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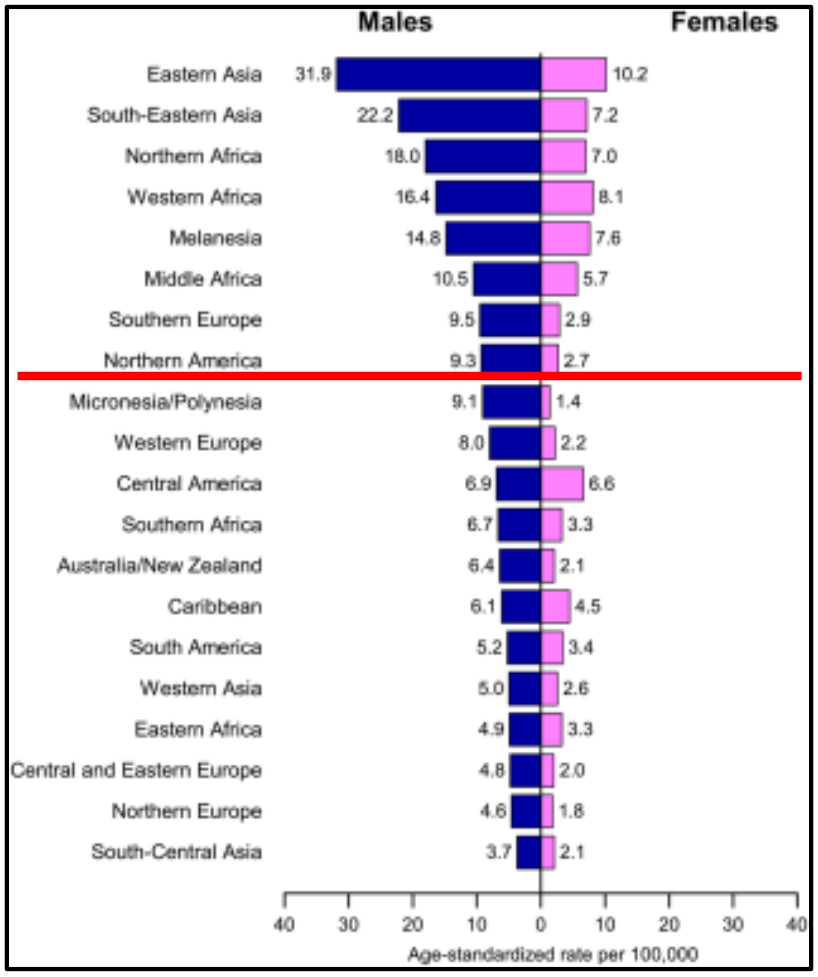
Hepatocellular Carcinoma (HCC)
Global Overview

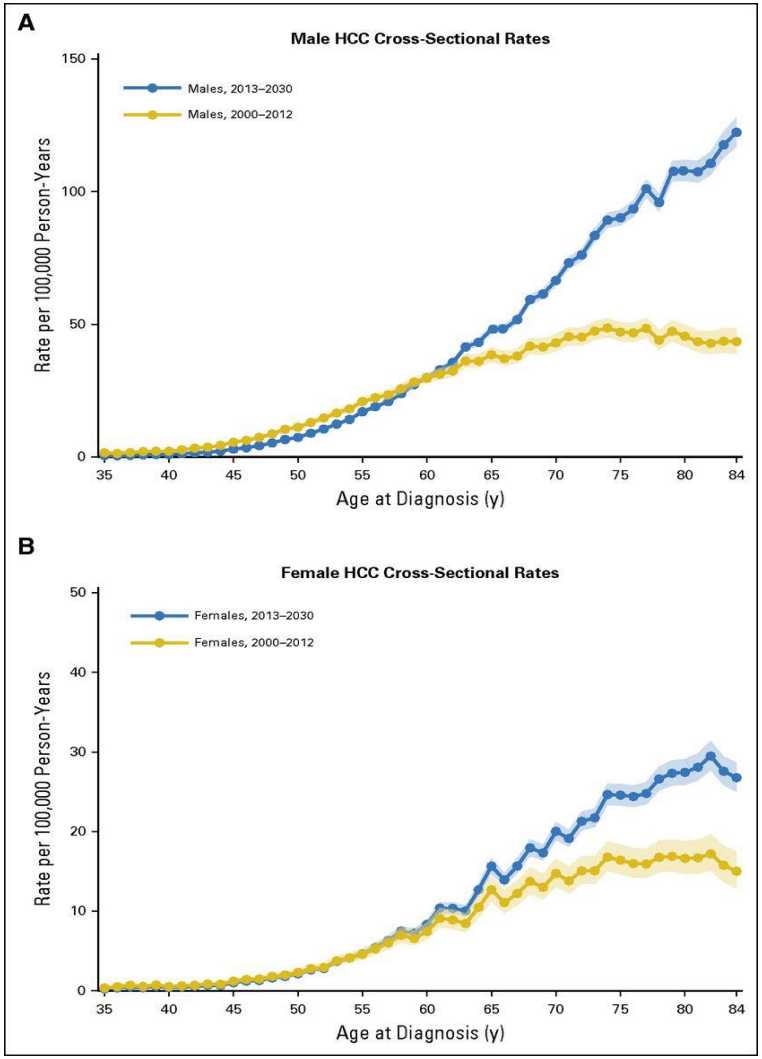
- 90% of primary liver cancers
- 4%-5% of all human cancers
- One million cases occur annually
- More common in men than women
- 7th commonest cancer in men
- 9th commonest cancer in women

