Attributable fraction of NAFLD and Related Disorders to Hepatocellular Carcinoma in the United States

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Disclosure Statement

- I have no financial disclosures or conflicts of interest
Liver Cancer Trends, 1978-2012  (Cancer Incidence in 5 Continents)

[Graphs showing liver cancer trends in Eastern Asia, Southern Europe, North-Western Europe, North America, and South America, with data for various countries such as China, Japan, Korea, Croatia, Italy, Malta, Slovenia, Spain, Denmark, Iceland, Ireland, Norway, Sweden, United Kingdom, Canada, Costa Rica, Puerto Rico, United States, Brazil, Colombia, and Ecuador.]
Liver Cancer Trends, 1978-2012  (Cancer Incidence in 5 Continents)

Age-Adjusted Rate per 100,000 person-years

- Eastern Asia
  - China
  - Japan
  - Korea

- Southern Europe
  - Croatia
  - Italy
  - Malta
  - Slovenia
  - Spain

- North-Western Europe
  - Denmark
  - Iceland
  - Ireland
  - Norway
  - Sweden
  - United Kingdom

- North America
  - Canada
  - Costa Rica
  - Puerto Rico
  - United States

- South America
  - Brazil
  - Colombia
  - Ecuador

Petrick JL et al., Int J Cancer, In press
Liver Cancer Trends, 1978-2012  (Cancer Incidence in 5 Continents)

Petrick JL et al., Int J Cancer, In press
HCC incidence rates, SEER-13, 1992-2016
HCC incidence rates, SEER-13, 1992-2016
HCC incidence rates, SEER-13, 1992-2016

- API: 9.07
- Hispanic: 9.28
- NHB: 9.66
- NHW: 4.06
HCC incidence rates, SEER-13, 1992-2016

- API: 9.28
- Hispanic: 9.66
- NHB: 9.07
- NHW: 4.06
Liver Cancer Incidence in the U.S. by state

Data Source: CDC WONDER
Risk Factors for HCC

- Hepatitis B Virus (HBV)
- Hepatitis C Virus (HCV)
- Aflatoxin
- Alcohol consumption
- Tobacco
- Rare Genetic Disorders
- Diabetes, Obesity, Metabolic Syndrome, Fatty Liver Disease

Inflammation leads to Fibrosis, then Cirrhosis, finally HCC.
NAFLD Questions

- What is the contribution of NAFLD to HCC incidence?
- What is the contribution of NAFLD to mortality?
NAFLD Questions

- What is the contribution of NAFLD to HCC incidence?
- What is the contribution of NAFLD to mortality?
SEER-Medicare Linked Database

Cancer diagnoses

Medicare insurance claims

SEER-Medicare Linked Database

Medicare HEALTH INSURANCE

Entitled to/Cuá derecho a
HOSPITAL (PART A) 03-01-2016
MEDICAL (PART B) 03-01-2016

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## HCC cases and controls in SEER-Medicare analysis

<table>
<thead>
<tr>
<th></th>
<th>HCC Cases (n=15,272)</th>
<th>Controls (n=396,897)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age, years</strong></td>
<td>77.3</td>
<td>77.0</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>10,180 (66.7)</td>
<td>156,872 (39.5)</td>
</tr>
<tr>
<td>Women</td>
<td>5,092 (33.3)</td>
<td>240,025 (60.5)</td>
</tr>
<tr>
<td><strong>Year of diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000-2003</td>
<td>2,973 (19.5)</td>
<td>112,147 (28.3)</td>
</tr>
<tr>
<td>2004-2007</td>
<td>3,639 (23.8)</td>
<td>74,178 (18.7)</td>
</tr>
<tr>
<td>2008-2011</td>
<td>4,160 (27.2)</td>
<td>74,919 (18.9)</td>
</tr>
<tr>
<td>2012-2015</td>
<td>4,500 (29.5)</td>
<td>135,653 (34.2)</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
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</tr>
<tr>
<td>White</td>
<td>10,876 (71.2)</td>
<td>330,861 (83.4)</td>
</tr>
<tr>
<td>Black</td>
<td>1,190 (7.8)</td>
<td>31,670 (8.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>1,692 (11.1)</td>
<td>13,273 (3.3)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>621 (4.1)</td>
<td>8,855 (2.2)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>893 (5.8)</td>
<td>12,238 (3.1)</td>
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</tbody>
</table>
HCC risk factors identified by ICD codes

**Hepatitis C virus**
- Chronic HCV infection
- Alcohol
- Any alcohol-related disorders

**Hepatitis B virus**
- Chronic HBV infection
- Smoking
- Chronic obstructive pulmonary disease

**Metabolic disorders**
- NAFLD
- Impaired fasting glucose
- Type II diabetes
- Obesity
- Metabolic syndrome

**Genetic disorders**
- Porphyrias
- Hemochromatosis
- Wilson's disease
- Alpha-1 Antitrypsin deficiency
- Glycogen storage disease
Odds ratios for HCC risk factors

- **HCV**: All - 52.2, Men - 34.8, Women - 78.6
- **HBV**: All - 18.5, Men - 24.8
- **Alcohol**: All - 10.8, Men - 7.0, Women - 6.3
- **Genetic**: All - 7.1, Men - 8.9
- **Metabolic**: All - 2.9, Men - 2.9, Women - 2.9
- **COPD**: All - 1.2, Men - 1.2, Women - 1.2
Odds ratios for HCC risk factors by race-ethnicity

