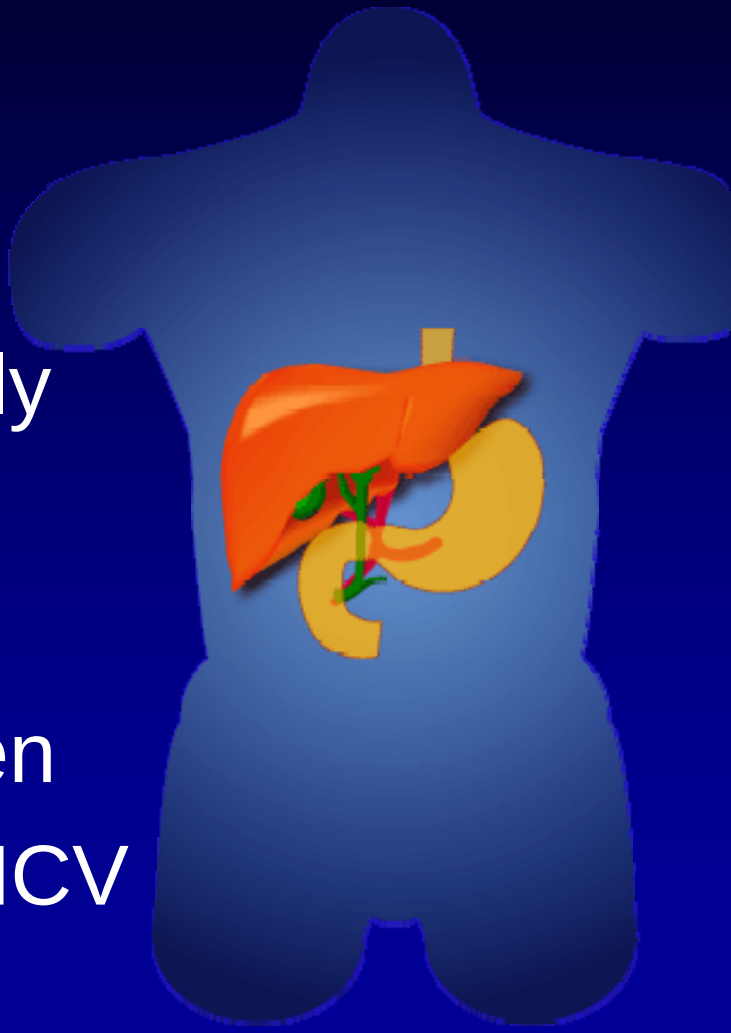
THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER
Making Cancer History™

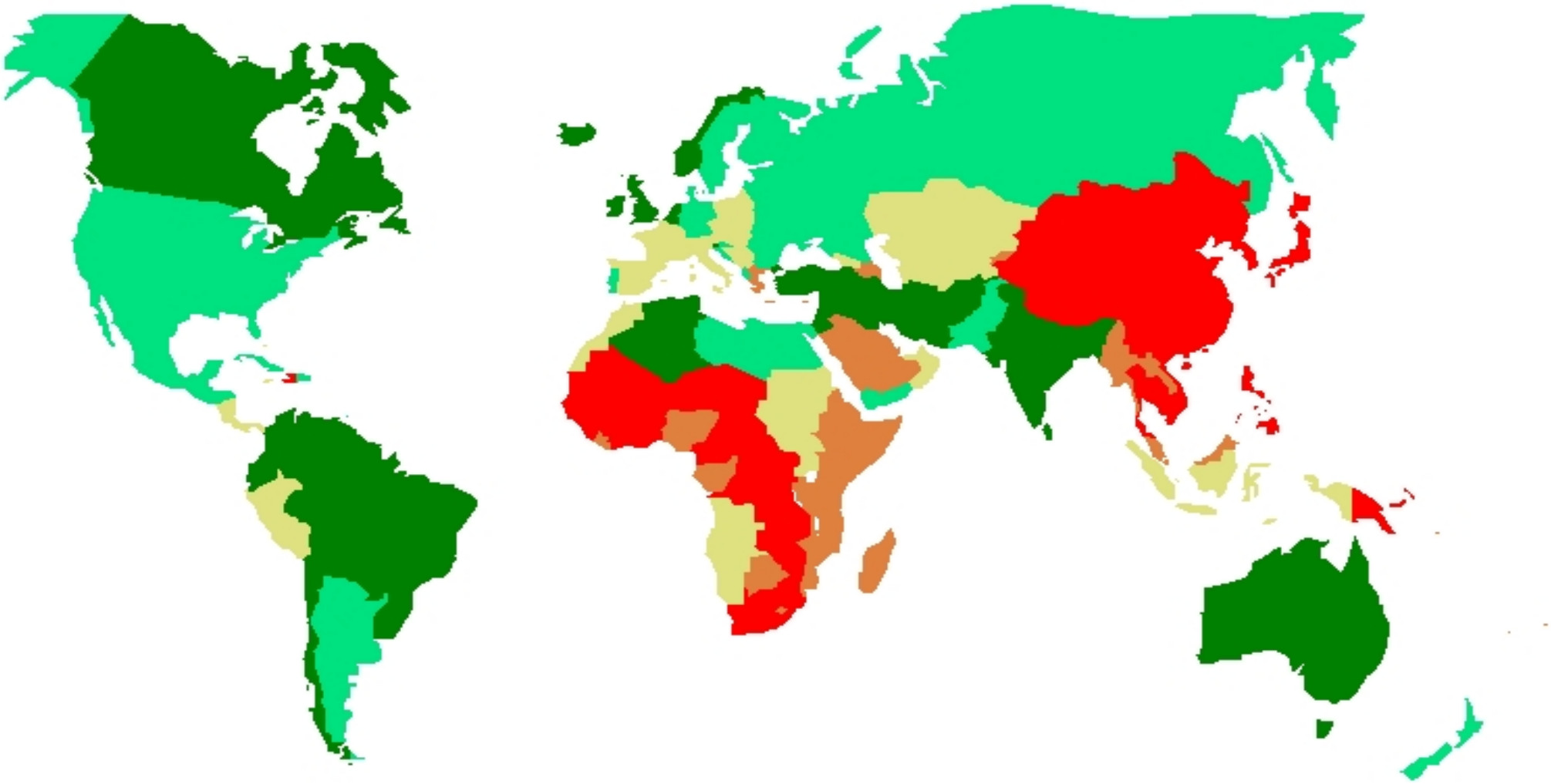
Epidemiology of Hepatocellular Carcinoma in USA

Hepatocellular Carcinoma
Global View

- 90% of primary liver cancer
- One million cases occur annually
- 4%-5% of all human cancer
- 7th commonest cancer in men
- 9th commonest cancer in women
- Significantly caused by HBV &HCV

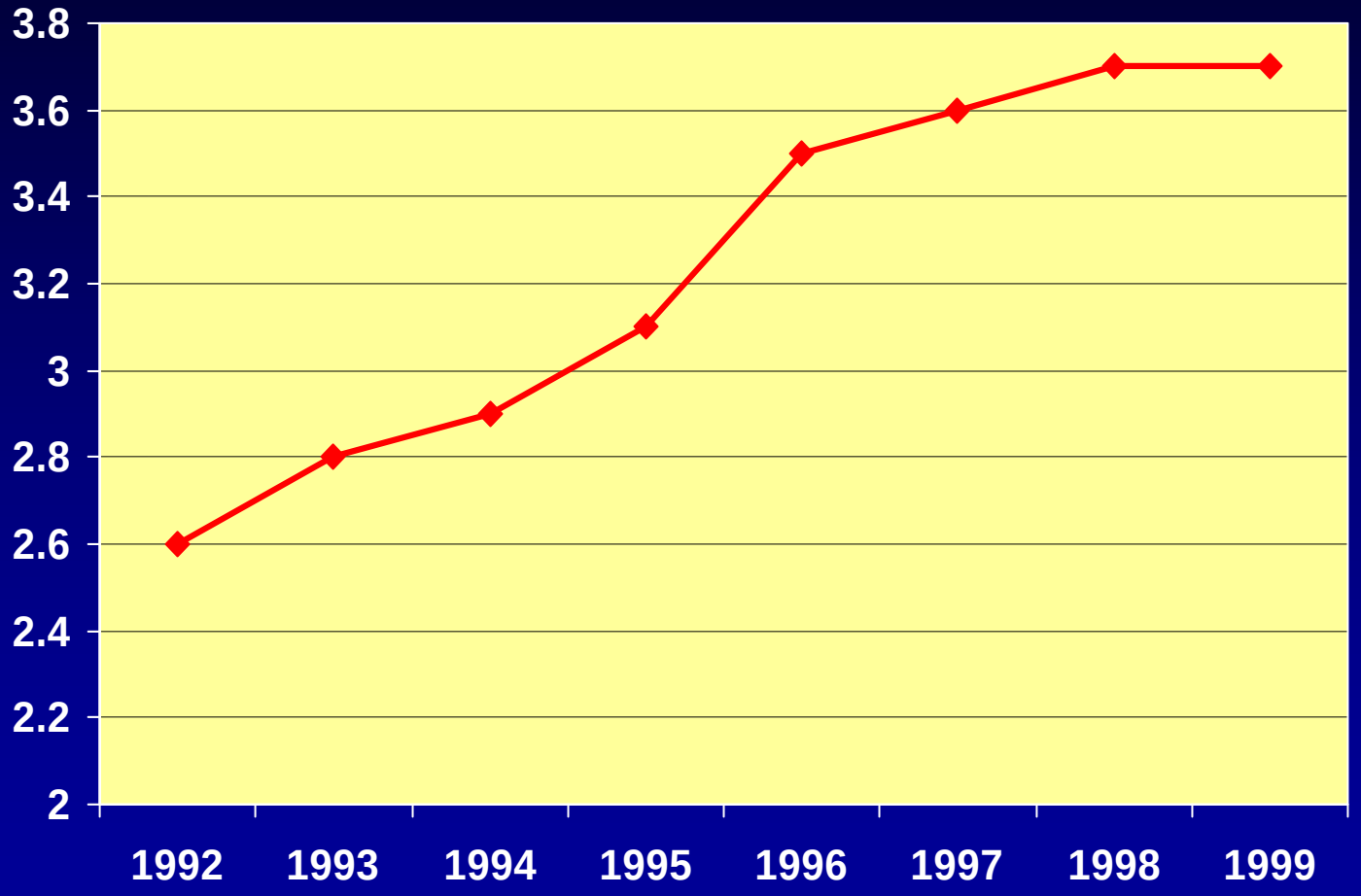


Incidence of Liver cancer: ASR (World)-Male (All ages)

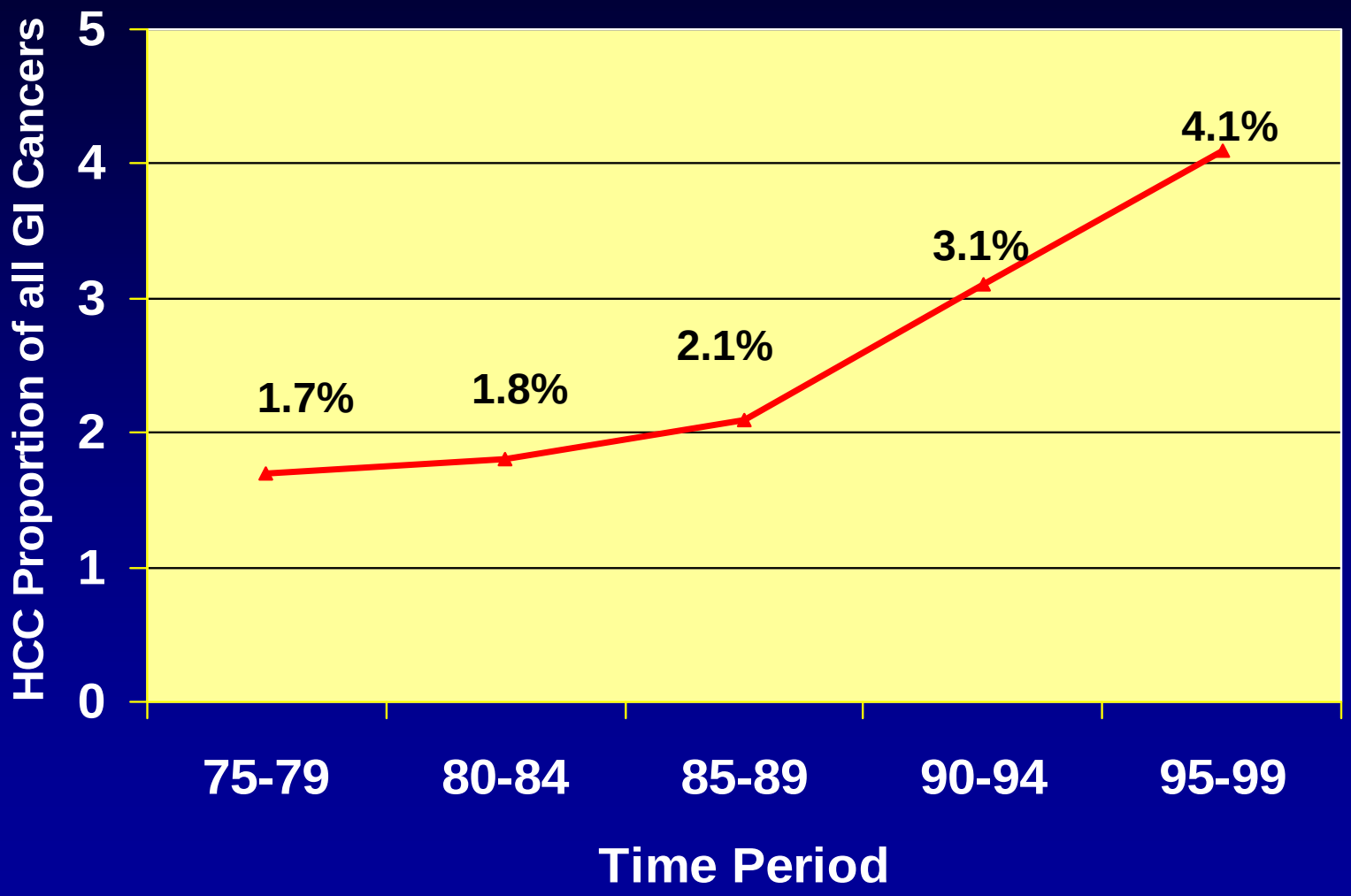


GLOBOCAN (IARC 1998)

