Epidemiology Trends: Evolving Etiologies and Risk Factors and Screening Guidelines for Populations at Risk

Tamar H. Taddei, MD
Disclosures:

None relevant to this talk
Objectives

• Learn about the shifting trends in the epidemiology of HCC
• Understand the risk factors for HCC
• Appreciate the importance of “screening” (surveillance)
• Explore tools that may refine our approach to surveillance
EPIDEMIOLOGY
HCC is Unique

• 1 patient, 2 diseases
  • Cirrhosis leads to
    • multifocal liver cancer
    • high recurrence rates
  • Cirrhosis complicates treatment and trial design
• HCC can be diagnosed by imaging alone
• HCC is the only solid organ malignancy for which transplantation offers a cure
HCC: An Epidemic…

• Hepatocellular carcinoma is rising in incidence globally, and tripled in the US in over the last three decades
• HCC is the leading cause of death in cirrhosis
• 5th most common cancer in men worldwide, 2nd leading cause of cancer death
  – Globally: 841,080 new cases and 781,631 deaths predicted in 2018
  – US: 42,220 new cases and 32,200 deaths predicted in 2018
2018 GLOBOCAN estimates of incidence and mortality worldwide for Liver Cancer
### Ten Leading Cancer Types for the Estimated Cancer Deaths by Sex, United States, 2019

<table>
<thead>
<tr>
<th>Estimated Deaths</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>76,650</td>
<td>66,020</td>
</tr>
<tr>
<td>Prostate</td>
<td>31,620</td>
<td>41,760</td>
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<tr>
<td>Colon &amp; rectum</td>
<td>27,640</td>
<td>23,380</td>
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<td>Pancreas</td>
<td>23,800</td>
<td>21,950</td>
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<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>21,600</td>
<td>12,160</td>
</tr>
<tr>
<td>Leukemia</td>
<td>13,150</td>
<td>9,690</td>
</tr>
<tr>
<td>Esophagus</td>
<td>13,020</td>
<td>8,460</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>12,870</td>
<td>7,850</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,510</td>
<td>8,460</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>9,910</td>
<td>7,850</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>321,670</strong></td>
<td><strong>285,210</strong></td>
</tr>
</tbody>
</table>

Notes:
- Lung & bronchus is the leading cause of cancer deaths in both males and females.
- Liver & intrahepatic bile duct is the fourth leading cause of cancer deaths in males and the fifth leading cause in females.
- Leukemia is the fourth leading cause in males and non-Hodgkin lymphoma in females.
- Non-Hodgkin lymphoma is the third leading cause of cancer deaths in males and females.
- Brain & other nervous system is the third leading cause in males and the fourth leading cause in females.
Five-Year Relative Survival Rates by Race and Stage at Diagnosis, United States, 2008 to 2014

Liver & intrahepatic bile duct

- All races
- White
- Black

<table>
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<tr>
<th>Stage</th>
<th>All races</th>
<th>White</th>
<th>Black</th>
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<td>Localized</td>
<td>3130</td>
<td>26</td>
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<tr>
<td>Regional</td>
<td>1111</td>
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<tr>
<td>Distant</td>
<td>8</td>
<td>2</td>
<td>3</td>
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<tr>
<td>All stages</td>
<td>1817</td>
<td>14</td>
<td></td>
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</tbody>
</table>
RISK FACTORS
Risk Factors for HCC

• **Chronic HBV** (5-100 fold ↑ risk)
  - 0.02-0.20 (per 100 person-years) carriers
  - 0.3-0.6 in chronic HBV without cirrhosis
  - 2.2-3.7 in chronic HBV with cirrhosis

• **HCV infection** (15-20 fold ↑ risk)
  - Advanced fibrosis/cirrhosis, 25-30 year latency
  - annual rate of developing HCC: 1% to 8%

Fattovich *J Hepatol* 2008, Yang *Nat Rev Gastroenterol Hepatol* 2011
Risk Factors for HCC

- **Alcoholic cirrhosis**
  - Second to HCV in the USA

- **No clear etiology** for 30–40% of cases in the West
  - NAFLD and the metabolic syndrome
  - 1.5–2.0-fold ↑ risk among obese
  - diabetes associated with a 2-fold ↑ risk

- **AGE** is a risk factor for all cancers…

Rui *Plos One* 2012, White *Clin Gastroenterol Hepatol* 2012
“SCREENING” (SURVEILLANCE) GUIDELINES
Routine Surveillance Recommended in High-risk Populations

• All patients with cirrhosis with US +/- AFP q 6 mos (AASLD)

• All patients with HCV with advanced fibrosis/cirrhosis (stage 3 and 4) (AASLD/IDSA)

• Non-cirrhotic patients with chronic hepatitis B
Non-Cirrhotic HBV Carriers at Risk: A Global Concern

