Chronic Hepatitis C Virus Infection and Cancer Risks: A Population-Based Cohort Study

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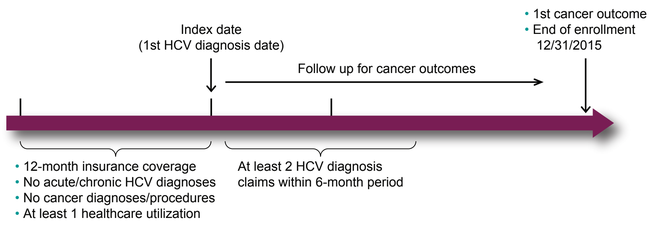
Background

- Chronic hepatitis C virus (HCV) infection is a major cause of up to 25% of hepatocellular carcinoma (HCC)
- It has been associated with non-liver cancers, but findings are conflicted and few studies are done in populations representative of a large US healthcare setting
- We aim to assess the incidence of major cancer types (colorectal cancer (CRC), lung, breast, prostate, liver, pancreas, non-Hodgkin's lymphoma (NHL), leukemia, thyroid, bladder, renal) using a large insurance claims database from the United States
- Humana is a claims insurance database, including both commercial and Medicare populations, with reimbursed claims on medical diagnoses and healthcare utilization

Methods

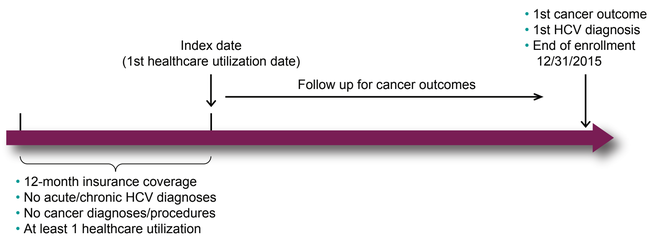
- We identified 20+-year-old Humana beneficiaries between 2007 and 2015, requiring a 12-month baseline of continuous insurance enrollment
- HCV cohort includes patients with at least 2 chronic HCV diagnosis claims in nonlaboratory settings within a 6-month period following baseline (**Figure 1**)
- Non-HCV cohort is based on a 1% random sample of the entire claims population and includes only patients free of HCV diagnoses by the index date, which is one of the healthcare utilization dates (**Figure 2**)
- Cancer outcomes identified using claims-based validated algorithm (at least 2 diagnosis claims in 6 months)

Figure 1. HCV† cohort construction timeline



†ICD-9-CM codes (070.44, 070.54, 070.70, 070.71).

Figure 2. Non-HCV cohort construction timeline



Non-HCV patients are eligible to be in HCV cohort after getting censored.

Statistical Analyses

- Incident cancer rates were estimated for each cancer type
- To control confounding by age and sex, standardized incident rates (95% approximate CI) were calculated after standardizing both HCV and non-HCV cohorts against 2000 US census population
- Standardized incident ratios were used to compare cancer rates in HCV vs non-HCV cohorts
- 95% CIs were estimated assuming gamma distribution of events
- Incident rates were also compared against standardized rates from 2007-2013 Surveillance, Epidemiology, and End Results (SEER) 18 cancer registries

Results

- We identified 13,315 patients with an HCV diagnosis and 38,991 patients without an HCV diagnosis who met inclusion criteria
- HCV cohort is slightly younger, more likely to be male, less likely to be white, and more likely to have Medicare Advantage plans than non-HCV cohort (**Table 1**)
- HCV cohort also has a higher prevalence of baseline comorbidities such as diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), liver disease, renal disease, acquired immunodeficiency syndrome (AIDS), and hepatitis B virus (HBV) infection
- Median follow-up (interquartile limits) is 1.4 years (0.6, 2.9) for HCV cohort and 1.5 years (0.7, 3.3) for non-HCV cohort

Table 1. Distribution of selected baseline characteristics between HCV and non-HCV cohorts