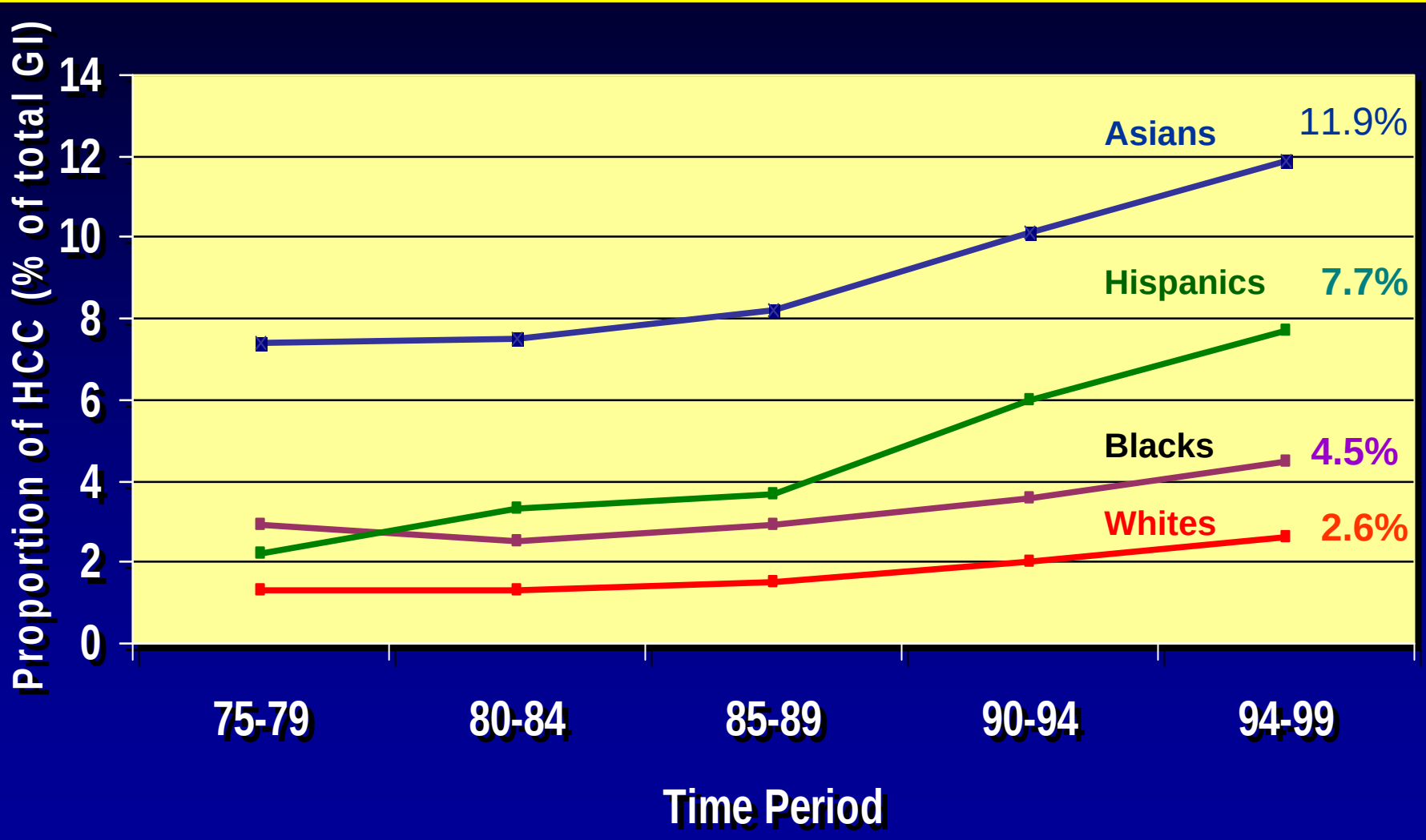
HCC Incidence /100,000 in USA
SEER 1992-1999



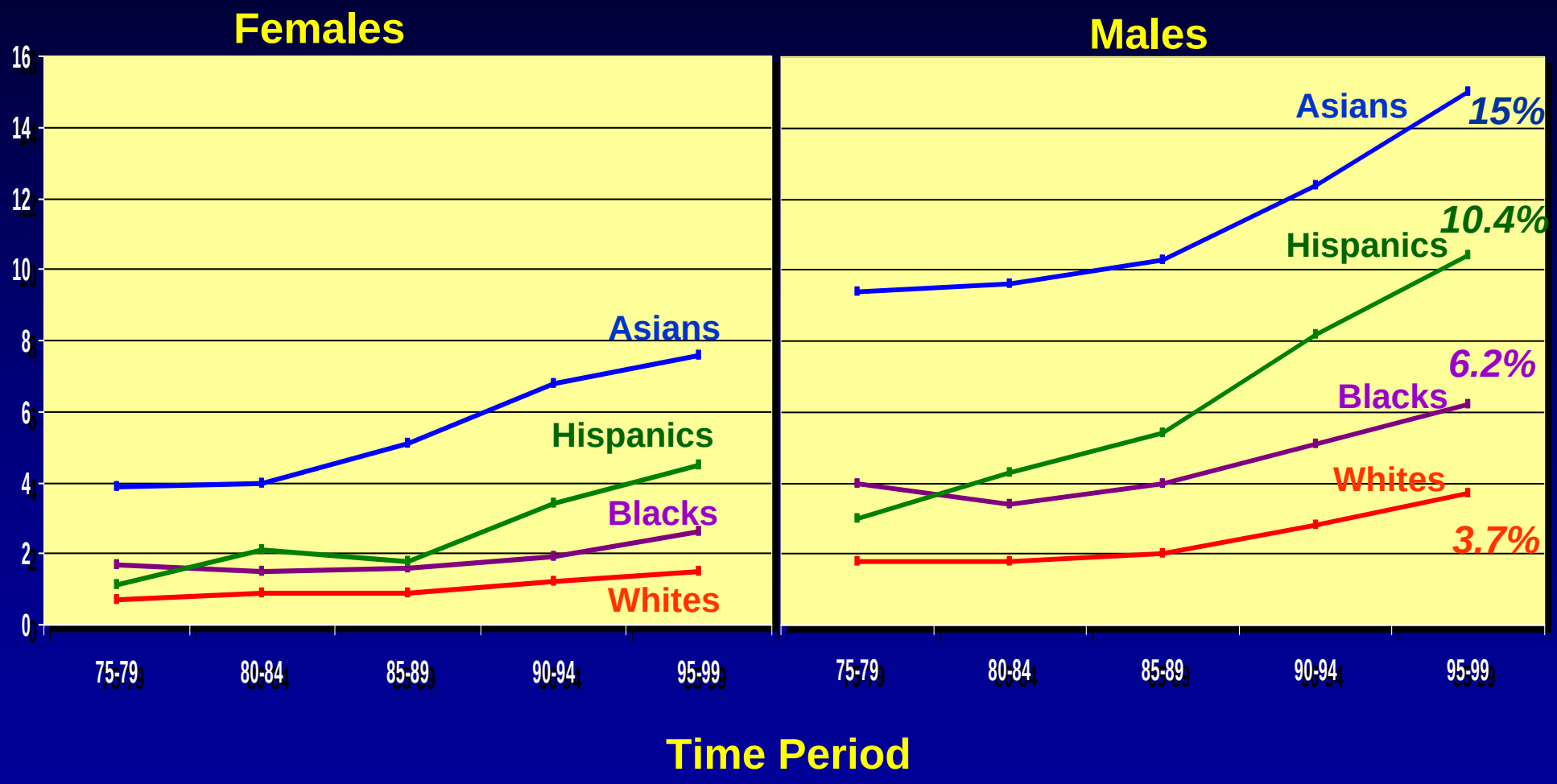
HCC Proportion of the Total GI Cancers
SEER- 1975-1999



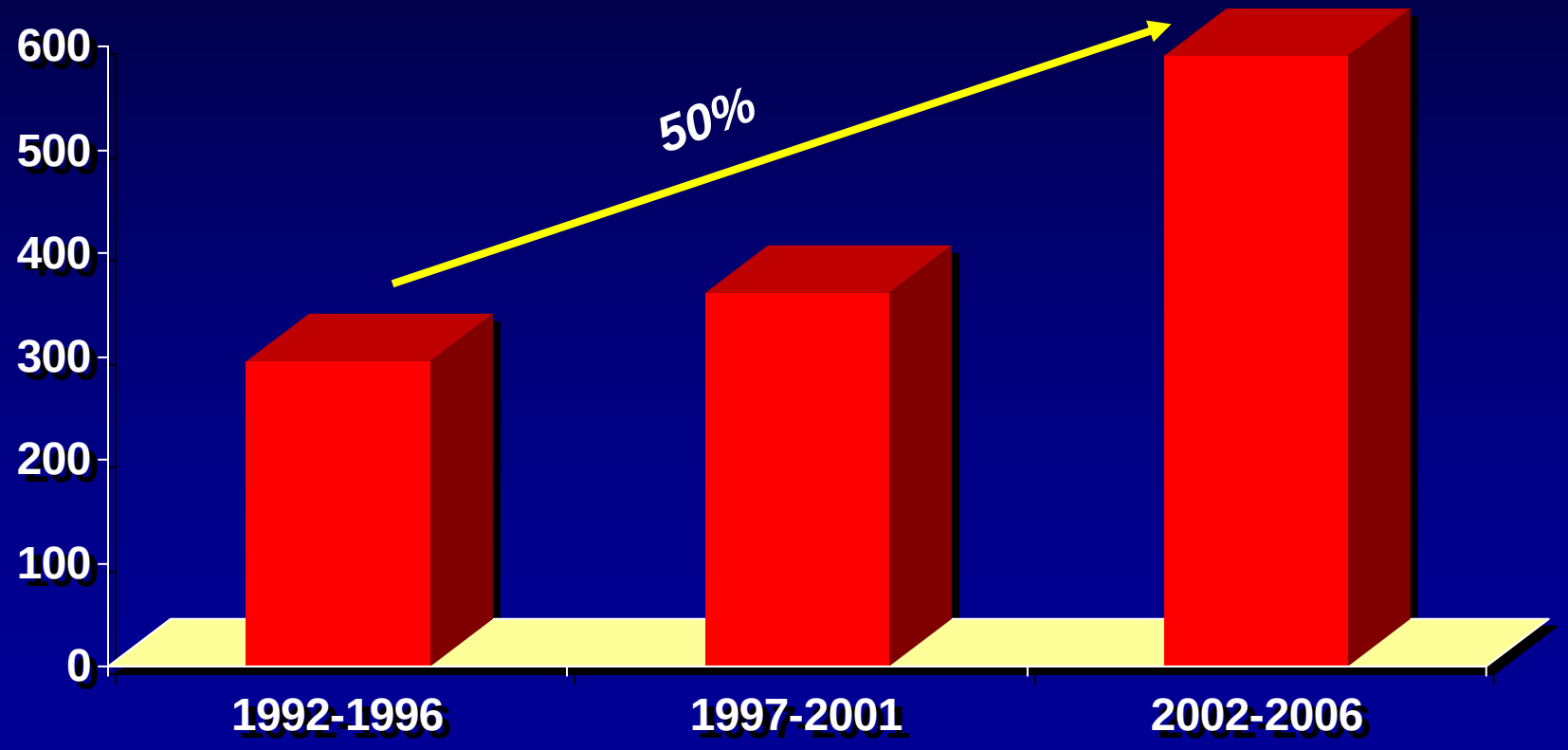
HCC Proportion of the Total GI Cancers
Racial Distribution: SEER 1975-1999



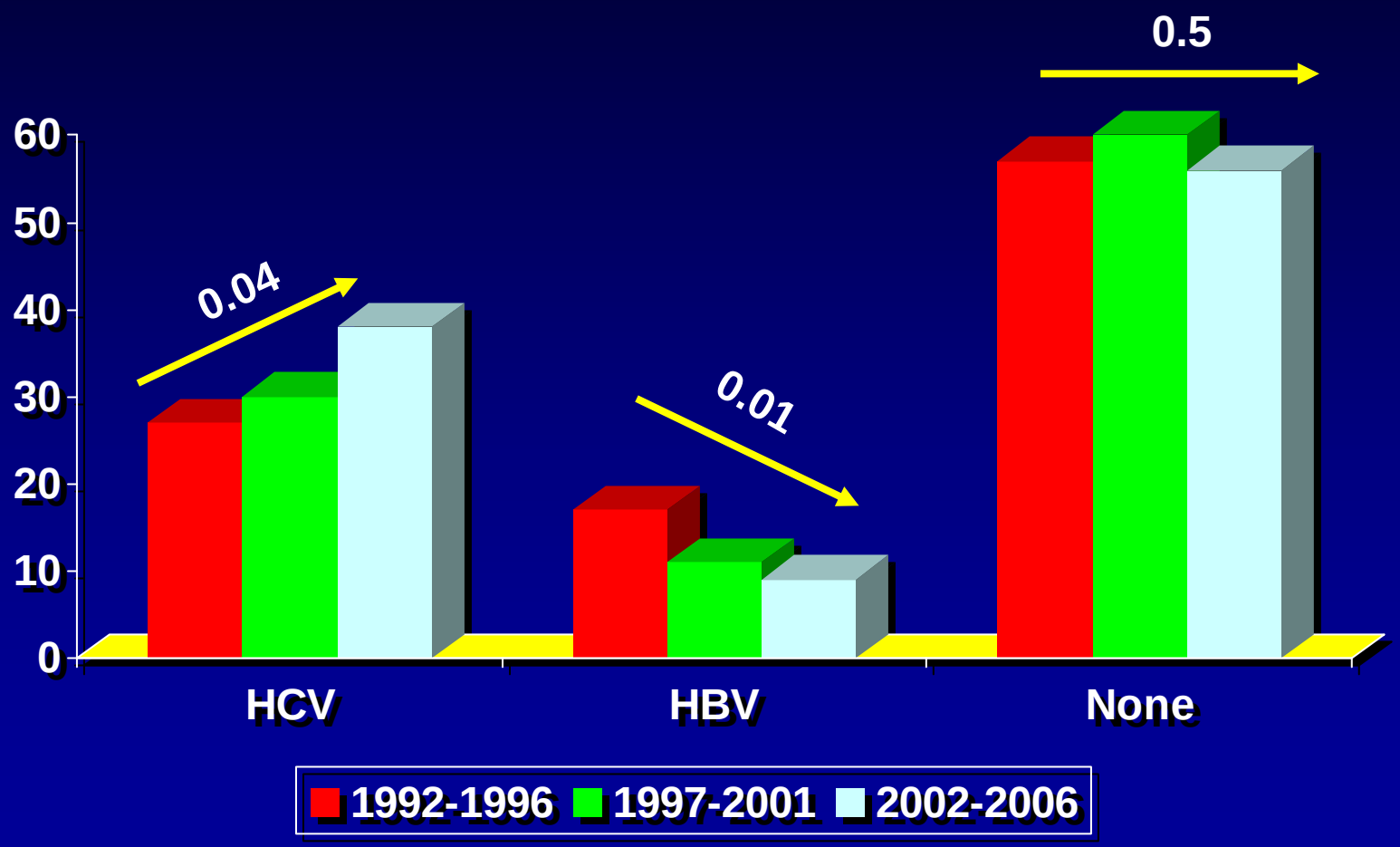
HCC Proportion of the Total GI Cancers Racial and Gender Distribution: SEER- 1975-1999