Liver Cancer Incidence Rates by Sex and World Area



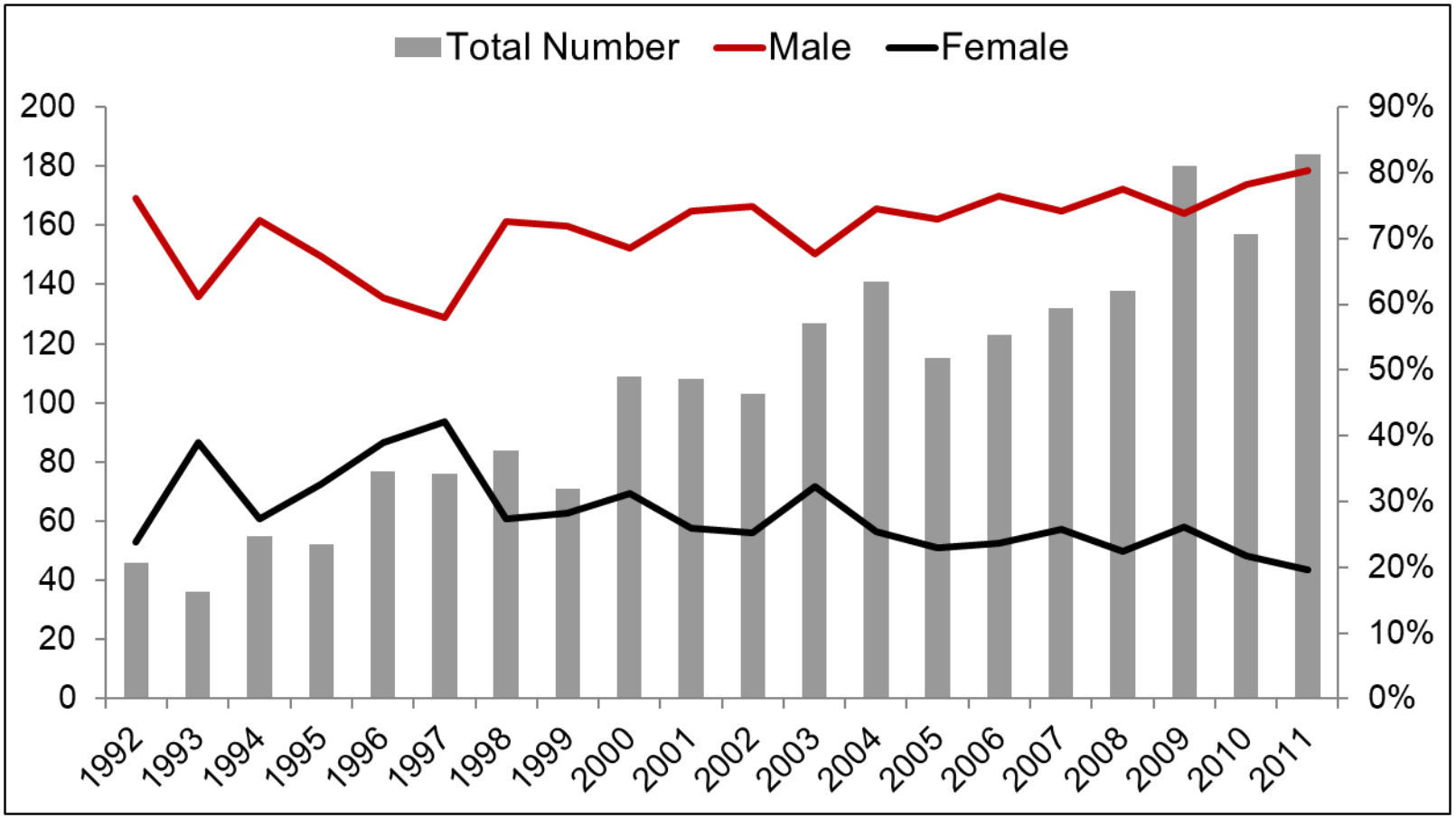
CA: A Cancer Journal for Clinicians
Volume 65, Issue 2,

Incidence rates (per 100,000 person-years) of HCC SEER 18, 2000 to 2012 and 2013 to 2030



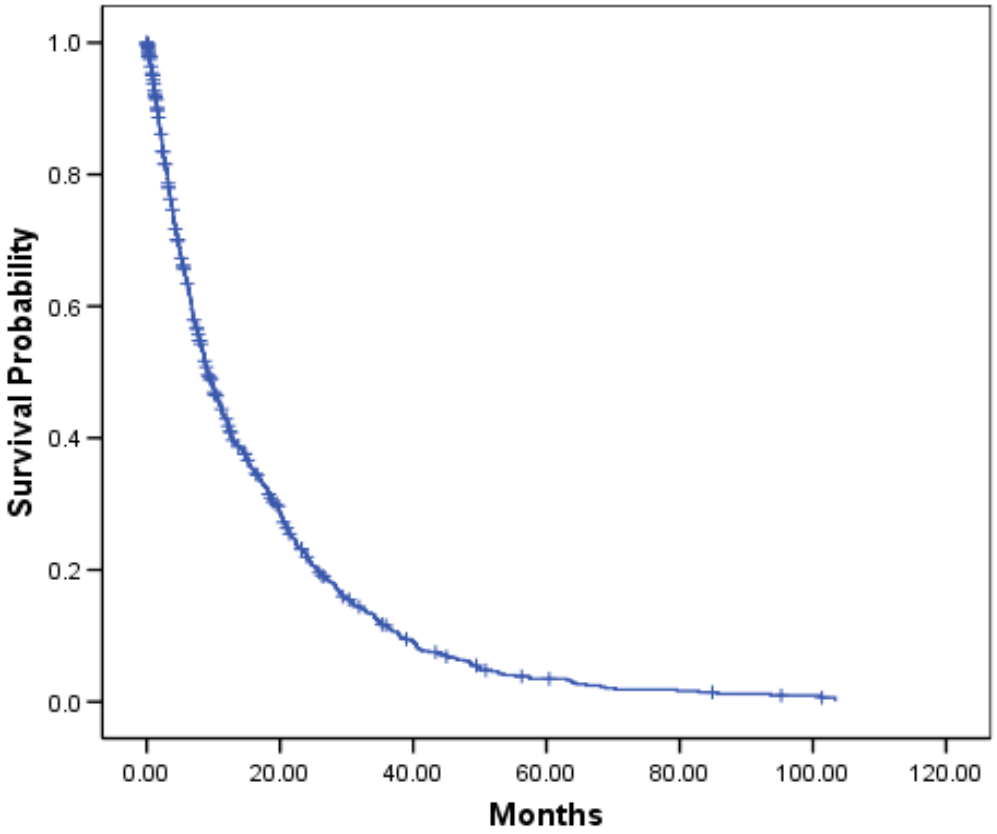
Jessica L. Petrick et al. JCO doi:10.1200/JCO.2016.64.7412

HCC Referral Pattern To UT MD Anderson over last 20 years by sex (N=2090)



Burden of HCC from clinical outcome

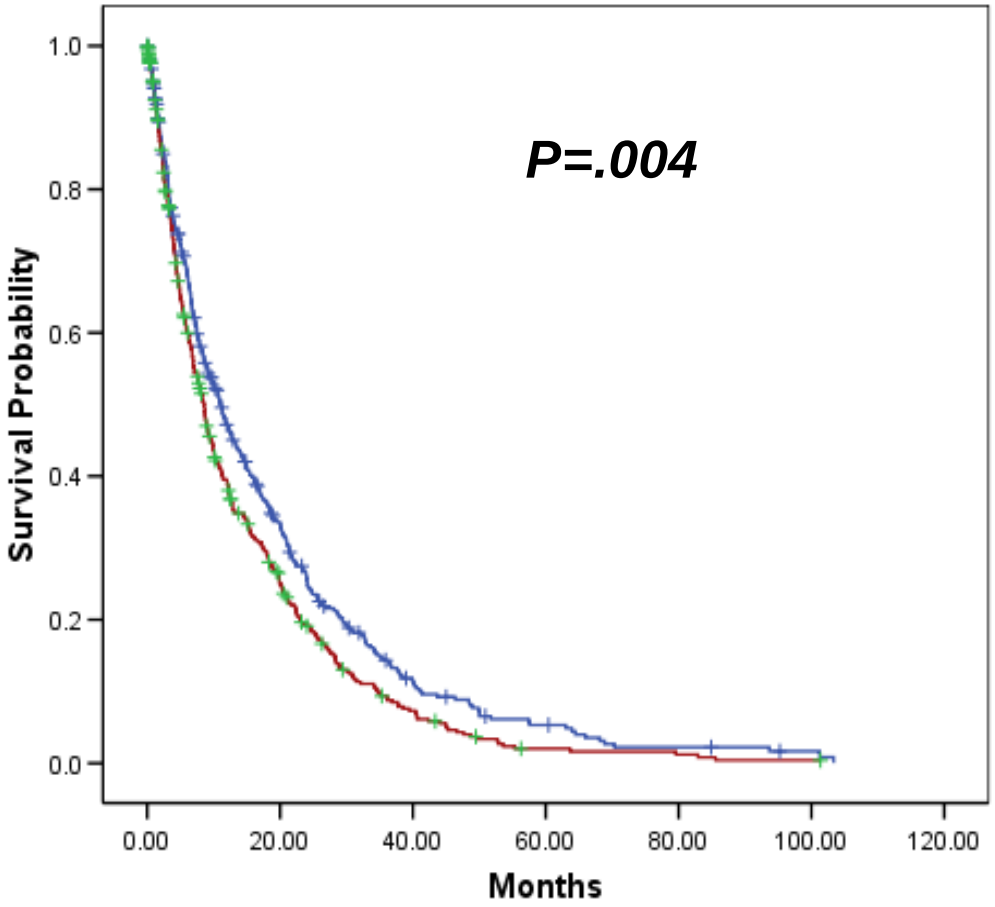
Overall Median Survival 9 months (8-10)



