SURVEILLANCE TO DETECT HEPATOCELLULAR CARCINOMA (HCC)

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ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

CONFLICTS OF INTEREST

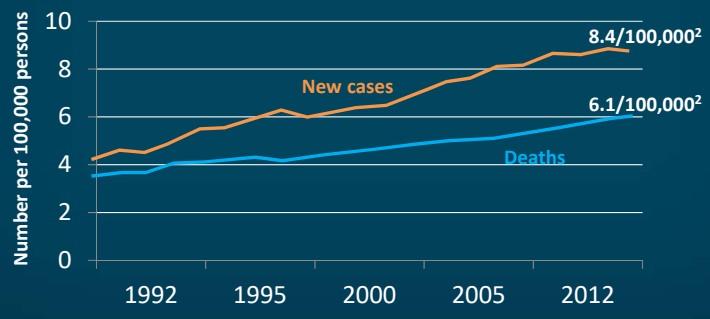
- Our program has two research grants for hepatitis C from Gilead Sciences
- None of these grants funds my salary

OUTLINE OF THIS PRESENTATION

- Incidence of HCC is rising in the USA
  - HCC incidence is rising faster in American Indian/Alaska Native people and persons of Asian/Pacific Islander descent than any other ethnic US populations
- Why it is important to detect HCC early
- Screening persons to detect liver disease is crucial
  - For those with chronic liver disease determining who has advanced fibrosis/cirrhosis or other high risk factors and need surveillance
- Who to enroll in regular surveillance
- What to screening methodologies to use for surveillance and how frequently
- Treatment of early HCC

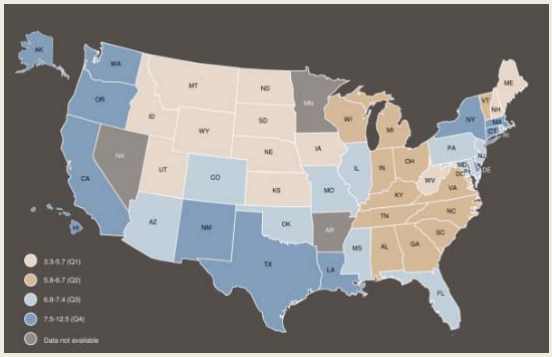
Incidence and Death Rates From Liver Cancer Have Doubled in the US

Since 1980, the incidence of liver and intrahepatic bile duct cancer has more than tripled.[1]



1. American Cancer Society. Available at www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf. Accessed September, 2016. 2. National Cancer Institute. Available at http://seer.cancer.gov/statfacts/html/livibd.html. Accessed September, 2016.

ANNUAL REPORT TO THE NATION ON THE STATUS OF CANCER, 1975-2012, FEATURING THE INCREASING INCIDENCE OF LIVER CANCER



Cancer
9 MAR 2016 DOI: 10.1002/cncr.29936
http://onlinelibrary.wiley.com/doi/10.1002/cncr.29936/full#cncr29936-fig-0001

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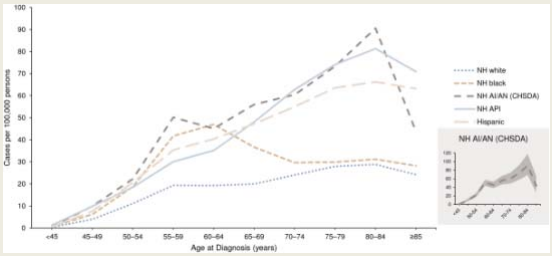
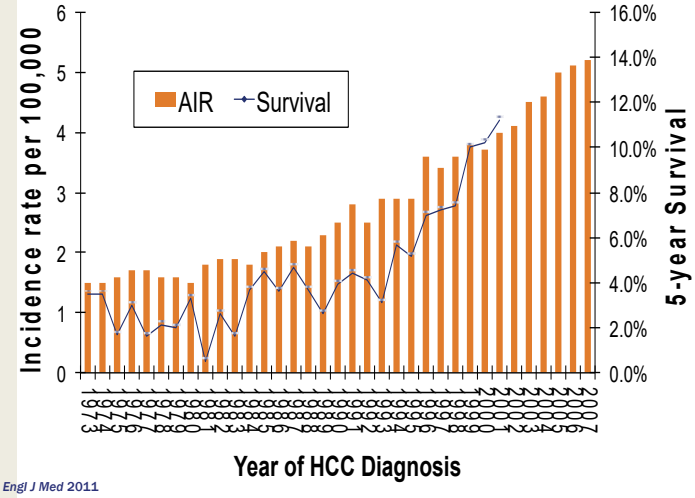