HCC Patients Referred to MDACC (1992-2006)
N=1200

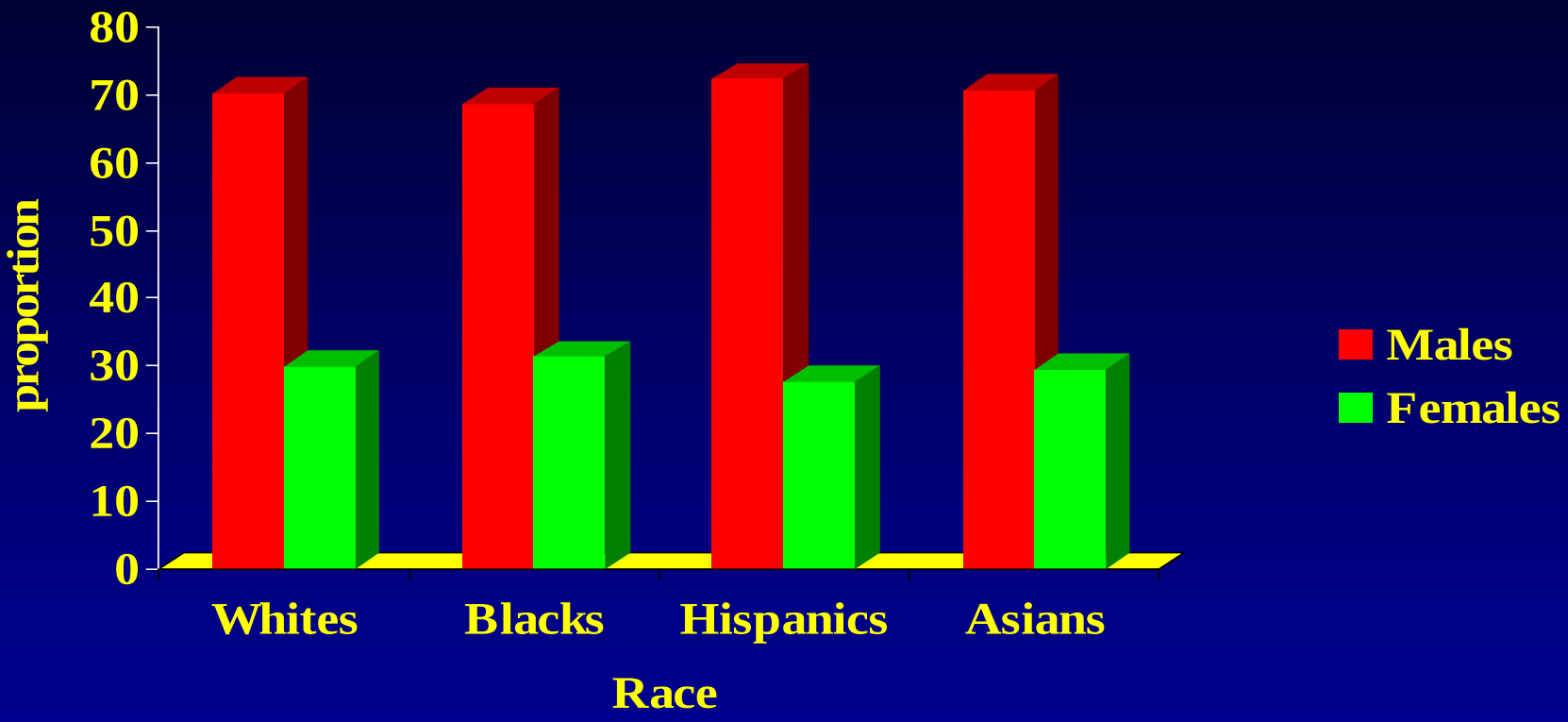


Proportion of HCC Associated With Viral Hepatitis (1992-2006)



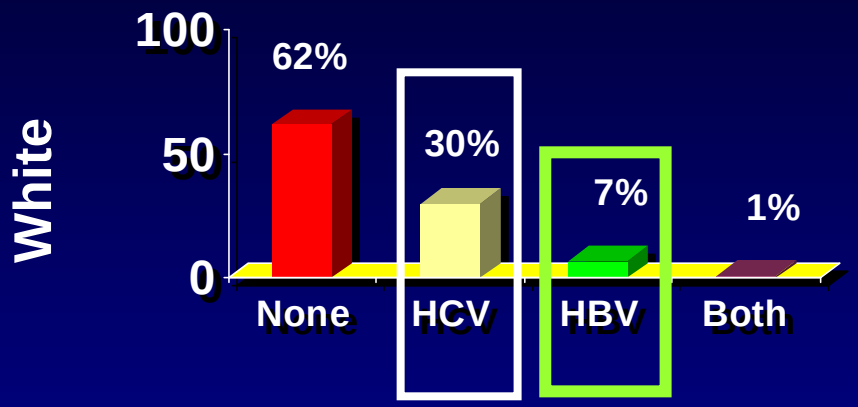
Hassan et al, CJ Gastroentrol

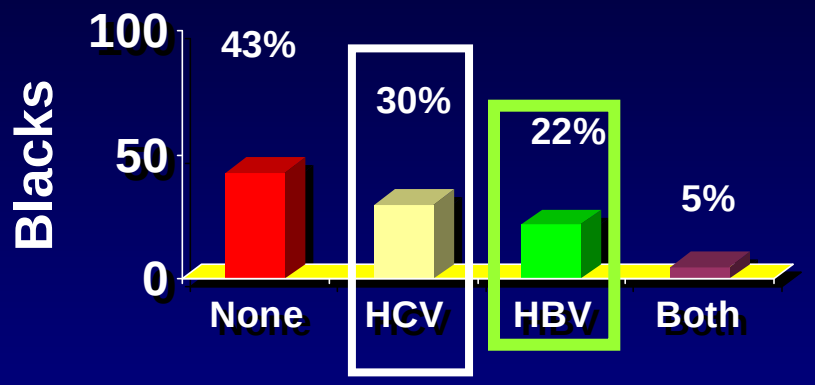
Demographic Characteristics of MDACC HCC Patients

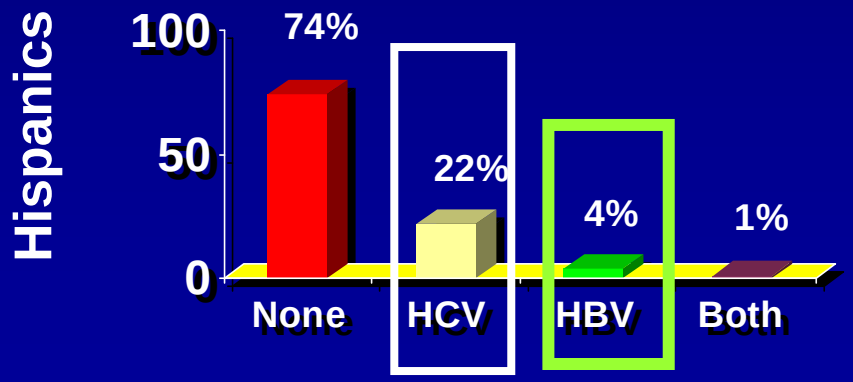


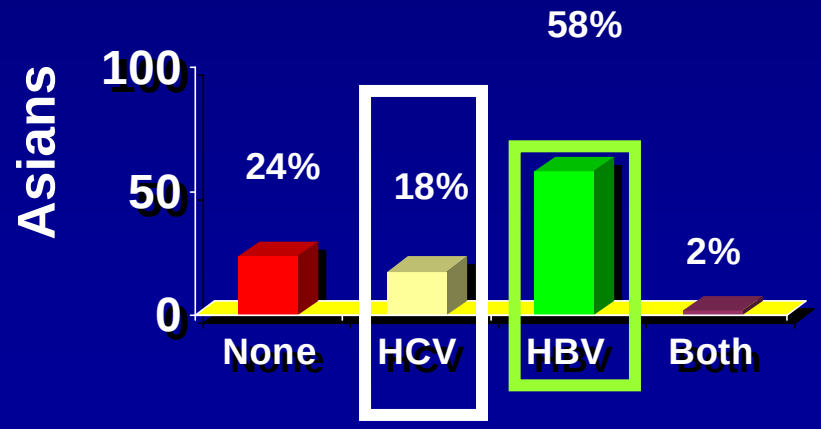
Age	Whites	Blacks	Hispanics	Asians
Mean (± SD)	63.2 ± 12.4	53.6 ± 13.6	63.4 ± 13.2	57.3 ± 12.4

Viral distribution by race in HCC in MDACC (1992-2006)

