Original Article

Hepatitis C Virus Infection and the Risk of Cancer Among Elderly US Adults: A Registry-Based Case-Control Study

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BACKGROUND: Hepatitis C virus (HCV) infection causes hepatocellular carcinoma (HCC) and subtypes of non-Hodgkin lymphoma (NHL). Associations with other cancers are not established. The authors systematically assessed associations between HCV infection and cancers in the US elderly population. **METHODS:** This was a registry-based case-control study using Surveillance, Epidemiology, and End Results (SEER)-Medicare data in US adults aged ≥66 years. Cases (n = 1,623,538) were patients who had first cancers identified in SEER registries (1993-2011). Controls (n = 200,000) were randomly selected, cancer-free individuals who were frequency-matched to cases on age, sex, race, and calendar year. Associations with HCV (documented by Medicare claims) were determined using logistic regression. **RESULTS:** HCV prevalence was higher in cases than in controls (0.7% vs 0.5%). HCV was positively associated with cancers of the liver (adjusted odds ratio [aOR] = 31.5; 95% confidence interval [CI], 29.0-34.3), intrahepatic bile duct (aOR, 3.40; 95% CI, 2.52-4.58), extrahepatic bile duct (aOR, 1.90; 95% CI, 1.41-2.57), pancreas (aOR, 1.23; 95% CI, 1.09-1.40), and anus (aOR, 1.97; 95% CI, 1.42-2.73); nonmelanoma nonepithelial skin cancer (aOR, 1.53; 95% CI, 1.15-2.04); myelodysplastic syndrome (aOR, 1.56; 95% CI, 1.33-1.83); and diffuse large B-cell lymphoma (aOR, 1.57; 95% CI, 1.34-1.84). Specific skin cancers associated with HCV were Merkel cell carcinoma (aOR, 1.92; 95% CI, 1.30-2.85) and appendageal skin cancers (aOR, 2.02; 95% CI, 1.29-3.16). Inverse associations were observed with uterine cancer (aOR, 0.64; 95% CI, 0.51-0.80) and prostate cancer (aOR, 0.73; 95% CI, 0.66-0.82). Associations were maintained in sensitivity analyses conducted among individuals without documented alcohol abuse, cirrhosis, or hepatitis B or human immunodeficiency virus infections and after adjustment for socioeconomic status. Associations of HCV with other cancers were not observed. **CONCLUSIONS:** HCV is associated with increased risk of cancers other than HCC in the US elderly population, notably bile duct cancers and diffuse large B-cell lymphoma. These results support a possible etiologic role for HCV in an expanded group of cancers. ***Cancer* 2017;000:000–000.** © *2017 American Cancer Society.*

KEYWORDS: cancers, cholangiocarcinoma, elderly, hepatitis C virus, hepatocellular carcinoma, lymphoma, Surveillance, Epidemiology, and End Results (SEER)-Medicare.

INTRODUCTION

Hepatitis C virus (HCV) infection is the most common chronic blood-borne infection in the United States, and approximately 3 million individuals are infected with this virus.[1] Approximately 55% to 85% of individuals newly infected with HCV develop chronic hepatitis, 20% to 30% of chronically infected individuals progress to cirrhosis and liver failure, and 2% to 5% develop hepatocellular carcinoma (HCC).[2]

Although HCV mainly affects the liver, extrahepatic manifestations are well documented.[3,4] On the basis of strong epidemiological and clinical evidence, the International Agency for Research on Cancer classified HCV as a proven cause not only of HCC but also of B-cell non-Hodgkin lymphomas (NHLs).[5] Furthermore, some epidemiological evidence suggests that chronic HCV infection is associated with cancers other than HCC and NHL, such as those of the oral

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See related editorial on pages 000-000, this issue.

Additional supporting information may be found in the online version of this article.