- Asian males > 40
- Asian females > 50
- Africans > 20
- Family history of HCC

- Lifetime risk 10-25%
- 35-87 million will die

http://globocan.iarc.fr/old/FactSheets/cancers/liver-new.asp
https://www.cdc.gov/globalhealth/immunization/othervpds/preventing_hepatitisb.html
Surveillance Algorithm

**SURVEILLANCE**

- Surveillance ultrasound with or without AFP
  - **Interpretation**
    - **Negative**
      - Repeat US with or without AFP in 6 mo
    - **Subthreshold** (≤ 10 mm lesions)
      - Repeat US with or without AFP in 3-6 mo
    - **Positive** (≥ 10 mm lesions or AFP ≥ 20 ng/mL)
      - **Interpretation**
      - **Multiphase CT or MRI in select patients**

**DIAGNOSIS**

- **Diagnostic imaging for HCC with multiphase CT or MRI**
  - **Interpretation**
Utility of Surveillance

• Surveillance with ultrasound is cost effective (annual incidence ≥ 1%)
• Associated with early stage at diagnosis and improved survival
• *Utilization* and sensitivity of surveillance test have been modeled (>32% and 42%, respectively)
## Evidence Favoring Surveillance

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>N of participants (studies)</th>
<th>Overall quality of evidence</th>
<th>Relative effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early tumor detection rate</td>
<td>10,904 (38 observational studies)</td>
<td>★★★★ ○○ LOW</td>
<td>OR 2.11 (1.88 to 2.33)</td>
</tr>
<tr>
<td>Early tumor detection rate (using BCLC to define early stage)</td>
<td>6,348 (23 observational studies)</td>
<td>★★★★ ○○ LOW</td>
<td>OR 2.08 (1.80 to 2.37)</td>
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<tr>
<td>Early tumor detection rate (using BCLC to define early stage)</td>
<td>6,573 (6 observational studies)</td>
<td>★★★★ ○○ LOW</td>
<td>OR 1.96 (1.41 to 2.73)</td>
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<tr>
<td>Curative treatment rate</td>
<td>24,374 (34 observational studies)</td>
<td>★★★★ ○★* MODERATE</td>
<td>OR 2.24 (1.99 to 2.52)</td>
</tr>
<tr>
<td>3-year survival rate*</td>
<td>10,850 (23 observational studies)</td>
<td>★★★★ ○★* MODERATE</td>
<td>OR 1.90 (1.67 to 2.17)</td>
</tr>
<tr>
<td>Early detection (ultrasound only)</td>
<td>(5 observational studies)</td>
<td>★★★★ ○○ LOW</td>
<td>OR 2.04 (1.55 to 2.68)</td>
</tr>
<tr>
<td>Early detection (ultrasound +/- AFP)</td>
<td>(14 observational studies)</td>
<td>★★★★ ○○ LOW</td>
<td>OR 2.16 (1.80 to 2.60)</td>
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<tr>
<td>Receipt of curative treatment (ultrasound only)</td>
<td>(8 observational studies)</td>
<td>★★★★ ○○ LOW</td>
<td>OR 2.23 (1.83 to 2.71)</td>
</tr>
<tr>
<td>Receipt of curative treatment (ultrasound +/- AFP)</td>
<td>(24 observational studies)</td>
<td>★★★★ ○○ LOW</td>
<td>OR 2.19 (1.89 to 2.53)</td>
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</tbody>
</table>

*Upgraded because of large effect size
5-Year Survival Is Substantially Higher When Liver Cancer Is Caught Early…

Percent of Cases by Stage

- Localized: 44%
- Regional: 27%
- Distant: 18%
- Unknown: 12%

5-Year Relative Survival

- Localized: 31.3%
- Regional: 10.8%
- Distant: 2.4%
- Unknown: 6.3%

National Cancer Institute
Even Very High-risk Patients Rarely Receive Routine HCC Surveillance

Annual HCC Surveillance With Either US or AFP in Patients With HCV and Cirrhosis (n=9369)

- Routine: 12%
- Inconsistent: 58.5%
- None: 29.5%

Routine testing=tests done during at least 2 consecutive years in the 4 years after diagnosis of cirrhosis; inconsistent testing=≥1 test during the same timeframe.

