Viral hepatitis and Hepatocellular Carcinoma

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Outline

• Risk of HCC in HCV and HBV infections
  • Risk estimates of HCC
  • Determinants of progression to HCC
  • Current and future trends

• Clinical Epidemiology
  • Anti-viral Treatment
  • Surveillance
  • Efficacy and Effectiveness
# Viral Hepatitis and the Attributable Risk of HCC

<table>
<thead>
<tr>
<th></th>
<th>Primary liver cancer cases</th>
<th>HBV (Attributable fraction, %)</th>
<th>HCV (Attributable fraction, %)</th>
<th>Cases attributable to HBV or HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developed countries</td>
<td>110,800</td>
<td>23.3</td>
<td>19.9</td>
<td>48,000</td>
</tr>
<tr>
<td>Developing countries</td>
<td>515,300</td>
<td>58.8</td>
<td>33.4</td>
<td>475,000</td>
</tr>
<tr>
<td>Total</td>
<td>626,100</td>
<td>54.4</td>
<td>31.1</td>
<td>535,000</td>
</tr>
</tbody>
</table>

Adapted from Parkin, 2006.
The Incidence and 5-Year Survival of HCC in United States

HCV Cirrhosis and HCC

Multiple small foci of HCC
Cirrhosis in Background of HCC

- Majority of HCC occurs in the setting of cirrhosis.
- Nearly all HCV patients have cirrhosis.
- Lower % with HBV have cirrhosis, especially in Asians.

Yang CGH 2011;64
Risk Factors and Ethnicity in the US

- Ethnicity of patients with HCC and serological testing for HBsAg and anti-HCV, in absolute numbers

White (n=410)
- Neither
- HBsAg
- Anti-HCV
- Both markers

Black (n=95)
- Neither
- HBsAg
- Anti-HCV
- Both markers

Asian (n=107)
- Neither
- HBsAg
- Anti-HCV
- Both markers

Tracing the Worldwide HCV Epidemic

Linear relationships between HCV seroprevalence and HCC annual mortality rates

Age-standardized death rates from HCC per 100,000 men

HCV prevalence among blood donors - %

Japan type 1920s~
Europe type 1940s~
USA type 1960s~

USA (white)
USA (black)
FSU
HCV Infection
Chronic Hepatitis
Cirrhosis
HCC

1%-3%/year
15%
(10%-30%)
90%
(60%-95%)
100

25 years

Goodgame B, et al., Am J Gastroenterol 2003
Risk Factors for HCC in Chronic HCV

- Older age
- Duration of HCV infection
- Male sex
- Race
- Alcoholism
- Obesity
- Diabetes
- HBV co-infection
- HIV co-infection
- Absence of antiviral treatment, coffee drinking
HCV Viral Factors and Risk of HCC

- HCV Viremia level (HCV RNA)
  - Any level (vs none)
  - High level (vs low):
    - Taiwan study show high HCC risk
    - US studies only as predictor of treatment response
- HCV Genotype GT
  - Possibly GT 1b
    - Meta analysis (1.78 increase in HCC odds)

El-Serag HB. Gastroenterology 2012
### Determinants of HBV Disease Progression

<table>
<thead>
<tr>
<th>HBeAg-positive</th>
<th>HBeAg-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged interval before e-seroconversion</td>
<td>Persistent viral replication</td>
</tr>
<tr>
<td>Age &gt; 40</td>
<td>HBV-DNA</td>
</tr>
<tr>
<td>Mildly, persistently abnormal ALT</td>
<td>Abnormal ALT</td>
</tr>
<tr>
<td>Genotype (C &gt; B)</td>
<td>Precore/BCP mutation</td>
</tr>
<tr>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
</tr>
<tr>
<td>Co-infection with HCV, HDV, HIV</td>
<td></td>
</tr>
</tbody>
</table>

Hepatitis B: Association between viral load and incidence of HCC

HBeAg negative, normal ALT, no liver cirrhosis at entry (n=2,925)

Baseline HBV DNA Level (copies/ml)

- ≥10^6: 13.50%
- 10^5–<10^6: 7.96%
- 10^4–<10^5: 3.15%
- 300–<10^4: 0.89%
- <300: 0.74%