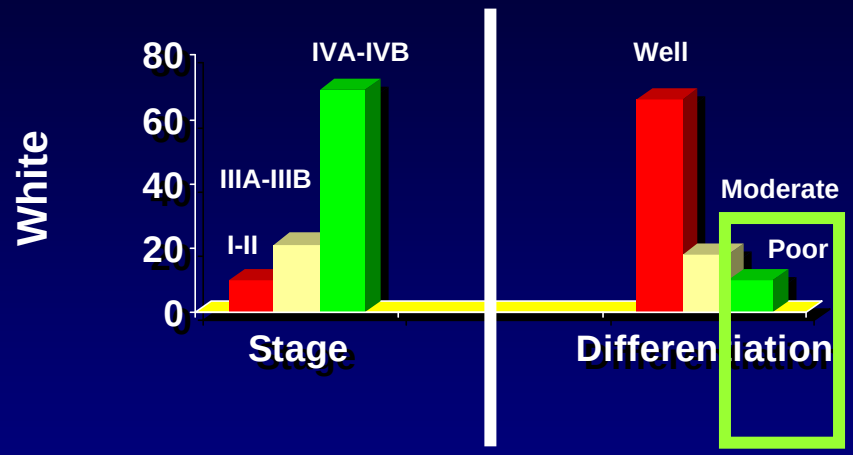


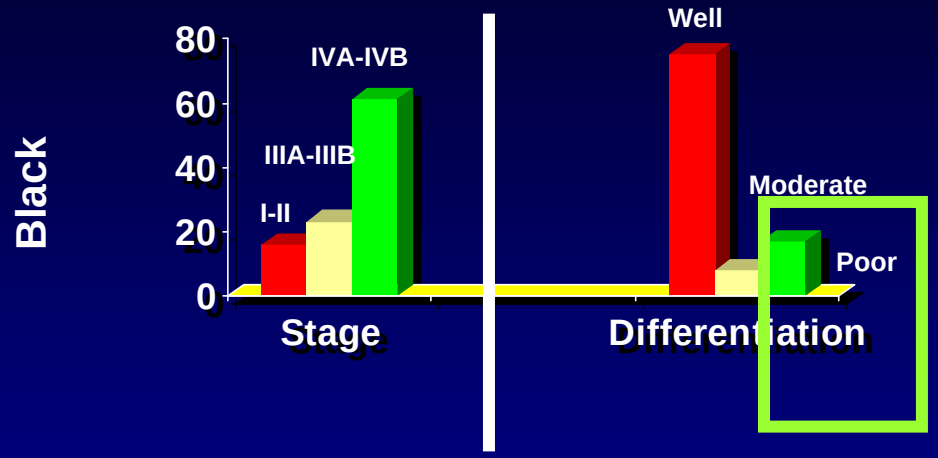


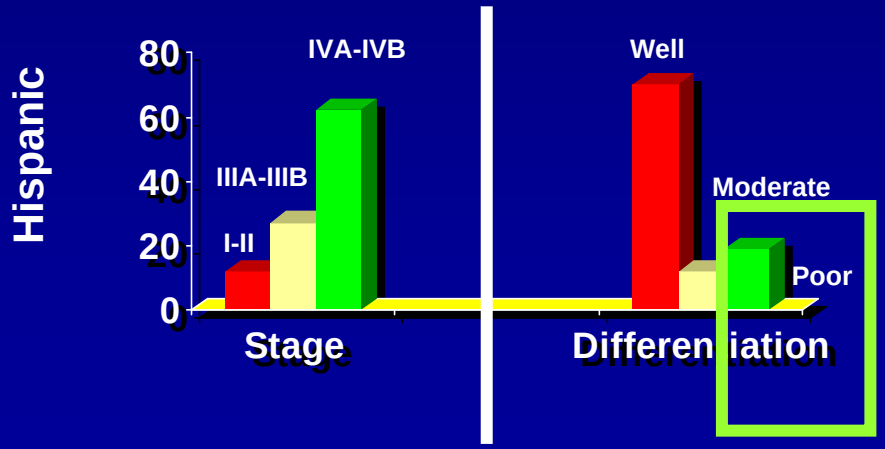


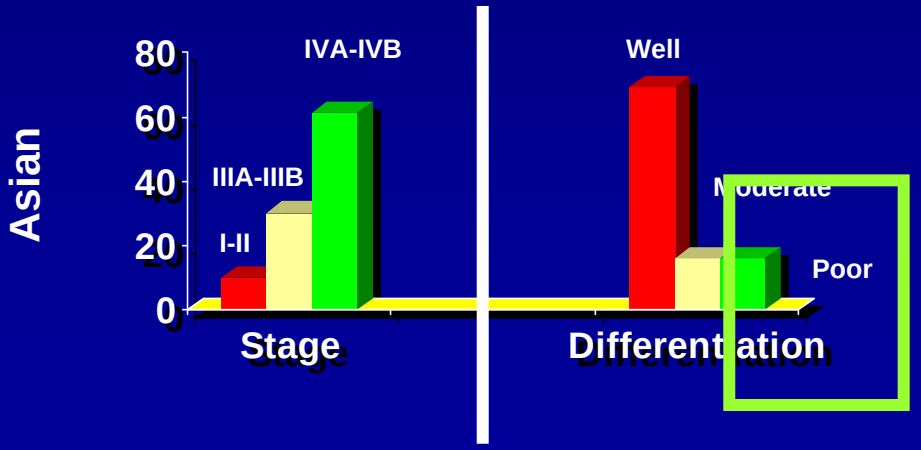


Clinical presentation of HCC in MDACC





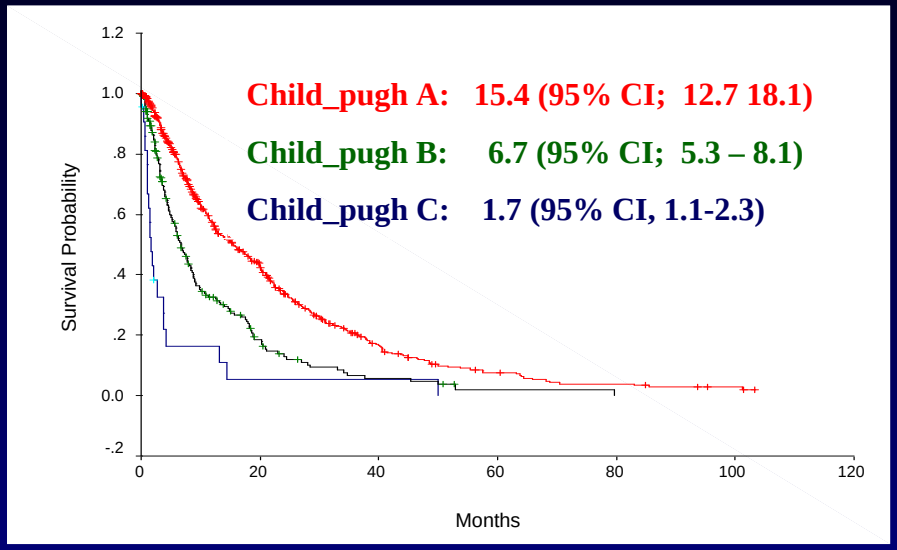


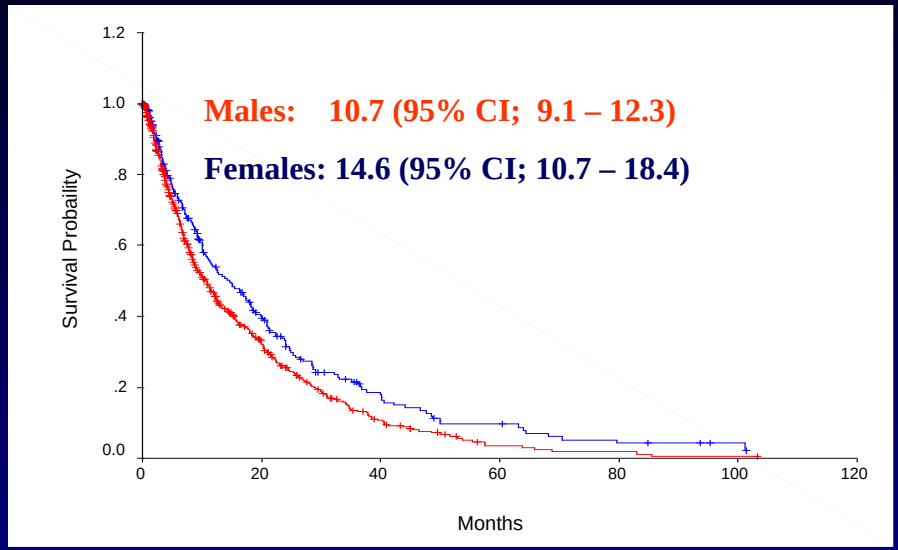


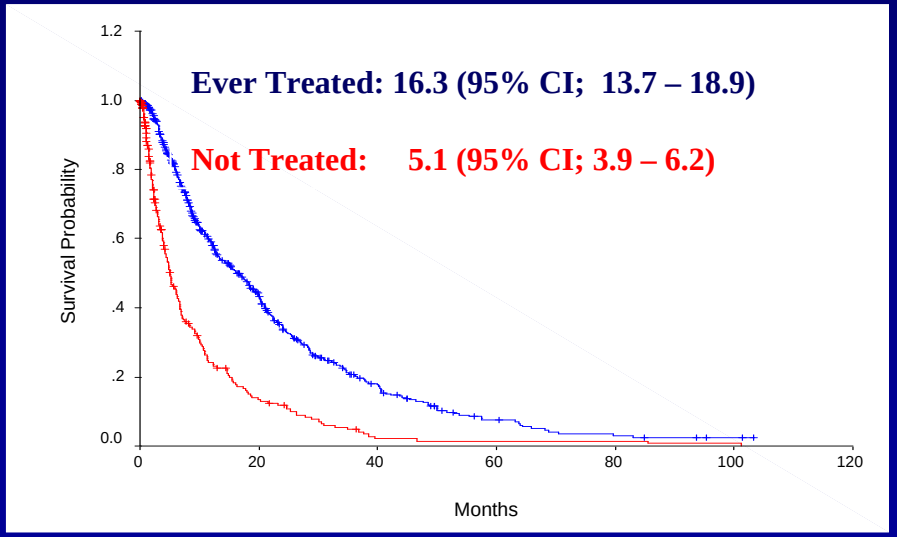
Predictors of HCC Survival
Multivariate Cox Regression

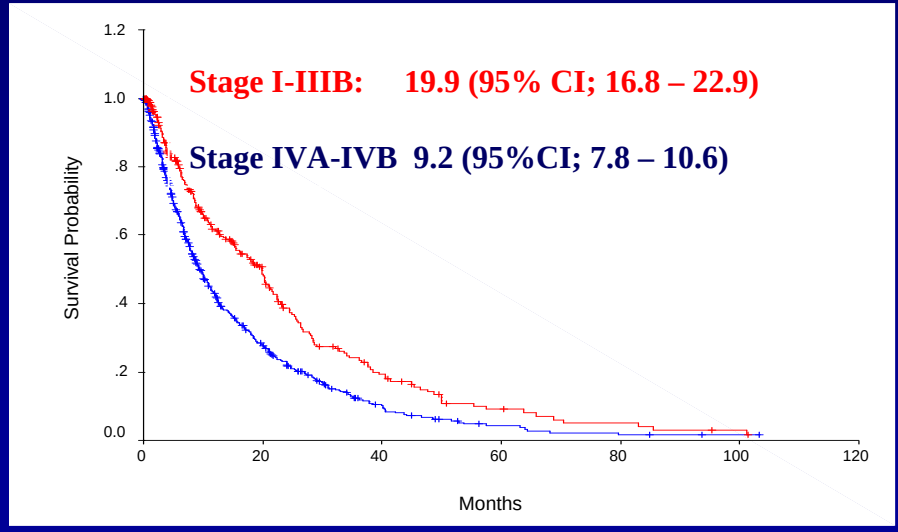
Variable	$\chi 2$ (Wald)	HRR*	95% CI**	P value
Treatment	76.304	0.4	0.3 – 0.5	< 0.0001
Cirrhosis	34.114	1.8	1.5-2.3	< 0.0001
AFP	9.360	1.3	1.1-1.6	0.002
TNM stage	7.832	1.3	1.1-1.6	0.005
Hispanic race	7.671	1.6	1.1-2.2	0.006
Sex (Male)	3.824	1.2	1.0-1.5	0.05
Virus (HCV or HBV)	2.256	1.0	0.8-1.5	0.09
Age (year unit)	0.257	0.8	0.7-1.1	0.6

Predictors of HCC survival



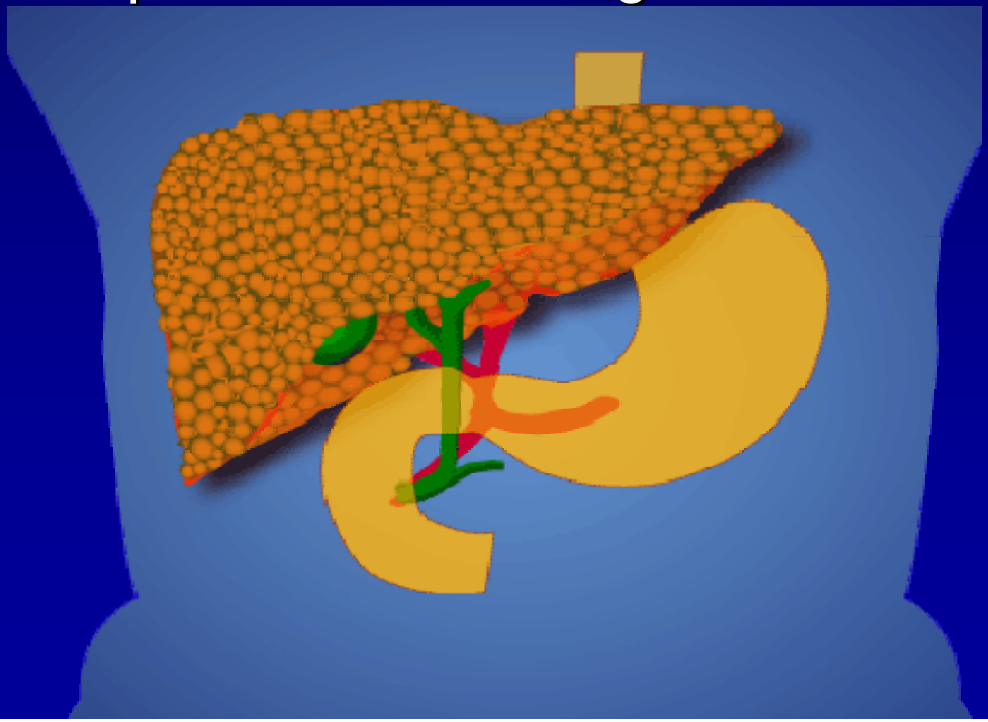






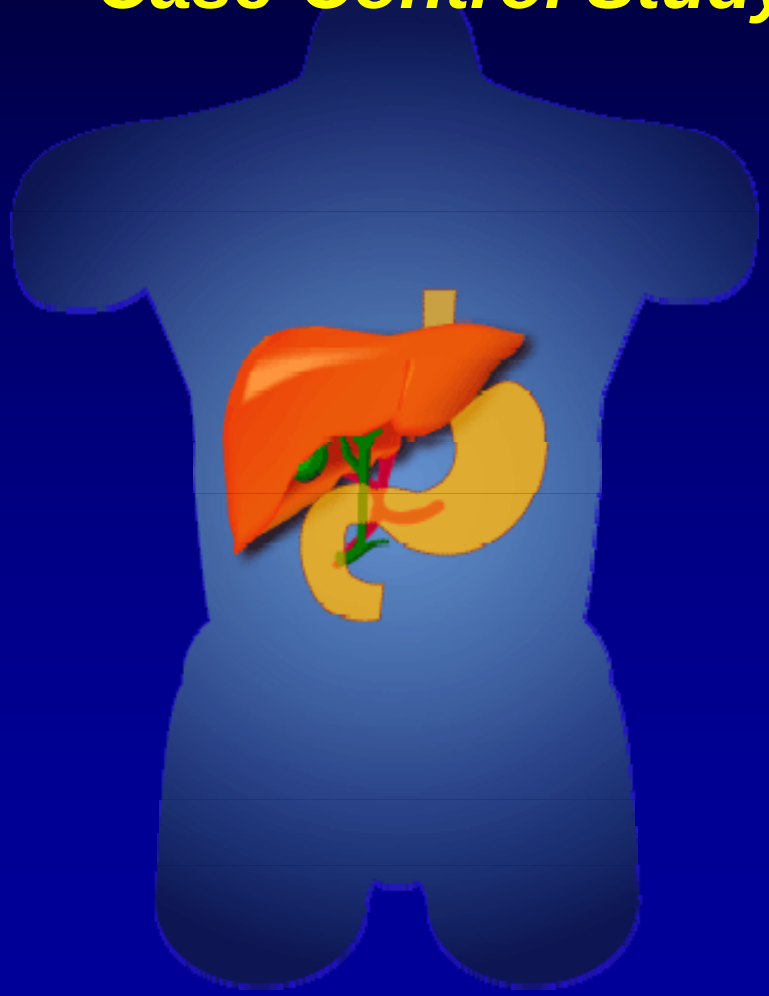
Summary

- The incidence and hospitalizations related to HCC are rising in the US
- Marked Ethnic and gender variations exist
- Younger ages are increasingly affected
- Early detection makes a different in disease prognosis
- The increase in the prevalence of chronic HCV infection is likely the explanation for rising the incidence of HCC in USA



Environmental Risk Factors of Hepatocellular Carcinoma in USA

Case-Control Study

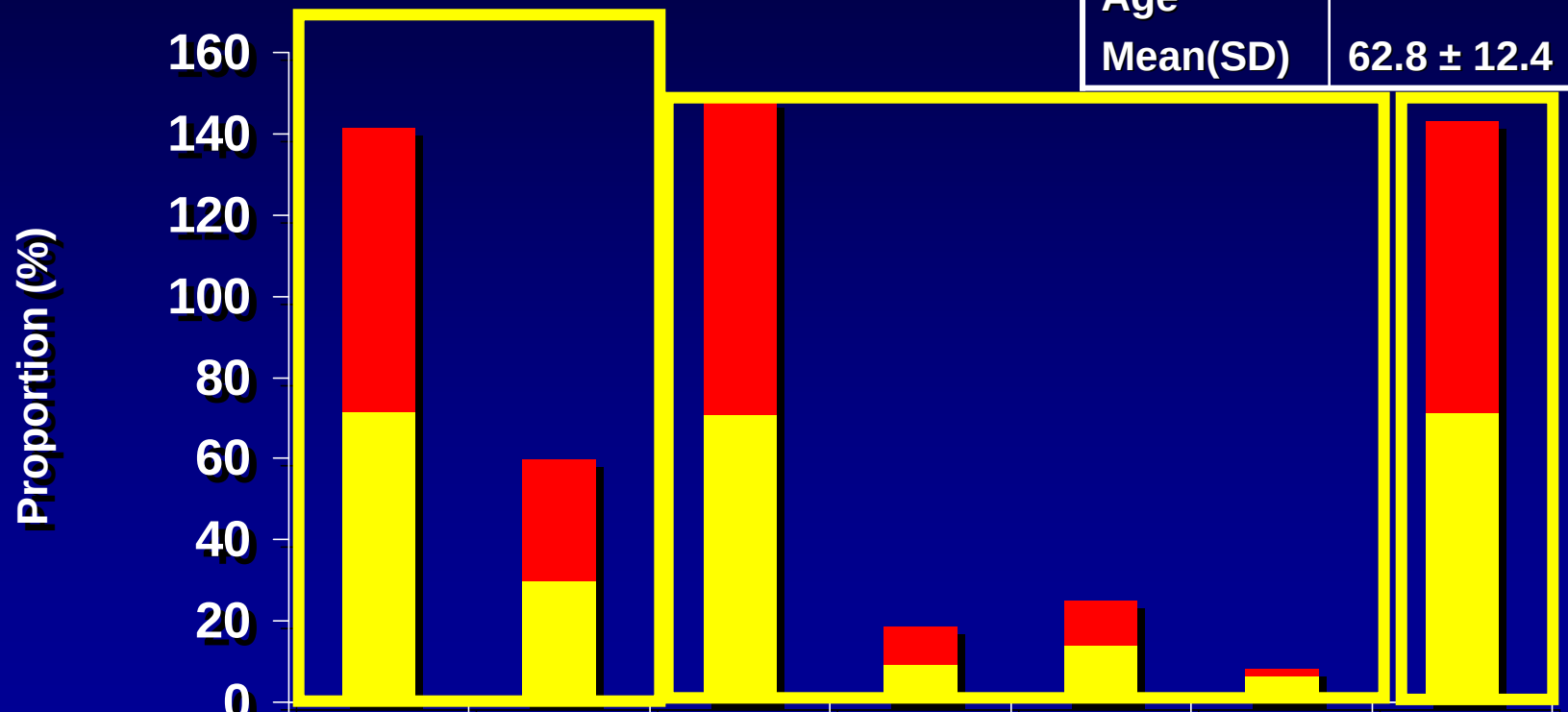


Study Design

- **Study Design:** Hospital-Based Case-Control
- **Place:** University of Texas M.D. Anderson
- **Time Period:** 2001-current
- **Cases:** Pathologically Confirmed New HCC
- **Controls:** Spouses/friends of other non-HCC cancers
- **Conduct:** IRB approved
  - Personal interview (risk & diet questionnaires)
  - Blood sample collection
  - Clinical data collection
- **Statistics:** Unconditional logistic regression