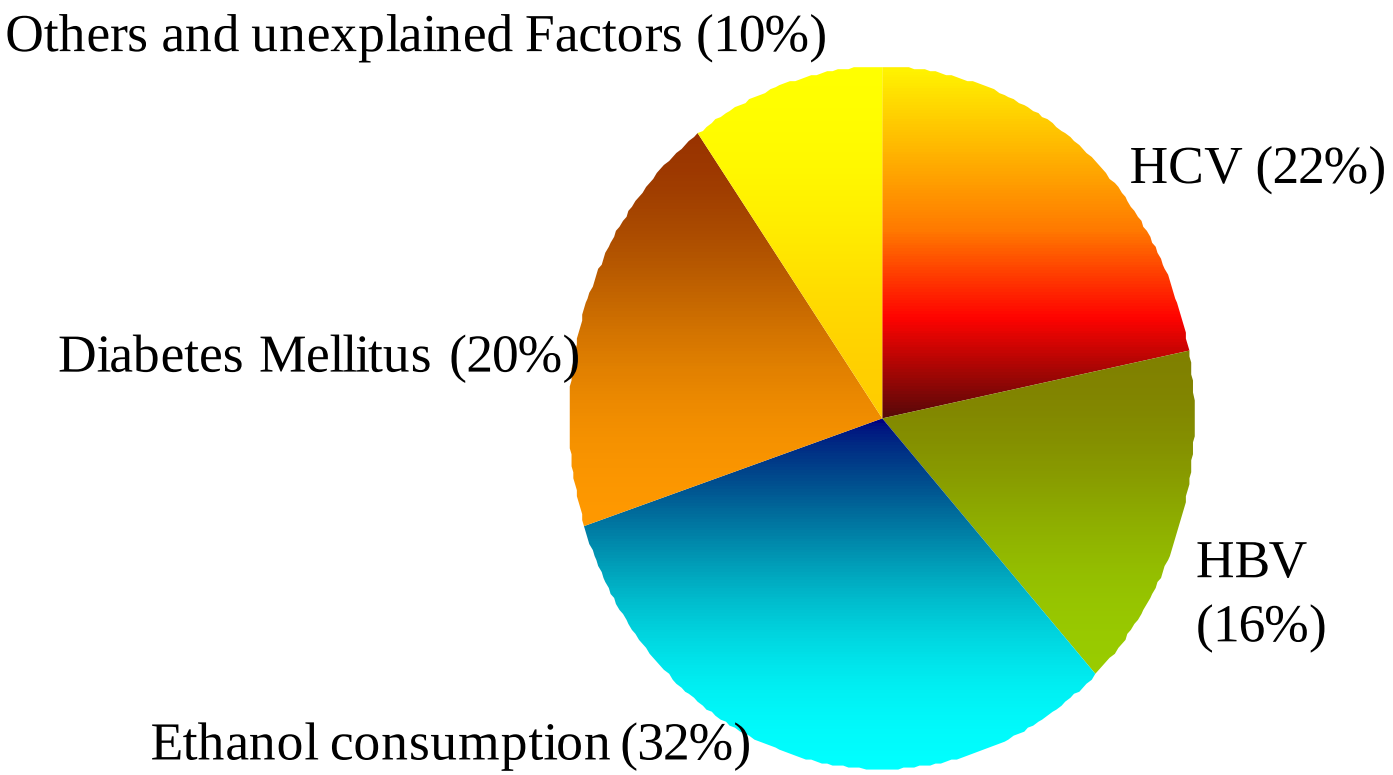
Burden of underlying chronic liver diseases

Cirrhosis : 6.5 months (5.3-8.7)

No cirrhosis: 11 months (8.9-12.9)