HCC is the only cancer in the US for which mortality is increasing.
Mortality for All other cancers has decreased over the last 2-3 decades

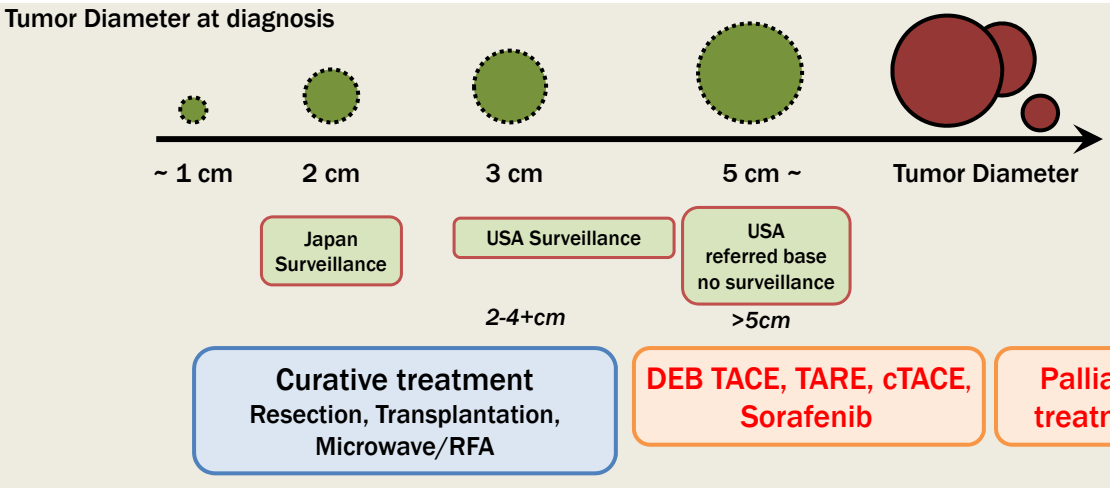
Cancer
9 MAR 2016 DOI: 10.1002/cncr.29936
http://onlinelibrary.wiley.com/doi/10.1002/cncr.29936/full#cncr29936-fig-0002

THE INCIDENCE AND 5-YEAR SURVIVAL OF HCC IN UNITED STATES



El-Serag HB. *N Engl J Med* 2011

WHY IS HCC SURVEILLANCE BENEFICIAL? HCC TREATMENT OPTIONS: EARLIER IS BETTER



FINDING PERSONS AT RISK FOR HCC AND BY IDENTIFYING THOSE AT RISK FOR LIVER DISEASE

- Annual risk for those at highest risk ranges between 1 and 3/100,000
- HBV: Screen all foreign born persons born in endemic countries for HBsAg
- HCV: Baby boomers
  - Evaluate HCV infected persons for advanced fibrosis and cirrhosis as they need surveillance: Baby Boomers are at highest risk, For recently infected young persons the risk is low
- NAFLD: Identify those with NASH: Risk is high for those with F3/F4 fibrosis
  - Important to note that NAFLD frequently is co-present in persons with HCV and HBV
- Alcoholic Liver Disease: Annual risk in those with cirrhosis is lower ~1%/year
  - Reason may be that persons with ALD who continue to drink may die of liver failure