- **HCV**: 53.5 (Black), 58.5 (White), 52.3 (Asian), 37.2 (Hispanic)
- **HBV**: 30.3 (Black), 7.9 (White), 4.2 (Asian), 11.3 (Hispanic)
- **Alcohol**: 8.0 (Black), 7.7 (White), 5.3 (Asian), 3.8 (Hispanic)
- **Genetic**: 2.9 (Black), 2.6 (White), 2.6 (Asian), 2.8 (Hispanic)
- **Metabolic**: 1.3 (Black), 1.9 (White), 1.3 (Asian), 3.3 (Hispanic)
- **COPD**: 1.1 (Black), 1.3 (White), 1.2 (Asian), 1.2 (Hispanic)
Attributable fractions of HCC risk factors by sex

- **Metabolic**
  - All: 34.6%
  - Men: 34.8%
  - Women: 34.0%
- **HCV**
  - All: 21.3%
  - Men: 18.5%
  - Women: 26.8%
- **Alcohol**
  - All: 13.8%
  - Men: 17.5%
  - Women: 6.5%
- **HBV**
  - All: 4.2%
  - Men: 4.5%
  - Women: 3.6%
- **COPD**
  - All: 3.4%
  - Men: 3.5%
  - Women: 2.8%
- **Genetic**
  - All: 1.3%
  - Men: 1.6%
  - Women: 0.6%
Attributable fractions of HCC risk factors by race/ethnicity

<table>
<thead>
<tr>
<th>Factor</th>
<th>White</th>
<th>Black</th>
<th>Asian</th>
<th>Hispanic</th>
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<td>21.6</td>
<td>21.6</td>
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<td>17.5</td>
<td>30.5</td>
<td>21.6</td>
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<td>Alcohol</td>
<td>4.6</td>
<td>14.2</td>
<td>19.6</td>
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<tr>
<td>COPD</td>
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<td>3.4</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>1.6</td>
<td>2.3</td>
<td>18.2</td>
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</tr>
<tr>
<td>Genetic</td>
<td>1.6</td>
<td>0.4</td>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>

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Attributable fractions of HCC risk factors by year-groups

- **Metabolic**
  - 2000-2003: 25.9
  - 2004-2007: 31.6
  - 2008-2011: 36.7
  - 2012-2015: 40.0

- **HCV**
  - 2000-2003: 17.9
  - 2008-2011: 21.4
  - 2012-2015: 23.3

- **Alcohol**
  - 2000-2003: 12.4
  - 2004-2007: 13.8
  - 2008-2011: 13.9
  - 2012-2015: 14.8

- **HBV**
  - 2000-2003: 3.9
  - 2004-2007: 4.1
  - 2008-2011: 4.8
  - 2012-2015: 3.9

- **Genetic**
  - 2000-2003: 1.9
  - 2004-2007: 1.5
  - 2008-2011: 1.1
  - 2012-2015: 0.7

- **COPD**
  - 2000-2003: -1.1
  - 2004-2007: 2.9
  - 2008-2011: 3.6
  - 2012-2015: 6.5
Summary

- The relative risk of metabolic disorders is fairly small compared to other risk factors.
- The attributable risk of metabolic disorders is substantial due to their prevalence in the population.
- The attributable risk of metabolic disorders appears to be increasing over time.
NAFLD Questions

- What is the contribution of NAFLD to HCC incidence?
- What is the contribution of NAFLD to mortality?
Prevalence of NAFLD by ultrasonography in the U.S.

NHANES III 1988-1994

Follow-up through 2015
21-27 years follow-up
Prevalence of NAFLD by ultrasonography in the U.S.

N=14,797 persons aged 20-74 years completed interview and physical exam

N=13,856 persons had a useable abdominal ultrasound image

N=1,241 persons excluded due to high alcohol consumption

N=324 persons excluded due to HBsAg(+) and/or anti-HCV(+)%

N=28 persons excluded due to iron overload

N=10 persons excluded due to lack of follow-up data

N=12,253 total analytical sample

N=4,355 with NAFLD, N=7,898 without NAFLD

Alvarez CS et al, Submitted
Prevalence of NAFLD by ultrasonography in the U.S.

Alvarez CS et al, Submitted
### Risk of mortality in association with NAFLD

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<th>Deaths</th>
<th>HR</th>
<th>95% CI</th>
</tr>
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<tr>
<td><strong>All causes</strong></td>
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<tr>
<td>No NAFLD</td>
<td>2,016</td>
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<td>NAFLD</td>
<td>1,493</td>
<td>1.20</td>
<td>(1.08, 1.34)</td>
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*NHANES III 1988-1994
Alvarez et al, *Submitted*
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Risk of mortality in association with NAFLD

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<th>95%CI</th>
<th>Deaths</th>
<th>Range</th>
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<tr>
<td><strong>All causes</strong></td>
<td>7.5</td>
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<td>(79,461, 320,769)</td>
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<td><strong>Cardiovascular disease</strong></td>
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<td>14,168</td>
<td>(-31,950, 60,286)</td>
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<td>38.0</td>
<td>(13.08, 63.00)</td>
<td>30,220</td>
<td>(10,390, 50,051)</td>
</tr>
<tr>
<td><strong>Kidney disease</strong></td>
<td>4.3</td>
<td>(-25.38, 33.93)</td>
<td>2,776</td>
<td>(-16,480, 22,031)</td>
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<tr>
<td><strong>Liver disease</strong></td>
<td>36.0</td>
<td>(-2.15, 74.05)</td>
<td>23,735</td>
<td>(-1,420, 48,890)</td>
</tr>
</tbody>
</table>
Percent of deaths in the U.S. associated with exposures

- Percent of U.S. deaths associated with:
  - Smoking: 18-26%
  - Overweight/obesity: 18%
  - Alcohol: 2-6%

Acknowledgements

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Mathieu Laversanne

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