HEPATOCELLULAR CARCINOMA:
AN OVERVIEW

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Dean of Research, Edith Cowan University
Death rates have decreased for almost all diseases

Exception: Liver disease (increased by 400% since 1970)

Williams et al. (2014) The Lancet
<table>
<thead>
<tr>
<th>Sex/Cancer Site or Type</th>
<th>Trend 1</th>
<th>Trend 2</th>
<th>Trend 3</th>
<th>Trend 4</th>
<th>Trend 5</th>
<th>Trend 6</th>
<th>AAPC 2003-2012</th>
<th>AAPC 2008-2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>Years</td>
<td>APC</td>
<td>Years</td>
<td>APC</td>
<td>Years</td>
<td>APC</td>
<td>Years</td>
<td>APC</td>
</tr>
<tr>
<td>Both sexes</td>
<td>1975-1984</td>
<td>0.5°</td>
<td>1984-1991</td>
<td>0.3°</td>
<td>1991-1994</td>
<td>-0.5</td>
<td>1994-1998</td>
<td>-1.3°</td>
</tr>
<tr>
<td>Men</td>
<td>1975-1979</td>
<td>1.0°</td>
<td>1979-1990</td>
<td>0.3°</td>
<td>1990-1993</td>
<td>-0.5</td>
<td>1993-2001</td>
<td>-1.5°</td>
</tr>
<tr>
<td>Women</td>
<td>1975-1990</td>
<td>0.6°</td>
<td>1990-1994</td>
<td>-0.2</td>
<td>1994-2002</td>
<td>-0.8°</td>
<td>2002-2012</td>
<td>-1.4°</td>
</tr>
<tr>
<td>Children (ages 0-14 years)</td>
<td>1975-1996</td>
<td>-2.9°</td>
<td>1996-2012</td>
<td>-1.3°</td>
<td>2002-2012</td>
<td>-2.0°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children (ages 0-19 years)</td>
<td>1975-1998</td>
<td>-2.7°</td>
<td>1998-2002</td>
<td>0.0</td>
<td>2002-2012</td>
<td>-2.0°</td>
<td></td>
<td></td>
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<tr>
<td>Top 17 cancers among men</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>1975-1978</td>
<td>0.8°</td>
<td>1978-1984</td>
<td>-0.3</td>
<td>1984-1990</td>
<td>-1.3°</td>
<td>1990-2002</td>
<td>-2.0°</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1975-1986</td>
<td>-0.8°</td>
<td>1986-2000</td>
<td>-0.3°</td>
<td>2000-2012</td>
<td>0.3°</td>
<td></td>
<td>0.3°</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1975-1980</td>
<td>0.5°</td>
<td>1980-1987</td>
<td>-0.7°</td>
<td>1987-1985</td>
<td>0.1</td>
<td>1985-2012</td>
<td>-0.9°</td>
</tr>
<tr>
<td>Liver and intrahepatic bile duct</td>
<td>1975-1979</td>
<td>0.3°</td>
<td>1979-1987</td>
<td>2.3°</td>
<td>1987-1996</td>
<td>3.9°</td>
<td>1996-1999</td>
<td>0.6</td>
</tr>
<tr>
<td>Top 17 cancers among women</td>
<td></td>
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<tr>
<td>Breast</td>
<td>1975-1990</td>
<td>0.4°</td>
<td>1990-1995</td>
<td>-1.8°</td>
<td>1995-1998</td>
<td>-3.3°</td>
<td>1998-2012</td>
<td>-1.9°</td>
</tr>
<tr>
<td>Colon and rectum</td>
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<td></td>
<td>-2.9°</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1975-1984</td>
<td>0.8°</td>
<td>1984-2000</td>
<td>0.1</td>
<td>2000-2012</td>
<td>0.4°</td>
<td></td>
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<td>0.7</td>
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<td>-0.4°</td>
<td>1999-2012</td>
<td>-1.2°</td>
<td></td>
<td>-1.2°</td>
</tr>
<tr>
<td>Corpus and uterus, NOS</td>
<td>1975-1989</td>
<td>-1.6°</td>
<td>1989-1997</td>
<td>-0.7°</td>
<td>1997-2009</td>
<td>0.3°</td>
<td>2009-2012</td>
<td>2.5°</td>
</tr>
<tr>
<td></td>
<td>2000-2008</td>
<td>1.4°</td>
<td>2008-2012</td>
<td>3.1°</td>
<td>2008-2012</td>
<td>3.1°</td>
<td></td>
<td>2.2°</td>
</tr>
</tbody>
</table>

Ryerson et al. Cancer 2016;122:1312
CURRENT STATUS

- 5th most common cancer
- 2nd most common cause of cancer death
- Accounts for 7% of all global cancers
  - 85% of all HCC occurs in SEA and African populations
- Peak incidence at age 70 years
RISK FACTORS FOR HCC

- SEER database study of 6,991 HCC cases compared with 255,000 controls
  - HCV OR 40
  - HBV OR 11
  - Alcohol OR 4.1
  - Diabetes/Obesity OR 2.5
- Treatment of the above reduces the risk of HCC

Welzel et al Am J Gastroenterol 2013

PREDICTORS OF HCC

- Prevalence + risk
- Population attributable fraction of known risk factors is 65%
  - Diabetes/Obesity 37%
  - Alcohol 28%
  - HCV 22%
  - HBV 6%

Welzel et al Am J Gastroenterol 2013
Mortality from cancer in obese US men.