WHO WITH CHRONIC HBV NEED SURVEILLANCE FOR HCC

- Persons with cirrhosis,
- Family history of HCC
- Men over 40 years and women above age 50 years
- Not effective for children <20 with the exception of those infected with HBV genotype F
  - Gounder et al. J of Pediatrics 2016:178:206-213

WHO TO INITIATE SURVEILLANCE WITH CHRONIC HEPATITIS C

- All persons with F3 or F4 fibrosis need regular HCC surveillance
- It's important to establish fibrosis stage in HCV infected persons
  - FIB4 and APRI are good first steps
  - Serologic Fibrosis scores such as FibroSure, FibroTest and FibroSpect2 are expensive but a little better than FIB4
    - Important to note that these test have good specificity at the low and high ends but in between suggest flipping a coin for less expensive accuracy
  - Liver Ultrasound with portal vein flow study
  - FibroScan
  - MRI elastography or MRE
  - Liver biopsy

WHAT SCREENING METHODOLOGIES TO USE AND HOW FREQUENTLY

- Ultrasound of the liver and AFP every 6 months. Insurers will cover this in patients with cirrhosis

AASLD Guideline for HCC Hepatology 2018;67:358-380
Download for free at AASLD.org under practice guidelines

IMAGING MODALITIES FOR HCC SURVEILLANCE

Imaging	Advantages	Disadvantages
Ultrasound	• Non-Invasive • Availability is ubiquitous • Low cost	• Highly operator & technique dependent -directly proportional to operator experience & skill • Low Sensitivity in Obesity • Soft tissue assessment • Low sensitivity in other Disease states
CT 4 Phase	• High sensitivity	• Risk of high radiation • High cost
MRI	• High sensitivity • High resolution	• Limited availability • Extremely high cost • GAD accumulation

SENSITIVITY OF HCC DETECTION

Size	US	CT	MRI
Per-nodule	92/200 (46%)	126/194 (65%)	126/175 (72%)
<2cm	20/96 (21%)	35/88 (40%)	33/70 (47%)
2-4cm	44/71 (62%)	59/74 (80%)	66/77 (86%)
≥4cm	28/33 (85%)	32/32 (100%)	27/28 (96%)
Per-patient	88/138 (64%)	113/149 (76%)	99/117 (85%)

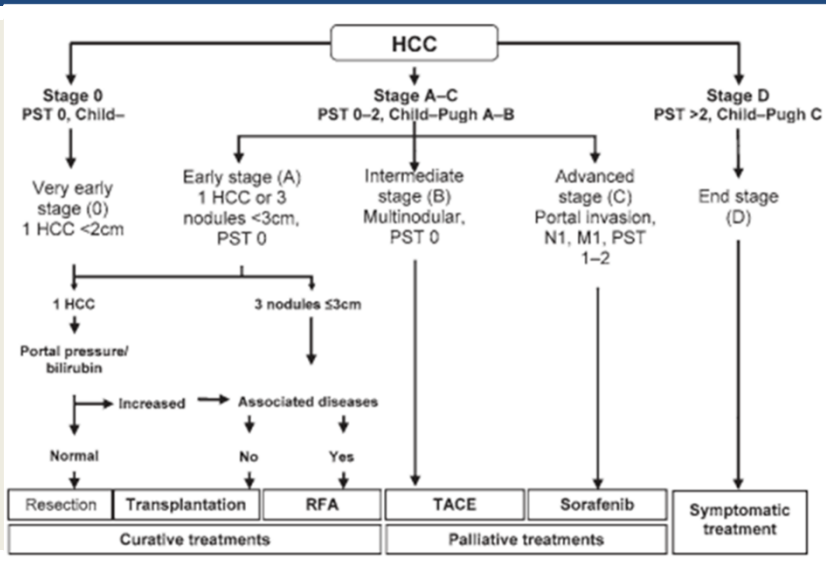
638 Liver transplant 225 (35%) HCC,
23 excluded *(infiltrative, multifocal)*