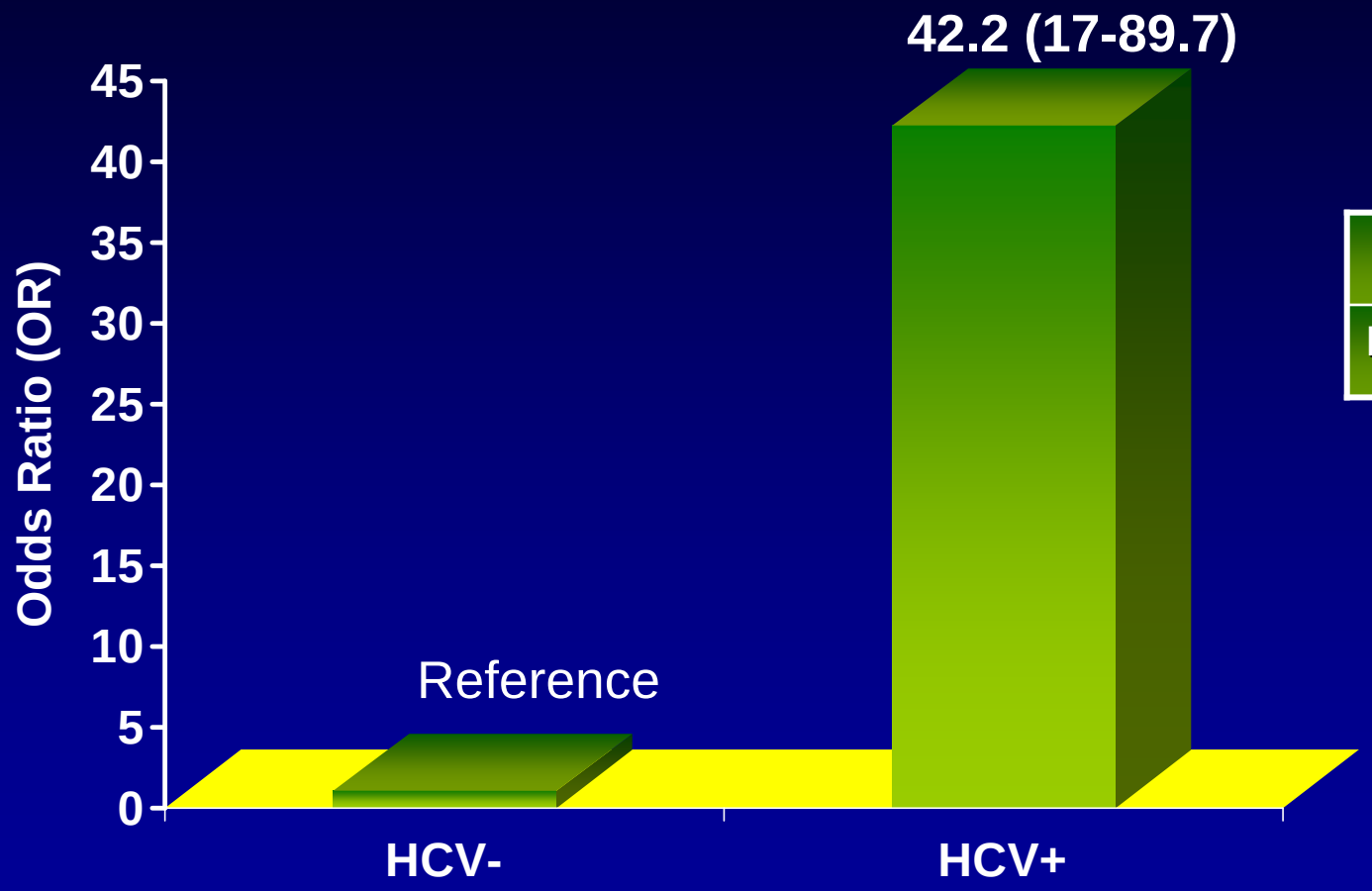
Demographic Characteristics
MDACC Case-Control Study (2001-2007)

	Cases N=355	Controls N=818
Age Mean(SD)	62.8 ± 12.4	60.7 ± 12.4



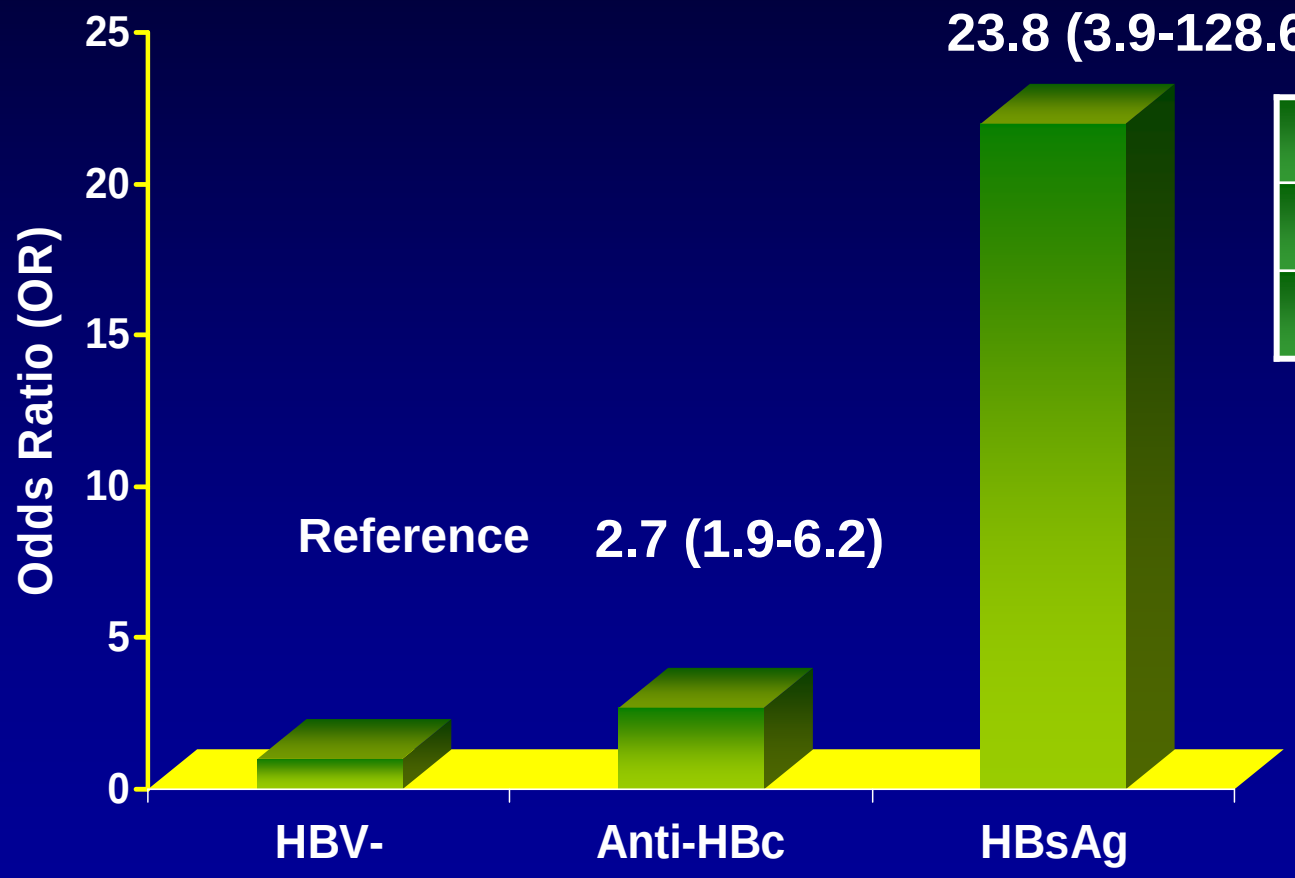
	Males	Females	White	Black	Hispanic	Asian	Texas
Controls	69.8	30.2	77.3	9.6	11	2.1	71.9
HCC	71.5	29.7	70.8	8.9	14	6.3	71.1

Risk of HCV in HCC



	HCC	Controls
HCV%	30.4	1

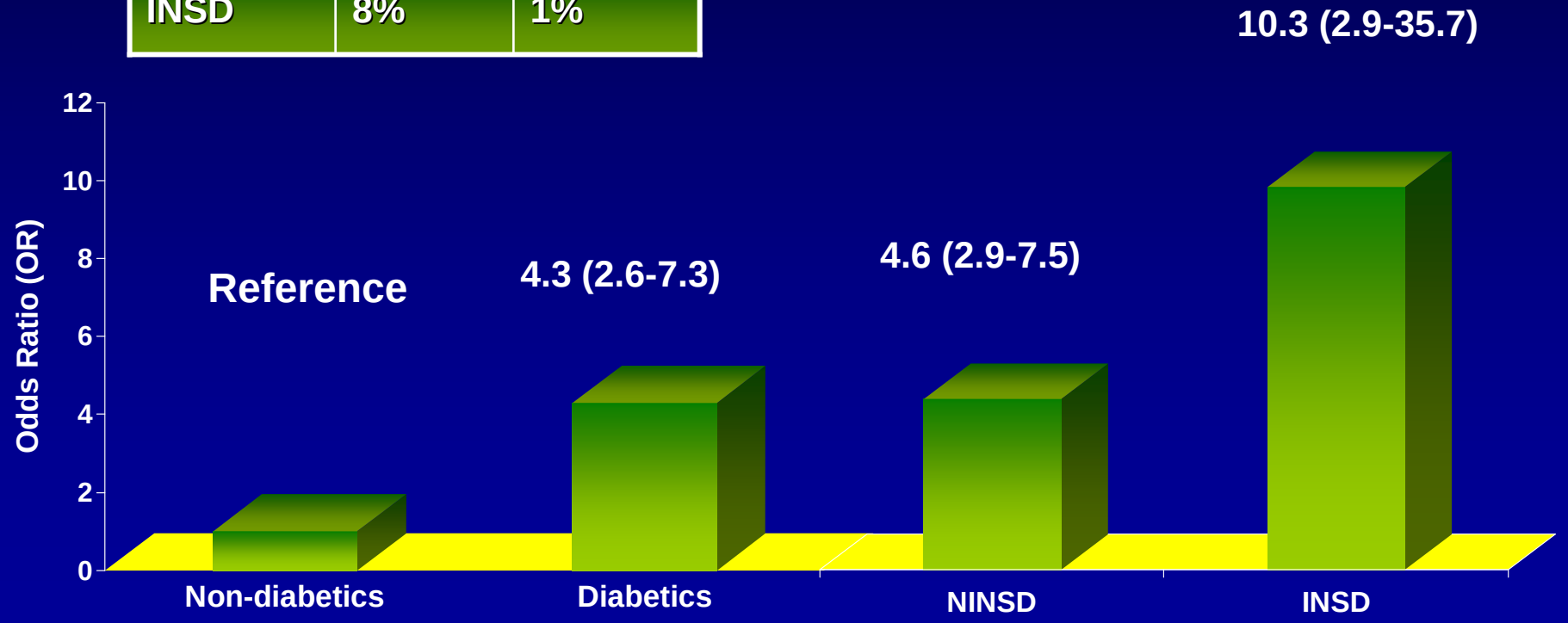
Risk of HBV in HCC



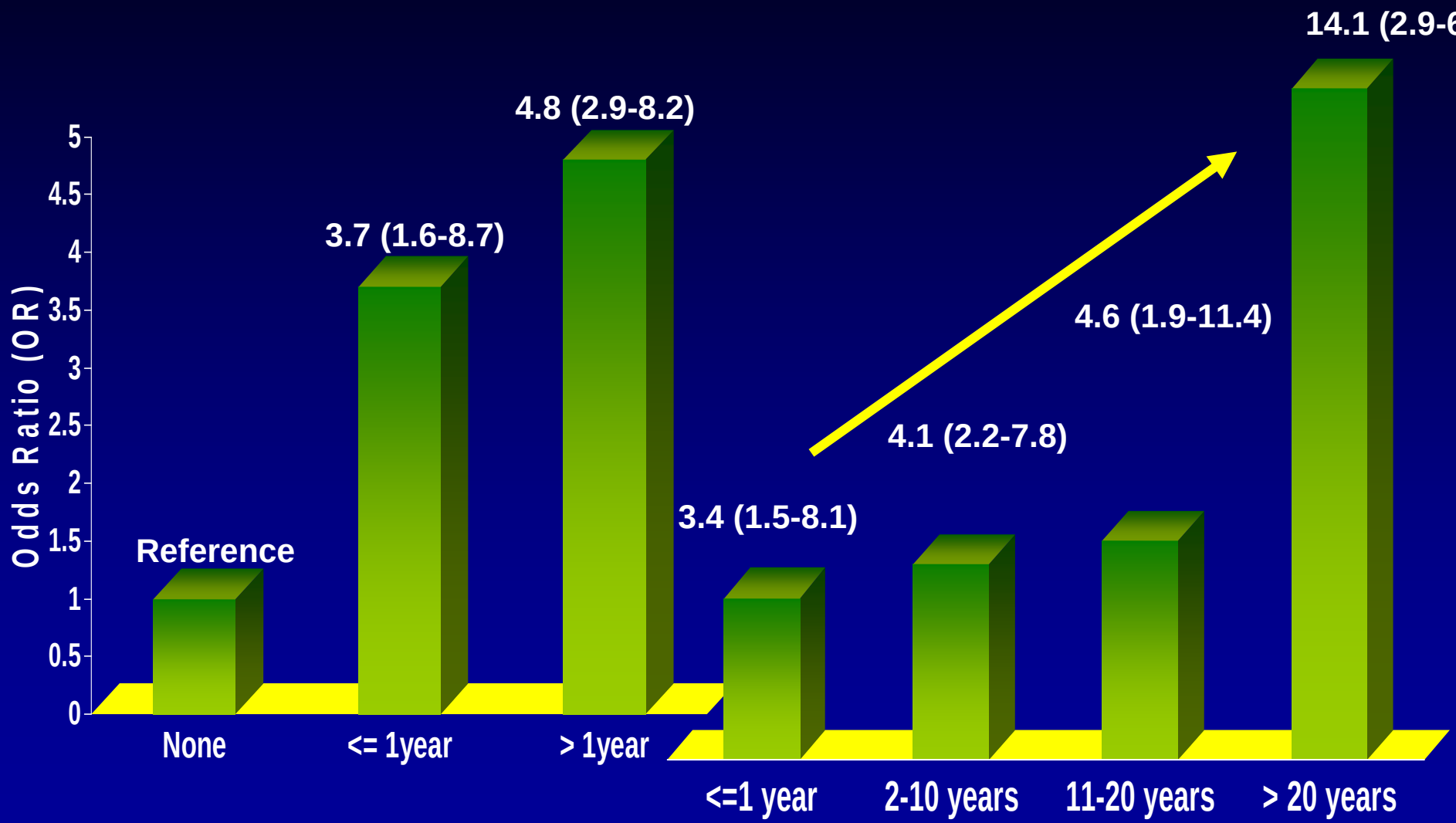
	HCC	Controls
Anti-HBc	22%	3%
HBsAg	7%	0.5%