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cavity,[6] oropharynx,[7] intrahepatic bile duct,[8] pancreas,[9] and kidney.[10] Adding biologic plausibility, HCV antigens and/or RNA have been detected in some of these cancers.[11-13] Whether the virus exerts direct oncogenic effects, through its various proteins and modulation of cell-signaling pathways, or indirect effects, by inducing chronic antigenic stimulation or inflammation, is mostly unknown. Few large studies have been conducted to systematically assess associations with these cancers in the United States.[14,15]

Approximately 70% of HCV-infected individuals in the United States were born between 1945 and 1965 ("baby boomers"), prompting the Centers for Disease Control and Prevention to recommend a 1-time screening for HCV in this birth cohort.[16] And, as baby boomers age, HCV-associated cancers in the elderly population may become an important public health issue in the United States in the near future. To identify the cancers for which older HCV-infected individuals may be at increased risk, we used a large, nationally representative database of elderly individuals in the United States and systematically evaluated the associations between HCV infection and all major cancer types.

MATERIALS AND METHODS

Data Source: Surveillance, Epidemiology, and End Results-Medicare–Linked Database

Surveillance, Epidemiology, and End Results (SEER) is a cancer surveillance program that collects information from 18 US cancer registries covering approximately 28% of the US population.[17] Medicare is a federally funded program that provides health insurance to approximately 97% of the US elderly (aged $\geq$ 65 years). All Medicare-eligible individuals are entitled to Part A coverage (for hospital inpatient care), and approximately 96% also subscribe to Part B coverage (for physician and outpatient care). Beneficiaries can elect to enroll in a health maintenance organization (HMO); Medicare does not receive claims for individual medical conditions for individuals enrolled in HMOs.

The SEER-Medicare database is an electronic linkage of SEER and Medicare that successfully links greater than 94% of patients with cancer aged $\geq$65 years in SEER with their Medicare claims data (from 1991 onward).[18] Claims data for an additional 5% random sample of Medicare beneficiaries residing in SEER geographic areas are provided.

Study Design and Study Population

We conducted a case-control study using the SEER-Medicare database to determine whether HCV was associated with cancer risk.[19] Eligible cases were patients who had a first cancer diagnosis identified in SEER, excluding basal cell and squamous cell skin carcinomas, which are not captured by cancer registries. Cancers diagnosed only at autopsy or by death certificate were excluded. Medicare did not cover claims for HCV infection before 1992. The 2014 SEER-Medicare linkage includes cancers diagnosed through 2011. To ensure adequate information on HCV status, we required that patients have at least 13 months of Medicare Part A and B, non-HMO coverage before cancer diagnosis. Therefore, only patients who were diagnosed between 1993 and 2011 at age $\geq$ 66 years were included. Cancer sites were defined using the SEER site recode variable, and morphology codes were used to define histologic subtypes for some cancers.

We randomly selected 200,000 controls from the 5% random sample of Medicare beneficiaries who were alive and cancer-free as of July 1 of the calendar year of their selection.[19] Like cases, controls were required to have at least 13 months of prior Medicare Part A and B, non-HMO insurance coverage. Controls were frequency matched to cases on age (age categories 66-69, 70-74, 75-79, 80-84, and 85-99 years), calendar year of selection, sex, and race (whites, blacks, others). Controls could be sampled repeatedly across multiple calendar years (47,407 controls were sampled more than once) and also later could become cases.

Ascertainment of HCV Status, Other Medical Conditions, and Socioeconomic Status

Medicare claims files were examined for International Classification of Diseases, version 9 (ICD-9) diagnosis codes for HCV infection (ICD-9 codes are provided in Supporting Table 1; see online supporting information). A diagnosis of HCV infection required at least 1 inpatient, physician, or outpatient claim before cancer diagnosis/control selection, excluding the 12-month period before cancer diagnosis/control selection. This exclusion period was used to minimize the possibility of differential assessment of HCV in cases as part of medical workup near the time of their cancer diagnosis. In a sensitivity analysis, we used a more stringent definition for HCV infection that required at least 1 inpatient claim or 2 physician or outpatient claims at least 30 days apart.

Because human immunodeficiency virus (HIV) and hepatitis B virus (HBV) infections are associated with HCV and also increase the risk of certain cancers, we identified cases and controls who had at least 1 Medicare claim for HIV or HBV infection any time before death or last follow-up (Supporting Table 1; see online supporting

information). Cirrhosis and diabetes mellitus were identified using ICD-9 codes (Supporting Table 1; see online supporting information) that required at least 1 inpatient claim or 2 physician/outpatient claims at least 30 days apart > 12 months before cancer diagnosis/control selection.