Inflammation and hyperinsulinemia increase risk of HCC independent of obesity


NAFLD IN ADULTS
WA DATA

- Estimate 28% of adult males and 23% of adult females have US detected NAFLD

Table 1. Baseline Characteristics of the Study Cohort Stratified by Sex and Age

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (N = 288)</td>
<td>All (N = 300)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>51 [37–68]</td>
<td>50 [35–67]</td>
</tr>
<tr>
<td>Serum ferritin (μg/L)</td>
<td>219 [133–349]</td>
<td>74 [40–131]</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.1 [24.7–29.7]</td>
<td>25.4 [22.7–29.6]</td>
</tr>
<tr>
<td>≥25</td>
<td>72%</td>
<td>54%</td>
</tr>
<tr>
<td>≥30</td>
<td>23%</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td>&lt;50 y (N = 300)</td>
<td>&lt;50 y (N = 300)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>37 [28–42]</td>
<td>35 [28–41]</td>
</tr>
<tr>
<td>Serum ferritin (μg/L)</td>
<td>209 [125–319]</td>
<td>71 [40–131]</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.4 [24.0–29.3]</td>
<td>24.3 [21.9–28.3]</td>
</tr>
<tr>
<td>≥25</td>
<td>69%</td>
<td>44%</td>
</tr>
<tr>
<td>≥30</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>≥50 y (N = 300)</td>
<td>≥50 y (N = 300)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>67 [58–72]</td>
<td>67 [57–72]</td>
</tr>
<tr>
<td>Serum ferritin (μg/L)</td>
<td>240 [139–373]</td>
<td>115 [70–177]</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.4 [25.1–30.0]</td>
<td>26.8 [23.5–30.1]</td>
</tr>
<tr>
<td>≥25</td>
<td>76%</td>
<td>63%</td>
</tr>
<tr>
<td>≥30</td>
<td>26%</td>
<td>26%</td>
</tr>
</tbody>
</table>

HCV Infection → Chronic Hepatitis → Cirrhosis → HCC/ESLD/Death

1-9 % per year
Hepatocellular Carcinoma in the Absence of Cirrhosis in United States Veterans Is Associated With Nonalcoholic Fatty Liver Disease

Sahil Mittal,*† Hashem B. El-Serag,*‡,§ Yvonne H. Sada,*‡ Fasiha Kanwal,*‡,§ Zhigang Duan,*§ Sarah Temple,*§ Sarah B. May,*§ Jennifer R. Kramer,*§ Peter A. Richardson,*§ and Jessica A. Davila*‡

Figure 1. Proportion of HCC patients with or without evidence of cirrhosis by risk factor.

Clinical Gastroenterology and Hepatology 2016;14:124–131
Majority of noncirrhotic HCC in NAFLD do not have significant fibrosis (F2 or less)
Mainly have steatosis and inflammation

Mittal et al Clin Gastroenterol Hepatol 2016; Baffy et al J Hepatol 2012
Human Liver Progenitor Cell Lines
Are Readily Established From Non-Tumorous Tissue
Adjacent to Hepatocellular Carcinoma

Aibin Zhang,1,3 Roslyn London,2 Frederik Michael Schulz,2 Philippe Wilfred Roger Giguère-Simmonds,2 Luc Delriviere,4 Harsha Chandraratana,4 Kathy Hardy,3 Shusen Zheng,1 John K. Olynuk,3,6,7 and George Yeoh2,3
Liver regeneration during acute and chronic injury

**ACUTE INJURY**

- Hepatocyte

**CHRONIC INJURY**

- Liver progenitor cell (LPC)
- Cholangiocyte
- Tumorigenic LPC

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**Healthy liver**

**Chronically injured liver**

H&E
**Control**

Mild

Mod

Severe

Mild

Mod

Severe

Mild

Mod

Severe

0

25

50

75

100

125

150

175

Hepatitis C

Hereditary Hemochromatosis

Alcoholic Liver Disease

LPC Count (n)

Lowes et al Am J Pathol 1999
WHAT IS IMPORTANT FOR CLINICIANS?

- Main risk = cirrhosis (advanced fibrosis)
- How to diagnose cirrhosis
  - Clinical – advanced liver disease
  - Biochemical – blood tests (e.g. hepascore, low platelets, AST/ALT ratio, low albumin, prolonged PT or INR)
  - Imaging – FibroScan/elastography, US/CT/MR (limitations)
- Biopsy
HCC - WHY DiAGNOSE EARLY?