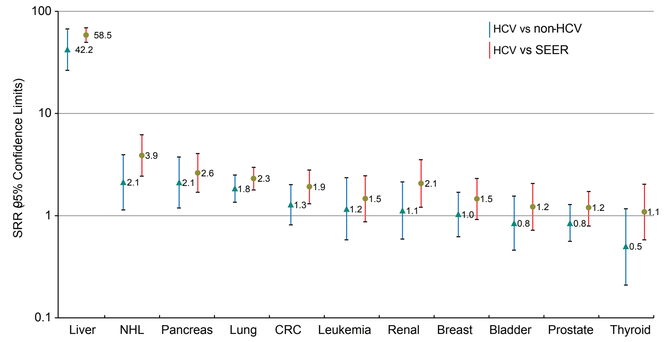
	HCV (N=13,315, %)	Non-HCV (N=38,991, %)
Age (mean, SD)	60.6 (10.9)	64.1 (16.5)
<50	1,932 (14.5)	7,546 (19.4)
51-55	2,163 (16.2)	2,423 (6.2)
56-60	2,875 (21.6)	2,583 (6.6)
61-70	4,303 (32.3)	13,051 (33.5)
>70	2,042 (15.3)	13,388 (34.3)
Sex		
Males	7,883 (59.2)	16,182 (41.5)
Race		
Whites	8,332 (74.6)	24,055 (83.8)
Blacks	2,189 (19.6)	3,484 (12.1)
Others	654 (5.9)	1,178 (4.1)
Insurance		
Commercial	2,132 (16.0)	10,039 (25.8)
Medicare	11,183 (84.0)	28,952 (74.2)
DM	4,031 (30.3)	9,704 (24.9)
COPD	2,839 (21.3)	4,373 (11.2)
Liver disease	3,241 (24.3)	213 (0.5)
HBV	302 (2.3)	25 (0.1)

SD=standard deviation

Table 2. Incidence of common cancer sites among chronic HCV, non-HCV, and SEER cohorts

Sites	Exposure	Crude Incidence per 1,000 Person-Years	Standardized Incidence per 1,000 Person-Years (95% CI)
Colorectal cancer	HCV	1.90	1.12 (0.73, 2.66)
	Non-HCV	1.89	0.87 (0.67, 1.16)
	SEER	0.60	0.58 (0.58, 0.59)
Lung	HCV	3.72	1.86 (1.41, 3.37)
	Non-HCV	2.79	1.01 (0.84, 1.25)
	SEER	0.82	0.80 (0.80, 0.81)
Breast	HCV	3.74	2.65 (1.58, 5.82)
	Non-HCV	4.68	2.58 (2.09, 3.19)
	SEER	1.87	1.81 (1.81, 1.82)
Prostate	HCV	3.58	2.03 (1.32, 5.23)
	Non-HCV	7.68	2.40 (2.03, 2.97)
	SEER	1.88	1.74 (1.74, 1.75)
Liver	HCV	13.93	6.52 (5.47, 8.35)
	Non-HCV	0.37	0.15 (0.09, 0.32)
	SEER	0.12	0.11 (0.11, 0.11)
Pancreas	HCV	1.01	0.44 (0.27, 2.03)
	Non-HCV	0.53	0.21 (0.14, 0.38)
	SEER	0.18	0.17 (0.17, 0.17)
NHL	HCV	1.64	1.03 (0.61, 2.62)
	Non-HCV	0.92	0.49 (0.31, 0.76)
	SEER	0.27	0.27 (0.27, 0.27)
Leukemia	HCV	0.67	0.24 (0.13, 1.89)
	Non-HCV	0.43	0.21 (0.12, 0.38)
	SEER	0.17	0.17 (0.17, 0.17)
Thyroid	HCV	0.41	0.20 (0.10, 1.87)
	Non-HCV	0.31	0.40 (0.20, 0.71)
	SEER	0.18	0.18 (0.18, 0.18)
Bladder	HCV	0.78	0.33 (0.18, 1.95)
	Non-HCV	1.02	0.39 (0.28, 0.60)
	SEER	0.28	0.27 (0.27, 0.27)
Renal	HCV	0.74	0.44 (0.23, 2.04)
	Non-HCV	0.74	0.39 (0.26, 0.61)
	SEER	0.22	0.21 (0.21, 0.21)

Figure 3. Comparison of standardized rate ratios between HCV vs non-HCV and SEER cohorts



Discussion and Conclusion

- This study provides additional support that HCV infection is associated with increased risk of liver and non-liver-related cancers (especially lung, pancreas, and NHL) vs non-HCV cohort or the general population (SEER)
- Cancer rates in the claims-based cohort are higher than the general population rates (SEER), which may be a reflection of the inclusion of a sicker population, excluding patients with no healthcare encounters (ie, no insurance claims) during the 1-year baseline period
- Validated algorithms, with high specificity (~99% for most cancers), were used for cancer diagnoses
- Study limitations include potential misclassification of HCV and cancer diagnoses, limited follow-up time, and unmeasured confounders
- Future studies should evaluate the potential mechanisms of increased cancer incidence (unmeasured confounding or detection bias) among patients with HCV infection
- Our findings suggest the need for follow-up care, including surveillance for cancer, among patients with chronic HCV

Conflicts of interest:

JH and JMA are employees and stockholders of Merck & Co., Inc.