Evidence for a rising burden of hepatocellular carcinoma

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• Epidemiology-general

• Causes:
  - Viral
  - Non-viral

• HCC Israel

• Prevention
Hepatocellular Carcinoma-facts (1)

- 700,000 cases/yr worldwide
  - 6th among cancers worldwide

- Leading cause of cancer-death Asia/Middle East

- 85% of HCC cases occur in Eastern and South-east Asia and Sub Saharan Africa

- Leading cause of death in cirrhotic patients

Liver Cancer Incidence: Sixth Most Common Cancer Worldwide¹

- HCC is the most common primary liver malignancy in adults²

Regional variation in incidence rates of HCC

El-Serag NEJM 2011
Regional variations in mortality rates of HCC

El-Serag H et al, Gastroenterology 2007
HCC standardised incidence rates per 100K population, world regions 2008
HCC European standardized incidence rates per 100K, EU-27 countries
Role of IL-6 in gender disparity in HCC

Karin M, Science 2007
HCC has the fastest growing death rate in the USA.

El-Serag H et al, Gastroenterology 2007
Hepatocellular Carcinoma-facts (2)

- 1985-2009 incidence has increased 3-fold
  - Estimation of new cases: 21,370
  - Estimation of deaths: 17,000

- Incidence increasing in United States and Europe
HCC number of new Cases per year and Incidence Rates per 100K (UK)
HCC European incidence rates per 100K by Sex, (UK) 1975-2009
Incidence and 5-Year Survival Rates for Patients with HCC in the USA, 1973–2007.

El-Serag H et al, Gastroenterology 2007
HCC incidence tripled over the last three decades in the USA
Incidence of HCC Is Increasing

*Primary liver cancer. UK=United Kingdom; US=United States.

Hepatocellular Carcinoma-facts (3)

• Most patients with HCC in have liver cirrhosis

• Hepatitis B virus is the most frequent underlying cause worldwide

• In the US, HCV-related HCC is the most prevalent (50-70% of cases)

• Other risk factors include alcohol use, NAFLD, inherited liver disease, hemochromatosis
Incidence of HCC in patients with cirrhosis according to etiology

Fattovich G, Gastroenterology 2004
Viruses enhance the carcinogenic effect of alcohol

El-Serag H et al, Gastroenterology 2011
Projected future incidence in HCC from HCV
Aging HCV population and the risk of HCC

Davis GL, Gastroenterology 2010
Why is the incidence rising?

Increasing prevalence of patients with cirrhosis

- Rising incidence of cirrhosis
  - HCV (main reason)
  - HBV
  - Other
- Improved survival of patients with cirrhosis

El-Serag HB, Gastroenterology 2004
Incidence of cirrhosis is increasing

El-Serag HB, Gastroenterology 2012
• USA HCV-infected population is estimated to decline from 3.15 million in 2005 to 2.47 million in 2021.
• Disease burden will increase as the population ages.
• Mortality rate will increase from 2.1% to 3.1%.
• Diagnosed population was 50% of the total infections, less than 2% of the total infections will be treated.
Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born during 1945–1965

- Adults born during 1945–1965 should receive one-time testing for HCV without prior ascertainment of HCV risk.
- All persons with identified HCV infection should receive a brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment services for HCV infection and related conditions.
Expected rise in HCV-HCC Tx candidates according to birth cohort
What are the settings for NAFLD

- **obesity**
  - steatosis
    - steatohepatitis
      - fibrosis
      - cirrhosis
      - liver-related morbidity and mortality

- metabolic disorders
  - T2DM
  - CVD, malignancy

Obesity kills -

Hepatocellular carcinomas in High Fat Diet (HFD) fed mice

Park EJ et al Cell 2010, Starlet BQ Hepatology 2010
Diabetes, MS, NAFLD and HCC
Obesity increases risk of cancer

Calle EE et al. NEJM 2003

[Graph showing relative risk of death for various cancers associated with obesity for men. The x-axis represents relative risk, with values ranging from 0 to 7, and the y-axis represents different types of cancer, such as prostate, non-Hodgkin's lymphoma, and others, with varying relative risk values indicated by markers.]
Risk estimates for the association between diabetes and risk of HCC