PAR% Explained by HCCC Risk Factors



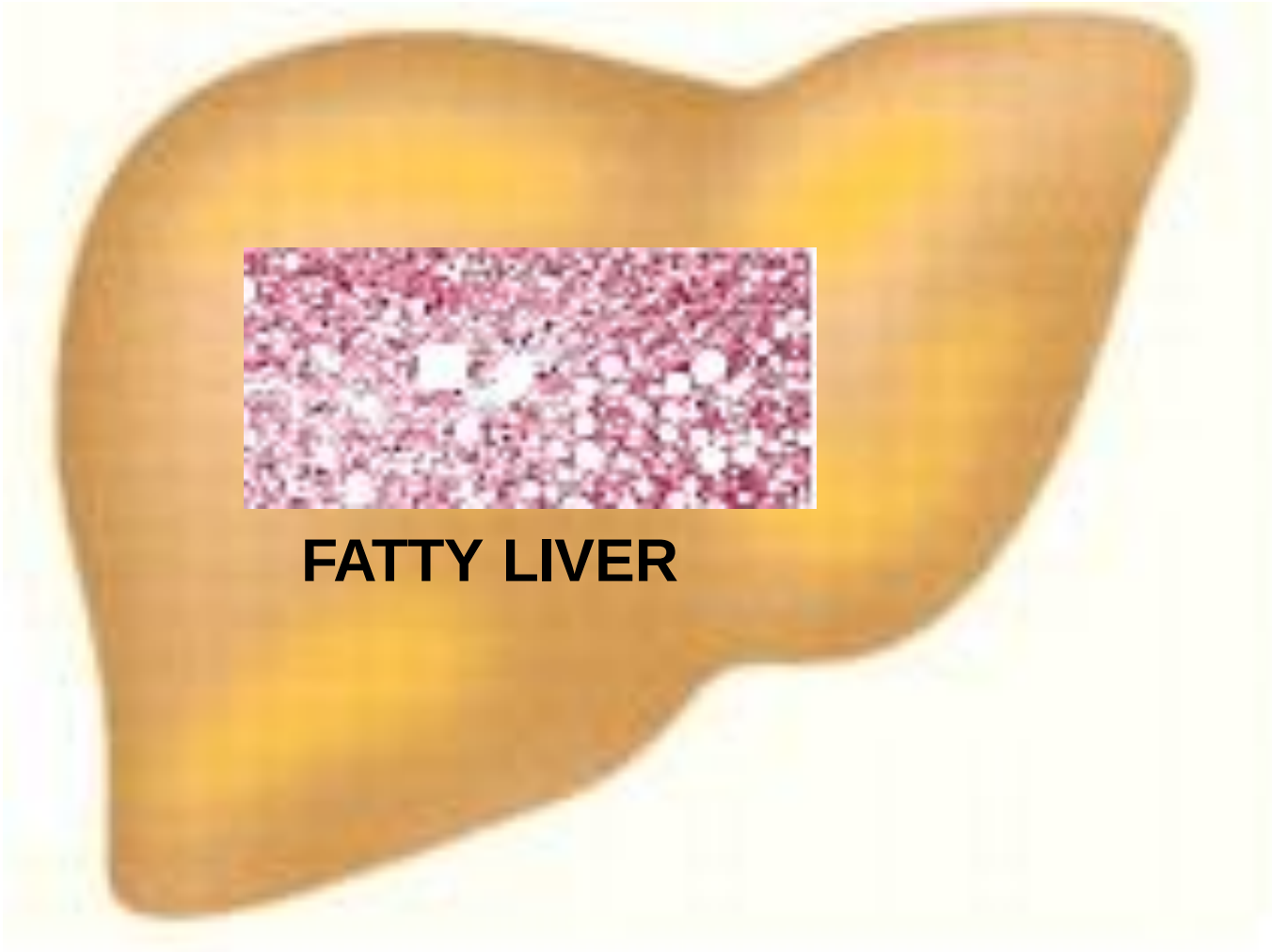
Hassan et al, hepatology

Nonalcoholic Fatty Liver Disease (NAFLD)

Chronic Liver disease which includes a spectrum of hepatic pathology including simple steatosis, steatohepatitis, fibrosis, and cirrhosis

Public Health Problem of NAFLD

- 25 to 30% of USA population
- 75% in Obese
- 16% in Normal weight individuals
- More prevalent in Hispanic Population
- Less prevalent in African Americans
- More prevalent in men < 50
- High in women > 50



“Fat in the Liver”

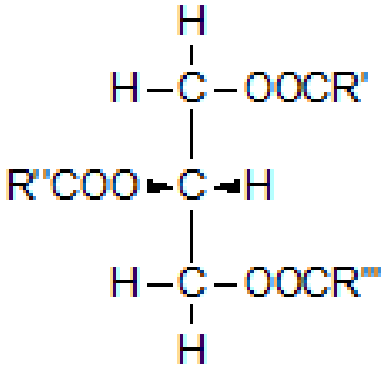
LIPIDS

- Natural molecules **(fat, oil, steroids, waxes)**
- Fatty acid is the building block
- Simple and complex compounds
- Insoluble in water
- Soluble in nonpolar solvents
- Mainly stored in adipose tissue
- Important diet constituent

- ✓High Energy value
- ✓Thermal insulator
- ✓Support organs
- ✓Electrical insulator
- ✓Fat-soluble vitamins
- ✓Essential fatty acids
- ✓Important cellular structure

FAT (Triglycerides)

- Ester derived from combination of glycerol and three fatty acids
- Major class and biological molecule in lipids
- Provide the highest caloric density
- Evolutionary it is the major energy reservoir



FAT (Triglycerides)

- The basis for such caloric difference drives from:
  - FA is much more highly reduced
  - Triglycerides are nonpolar (insoluble in water) so they are stored in anhydrous form without adverse osmotic effect
- Utilization of fat and energy production from TG by Lipase (lipolysis)
- Accumulate in cytoplasm of adipose cells (fat cell)
- TG droplets coalesce to form large globule to occupy most cell volume
- Under unusually circumstances it may accumulate in the liver cell

The importance of liver in lipid metabolism

- Facilitate the digestion absorption of lipids
- Synthesis and oxidizing fatty acids
- Synthesis of Triglycerides and phospholipids
- Conversion of fatty acids to ketone bodies
- Synthesis and metabolism of lipoprotein

Fatty Liver (Steatosis)

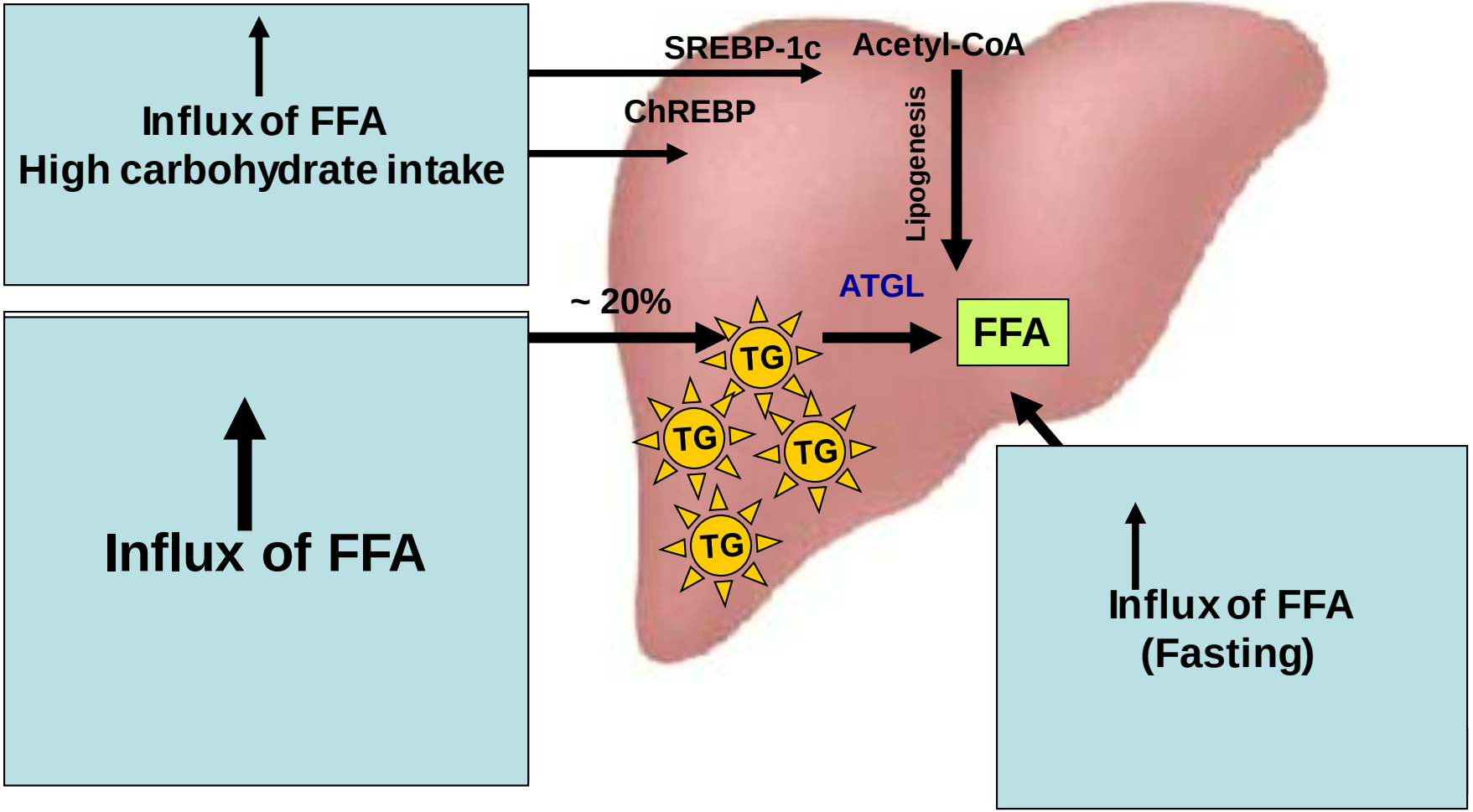
Continuing accumulation of Fat (TG) in hepatocytes until fat accounts for more than 5% of Liver weight (hepatocytes)

