Risk of incident extrahepatic cancers among Medicare patients with non-alcoholic steatohepatitis (NASH)

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Background

- NASH, also referred to as metabolic dysfunction-associated steatohepatitis (MASH), is a severe form of non-alcoholic fatty liver disease (NAFLD) or metabolic dysfunction-associated steatotic liver disease (MASLD) [1].
- NAFLD is associated with increased risk of extrahepatic malignancies which have high patient burden; however, evidence is lacking for NASH specifically and for progression to more advanced liver disease including compensated cirrhosis (CC), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), and liver transplant (LT) [2,3].
- This study aimed to characterize the risk of incident extrahepatic cancers among Medicare patients with NASH up to 5 years following diagnosis.

Methods

Data Source

- This retrospective non-interventional study used 100% Medicare fee-for-service claims data, which covers inpatient hospital and outpatient facility services (Part A), physician services (Part B), and outpatient prescription drugs (Part D) for Oct. 1, 2015 through Dec. 31, 2021.

Sample Criteria

- Diagnosis for NASH (ICD-10: K75.81) as the primary or secondary diagnosis in an inpatient visit or in two separate outpatient visits [earliest is index date]
- Medicare-age adult throughout the study period (≥66 years on index date)
- Continuous enrollment in Medicare Parts A, B, and D of for ≥12 months prior to the index date and ≥6 months following the index date (unless death)
- No enrollment in Medicare Part C (Medicare Advantage)
- No evidence prior to the index date of other causes of liver disease*

** Includes alcoholism, alcoholic liver disease, toxic liver disease, viral hepatitis, Wilson's disease, autoimmune hepatitis, Gaucher disease, lysosomal acid lipase deficiency, primary biliary cholangitis, hemochromatosis, primary sclerosing cholangitis, exposure to heavy metals, and HIV*

Analysis

- Progression to and index dates for CC/DCC/HCC/LT were based on the earliest corresponding diagnosis/procedure claim. Patients were included in each cohort for which they qualified.
- Incidence of cancer was identified using diagnosis codes on medical claims among patients without evidence of each cancer type prior to their index date.
- A control cohort of Non-NAFLD patients (defined as the absence of ICD-10: K75.81 and K76.0 from all medical claims during the study period) was 3:1 matched to the NASH sample on age and sex.
- Kaplan-Meier survival analyses were conducted for time to cancer incidence.
- Pairwise Cox proportional hazards models estimated the hazard ratios (HRs) and 95% confidence intervals (CIs) of cancer incidence associated with liver disease progression relative to NASH, controlling for baseline characteristics.

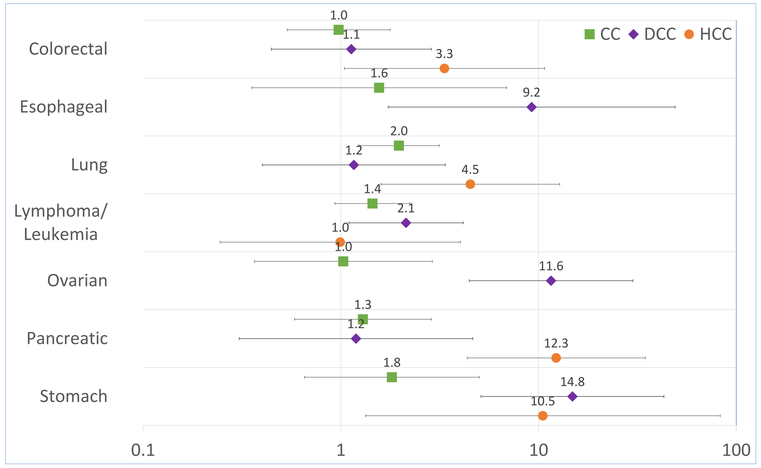
Results

- In 14,806 unique patients (N=12,990 NASH; 1,899 CC; 997 DCC; 209 HCC; 140 LT), mean age and follow-up were 72.2 and 2.8 years (**Table 1**).
- For NASH, 5-year cumulative incidence was highest for breast cancer followed by lymphoma/leukemia, prostate, and lung cancers (**Table 2**).
- Relative to Non-NAFLD control patients (N=38,970), the greatest increase in 5-year incidence was observed for breast, liver, lung, lymphoma/leukemia, pancreatic, and prostate cancers (**Table 2**).