We used ICD-9 codes for diagnoses related to smoking and alcohol abuse to capture these behaviors (Supporting Table 1; see online supporting information), because direct information is not available in the SEER-Medicare database. Individuals were classified as smokers or alcohol abusers if at least 1 specified ICD-9 code was present > 12 months before cancer diagnosis/control selection.

Socioeconomic status (SES) is an important predictor of cancer incidence,[20] and HCV infection is more common in low-income demographic groups.[21] We used 3 variables available in SEER-Medicare that capture SES based on an individual's residential zip code: median household income, the percentage of individuals aged >25 years with < 12 years of education, and the percentage of residents living below the poverty line.

Statistical Analyses

Characteristics of cases and controls were compared using chi-square tests. To select cancer sites for evaluation, we computed the expected number of individuals with HCV infection by multiplying the number of cases for each cancer site by the prevalence of HCV infection in controls in our study (0.5%). We included only those cancer sites for which the expected count of individuals with HCV infection was >11 to be in compliance with the SEER-Medicare data use agreement, which requires suppression of cell sizes >11. Major subtypes of NHL were selected for evaluation if they were common or consistently associated with HCV in prior studies. In all, 43 cancer sites were evaluated.

We compared HCV prevalence in cases and controls by fitting separate, unconditional logistic regression models for each cancer type. Odds ratios were adjusted (aOR) for age, sex, race, year of cancer diagnosis/control selection, average annual number of physician claims >12 months before cancer diagnosis/control selection (a measure of health care use), and smoking status. The variance of aORs obtained from these models was adjusted for repeated selection of some controls across calendar years and inclusion of some controls who later became cases.[19] We used a 2-sided α value of .05 to describe confidence intervals (CIs); but, to account for multiple testing, we selected cancers for further evaluation by using a false-discovery rate of 10% according to the Benjamini and Hochberg method.[22] We also used a more stringent Bonferroni criterion, which, based on assessment of 43 cancer outcomes, used a P value threshold for statistical significance of .05/43 = .0012.

Cancers identified as significantly associated with HCV using the false-discovery rate method were analyzed further. Specifically, we assessed associations of HCV with histologic subtypes of nonmelanoma nonepithelial skin cancers and nodal versus extranodal NHL. We conducted sensitivity analyses in which we assessed the associations of cancers in individuals without cirrhosis, in nonalcohol abusers, and in individuals without HBV or HIV infections. We conducted additional analyses to adjust for potential confounding by SES by introducing each SES variable individually in the models. We explored whether diabetes modified the association between HCV and selected cancers by calculating stratum-specific ORs and testing for heterogeneity. We also analyzed the data by using the more stringent definition of HCV infection. Finally, we calculated the population-attributable fractions for certain cancers associated with HCV infection for which there was a biologically plausible explanation for a causal association.[23]

RESULTS

We studied 1,623,538 patients with cancer (cases) and 200,000 cancer-free controls (Table 1). Cases and controls were perfectly matched on age categories, sex, race, and calendar year of cancer diagnosis/control selection. Cases had slightly shorter duration of Medicare coverage and slightly fewer annual physician claims than controls. Although differences compared with controls were small, cases were also more likely to have HBV infection, cirrhosis, or diabetes mellitus; to be smokers or alcohol abusers; and to reside in zip codes with higher median incomes and greater proportions of high school graduates. (Table 1). Cases and controls did not differ with respect to the proportion with HIV infection.

Overall, HCV prevalence was higher in cases than in controls (0.7% vs 0.5%; aOR, 1.32; 95% CI, 1.22-1.42; $P < .0001$). We present results for 43 cancers separately in Figure 1. After correction for multiple comparisons using the Benjamini and Hochberg method, we observed significant positive associations between HCV infection and cancers of the liver (aOR, 31.5; 95% CI, 29.0-34.3), intrahepatic bile duct (aOR, 3.40; 95% CI, 2.52-4.58), extrahepatic bile duct (aOR, 1.90; 95% CI, 1.41-2.57), pancreas (aOR, 1.23; 95% CI, 1.09-1.40), and anus (aOR, 1.97; 95% CI, 1.42-2.73); nonmelanoma

TABLE 1. Characteristics of Cancer Cases and Controls (1993-2011)