Yu NC. et al Clin Gastroenterol Hepatol 2011;9:161-167

TREATMENT OF EARLY HCC

- Ablative therapies, Radiofrequency and Microwave can be curative HCC tumors 3cm or less.
  - If tumor is reachable in left lobe or in medial segments of the right lobe, procedure can be done in radiology suite using percutaneous US or CT guidance with conscious sedation
    - Patient will be out the door in 2-3 hours and back to full activity in 3 days
  - If tumor is deep in right lobe or near diaphragm or major vessel, ablation via laparoscopic approach is necessary and patient hospitalized overnight and back to full activities in 1 week
- Surgical resection of single lesions usually under 5 cm
- Liver Transplantation
  - 3 or less lesions,
  - All in one lobe,
  - Total diameter <7cm,
  - Largest <5cm

EARLY DETECTION ALLOWS CURATIVE TREATMENTS



ABLATION DEMO

SECONDARY PREVENTION AND ADJUVANT THERAPY

- Secondary prevention of recurrence of HCC after initial treatment
  - HCV: Treat for SVR
  - HBV: Suppress HBV DNA with tenofovir or entecavir
- Adjuvant therapies
  - Coffee
  - Statins

Coffee

- Protective effect in NASH (bx. proven) through a reduction in inflammation and fibrosis
- Reduces insulin levels and risk of Type II DM
- 40% Risk Reduction of HCC:
  - dose response: 1 to 2 cups = 20% reduction
  - 75% > 5 cups

Hepatology 2007

J Natl Cancer Inst 2005

Clin Gastroenterol 2013

Lipophilic statins and risk of hepatocellular carcinoma (HCC) and mortality in chronic viral hepatitis

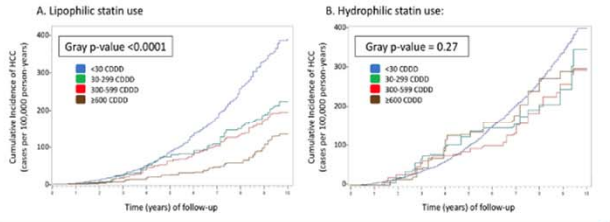
Aim:
To examine the associations between lipophilic and hydrophilic statin use and risk for incident HCC and death, in a prospective, nationwide population with confirmed chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection

Methods:
- Using validated Swedish nationwide registers, we conducted a prospective, nationwide cohort study, using a 1:1 propensity score-matched, new-user design.
- Using Cox proportional hazards modeling that accounted for competing risks, we estimated the subdistribution hazard ratios and 95% confidence intervals for incident HCC and death.

Conclusions:
Lipophilic but not hydrophilic statin use is associated with dose-dependent reductions in risk for incident HCC and death.

Simon TG, et al., Abstract 93

Cumulative incidence of HCC with lipophilic statins (A) or hydrophilic statins (B)



Cumulative defined daily dose (cDDD) of lipophilic statins and risk for HCC:

	Non-use	30-299 cDDD	300-599 cDDD	≥ 600 cDDD	*P*-trend
No. Cases / Person-Years	341/88,695	63/22,250	46/21,094	76/33,822	--
Crude	1 (Reference)	0.81 (0.49-1.14)	0.59 (0.48-0.82)	0.43 (0.29-0.67)	<0.001
Adjusted*	1 (Reference)	0.85 (0.51-1.22)	0.57 (0.47-0.79)	0.46 (0.31-0.72)	<0.001

* Model adjusted for age (years), sex, duration of HBV/HCV (years), cirrhosis (yes vs no), ever-use of antiviral therapy, type 2 diabetes (yes vs no), obesity (yes vs no), use of aspirin (yes vs no), use of metformin (yes vs no).

CONCLUSION

- Identify patients at risk for liver disease and screen for diagnosis
- Identify stage of liver fibrosis
- Initiate every 6 month surveillance with liver US and AFP for those at highest risk of HCC
- Remember that there are significant limitations to our screening modalities and to keep a high level of suspicion
- Detecting HCC tumors early can lead to long-term survival
- HCC that is to advanced to ablate, resect or transplant is ultimately fatal as unlike other cancers, no chemotherapy for cure is available