- Symptomatic HCC - 0-10% 5 year survival
- Epidemiological data supporting screening
  - 37% reduction in mortality in Chinese study of 19,000 subjects randomised to screening vs no screening
- Screen detected HCC often smaller and more likely to be treatable

Zhang et al J Cancer Res Clin Oncol 2004
SCREENING FOR HCC

- US National Cancer Institute
  - Based on fair evidence, screening of persons at elevated risk does not result in a decrease in mortality from hepatocellular cancer

http://www.cancer.gov/cancertopics/pdq/screening/hepatocellular/HealthProfessional/page1
**Table 3. Groups for whom HCC surveillance in recommended or in whom the risk of HCC is increased, but in whom efficacy of surveillance has not been demonstrated**

<table>
<thead>
<tr>
<th>Population group</th>
<th>Threshold incidence for efficacy of surveillance (&gt;.25 LYG)(%/year)</th>
<th>Incidence of HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian male hepatitis B carriers over age 40</td>
<td>0.2</td>
<td>0.4-0.6%/year</td>
</tr>
<tr>
<td>Asian female hepatitis B carriers over age 50</td>
<td>0.2</td>
<td>0.3-0.6%/year</td>
</tr>
<tr>
<td>Hepatitis B carrier with family history of HCC</td>
<td>0.2</td>
<td>Incidence higher than without family history</td>
</tr>
<tr>
<td>African/North American Blacks with hepatitis B</td>
<td>0.2</td>
<td>HCC occurs at a younger age</td>
</tr>
<tr>
<td>Cirrhotic hepatitis B carriers</td>
<td>0.2-1.5</td>
<td>3-8%/yr</td>
</tr>
<tr>
<td>Hepatitis C cirrhosis</td>
<td>1.5</td>
<td>3-5%/yr</td>
</tr>
<tr>
<td>Stage 4 primary biliary cirrhosis</td>
<td>1.5</td>
<td>3-5%/yr</td>
</tr>
<tr>
<td>Genetic hemachromatosis and cirrhosis</td>
<td>1.5</td>
<td>Unknown, but probably &gt; 1.5%/year</td>
</tr>
<tr>
<td>Alpha 1-antitrypsin deficiency and cirrhosis</td>
<td>1.5</td>
<td>Unknown, but probably &gt; 1.5%/year</td>
</tr>
<tr>
<td>Other cirrhosis</td>
<td>1.5</td>
<td>Unknown</td>
</tr>
<tr>
<td>Surveillance benefit uncertain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B carriers younger than 40 (males) or 50 (females)</td>
<td>0.2</td>
<td>&lt;0.2%/yr</td>
</tr>
<tr>
<td>Hepatitis C and stage 3 fibrosis</td>
<td>1.5</td>
<td>&lt;1.5%/yr</td>
</tr>
<tr>
<td>Non-cirrhotic NAFLD</td>
<td>1.5</td>
<td>&lt;1.5%/yr</td>
</tr>
</tbody>
</table>

6 monthly US + AFP

Bruix and Sherman Hepatology 2011

WHICH TESTS?

- **AFP**
  - Raised or rising
  - Low sensitivity 39-97% (66%)
  - Low PPV 9-36%

- **Mass on imaging**
  - US
  - 4 phase multi-detector CT
  - Contrast enhanced MR (primovist)

Bruix and Sherman Hepatology 2011; http://www.cancer.gov/cancertopics/pdq/screening/hepatocellular/HealthProfessional/page1
Figure 2. Diagnostic algorithm and recall policy in cirrhotic liver. *Using extracellular MR contrast agents or gadobenate dimeglumine. **Using the following diagnostic criteria: arterial phase hyperenhancement (APHE) and washout on the portal venous phase. ***Using the following diagnostic criteria: arterial phase hyperenhancement (APHE) and mild washout after 60 s. ****Lesion <1 cm stable for 12 months (three controls after four months) can be shifted back to regular six months surveillance. *****Optional for centre-based programmes.
STAGING & TREATMENT

HCC in cirrhotic liver

Very early stage (0)
Single <2 cm
Preserved liver function\(^1\), PS 0

Early stage (A)
Single or 2-3 nodules <3 cm
Preserved liver function\(^1\), PS 0

Intermediate stage (B)
Multinodular, unresectable
Preserved liver function\(^1\), PS 0

Advanced stage (C)
Portal invasion/extrahepatic spread
Preserved liver function\(^1\), PS 1\(^2\)-2

Terminal stage (D)
Not transplantable HCC
End-stage liver function
PS 3-4

Prognostic stage

Solitary
Optimal surgical candidate\(^2\)

2-3 nodules ≤3 cm
Transplant candidate

Yes
No

Treatment\(^4\)
Ablation
Resection
Transplant
Ablation
Chemoembolization
Systemic therapy\(^5\)
BSC

Survival
>5 years
>2.5 years
≥10 months
3 months

SUMMARY

- HCC is becoming the commonest cause of death in end stage liver disease
- High index of suspicion for early detection and diagnosis
  - Need to know which patients are cirrhotic
  - ?? NAFLD – when to assess ??
- Any time a cirrhotic deteriorates - ? Is HCC present
PREVENTION OF HCC
PREVENTION OF HCC? THE FUTURE

- 100 mg day in cirrhotic HBV subjects
- RR 0.44 compared with no antiplatelet
- No increased risk of bleeding

Lee et al Hepatology 2017
QUESTIONS?