Table 1. Baseline Characteristics

Overall Sample (N=14,806)	
Follow-up months, mean (SD) [median]	33.8 (17.5) [33.5]
Age, mean (SD) [median]	72.2 (5.5) [71.0]
Sex, female, n (%)	9,312 (63)
Race, n (%)	
White	12,418 (84)
Black	496 (3)
Hispanic	912 (6)
Asian	513 (3)
Other	467 (3)

Figure 1. Hazard Ratio of Cancer Incidence (relative to NASH)



- Progression to CC significantly increased the hazard of lung cancer while progression to DCC increased the hazard of esophageal, lymphoma/leukemia, ovarian, and stomach cancers (all p<0.05) (**Figure 1**).
- Onset of HCC increased the hazard of colorectal, lung, pancreatic, stomach cancers (all p<0.05) (**Figure 1**).
- Patients with NASH that underwent liver transplant also experienced increased hazard for extrahepatic cancer. Among these patients, the hazard ratio for lymphoma/leukemia was 10.5 (CI: 1.8 – 61.0; p<0.05).

Table 2. Cumulative Incidence of Cancer

	Bladder	Breast	Colorectal	Esophageal	Gallbladder	Kidney	Liver	Lung	Lymphoma / Leukemia	Ovarian	Pancreatic	Prostate	Small Intestine	Stomach	Uterine
NASH															
Year 1	0.1%	0.7%	0.4%	0.0%	0.0%	0.3%	0.2%	0.4%	0.5%	0.2%	0.2%	0.6%	0.0%	0.1%	0.3%
Year 2	0.3%	1.4%	0.8%	0.1%	0.0%	0.4%	0.5%	0.7%	1.2%	0.3%	0.4%	1.0%	0.1%	0.2%	0.4%
Year 3	0.4%	1.9%	1.2%	0.2%	0.1%	0.6%	0.8%	1.1%	1.6%	0.4%	0.6%	1.6%	0.1%	0.3%	0.6%
Year 4	0.6%	2.5%	1.5%	0.2%	0.1%	0.7%	1.0%	1.6%	2.0%	0.5%	0.9%	2.2%	0.2%	0.4%	0.7%
Year 5	1.0%	3.1%	1.8%	0.2%	0.1%	1.0%	1.4%	2.3%	2.8%	0.5%	1.1%	2.6%	0.2%	0.5%	0.8%
Non-NAFLD Year 5	0.5%	2.1%	1.3%	0.2%	0.0%	0.6%	0.4%	1.4%	1.8%	0.3%	0.4%	1.8%	0.1%	0.2%	0.4%

CONCLUSIONS

- High incidence of extrahepatic cancers was found following NASH diagnosis.
- Cancer incidence was higher among NASH patients than Non-NAFLD individuals.
- Progression to more advanced liver disease was associated with increased risk for several extrahepatic cancer types.

References/Acknowledgements

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Limitations

- Use of administrative claims data relies on accurate diagnosis codes and lacks potentially relevant clinical information on patients prior to their entry into the database.
- We were unable to identify fibrosis staging or confirm disease states due to lack of lab and biopsy results in the data.
- There is limited generalizability of the results outside of the Original Medicare population or to populations later than the study period.
- Results are from descriptive analysis and thus we cannot infer causality.

Disclosures

- YK and JM are employees of Madrigal Pharmaceuticals, Inc.
- MD and DN are employees of Medicus Economics, LLC, which received funding from Madrigal Pharmaceuticals, Inc. to participate in this research.
- RG has performed as Consultant and/or Advisor to (in the last two years): Abacus, Abbott, AbbVie, Albireo, Aligos, Altimmune, Arrowhead, AstraZeneca, Audentes Therapeutics, Corcept, Dynavax, Effectus, Eiger, Eisai, Genentech, Genlantis, Gerson Lehrman Group, Gilead Sciences, GlaxoSmithKline, Helios, HepaTX, HepQuant, Intercept, Janssen, JBS Science, Kinnate Bio, Madrigal, Merck, Precision BioSciences, Pfizer, Seres Therapeutics, Topography Health, Tune Therapeutics, Venatorx, Virion.