Risk of Diabetes Mellitus in HCC

	HCC	Controls
Diabetes	33.8%	10%
NINSD	29.1%	9.7%
INSD	8%	1%



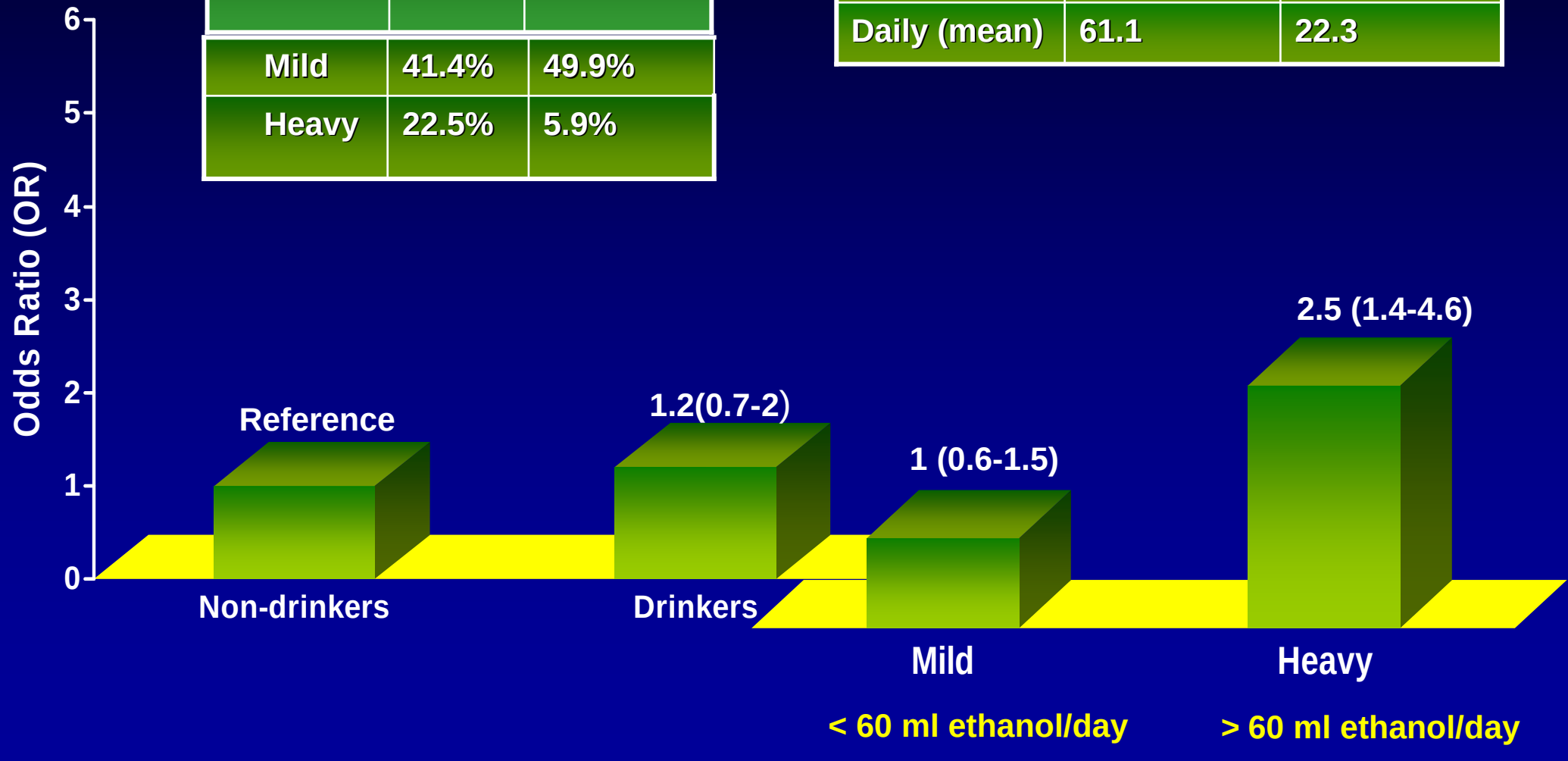
Risk of Diabetes Mellitus in HCC



Risk of Alcohol Consumption in HCC

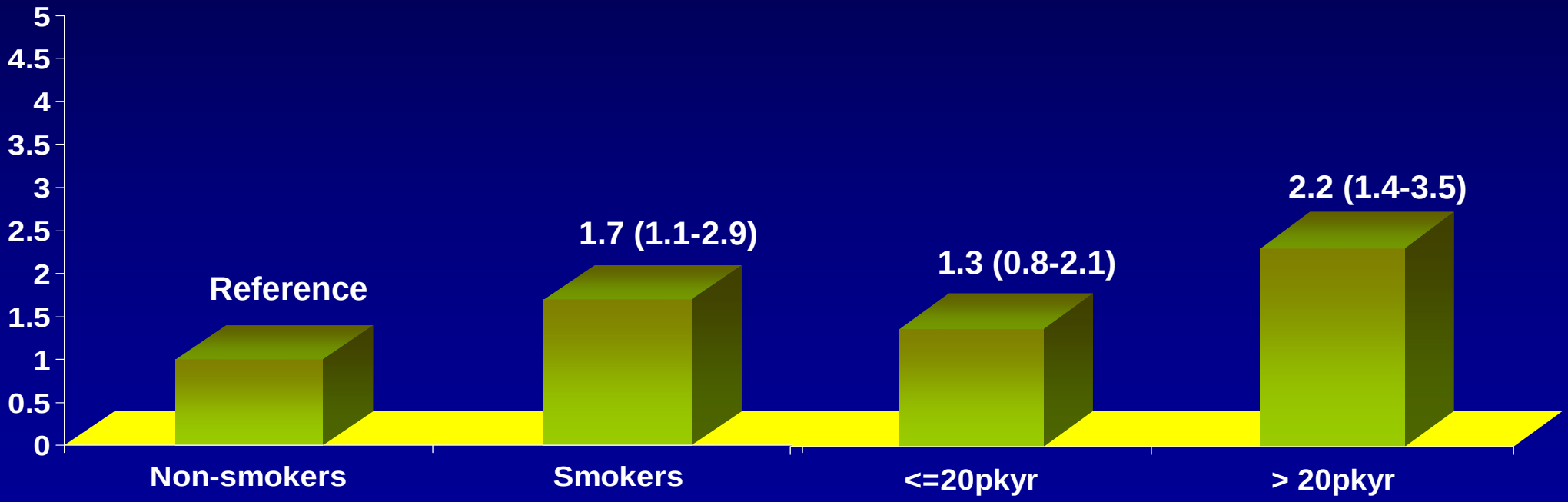
	HCC	Controls
Drinkers	63.9%	55.7%
Mild	41.4%	49.9%
Heavy	22.5%	5.9%