Year of follow-up

Chen CJ et al. JAMA. 2006;295:65–73
Occult HBV Infection and HCC risk

- HBV DNA in serum or liver in persons with serologic recovery from transient HBV infection
- Systematic review of 16 studies
  - none was population-based
  - most had a small number of cases or controls
  - 11 were from Asia (only 1 was in the United States)
  - Pooled adjusted estimate for only 4 longitudinal studies indicated a modest association (RR: 2.83)
  - No convincing evidence that occult HBV is an independent risk factor for HCC or a cofactor with HCV infection in most regions of the world
Alcohol and Viral Hepatitis

![Graph showing the relationship between alcohol intake and infection with HCV or HBV. The graph compares the odds ratio of liver disease progression with and without viral infection, demonstrating higher odds with viral infection.](Gastroenterology 2012; 142:1264-1273.e1)
Tobacco Smoking

- Positive associations and no associations have been reported in different studies.
- Meta-analysis of 16 publications that evaluated the epidemiologic interactions between HBV and HCV infection, cigarette smoking:
  - more than additive interaction between HBV infection and cigarette smoking
  - more than multiplicative interaction between HCV infection and cigarette smoking

Diabetes Is Associated with a Two-fold Increase in Risk of HCC

El-Serag HB, et al, Gastroenterology 2004
Mortality from Cancer in Obese US Men (n=900,053)

Type of Cancer (Highest BMI Category)

- Prostate (≥35) 1.34
- Non-Hodgkin’s Lymphoma (≥35) 1.49
- All Cancers (≥40) 1.52
- All Other Cancers (≥30) 1.68*
- Kidney (≥35) 1.70
- Multiple Myeloma (≥35) 1.71
- Gall Bladder (≥30) 1.76
- Colon and Rectum (≥35) 1.84
- Esophagus (≥30) 1.91*
- Stomach (≥35) 1.94
- Pancreas (≥35) 2.61*
- Liver (≥35) 4.52

Relative Risk of Death (95% Confidence Interval)

Calle, NEJM 2003
### Statins and HCC

(1303 cases, 5212 controls)

<table>
<thead>
<tr>
<th>Statin Use</th>
<th>Unadjusted OR</th>
<th>Adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>0.46</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>(0.40, 0.52)</td>
<td>(0.54, 0.73)</td>
</tr>
<tr>
<td>At least 6 months</td>
<td>0.44</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>(0.38, 0.50)</td>
<td>(0.521, 0.71)</td>
</tr>
<tr>
<td>At least 12 months</td>
<td>0.45</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>(0.39, 0.52)</td>
<td>(0.55, 0.76)</td>
</tr>
<tr>
<td>At least 18 months</td>
<td>0.43</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>(0.36, 0.51)</td>
<td>(0.52, 0.75)</td>
</tr>
</tbody>
</table>

El-Serag HB, et al Gastroenterology 2009
Past and Future (Estimated) US Incidence and Prevalence of HCV Infection

Histologic Fibrosis Stage by Year

Prevalence of Cirrhosis, Decompensated Cirrhosis, and Hepatocellular Cancer 1996–2006

Coffee and Hepatocellular Carcinoma

- Epidemiologic studies: coffee consumption is inversely related to
  - serum liver enzyme activity
  - liver cirrhosis
  - HCC
- For each additional 1 cup of coffee:
  - Case-control studies
    - (0.77, 0.72-0.83)
  - Cohort studies
    - (0.75, 0.65-0.85)
Prevention of HCC

- HBV Vaccination
- Surveillance for HCC
- Treatment of viral hepatitis
HCC Surveillance: Randomized Trials

- Cirrhosis (NONE)
- Hepatitis C infection (NONE)
- Hepatitis B infection (carriers)
  - China
  - Two trials
  - One showed benefit
  - One did not show benefit
Screening for HCC: AASLD Recommendations

- Surveillance for HCC should be performed with ultrasonography (level II)

- Screening should occur every 6 months intervals (level II)

- The surveillance interval does not need to be shortened for patients at higher risk of HCC (level III)

HCC Risk is Reduced after Successful Antiviral Therapy for HCV

Cumulative Incidence of HCC (%)

Follow-up (yr)

No Response
Relapse
Sustained Response

Sustained Response to Interferon Therapy is Associated with Reduced Clinical Endpoints in Patients with Advanced Fibrosis

Veldt, Heathcote, Wedemeyer et al., Ann Inn Med 2007
Sustained Response to Interferon Therapy: HCCs still occur

