Risk of HCC in NAFLD/NASH

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• Simple fatty liver is histologically characterized by macrovesicular steatosis with no additional pathology.
• Fatty liver is generally considered benign.

• NASH is histologically advanced fatty liver. It is characterized by steatosis, inflammation, ballooning, Mallory's hyaline, and fibrosis.
• It can lead to cirrhosis and liver failure.
NAFLD is becoming one of the most important causes of liver disease, with an estimated global prevalence rate of 24%.

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Risk of Hepatocellular Cancer in Patients With Non-Alcoholic Fatty Liver Disease

Fasiha Kanwal, Jennifer R. Kramer, Srikar Mapakshi, Yamini Natarajan, Maneerat Chayanupatkul, Peter A. Richardson, Liang Li, Roxanne Desiderio, Aaron P. Thrift, Steven M. Asch, Jinna Chu, and Hashem B. El-Seraq

Gastroenterology 2018;155:1828–1837
Baseline Characteristics of 237,683 NAFLD Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>55.5 (13)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>69.0</td>
</tr>
<tr>
<td>African American</td>
<td>11.4</td>
</tr>
<tr>
<td>Hispanic</td>
<td>5.4</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>94.5</td>
</tr>
<tr>
<td>Women</td>
<td>5.5</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>30.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>71.8</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>72.0</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>31.5 (5.6)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>21.3</td>
</tr>
<tr>
<td>Chronic obstructive lung disease</td>
<td>9.6</td>
</tr>
<tr>
<td>APRI, mean (SD)</td>
<td>0.4 (0.46)</td>
</tr>
</tbody>
</table>

APRI: AST to platelet ratio index
HCC in Patients with NAFLD

237,683 patients with NAFLD
237,683 matched controls

Mean 9.1 (SD 2.9) year follow-up
HCC in Patients with NAFLD

237,683 patients with NAFLD
237,683 matched controls

Hazard ratio
7.6 (95% CI=5.7-10.1)
Annual incidence rate of HCC:

- **0.02** per 1000 PY in controls
- **0.08** per 1000 PYs in NAFLD without cirrhosis
- **10.6** per 1000 PYs in NAFLD with cirrhosis

Among patients with NAFLD cirrhosis:
HCC risk ranged from **1.6** to **23.7** per 1000 PYs based on other demographic characteristics.

Kanwal F, Gastroenterology 2018
Trends in metabolic traits in NAFLD

Follow up year

None

Hypertension

Dyslipidemia

Diabetes, dyslipidemia & hypertension

Diabetes with hypertension or dyslipidemia

Percentage

0 1 2 3 4 5 6 7 8 9 10 11 12

Follow up year

Diabetes with hypertension or dyslipidemia
Diabetes, dyslipidemia & hypertension
Dyslipidemia & hypertension
Dyslipidemia
Hypertension
None
Trends in metabolic traits in NAFLD
Factors associated with risk of progression to HCC in NAFLD

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Adjusted hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.07 (1.06-1.08)</td>
</tr>
<tr>
<td>Female</td>
<td>0.55 (0.24-1.23)</td>
</tr>
<tr>
<td>Race (ref: white)</td>
<td></td>
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<tr>
<td>African Americans</td>
<td>0.78 (0.51-1.19)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.54 (1.01-2.35)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.80 (2.18-3.59)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.28 (0.76-2.16)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.05 (0.76-1.44)</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.44 (1.14-1.82)</td>
</tr>
</tbody>
</table>
Additive effect of metabolic traits on progression to HCC

Adjusted hazard ratio

- No trait: 1.0 (0, 6.0)
- Diabetes & hypertension: 1.87 (0.49, 7.11)
- Diabetes, hypertension & dyslipidemia: 2.76 (0.86, 8.85)
- Diabetes, hypertension & obesity: 5.70 (1.70, 19.12)

Kanwal, Hepatology 2020
The absolute risk of progression in this subgroup was 2.5-2.8% at 10 years, approaching the risk in community-based cohorts with HCV (estimated ~3-4% at 10 years following infection).

Additive effect of metabolic traits on progression to HCC

Diabetes, hypertension & obesity

Adjusted hazard ratio: 5.70 (1.70, 19.12)

Kanwal, Hepatology 2020
Summary - 1

- Risk of HCC was higher in NAFLD patients than that observed in general clinical population.
- The absolute risk of HCC was higher than the accepted thresholds for HCC surveillance for most patients with NAFLD cirrhosis.
- Among metabolic traits, diabetes had the strongest association with HCC.
- Diabetic patients with co-existing hypertension and obesity may be important targets for secondary prevention of NAFLD-related HCC.
HCV vs. NAFLD

• **Relative Risk of HCC**
  – Compared to NAFLD-controls (7.6 fold)

• **Absolute Risk of HCC**
  – HCC in NAFLD
    • 0.02 per 100 at 9 years
  – HCC in NAFLD-related cirrhosis
    • 1.0 to 2.0 per 100

• **Relative Risk of HCC**
  – Compared to HCV-controls (25 fold)