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lawson et al. 1986</td>
<td>3.9%</td>
<td>4.88 [1.83, 13.00]</td>
<td></td>
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<tr>
<td>Yu et al. 1991</td>
<td>4.9%</td>
<td>3.30 [1.51, 7.23]</td>
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<tr>
<td>Fukuda et al. 1993</td>
<td>7.1%</td>
<td>0.92 [0.60, 1.41]</td>
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<tr>
<td>Hadziyannis et al. 1995</td>
<td>5.0%</td>
<td>1.30 [0.60, 2.79]</td>
<td></td>
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<tr>
<td>La Vecchia et al. 1997</td>
<td>7.2%</td>
<td>2.10 [1.39, 3.17]</td>
<td></td>
</tr>
<tr>
<td>Shibata et al. 1998</td>
<td>4.9%</td>
<td>3.54 [1.63, 7.67]</td>
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</tr>
<tr>
<td>Lagiou et al. 2000</td>
<td>5.8%</td>
<td>1.86 [0.99, 3.50]</td>
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</tr>
<tr>
<td>El-Serag et al. 2001</td>
<td>8.2%</td>
<td>1.27 [1.02, 1.58]</td>
<td></td>
</tr>
<tr>
<td>Hassan et al. 2002</td>
<td>4.7%</td>
<td>4.30 [1.88, 9.82]</td>
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</tr>
<tr>
<td>Matsuo et al. 2003</td>
<td>6.3%</td>
<td>2.51 [1.46, 4.32]</td>
<td></td>
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<tr>
<td>Yuan et al. 2004</td>
<td>6.6%</td>
<td>2.70 [1.65, 4.43]</td>
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<tr>
<td>Davila et al. 2005</td>
<td>8.6%</td>
<td>3.08 [2.74, 3.46]</td>
<td></td>
</tr>
<tr>
<td>Rousseau et al. 2006</td>
<td>3.7%</td>
<td>3.10 [1.10, 8.77]</td>
<td></td>
</tr>
<tr>
<td>Polesel et al. 2009</td>
<td>4.8%</td>
<td>3.70 [1.66, 8.22]</td>
<td></td>
</tr>
<tr>
<td>Tung et al. 2010</td>
<td>3.6%</td>
<td>1.20 [0.42, 3.45]</td>
<td></td>
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<tr>
<td>Donadon et al. 2010</td>
<td>7.3%</td>
<td>2.50 [1.70, 3.68]</td>
<td></td>
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<tr>
<td>Hassan et al. 2010</td>
<td>7.4%</td>
<td>4.40 [3.04, 6.38]</td>
<td></td>
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</tbody>
</table>

**Total (95%, CI)**

100.0%

2.40 [1.85, 3.11]

Heterogeneity: Tau² = 0.20; Chi² = 92.29, df = 16 (P < 0.00001); I² = 83%

Test for overall effect: Z = 6.68 (P < 0.00001)
Association Between NAFLD and Risk for HCC: Systematic Review

- 17 cohort studies, 18 case-control and cross-sectional studies, and 26 case series.

- NAFLD/NASH without cirrhosis cases had a minimal risk for HCC (cumulative HCC mortality 0%–3% for periods up to 20 y).

- NASH and cirrhosis (cumulative incidence ranging from 2.4%-12.8%).

- There is an association between NAFLD/NASH and increased risk of HCC, limited to individuals with cirrhosis.

White D et al, CGH 2012
HCC In Israel
Reported annual incidence of HCC in Israel
Hadassha-TLVMC-HCC database

- Database for HCC patients shared by two liver units in Israel since 6/2011

  • Newly diagnosed HCC (6/2011 to 9/2012 (15 months))

  • Each center individually manage its own cohort

  • The diagnosis of HCC is according with the EASL criteria.
### Basic Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>80 HCC patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67.6±11</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>65(81)</td>
</tr>
<tr>
<td>HCV</td>
<td>42 (52)</td>
</tr>
<tr>
<td>NASH</td>
<td>20(25)</td>
</tr>
<tr>
<td>HBV</td>
<td>11(13.7)</td>
</tr>
<tr>
<td>Alc comorbidity</td>
<td>10(12)</td>
</tr>
<tr>
<td>Alc alone</td>
<td>3(3.7)</td>
</tr>
<tr>
<td>Crypto</td>
<td>4(5)</td>
</tr>
<tr>
<td>CPS A/B/C</td>
<td>65/13/2</td>
</tr>
<tr>
<td>CLIP 0/1/2+</td>
<td>34/27/19</td>
</tr>
<tr>
<td>BCLC A/B/C/D</td>
<td>19/23/36/2</td>
</tr>
</tbody>
</table>
• Etiology of HCC
  – HCV 52%,
  – **NASH 25%**
  – Alcohol (alone + comorbidity) 16%
  – HBV 13.5%
  – Cryptogenic 4.9%.