5-year occurrence
SVR: 9.2% (CI, 0.0%–19.6%)
No SVR: 13.1% (CI, 7.6%–18.6%)
\(P = 0.192\) (log likelihood)

<table>
<thead>
<tr>
<th>No SVR</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>At risk</td>
<td>337</td>
</tr>
<tr>
<td>Events</td>
<td>0</td>
</tr>
</tbody>
</table>

H. Wedemeyer – 8-2010: Antiviral Treatment and Incidence of HCC

Veldt, Heathcote, Wedemeyer et al., Ann Inn Med 2007
HALT-C Data

- No SVR = No Benefit

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.05</td>
</tr>
<tr>
<td>Black</td>
<td>2.04</td>
</tr>
<tr>
<td>Alk Phos</td>
<td>1.01</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.11</td>
</tr>
<tr>
<td>Varices</td>
<td>2.16</td>
</tr>
<tr>
<td>Platelets</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Not readily modifiable with antiviral Tx
Efficacy of HBV Treatment on HCC
Proof of Concept: Cirrhotics

- Randomized controlled trial comparing lamivudine versus placebo
  - Patients with advanced fibrosis or cirrhosis
  - HBV-DNA ($>10^5$ copies/mL) or HBeAg+
  - Study terminated prematurely by DSMB (median Tx=32 mo)

Risk of HCC reduced by 51% by lam (p=0.047).

Results unchanged when 5 HCCs detected in the first year were excluded (p=0.052).

Liaw, NEJM 2004;1521
Prevention of HCC
(Antiviral Treatment or Surveillance)

Efficacy in Clinical Trials and Research Centers

Effectiveness in Community Practice

Efficacy x Access x Correct Diagnosis x Recommendation x Acceptance x Adherence

## Efficacy and Effectiveness

### A Demonstration of the Multiplicative Effect of Factors

<table>
<thead>
<tr>
<th>Example 1: Rx “X”</th>
<th>Example 2: Rx “Y”</th>
<th>Example 3: Rx “X” Modified</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy of Rx “X”</strong></td>
<td><strong>Efficacy of Rx “X”</strong></td>
<td><strong>Efficacy of Rx “X”</strong></td>
</tr>
<tr>
<td>60%</td>
<td>80%</td>
<td>60%</td>
</tr>
<tr>
<td>Access</td>
<td>Access</td>
<td>Access</td>
</tr>
<tr>
<td>x 80%</td>
<td>x 80%</td>
<td>x 90%</td>
</tr>
<tr>
<td>Correct diagnosis</td>
<td>Correct diagnosis</td>
<td>Correct diagnosis</td>
</tr>
<tr>
<td>x 85%</td>
<td>x 85%</td>
<td>x 90%</td>
</tr>
<tr>
<td>Recommend</td>
<td>Recommend</td>
<td>Recommend</td>
</tr>
<tr>
<td>x 85%</td>
<td>x 85%</td>
<td>x 90%</td>
</tr>
<tr>
<td>Acceptance</td>
<td>Acceptance</td>
<td>Acceptance</td>
</tr>
<tr>
<td>x 85%</td>
<td>x 85%</td>
<td>x 90%</td>
</tr>
<tr>
<td>Adherence</td>
<td>Adherence</td>
<td>Adherence</td>
</tr>
<tr>
<td>x 70%</td>
<td>x 70%</td>
<td>x 80%</td>
</tr>
<tr>
<td><strong>Effectiveness of Rx “X”</strong></td>
<td><strong>Effectiveness of Rx “Y”</strong></td>
<td><strong>Effectiveness of Rx “X” modified</strong></td>
</tr>
<tr>
<td>= 21%</td>
<td>= 28%</td>
<td>= 32%</td>
</tr>
</tbody>
</table>

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*El-Serag HB. Gastroenterology. 2007;132:8-10.*
Reasons for Lack of Treatment Among Respondents to the NHANES Hepatitis C Follow-Up Questionnaire

Overall Effectiveness of HCV Treatment in VA

100 with HCV

60 tested for genotype

11 received PEG- INF/ribavirin

6 completed treatment

3 SVR

Kramer: HCV Treatment and SVR in the VA
Viral Hepatitis and HCC

- HCV and HBV-related HCC
  - Modifiable risk factors (alcohol, obesity, diabetes) for individual management
  - Non modifiable risk factors (age, duration, sex) are shaping the current HCC trends
  - Likely to increase in the near future