When TG level exceeding 95th percentile for lean healthy individuals (> 55mg per gram of liver)

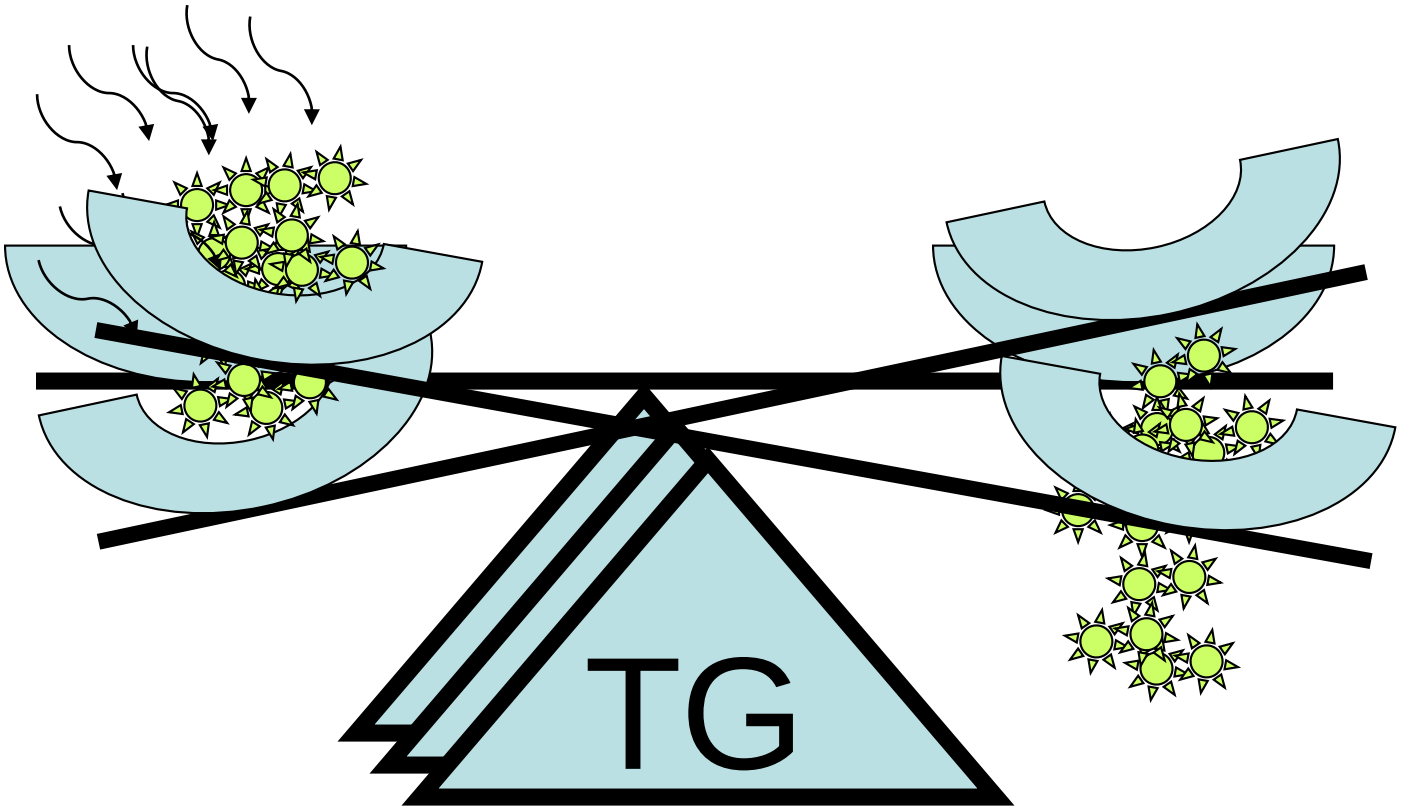
Simple Steatosis < 30% of hepatocytes

Sever Steatosis > 60% of hepatocytes

Source of Hepatic FA



The Fatty Liver Problem



It leads to inability of the hepatocytes to metabolize excess free fatty acids

Fatty Liver Prognosis

Non-Alcoholic Liver Diseases

(NAFLD)

Diagnosis

- Invasive (liver biopsy)
  - Expensive
  - Serious complication
  - Not suitable for followup and monitoring progression
- Radiologic (US) showing bright liver (sensitive)
- Magnetic Resonance Spectroscopy (TG Content)
- Plasma markers e.g. ALT/AST >1 or AST/platelets Ratio
- Sophisticated formula FibroIndex, FibroTest, ActiTest)
- Innovative procedure e.g. Breath Test and FibroScan

Case-Control of HCC

Hospital-Based at MDACC/ GI Med Oncology

Ongoing since 2000

Aimed to address environmental, nutritional, and genetic factors

Personal interview and medical chart review

Funded by NCI/NIH, IRG, Tobacco Settlement, Onyx, Chugi

Hospital Based Case-Control of HCC in USA IRB-Approved

Cases

- Newly diagnosed HCC
- pathologically confirmed
- No prior cancers
- USA residents
- Oncologist Approval