Ethanol/ml	HCC	Controls
Life (mean)	773,214	305,872
Daily (mean)	61.1	22.3



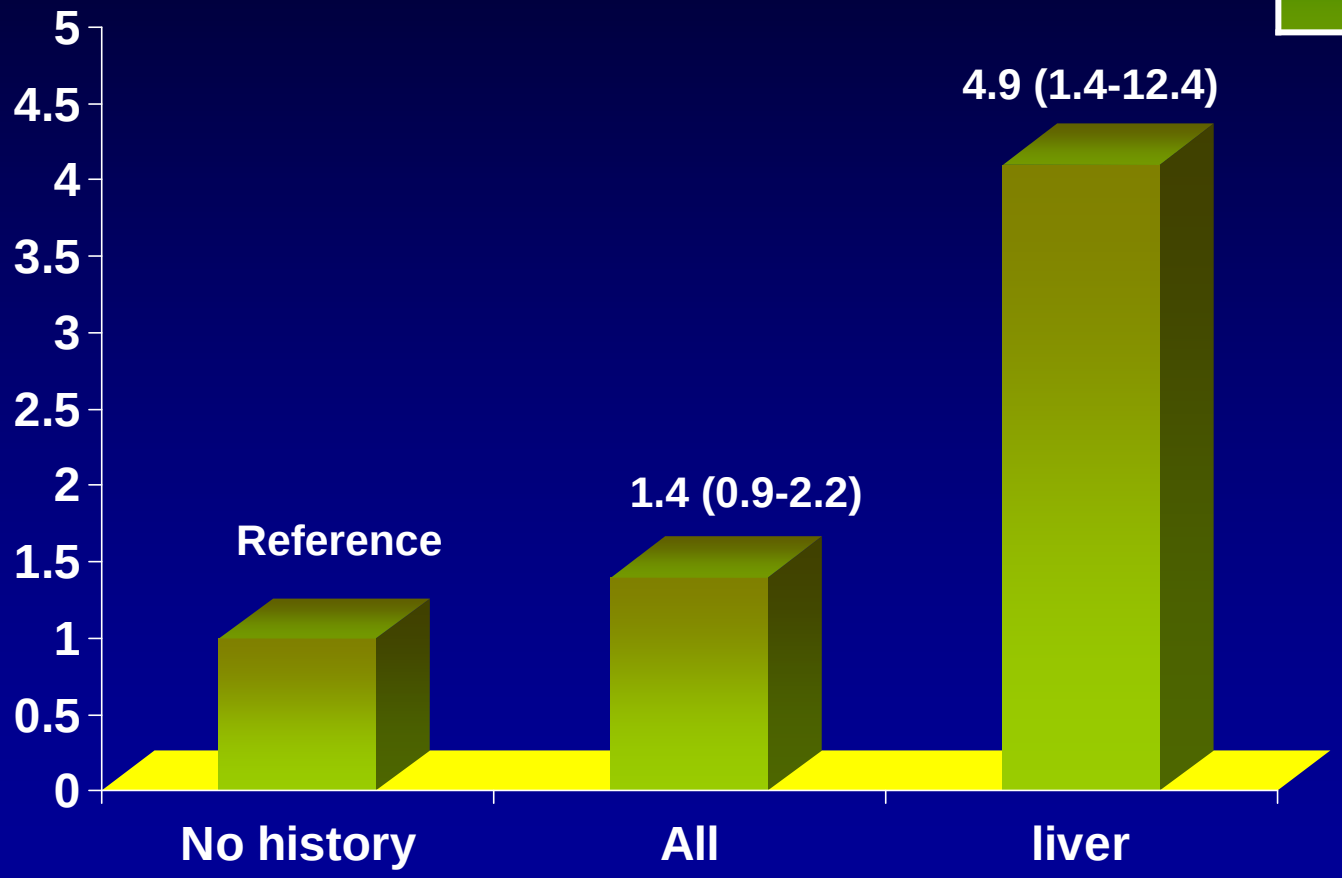
Risk of Cigarette Smoking in HCC

	HCC	Controls
Smoking	67.8%	50.9%

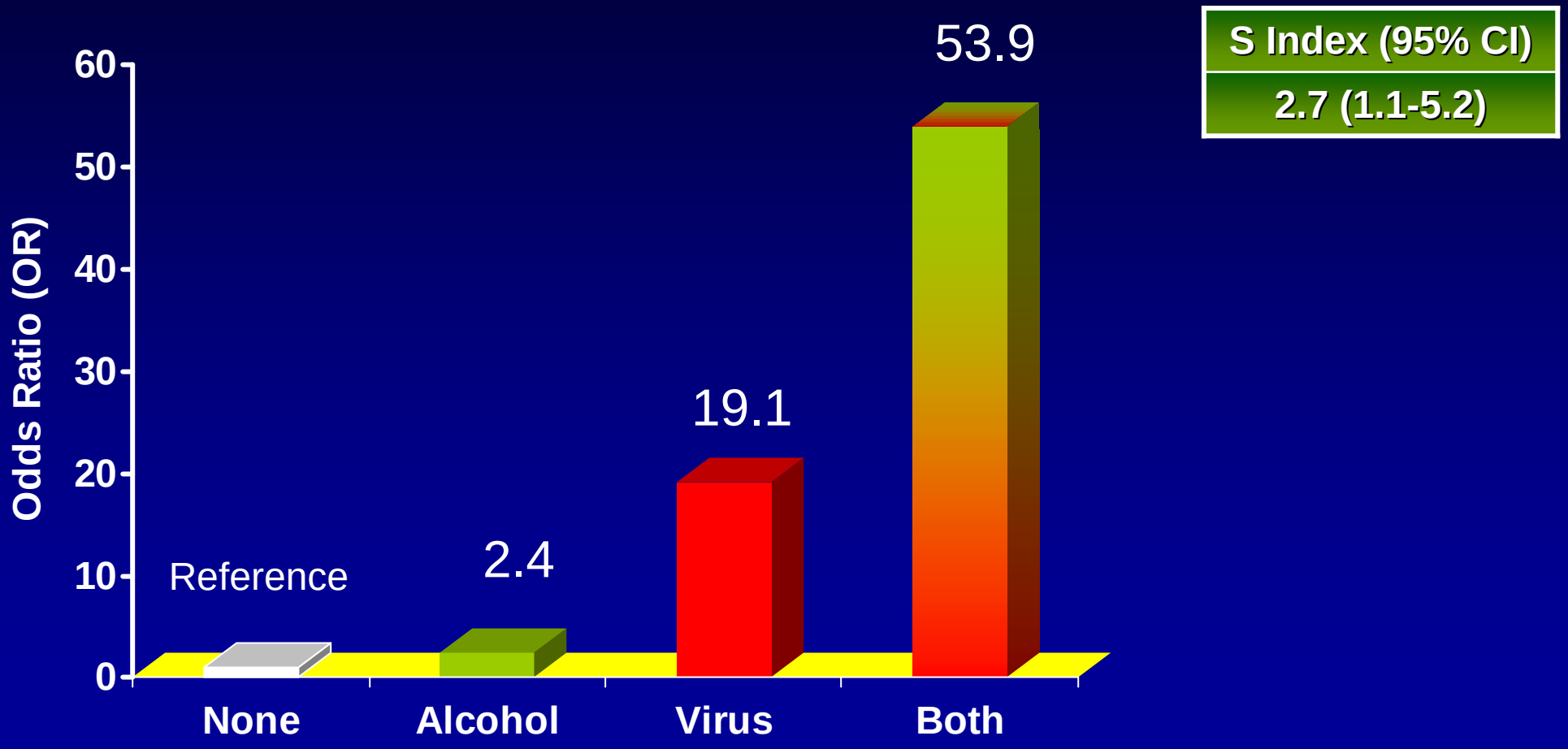


F.D. Family history of cancer & HCC development

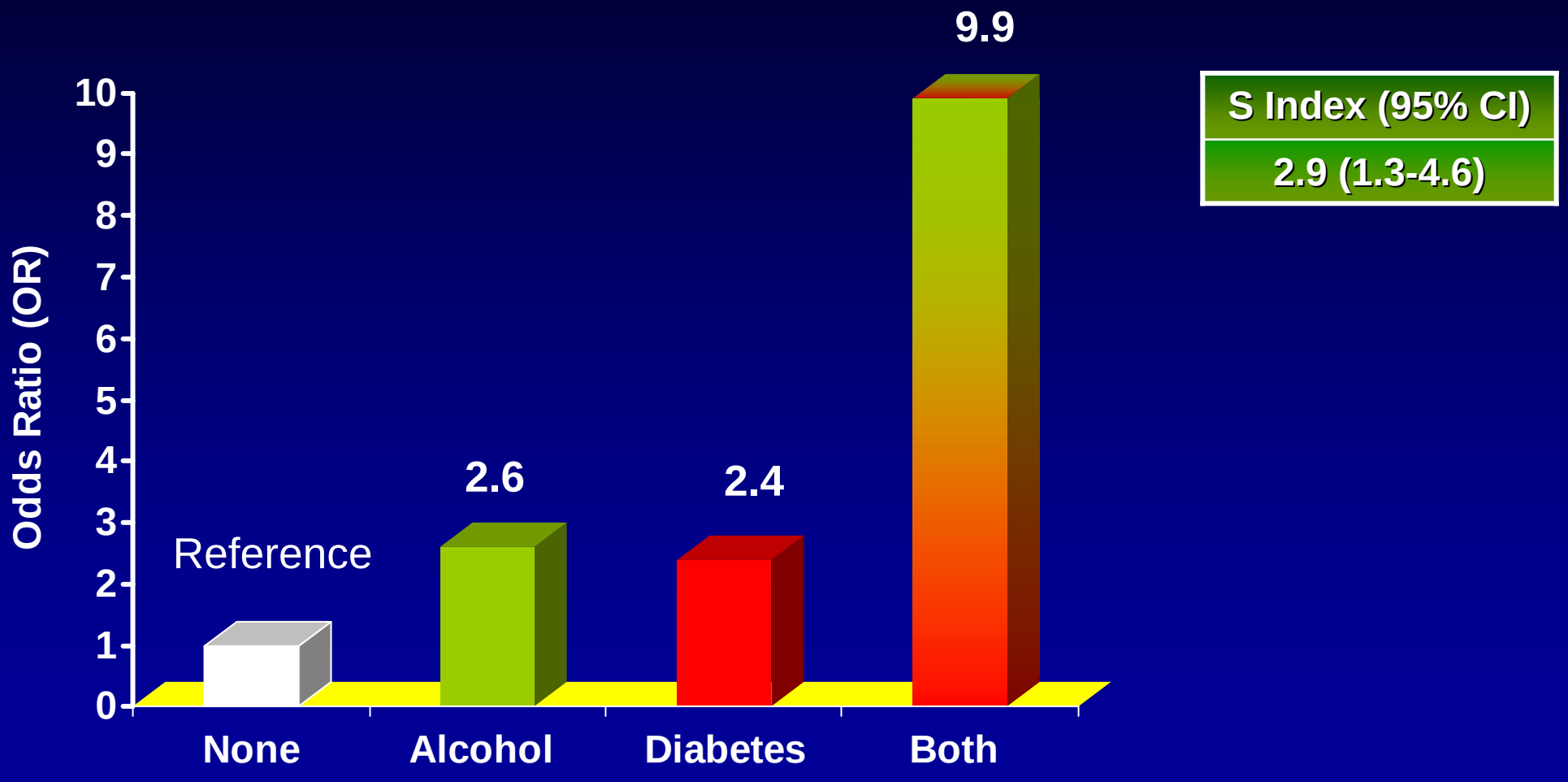
	HCC	Controls
FDHX_Liver	6.8%	1.6%



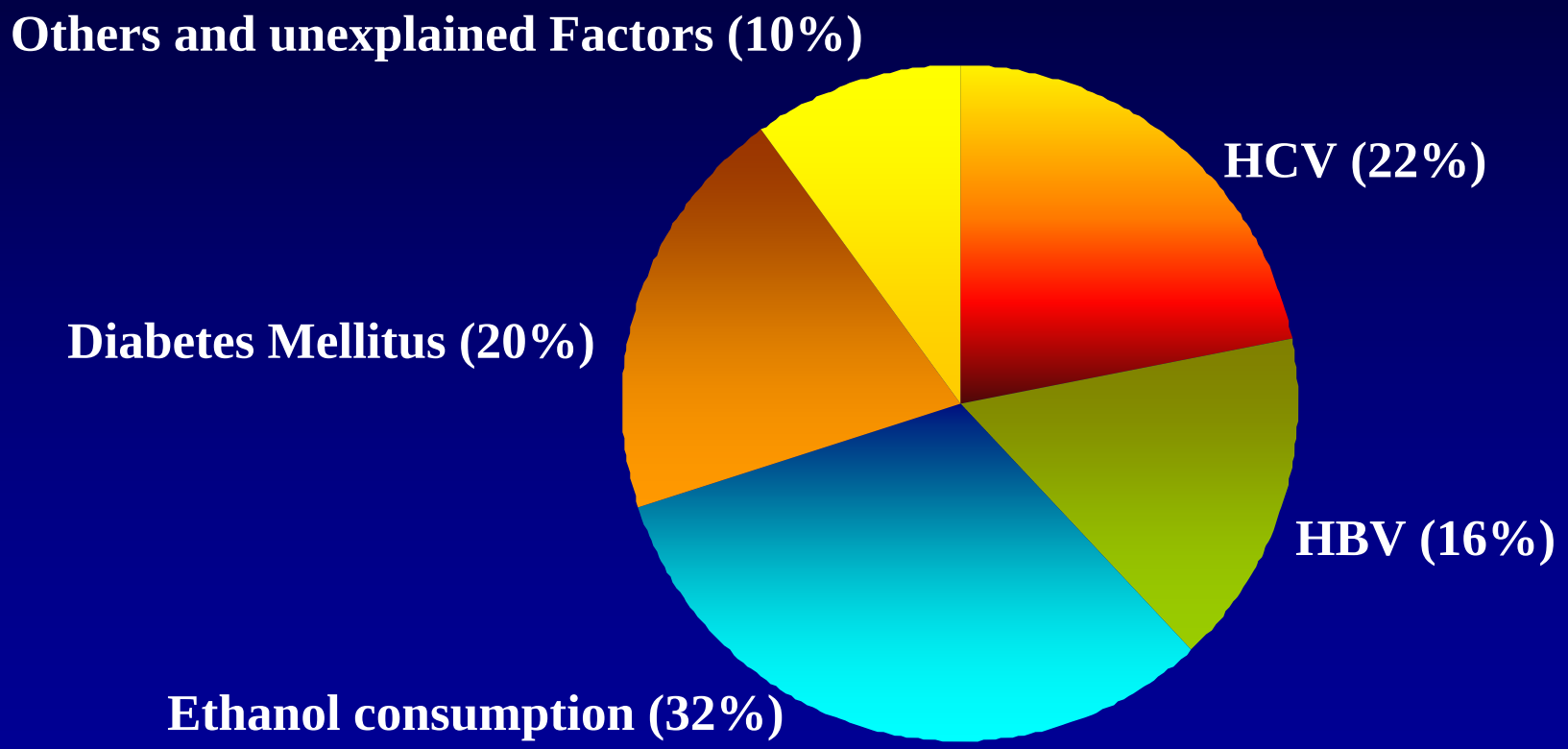
Synergistic Interaction in HCC
Alcohol Consumption with Virus Infection



Synergistic Interaction in HCC
Alcohol Consumption with Diabetes Mellitus



PAR% Explained by HCCC Risk Factors



Summary

- The most significant risk factors of HCC in USA are:
  - ✓ Chronic hepatitis C and B
  - ✓ Heavy alcohol consumption
  - ✓ Diabetes mellitus
  - ✓ Cigarette smoking
  - ✓ Family history of liver cancer
- Significant interaction on the additive scale was noted for
  - ✓ Alcohol consumption with viral hepatitis and
  - ✓ Alcohol consumption with diabetes mellitus
- Other risk factors including obesity, occupational, female hormones, and nutritional have been collected for publication

Evidences for the Genetic role in HCC

- Family history of liver cancer is a significant risk factor of HCC
- Genetic diseases (hemochromatosis and alpha-1-antitrypsin deficiency are related to HCC
- Chromosomal abrasions have been detected in HCC patients
- Alcohol play role in virus mediated carcinogenesis

Rational (Advantages) to study genetic factors of HCC

- Early detection
- Identify methods for screening
- Establish cancer diagnosis
- Predict clinical outcome
- Identify appropriate treatment and prevention
- Identify high risk population

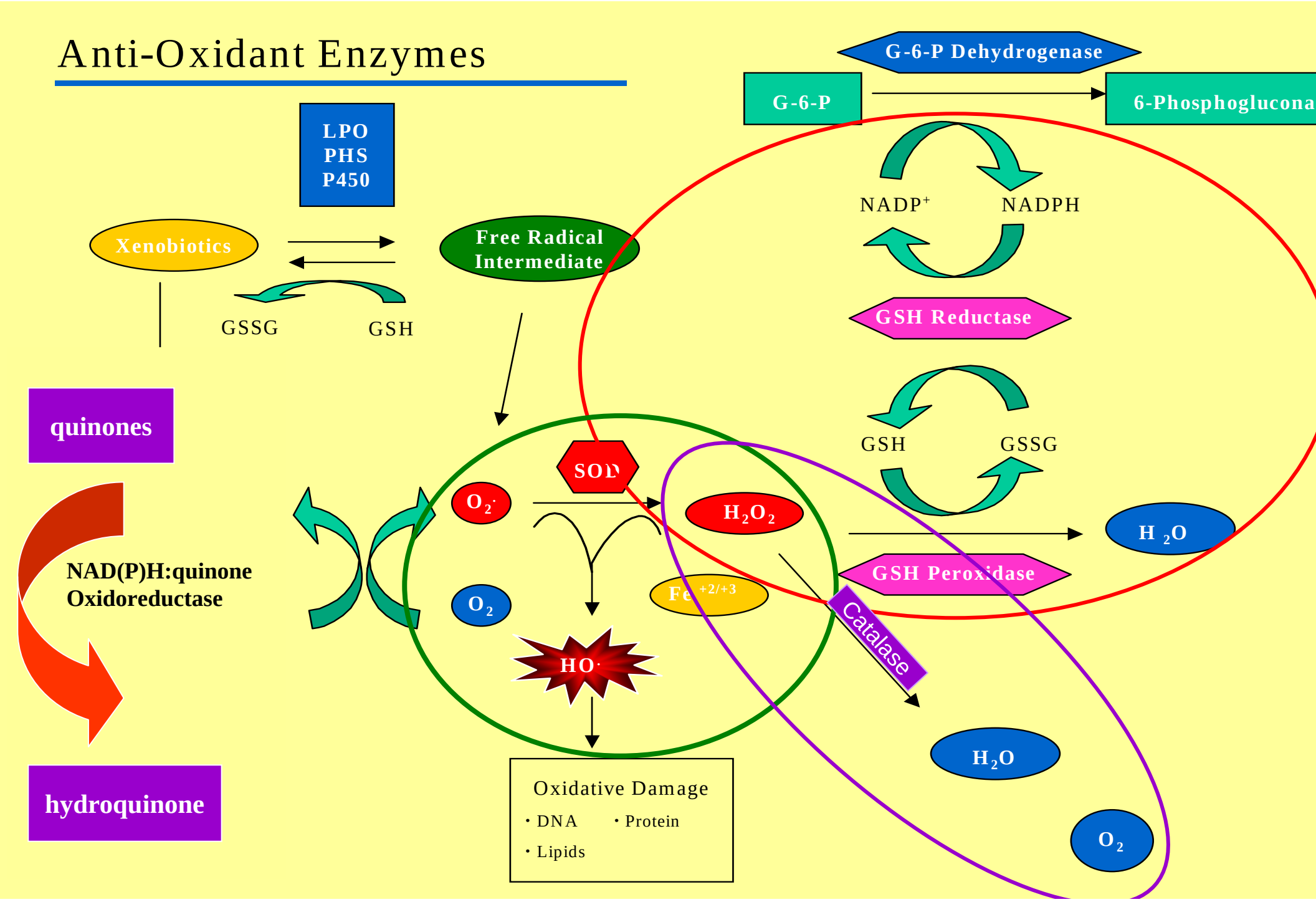
Molecular Epidemiology of HCC
MDACC case-control study

- Oxidative stress and inflammation have been suggested to play important roles in the liver injury induced by most HCC risk factors

- Oxidative stress, imposed either directly by HCC risk factors or by the host- immune response will lead to inflammatory liver injury

- During chronic inflammation, hepatocytes are destroyed and regenerated incessantly. These processes cause perpetual damage to DNA of the host and induce genomic instability, along with enhanced cell proliferation, resistance to apoptosis as well as stimulation of angiogenesis

Anti-Oxidant Enzymes

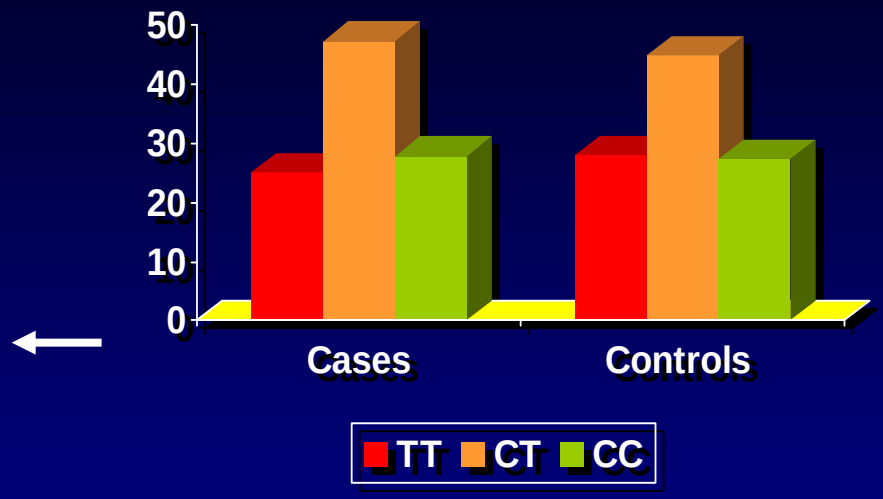


Catalase Gene (*CAT*)