- Prevention:
  - HBV vaccination
  - Antiviral treatment
  - HCC surveillance
  - Major gaps in effectiveness
Meta-analysis: Effect of SVR vs. no SVR on HCC Risk

- 14 studies (3310 pts with cirrhosis)
- RR = 0.35 (0.26-0.46, 95% CI)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>SVR Events</th>
<th>Total</th>
<th>NSVR Events</th>
<th>Total</th>
<th>Weight</th>
<th>M-H, random, 95% CI</th>
<th>Risk ratio M-H, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azzaroli 2004</td>
<td>0</td>
<td>21</td>
<td>2</td>
<td>50</td>
<td>1.0%</td>
<td>0.46 [0.02, 9.27]</td>
<td></td>
</tr>
<tr>
<td>Braks 2007</td>
<td>1</td>
<td>37</td>
<td>24</td>
<td>76</td>
<td>2.3%</td>
<td>0.09 [0.01, 0.61]</td>
<td></td>
</tr>
<tr>
<td>Bruno 2007 (1)</td>
<td>7</td>
<td>124</td>
<td>122</td>
<td>759</td>
<td>16.0%</td>
<td>0.35 [0.17, 0.73]</td>
<td></td>
</tr>
<tr>
<td>Floreani 2008 (2)</td>
<td>0</td>
<td>40</td>
<td>5</td>
<td>38</td>
<td>1.1%</td>
<td>0.09 [0.00, 1.51]</td>
<td></td>
</tr>
<tr>
<td>Hasegawa 2007 (3)</td>
<td>3</td>
<td>48</td>
<td>16</td>
<td>57</td>
<td>6.3%</td>
<td>0.22 [0.07, 0.72]</td>
<td></td>
</tr>
<tr>
<td>Hung 2006</td>
<td>5</td>
<td>73</td>
<td>11</td>
<td>59</td>
<td>8.7%</td>
<td>0.37 [0.14, 1.00]</td>
<td></td>
</tr>
<tr>
<td>Nishiguchi 1995</td>
<td>0</td>
<td>7</td>
<td>2</td>
<td>38</td>
<td>1.0%</td>
<td>0.97 [0.05, 18.43]</td>
<td></td>
</tr>
<tr>
<td>Okanoue 1999</td>
<td>0</td>
<td>2</td>
<td>7</td>
<td>38</td>
<td>1.3%</td>
<td>0.87 [0.06, 11.79]</td>
<td></td>
</tr>
<tr>
<td>Shioda 1999</td>
<td>4</td>
<td>204</td>
<td>18</td>
<td>448</td>
<td>7.6%</td>
<td>0.49 [0.17, 1.42]</td>
<td></td>
</tr>
<tr>
<td>Shiratori 2005</td>
<td>11</td>
<td>64</td>
<td>73</td>
<td>207</td>
<td>26.9%</td>
<td>0.49 [0.28, 0.86]</td>
<td></td>
</tr>
<tr>
<td>Tanaka 1998</td>
<td>0</td>
<td>8</td>
<td>10</td>
<td>47</td>
<td>1.2%</td>
<td>0.25 [0.02, 3.96]</td>
<td></td>
</tr>
<tr>
<td>Velct 2006</td>
<td>3</td>
<td>142</td>
<td>32</td>
<td>337</td>
<td>6.4%</td>
<td>0.22 [0.07, 0.71]</td>
<td></td>
</tr>
<tr>
<td>Yoshida 1999 (4)</td>
<td>1</td>
<td>53</td>
<td>30</td>
<td>168</td>
<td>2.2%</td>
<td>0.11 [0.01, 0.76]</td>
<td></td>
</tr>
<tr>
<td>Yu 2006</td>
<td>9</td>
<td>85</td>
<td>27</td>
<td>80</td>
<td>18.3%</td>
<td>0.31 [0.16, 0.63]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>908</strong></td>
<td><strong>2402</strong></td>
<td><strong>2402</strong></td>
<td><strong>2402</strong></td>
<td><strong>0.35 [0.26, 0.46]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\text{Chi}^2 = 8.67, \text{df} = 13 (P = .80)$
Test for overall effect: $Z = 7.06 (P < .00001)$