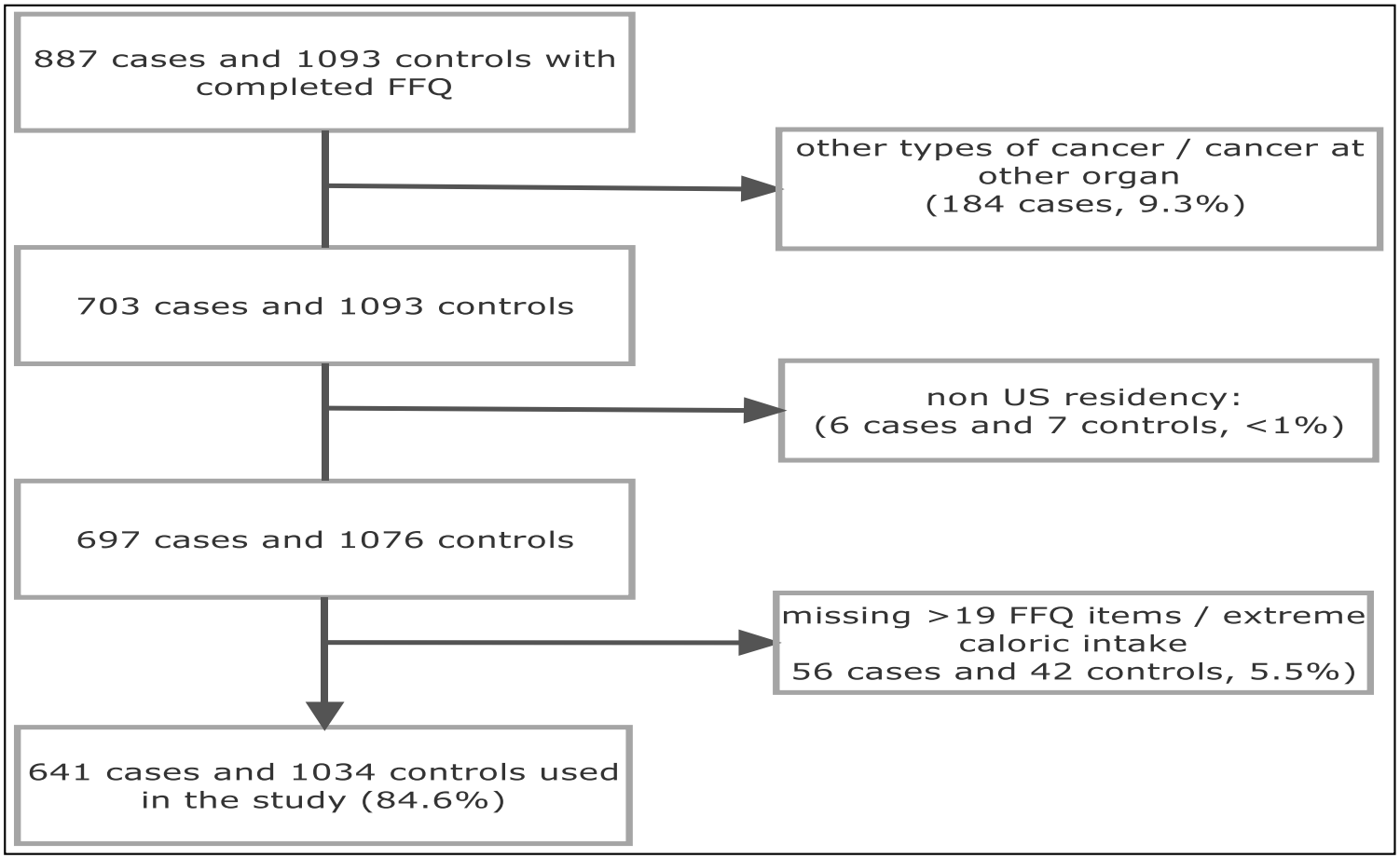
Controls

- Healthy individual
- Accompany other patients
- Not-blood related
- USA residents
- Test blood for HBV and HCV
- Frequency matched to cases by age, sex, and race

Hospital Based Case-Control of HCC in USA
Food Frequency Questionnaire (FFQ)

- The Willet semi-quantitative FFQ was used to assess the usual dietary intake of participants during the past year (the year prior to cancer diagnosis for the cases and prior to recruitment for the controls).
- The FFQ was developed and validated by the Department of Nutrition at the Harvard School of Public Health.
- The FFQ forms included the following categories: dietary supplements, dairy foods, fruits, vegetables, eggs and meat, breads and cereals, beverages, and sweets.
- The FFQ included standard portion sizes and frequency of consumption options ranging from "never, or less than once per month" to "≥ 6 per day" during the past year.
- Completed FFQs were processed by Department of Nutrition at the Harvard School of Public Health.

Hospital Based Case-Control of HCC in USA Responders to FFQ (2000-2019)



Prior History of Obesity (early adulthood weight/height) started in 2005
Total of 502 and 669 had completed the weight questionnaire prior to cancer diagnosis or recruitment

Hospital Based Case-Control of HCC in USA Demographic Characteristics

Characteristic	HCC N=502 (%)		Controls N =669 (%)		Adjusted OR[a] (95% CI)	*P*
Gender						
Female	133	26.5	265	39.5	1(reference)	
Male	369	73.5	406	60.5	1.02 (0.72-1.44)	.909
Age, years						
<60	177	35.3	295	44.0	1(reference)	
≥60	325	64.7	376	56.0	2.57 (1.8-3.66)	<.001
Ethnicity						
White	378	75.3	619	92.3	1(reference)	
Non-white	124	24.7	52	7.7	2.65 (1.63-4.30)	<.001
Education						
<College	197	39.2	173	25.8	1(reference)	
≥ College	305	60.8	498	74.2	0.75 (0.54-1.05)	.096

Hospital Based Case-Control of HCC in USA
HCC Risk Factors

Risk Factor	HCC Patients N=502 (%)		Controls N =669 (%)		Adjusted Or[a] (95% CI)	*P*
Alcohol drinking						
No drinking	136	27.1	286	42.6	1(reference)	
<60 ml E/D	266	53.0	321	47.8	1.37 (0.98-1.92)	.065
≥60 ml E/D	100	19.9	64	9.5	1.99 (1.23-3.24)	.005
Cigarette smoking						
No smoking	178	35.5	368	54.8	1 (reference)	
≤ 20 pack-years	148	29.5	138	20.6	1.39 (0.94-2.05)	.105
>20 pack-years	176	35.1	165	24.6	1.62 (1.12-2.33)	.010
FHX Cancer						
No	134	26.7	213	31.7	1(reference)	
Yes	368	73.3	458	68.3	2.06 (1.45-2.94)	.0001
Diabetes						
No	337	67.1	591	88.1	1 (reference)	
≤ 1 year	8	1.6	15	2.2	1.20 (0.46-3.13)	.705
>1 year	157	31.3	65	9.7	3.72 (2.54-5.45)	<.0001
Prior BMI Status						
Normal weight	297	59.2	440	65.6	1(reference)	
Overweight	141	28.1	192	28.6	1.02 (0.71-1.45)	.924
Obese	64	12.7	39	5.8	3.18 (1.87-5.43)	<.0001
Hepatitis						
No	275	54.8	658	98.1	1 (reference)	
HCV/ HBV	227	45.2	13	1.9	53.74 (28.74-100.47)	<.0001

Multivariate adjusted ORs and 95% CI for HCC according to tertiles of energy-adjusted fat subtype

Variable (Tertiles*)	Mean[a] gm (±SD)	Cases / Controls	Adjusted OR (95% CI)	*P*
Total fat				
T1*	65.7 (± 9.9)	176 /206	1[b](reference)	
T2	80.8(±2.7)	164/219	0.94 (0.64-1.37)	0.7525
T3	95.8 (±11.7)	147/244	0.59 (0.40-0.87)	0.0082
P_{trend}	0.1963			
Saturated Fat				
T1	24.1 (±3.7)	176/223	1[b](reference)	
T2	30.1 (±1.2)	153/234	0.87 (0.60-1.26)	0.4602
T3	36.3 (±4.6)	158/212	0.79 (0.54-1.17)	0.2435
P_{trend}	0.8389			
Polyunsaturated fat				
T1	20.9 (±0.7)	112/198	1[b](reference)	
T2	24.4 (±3.9)	130/225	1.05 (0.68-1.1)	0.8275
T3	28.8 (±4.1)	245/246	1.82 (1.23-2.70)	0.0027
P_{trend}	0.0027			