• Fatty liver is becoming the second risk factor for HCC in Israel
  – NASH: cryptogenic cirrhosis with metabolic syndrome, while viral, alcohol and all other etiology are ruled out.
# Results – Treatment

<table>
<thead>
<tr>
<th>Treatments</th>
<th>80 HCC patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TACE</td>
<td>39(48.8)</td>
</tr>
<tr>
<td>Resection</td>
<td>14(17.5)</td>
</tr>
<tr>
<td>OLT</td>
<td>7(8.7)</td>
</tr>
<tr>
<td>RFA</td>
<td>11(13.5)</td>
</tr>
<tr>
<td>NEXAVAR</td>
<td>17(21)</td>
</tr>
<tr>
<td>SIRT</td>
<td>3(3.7)</td>
</tr>
<tr>
<td>No Treatment</td>
<td>8(9.9)</td>
</tr>
</tbody>
</table>
Prevention
Effect of SVR on HCC development

Morgan TR et al, Hepatology 2011
Ogawa H et al, J Hep 2012
Eradication of HCV and the development of HCC

Figure 1. Forest plot of adjusted hazard effects in persons at all stages of fibrosis.

Figure 2. Forest plot of adjusted hazard effects in persons with advanced liver disease.

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>log(Hazard Ratio)</th>
<th>SE</th>
<th>Total</th>
<th>Weight, %</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>SVR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Braks et al, 2007 (37)</td>
<td>-1.966</td>
<td>0.601</td>
<td>37</td>
<td>76</td>
<td>0.14 (0.04–0.45)</td>
</tr>
<tr>
<td>Bruno et al, 2007 (38)</td>
<td>-0.954</td>
<td>0.425</td>
<td>124</td>
<td>759</td>
<td>0.39 (0.17–0.89)</td>
</tr>
<tr>
<td>Cardoso et al, 2010 (40)</td>
<td>-1.120</td>
<td>0.514</td>
<td>103</td>
<td>204</td>
<td>0.33 (0.12–0.89)</td>
</tr>
<tr>
<td>Hasegawa et al, 2007 (64)</td>
<td>-1.690</td>
<td>0.755</td>
<td>48</td>
<td>57</td>
<td>0.18 (0.04–0.81)</td>
</tr>
<tr>
<td>Hung et al, 2006 (65)</td>
<td>-1.468</td>
<td>0.622</td>
<td>73</td>
<td>59</td>
<td>0.23 (0.07–0.78)</td>
</tr>
<tr>
<td>Morgan et al, 2010 (52)</td>
<td>-1.721</td>
<td>0.764</td>
<td>140</td>
<td>309</td>
<td>0.18 (0.04–0.80)</td>
</tr>
<tr>
<td>van der Meer et al, 2012(63)</td>
<td>-1.592</td>
<td>0.416</td>
<td>192</td>
<td>338</td>
<td>0.20 (0.09–0.46)</td>
</tr>
<tr>
<td>Velosa et al, 2011 (60)</td>
<td>-2.433</td>
<td>1.108</td>
<td>39</td>
<td>91</td>
<td>0.09 (0.01–0.77)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>756</td>
<td>1893</td>
<td>0.23 (0.16–0.35)</td>
</tr>
</tbody>
</table>

Heterogeneity: tau-square = 0.00; chi-square = 3.64; P = 0.82; I² = 0%
Test for overall effect: Z = 7.21; P < 0.001

Test for overall effect: Z = 10.80; P < 0.001

Morgan RL, Ann Int Med 2013
Effect of HBV vaccination on annual incidence of HCC in Alaska

McMahon BJ et al, Hepatology 2011
Primary Prevention of HCC

- Vaccinate to HBV!
- Treat HCV with effective treatment
- Suppress HBV
- Abstain from alcohol?
- Weight loss?
Ten studies were retrieved (2,260 HCC cases), 6 case– control studies from Europe and Japan (1551 cases) and 4 cohort studies from Japan (709 cases).

The overall Relative risk RR was 0.59 (95% CI 0.49-0.72). RR for low or moderate coffee drinkers was 0.70 (95% CI 0.57-0.85), and for high drinkers was 0.45 (95% CI 0.38-0.53).

The present analysis provides evidence that the inverse relation between coffee and HCC is real, though inference on causality remains open to discussion.
Conclusion

• Burden of HCC is increasing

• Common risk factors are cirrhosis from any cause (main reasons HCV, HBV, NASH)

• Primary prevention is paramount

• Data about incidence of epidemiology of HCC in Israel is lacking
Recipe

IRISH (HOT) 2 SERVINGS

- 2 cups strong coffee
- 2 tablespoons orange juice
- 2 teaspoons lemon juice
- whipped cream

Mix coffee, orange juice and lemon juice.

Pour into Irish whiskey glass.

Top with whipped cream.
Thank You For Your Attention