AFP=alpha-fetoprotein; US=ultrasound.
Barriers to Surveillance

Provider

Cirrhosis? Guidelines? Clinical concerns

System/Patient

Availability Scheduling Patient f/u

Test

Operator-dependence
- Tech v. MD
- Obesity

Underutilization
SHIFTING TRENDS
The “Birth Cohort” – The Present US Problem

 Deaths per 100,000 persons  

- Born before 1945 (aged > 55 years at death)
- Born 1945-1965 (aged 35-68 years at death)
- Born 1966-1970 (aged 35-47 years at death)

Death Year

Ryerson Cancer 2016
Pre-DAA Snapshot: HCC in the VA System: 2013
DAA-induced SVR is associated with a 71% reduction in HCC risk

Kaplan-Meier curves of survival free of HCC by cirrhosis and SVR status after DAA-only antiviral treatment:
SVR is associated with a reduction in HCC risk both among patients with cirrhosis and those without cirrhosis.
Don’t Stop Surveillance Post-SVR in Patients with Advanced Fibrosis

• Natural history is evolving
• Many studies suggest that although liver stiffness may improve after SVR, cirrhosis and attendant HCC risk remains
• Probability of HCC seems to plateau in the second year following SVR (Kanwal et al. #0888)
• 1.6-fold increase in HCC incidence in the 7 year interval between 2001-2007 compared to 2008-2014 (Ioannou PLoS One 2018)
Once HCC is Successfully Treated, Don’t Forget to Treat HCV!

DAA group vs no DAA group

HR=0.39 (p=0.03)

Survival

Time (months)

DAA group
No DAA group

Number at risk
DAA group 102 88 39 1
No DAA group 102 81 59 34
Direct-Acting Antiviral Therapy is not Associated with HCC Recurrence: A Multicenter North American Cohort Study

**Aim:** Do DAAs impact the risk of HCC recurrence?

- HCV related HCC
- HCC with complete response
- DAA therapy for HCV
- Recurrent HCC

**Methods:**
31 centers in North America including patients with HCV-related HCC with complete radiographic response

**Results:**
- Landmark analysis of risk of HCC recurrence by DAA treatment status
- 304 HCV treated with DAAs
- 489 Treatment-naive HCV

DAA therapy has no impact on:
- Overall HCC recurrence (aHR: 0.90 95% CI: 0.90-1.17)
- Early HCC recurrence (aHR: 0.96 95% CI: 0.69-1.33)

Singal AG et al. Gastroenterology. 2019
296,707 NAFLD patients; 296,707 matched controls.

Over 2,382,289 PY of follow-up, 490 HCCs (0.21/1000 PY).

Incidence significantly higher among NAFLD patients vs controls (0.02/1000 PY; HR 7.62; 95% CI 5.76–10.09).

Cirrhotics had the highest annual incidence of HCC (10.6/1000 PYs, ranging 1.6 to 23.7 per 1000 PY).

Highest risk in older Hispanics with cirrhosis.

20% of NAFLD patients with HCC had no evidence of cirrhosis.

Absolute risk of HCC higher than accepted thresholds for most patients with NAFLD cirrhosis.

Kanwal F, et al. Gastro 2018
Prevalence of Obesity Not Entirely to Blame…

Age-adjusted incidence of HCC in the US

Kulik Gastroenterology 2019
White Gastroenterology 2017
Observations...

• The natural history of HCV-related HCC continues to evolve in the DAA area; patients with HCV cirrhosis still are at high risk, despite cure
• NAFLD/NASH will likely become the most common underlying cause of HCC in the future
• The prevalence of HCC in NAFLD/NASH patients without cirrhosis is unclear
• There is no guidance on surveillance for non-cirrhotic NASH patients
• Ultrasound is likely to be less sensitive in this population
• This population is likely to be older and have more comorbidities which will limit treatment and affect survival
How Do We Prioritize Those Most In Need?

- Can we develop more rational, “living models” of risk, to inform those most in need of surveillance?
- Risk stratification
- Prioritize resources
- Prioritize workflow
- Diminish psychological harm
# HCC Risk Models for HCV

<table>
<thead>
<tr>
<th>CIRRHOSIS + No SVR</th>
<th>CIRRHOSIS + SVR</th>
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<tr>
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<tr>
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</tbody>
</table>

Available at [www.hccrisk.com](http://www.hccrisk.com)

Courtesy of G. Ioannou
Ioannou AASLD #0094
Ioannou GN et al. J Hepatol 2018
**Online HCC Risk Prediction**

**Web-based tool:**

[www.hccrisk.com](http://www.hccrisk.com)

<table>
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<th></th>
<th>1</th>
<th>2</th>
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<td>Cirrhosis</td>
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<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>SVR</td>
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<td>145</td>
<td>201</td>
<td>250</td>
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<tr>
<td>3-yr HCC risk</td>
<td>25.9%</td>
<td>1.6%</td>
<td>11.1%</td>
<td>7.0%</td>
<td>0.6%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

- **Screening “Recommended”**
- **Screening Not “Recommended”**

Web Developer: Ted James, MD (UNC)
Summary

• Incidence and death rates of HCC continue to increase
• Epidemiology is shifting and will continue to shift in the setting of
  • Effective HCV therapy
  • Increasing obesity
  • An aging population
• Diagnosing HCC at early stages requires identifying at-risk individuals and enrolling them in a surveillance program
• New tools can help us prioritize those at highest risk
• Implementation of HCC surveillance programs has been challenging