Multivariate adjusted ORs and 95% CI for HCC according to tertiles of energy-adjusted fat subtype

Fat variable (Tertiles*)	mean intake [a] gm (±SD)	Cases / Controls	Adjusted OR (95% CI)	P-value
Monounsaturated fat				
T1	34.0 (±)	207/208	1[c](reference)	
T2	40.3 (±)	158/225	0.74 (0.52-1.07)	0.1094
T3	47.5 (±)	122/236	0.49 (0.33-0.72)	0.0003
P_{trend}	0.0793			
ω- 3 fatty acids (EPA 20:5 + DHA 22:6)				
T1	1.8 (±0.1)	225/208	1[d](reference)	
T2	1.9 (±0.1)	131/222	0.49 (0.34-0.72)	0.0001
T3	2.36 (±0.4)	131/239	0.49 (0.33-0.70)	0.0002
P_{trend}	0.0972			

[a]Calculated among controls.

Multivariate adjusted ORs and 95% CI for HCC according to tertiles of energy-adjusted fat subtype among **non-cirrhotic HCC cases**

Fat variable (Tertiles)	Cases/Controls	Adjusted OR [a] (95% CI)	*P*
Total fat			
T1	90/206	1(reference)	
T2	82/219	0.95 (0.62-1.4)	0.9456
T3	76/214	0.73 (0.48-1.13)	0.1575
Saturated Fat			
T1	98/223	1(reference)	
T2	76/234	0.84(0.56-1.27)	0.4046
T3	74/212	0.79(0.52-1.21)	0.2751
Polyunsaturated fat			
T1	60/198	1(reference)	
T2	61/225	1.07 (0.66-1.74)	0.7932
T3	127/246	2.05 (1.32-3.18)	0.0014
Monounsaturated fat			
T1	106/208	1(reference)	
T2	73/225	0.67 (0.44-1.01)	0.0585
T3	69/236	0.57(0.37-0.87)	0.0095
ω- 3 fatty acids (EPA 20:5 + DHA 22:6)			
T1	102/208	1(reference)	
T2	69/222	0.59 (0.39-0.90)	0.0142
T3	77/239	0.58 (0.38-0.88)	0.0101

Multivariate adjusted ORs and 95% CI for HCC according to tertiles of energy-adjusted fat intake, stratified by gender

	Males		Females	
Fat variable (Tertiles)	OR (95% CI)	*P*	OR (95% CI)	*P*
Polyunsaturated fat				
T1	1[a] (reference)		1 (reference)	
T2	1.18 (0.69-2.01)	0.5471	0.69(0.32-1.45)	0.3319
T3	2.11(1.31-3.42)	0.0002	1.04(0.52-2.10)	0.9065
Monounsaturated fat				
T1	1[a] (reference)		1 (reference)	
T2	0.85 (0.53-1.35)	0.4821	0.62(0.35-1.10)	0.1039
T3	0.54 (0.34-0.87)	0.0116	0.40(0.20-0.77)	0.0059
ω- 3 fatty acids (EPA 20:5 + DHA 22:6)				
T1	1[a](reference)		1 (reference)	
T2	0.41 (0.25-0.66)	0.0002	0.71(0.39-1.27)	0.2464
T3	0.52 (0.33-0.82)	0.0055	0.45(0.24-0.84)	0.0121

Multivariate adjusted ORs and 95% CI for HCC according to tertiles of energy-adjusted fat intake, stratified by Diabetes

	Diabetics		Non-Diabetics	
Fat variable (Tertiles)	OR (95% CI)*	*P*	OR (95% CI)±	*P*
Polyunsaturated fat				
T1	1[b] (reference)		1 (reference)	
T2	1.69 (0.57-5.0)	0.3421	1.09(0.69-1.76)	0.7406
T3	3.22 (1.21-8.61)	0.0195	1.78 (1.14-2.78)	0.0116
Monounsaturated fat				
T1	1[b] (reference)		1 (reference)	
T2	1.19 (0.52-2.73)	0.6771	0.68 (0.45-1.02)	0.0628
T3	0.5 (0.23-1.10)	0.0862	0.53 (0.34-0.83)	0.005
ω- 3 fatty acids (EPA 20:5 + DHA 22:6)				
T1	1[b] (reference)		1 (reference)	
T2	0.87 (0.39-1.91)	0.7245	0.44 (0.29-0.67)	0.0001
T3	0.53 (0.25 -1.12)	0.0946	0.48(0.32-0.74)	0.0009

* OR adjusted for age, ethnicity, alcohol drinking, cigarette smoking, diabetes, BMI, family history of cancer, multivitamin use, and hepatitis virus infection.

± OR adjusted for gender, age, ethnicity, alcohol drinking, cigarette smoking, BMI, family history of cancer, multivitamin use, and hepatitis virus infection.

Multivariate adjusted OR of HCC according to dietary fat, HCV/HBV infection and diabetes with interaction indexes

	HCV/HBV	AOR (95%CI)	Diabetes	AOR (95%CI)
Polyunsaturated fat				
T1	No	1[a]	No	1[b]
T1	yes	68.64 (22.62-208.25)	yes	2.44 (1.07-5.56)
T3	No	1.93 (1.28-2.91)	No	1.66 (1.07-2.57)
T3	yes	61.81 (24.36-156.86)	yes	6.35 (3.61-11.18)
Interaction index (95%CI)		**0.9 (0.24-3.36)**	**3.0 (1.3-7.2)**	
Monounsaturated fat				
T1	No	1[a]	No	1[b]
T1	yes	69.21 (23.42-204.57)	yes	2.88(1.50-5.52)
T3	No	0.50 (0.33-0.75)	No	0.48(0.30-0.74)
T3	yes	11.98 (5.01-28.71)	yes	1.46 (0.79-2.68)
Interaction index (95%CI)		**0.2 (0.15-0.23)**	**1.1(0.20-.92)**	
ω- 3 Fatty acids				
T1	No	1[a]	No	1[b]
T1	yes	134.44 (30.99-583.25)	yes	2.28 (1.27-4.08)
T3	No	0.54 (0.36-0.80)	No	0.45(0.29-0.70)
T3	yes	16.40 (6.69-40.21)	yes	1.40 (0.74-2.63)
Interaction index (95%CI)		**0.1 (0.02-0.53**	**1.9(0.24-5.5)**	