- CAT is a heme-containing peroxisomal enzyme
- It has 13 exons and located on chromosome 11p13
- Most abundant in the liver, kidney and RBCs
- Primary defense against oxidative stress (decompose H_2O_2 to O_2 and H_2O)
- Several mutations and polymorphisms reported
- Mostly associated with acatalasemia (↓ RBCs catalase 0.2-4%)
- A C→T polymorphism at – 262 base pair from transcription start site
- CC and CT alleles correlated with lower level of transcription factor binding, reporter gene transcription and blood catalase

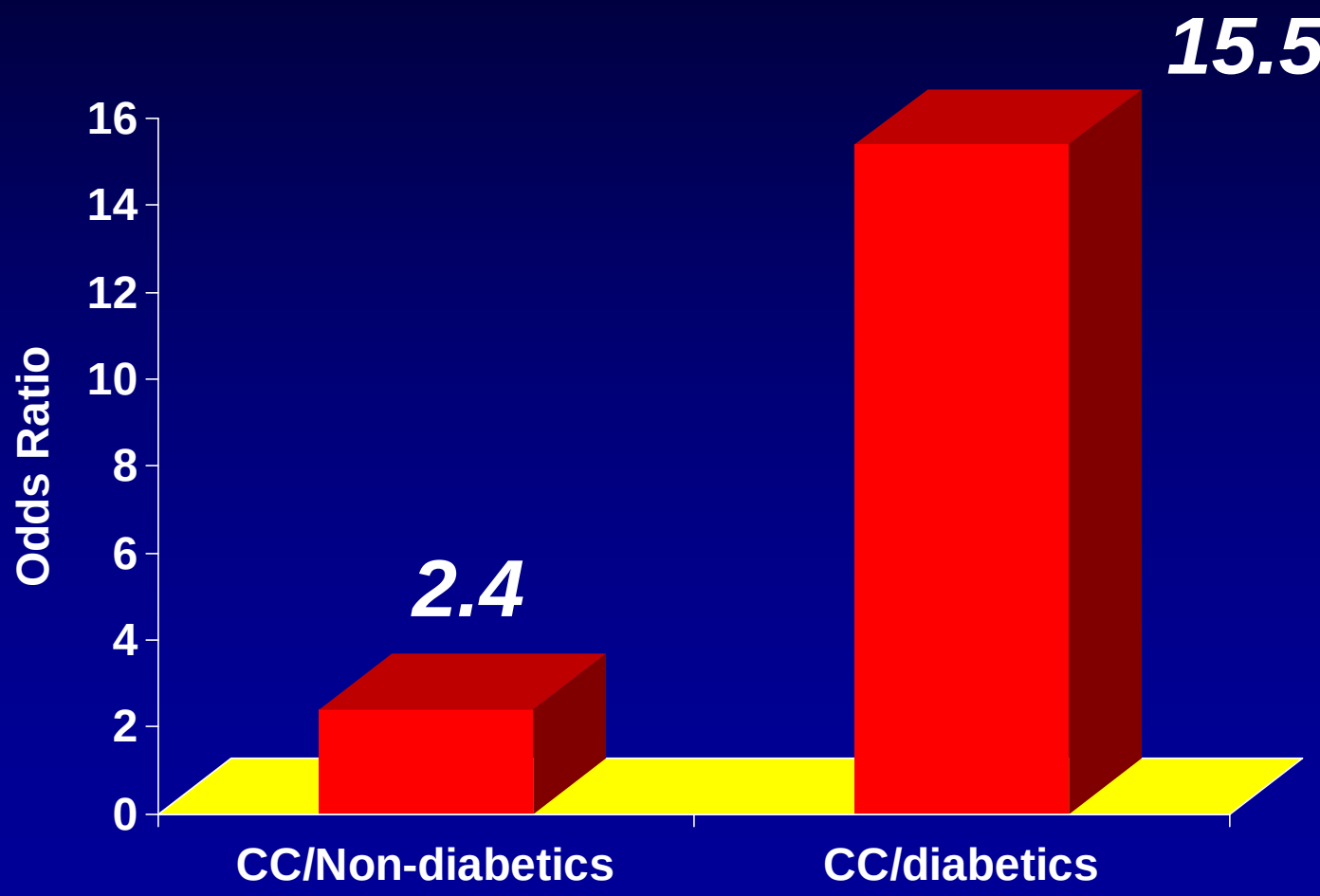
Genetic Polymorphisms of *CAT* and HCC development

Genotype	Univariable OR (95% CI)	Multivariable OR (95% CI)
TT	1	1
CT	1.4 (0.7-2.9)	1.5 (0.6-3.6)
CC	3.4 (1.7-6.8)	3.2 (1.4 -7.3)



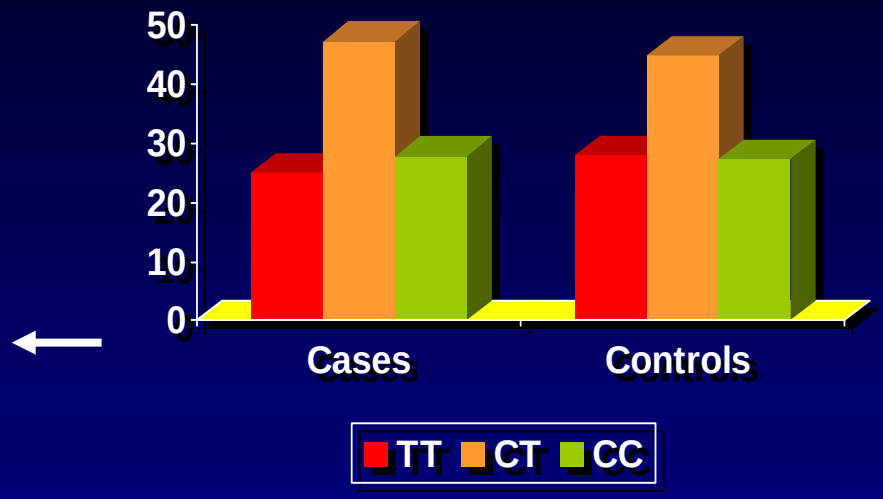
Cases N=115	14.8%	31.3%	53.9%
Controls N=128	28.1%	30.5%	41.4%

Effect Modification of *CAT* Genotypes (-262) By Diabetes



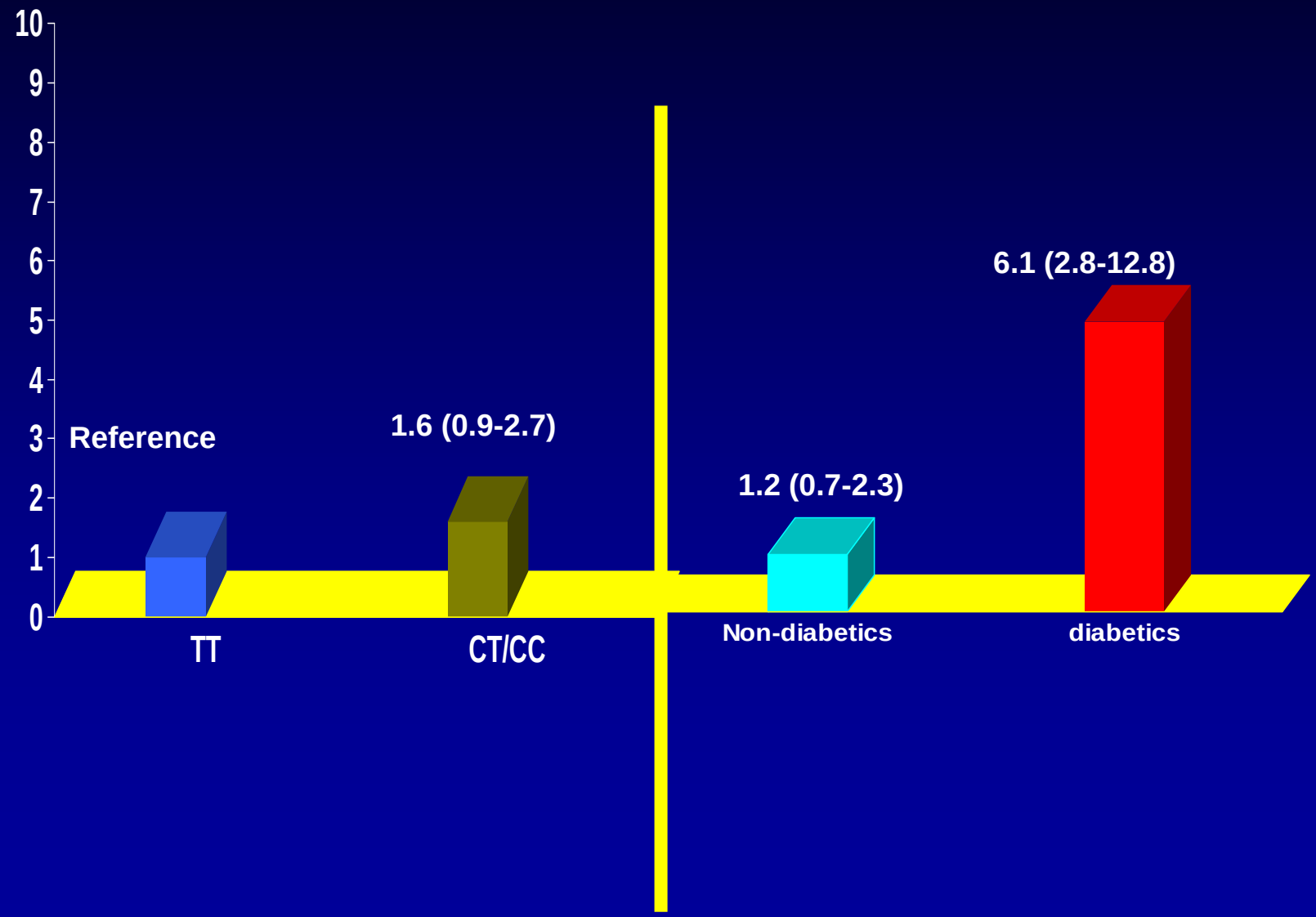
Genetic Polymorphisms of *CAT* and HCC development

Genotype	Univariable OR (95% CI)	Multivariable OR (95% CI)
TT	1	1
CT	1.2 (0.8-1.7)	1.4 (0.9-2.2)
CC	1.1 (0.8-1.7)	0.9 (0.4-2.1)



Cases N=250	7.1%	30.9%	61.9%
Controls N=700	11%	27.8%	61.1%

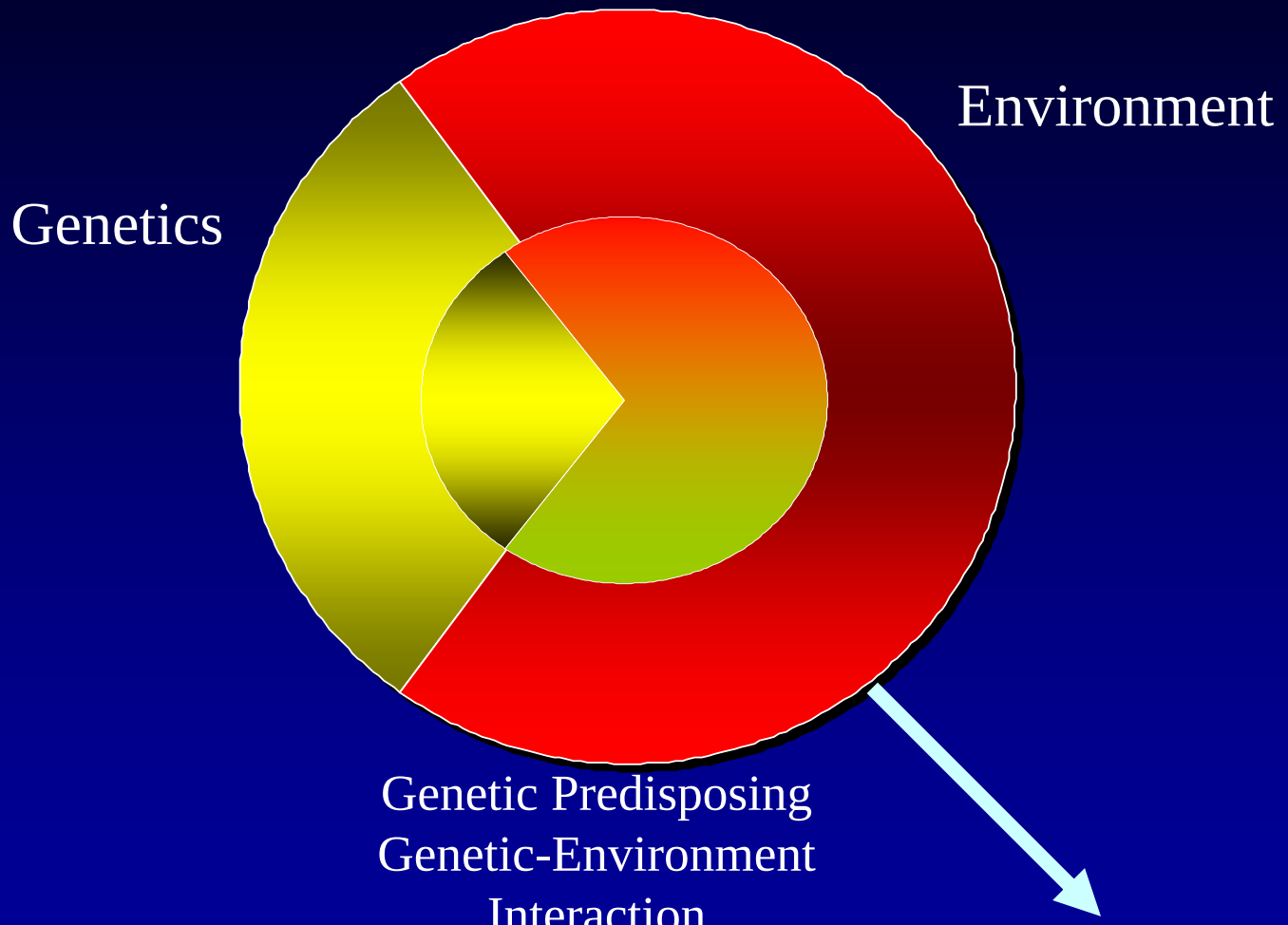
The Effect of Variant Alleles (CT/TT) of *CAT* Gene on HCC



Summary

- Hepatocarcinogenesis is long term, slow process, complex, and heterogeneous
- Hepatocarcinogenesis is multi-phase process
- Possible overlapping in molecular pathways
- Hepatocarcinogenesis depends on combination of genetic, viral, environmental factors

Molecular Epidemiology of HCC



Risk of developing HCC is determined by both cumulative carcinogenic exposure and by individual genetic variation

Obstacles
Facing Molecular Epidemiology Studies of HCC

- Rare disease
- Sever clinical complications and short survival
- Limited access to tissue biopsy
- Multifactorial in origin
- Strong effect of environmental risk factors
- Low prevalence of HCV in the general population
- Overlapping in clinical management of this disease between oncologists and hepatologists

Acknowledgment

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