• **Absolute Risk of HCC**
  – HCC in HCV
    • 1 per 100 at 30 years
  – HCC in HCV-related cirrhosis
    • 3.5 per 100 [1-7]
NAFLD is becoming one of the most important causes of liver disease, with an estimated global prevalence rate of 24%.
Contemporary risk factors for cirrhosis in the U.S
Data from Trans-Texas HCC Consortium (THCCC)

- Large prospective cohort of patients with cirrhosis
- Started in 5 centers (2016)
  - Extended to 7 centers (2019)

Etiology of cirrhosis
- 33.1% cured hepatitis C virus infection (HCV)
- 30.0% alcohol
- **23.3%** nonalcoholic fatty liver disease
- 16.1% active HCV
- 2.5% hepatitis B virus (HBV) infection

Contemporary risk factors for cirrhosis in the U.S
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75% has metabolic dysfunction without other active risk factors

Mathematical models project that NAFLD will account for 48% of the HCC burden, becoming the leading cause of HCC in the U.S in the next 2 decades.

- Dyson observed a 10-fold increase in MAFLD-HCC between 2000 and 2010 in Newcastle, U.K.
- A recent study estimated MAFLD will result in 135,000 HCC cases in the U.S. between 2015 and 2030.
HCC can occur in the absence of cirrhosis in NAFLD

- 1500 patients with HCC seen in the VA (2005-2020)
- About 13% of patients with HCC in the VA did not have cirrhosis.
- NAFLD was the main risk factor for HCC in the absence of cirrhosis (odds ratio, 5.4, 95% CI, 3.4-8.5)
Challenges in reducing NAFLD HCC-related mortality

90% patients with NAFLD and fibrosis are undiagnosed

Systematic **risk assessment** of patients with risk factors for NAFLD to diagnose cirrhosis

0.2-2.4% In patients with NAFLD cirrhosis, the annual risk of HCC is variable

Better **risk stratification** to match prevention and early detection efforts to patients’ risk of HCC

20-30% patients with NAFLD HCC do not have cirrhosis

Novel **biomarkers** and tools needed for the newer groups of patients (with NAFLD)

Quality of Cancer Care Continuum (QCCC)

Risk Assessment → Prevention → Detection → Diagnosis → Cancer Treatment

Zaman SN,. Cancer 1990;65:1607-1
Walker M, Kanwal F. APT 2016
Kanwal F, El-Serag H, Gastroenterology 2018
Challenges in reducing NAFLD HCC-related mortality

Quality of Cancer Care Continuum (QCCC)

Risk Assessment → Prevention → Detection → Diagnosis → Cancer Treatment

- No curative treatment for NAFLD
  - New liver directed treatments in the pipeline, but none holds substantial promise
- Chemoprevention using other agents that may block carcinogenesis
  - Plausible but remains unexamined

Zaman SN,. Cancer 1990;65:1607-1
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Challenges in reducing NAFLD HCC-related mortality

- Risk Assessment
- Prevention
- Detection
- Diagnosis
- Cancer Treatment

Quality of Cancer Care Continuum (QCCC)

- 32% Sensitivity of ultrasound for detection of early stage HCC
- 41%–65% Sensitivity of AFP for detecting HCC

Early detection **biomarkers** needed for early detection of HCC
NAFLD is projected to become the leading etiology of HCC in the U.S.

The absolute risk of HCC is higher than the accepted thresholds for HCC surveillance for most patients with NAFLD cirrhosis.

However, 20-30% of NAFLD-HCC develop in patients without cirrhosis. However, the absolute risk is low in the subgroup without cirrhosis.

Diabetes had the strongest association with HCC; these patients may be important targets for secondary prevention.

Several gaps exist in the NAFLD-HCC care continuum. The early steps in the continuum serve as important, high-yield targets for research.
NAFLD and Risk of HCC
Based on Cohort Studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>NAFLD (N)</th>
<th>Cirrhosis %</th>
<th>HCC (N)</th>
<th>Mean follow up (yr)</th>
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<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
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<tr>
<td>Hui</td>
<td>Australia</td>
<td>23</td>
<td>100</td>
<td>0</td>
<td>7</td>
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<td>100</td>
<td>9</td>
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<td>Ratziu</td>
<td>France</td>
<td>41</td>
<td>100</td>
<td>8 (3 incident)</td>
<td>Max 5</td>
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<td>Yatsuji</td>
<td>Japan</td>
<td>68</td>
<td>100</td>
<td>21 (7 incident)</td>
<td>3.1</td>
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<td>Ekstedt</td>
<td>Sweden</td>
<td>129</td>
<td>3</td>
<td>0</td>
<td>13.7</td>
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<tr>
<td>Sanyal</td>
<td>USA</td>
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<td>Dam-Larsen</td>
<td>Copenhagen</td>
<td>170</td>
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<td>Ascha</td>
<td>USA</td>
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<td>Bhala</td>
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<td>247</td>
<td>52</td>
<td>6</td>
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<td>Soderberg</td>
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<td>256</td>
<td>7</td>
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<tr>
<td>Angulo</td>
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<td><strong>Population based</strong></td>
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<td>Adams(^{36})</td>
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<td>817</td>
<td>NR</td>
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</tr>
</tbody>
</table>

White D, Kanwal F, El-Serag HB. Clin Gastroenterol Hepatol 2012