Population Attributable Risk %

$$PAR\% = \frac{P_e(OR-1)}{P_e(OR-1)+1} \times 100,$$

Adjusted OR for the third tertile =1.82

Pe =246/669= 0.37

PAR for the highest tertile of PUFA intake for **23.3%**

Additional Points with ongoing investigation

- Restricted analysis among HCC cases by cirrhosis (cirrhosis vs non cirrhosis)
  - ω- 3 Fatty acids associated with reduced cirrhosis in HCC OR=.54
- Excluding people who used omega supplements (13.7% cases. 12.6% controls) did not make any differences
  - ω- 3 Fatty acids OR= 0.48 (high T vs low T) and .41 (second T vs Low T)
- Excluding patients and controls with diabetes <= 1 year prior to diagnosis or recruitment did not make any difference
- Minority Samples are small But
  - 65.4% AA and 70% of Hispanics their mean intake of omega 3 was bellow control values
  - 75% AA and 57% Hispanics their mean intake of MUFA was bellow controls values

Limitation

- Retrospective nature of the study as case-control design and possible recall bias/ reverse causation as patients could alter their dietary habits following disease diagnosis.
- Analysis among no cirrhotic cases vs healthy controls
- Comparison of % of fat intake in our controls versus US population

	Study controls	NHANES DATA (1999-2000) to (2015-2016)
Total fat	35.5%	32.5 to 33.6 % 32.5% in the 1999-2000 cycle 33.6% in the 2015-2016 cycle
MUFA	13.6%	12.9 to 13.1 %
PUFA	6.7%	7.5 to 8.2 %
SFA	11.9%	11.5 to 11.9 %

Participants' height and weight were not collected from the beginning of the study, a total of 496 subjects (134 cases and 362 controls) did not have data limiting use of this measure. However, the demographic characteristics and dietary intake of those missing BMI data did not differ from those with BMI data.

Small number of non white population

Conclusion

- Positive association between PUFA and HCC
- Inverse association between HCC with MUFA and omega-3 fatty acids .
- Saturated fat intake was not associated with HCC.
- In stratified analysis, we found that the increased odds of PUFA intake among HCC cases was stronger among males than females and stronger among diabetics than non-diabetics.
- The magnitude of association between virus and HCC was attenuated by MUFA and omega-3 intake (unexplained)
- Our results indicated that approximately 23% of our HCC cases could be explained by high polyunsaturated fat intake after considering other known risk factors, most notably HBV/HCV.

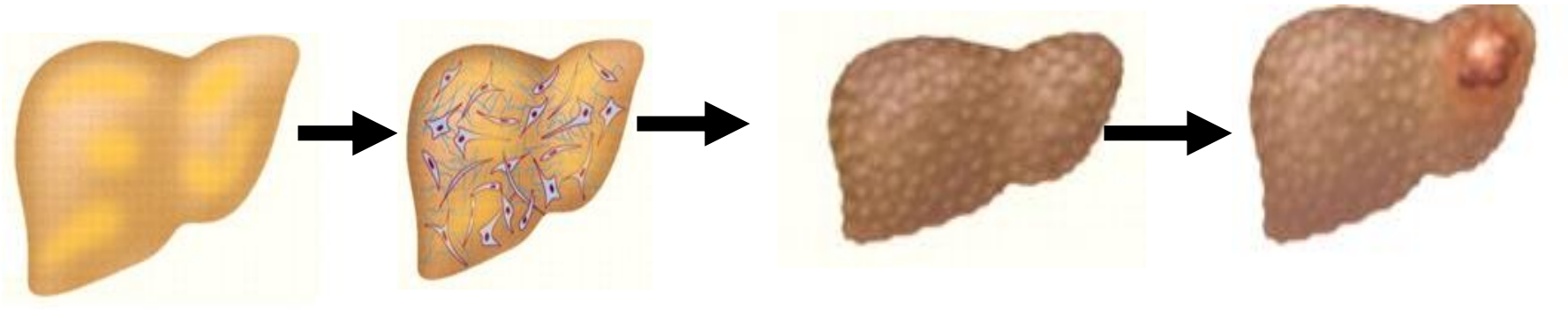
Our Results vs Others

- European Investigation into Cancer (EPIC): *Int J Cancer*. 2015;137(11):2715-2728
  - -ve association with MUFA
  - No association with Saturated Fat
- The Singapore Chinese Health Study: *Liver Int*. 2016;36(6):893-901
  - +ve association with PUFA
  - Decreased risk of MUSFA
- The NIH-AARP diet and Health study: *Int J Cancer*. 2015;137(11):2715-2728.
  - +ve association with Saturated Fat
  - No association with PUFA or MUFA
- Meta-analysis (Gao M et al): *Cancer Causes Control*. 2015;26(3):367-376.
  - -ve association with omega 3
  - No association between HCC and PUFA

Discussion

- Limited Population study aimed to study diet in HCC
- Relationship between fatty diet and HCC is controversial
- Dietary fat might be associated with predisposing factors of HCC such as insulin resistance, inflammation and NAFLD

Steatosis Steatohepatitis Cirrhosis HCC



Discussion

- Different types of dietary fat act differently; products of PUFA peroxidation as epoxides and aldehydes could enhance tumor formation via oxidative DNA damage. Whereas n-3 PUFAs are thought to increase accumulation of lipid peroxidation products in tumor cells inhibiting their growth.

- The carcinogenic effects of dietary lipids could be exerted by modulating the immune system, n-6 PUFA promotes the formation of inflammatory cytokines such as tumor necrosis factor α (TNF-α), and interleukin-6 (IL-6), however, n-3 PUFA in the diet decreases the release of inflammatory cytokines such as TNF-α and interleukin 1β (IL-1β).

- In animal models, diets high in saturated fatty acids promoted breast, colorectal and prostate tumor and diets high in n-3 PUFA particularly (EPA and DHA) inhibited breast and colon tumor growth and metastasis.

- **Diet is behavioral risk factor hard to modify and may continue to be a risk factor for HCC despite controlling for other factors**

Watch the fat level in the food

- Circulation Flux of FFA ~ 100 g/day
- 20% extracted by Liver (Dietary Source)
- 20% From Adipose tissue to Liver
- Total TG content in Average Liver ~ 40 g/day

✓ One Burger King Whopper with cheese= 48 g

✓ One Medium-sized Burger King French fries = 20 g

✓ Medium-sized Burger King vanilla shake =35 g

✓ Total fat intake from Burger King= 103 g

✓ 20% goes to liver = 20.6 g **~ ½ total liver TG content**

Acknowledgment

Study Team

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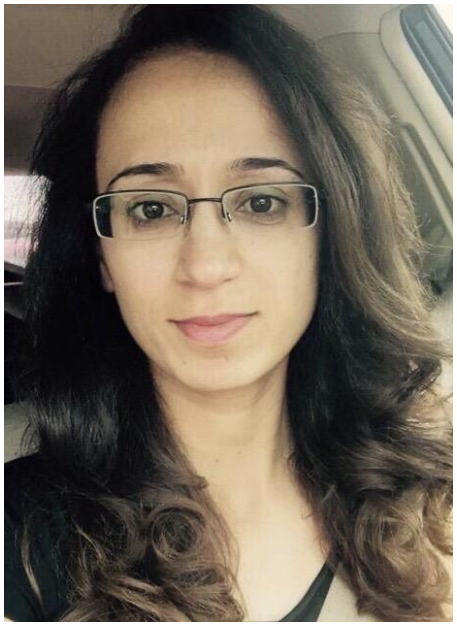

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