Characteristic	No. (%) or Median [IQR]		*P*
	Cases, N = 1,623,538	Controls, N = 200,000	
Age, y[a]			—
66-69	265,364 (16.3)	32,690 (16.4)	
70-74	418,536 (25.8)	51,553 (25.8)	
75-79	393,987 (24.3)	48,536 (24.3)	
80-84	299,444 (18.4)	36,888 (18.4)	
≥85	246,207 (15.2)	30,333 (15.2)	
Sex[a]			—
Women	777,936 (47.9)	95,827 (47.9)	
Men	845,602 (52.1)	104,173 (52.1)	
Race/ethnicity[a]			—
White	1,383,341 (85.4)	170,414 (85.3)	
Black	131,955 (8.1)	16,251 (8.1)	
Other	105,312 (6.5)	13,030 (6.5)	
Year of cancer diagnosis/control selection[a]			—
1993-1999	367,339 (22.6)	45,242 (22.6)	
2000-2003	357,559 (22.0)	44,048 (22.0)	
2004-2007	454,391 (28.0)	55,978 (28.0)	
2008-2011	444,249 (27.4)	54,732 (27.4)	
Total part A, part B, non-HMO Medicare coverage, mo[b]			
Median [IQR]	53 [28-70]	54 [30-66]	
<28	397,457 (24.5)	46,320 (23.2)	<.0001
28-52	406,400 (25.0)	48,218 (24.1)	
53-69	392,033 (24.2)	58,341 (29.2)	
≥70	427,648 (26.3)	47,121 (23.6)	
Total no. of physician claims/y[b]			
Median [IQR]	22 [8-47]	23 [8-48]	
<2.56	392,132 (24.2)	47,213 (23.6)	<.0001
2.56 to <5.57	399,687 (24.6)	49,077 (24.5)	
5.57 to <10.07	418,491 (25.8)	51,382 (25.7)	
≥10.07	413,228 (25.5)	52,328 (26.2)	
Hepatitis C	11,067 (0.7)	1040 (0.5)	<.0001
Hepatitis B	19,254 (1.2)	2217 (1.1)	.0025
HIV	6976 (0.4)	880 (0.4)	.5061
Cirrhosis	11,261 (0.7)	884 (0.4)	<.0001
Diabetes mellitus	403,429 (24.9)	48,926 (24.5)	.0002
Smoking	632,428 (38.9)	69,694 (34.8)	<.0001
Alcohol abuse	159,001 (9.8)	14,253 (7.1)	<.0001
Median household income for the zip code, US $			
Median [IQR]	45,561 [35,114-59,202]	45,013 [34,764-58,437]	
<35,097	396,608 (24.8)	50,371 (25.6)	<.0001
35,097-45,537	398,753 (25.0)	49,811 (25.4)	
45,538-59,164	400,258 (25.1)	48,283 (24.6)	
≥59,164	400,577 (25.1)	47,829 (24.4)	
Percentage of non-high school graduates aged ≥25 y in the zip code			
<9.96	396,438 (24.8)	49,565 (25.2)	.0010
9.96-15.78	399,793 (25.1)	48,676 (24.8)	
15.79-25.17	399,241 (25.0)	49,076 (25.0)	
≥25.18	399,750 (25.1)	48,867 (24.9)	
Percentage of residents living below the poverty line in the zip code			
<5.23	392,548 (24.6)	47,861 (24.4)	<.0001
5.23-8.91	402,349 (25.2)	48,786 (24.8)	
8.92-15.40	399,721 (25.0)	50,097 (25.5)	
≥15.41	399,452 (25.0)	49,297 (25.1)	

Abbreviations: HIV, human immunodeficiency virus; HMO, health maintenance organization; IQR, interquartile range.
[a] Cases and controls were frequency-matched on age categories, sex, race/ethnicity, and year of cancer diagnosis/control selection.
[b] Medicare coverage and physician claims were calculated excluding the 12-month period immediately before cancer diagnosis/control selection.

nonepithelial skin cancer (aOR, 1.53; 95% CI, 1.15-2.04); myelodysplastic syndrome (MDS) (aOR, 1.56; 95% CI, 1.33-1.83); and diffuse large B-cell lymphoma (DLBCL) (aOR, 1.57; 95% CI, 1.34-1.84). We also observed inverse associations between HCV and cancers of the uterus (aOR, 0.64; 95% CI, 0.51-0.80) and prostate

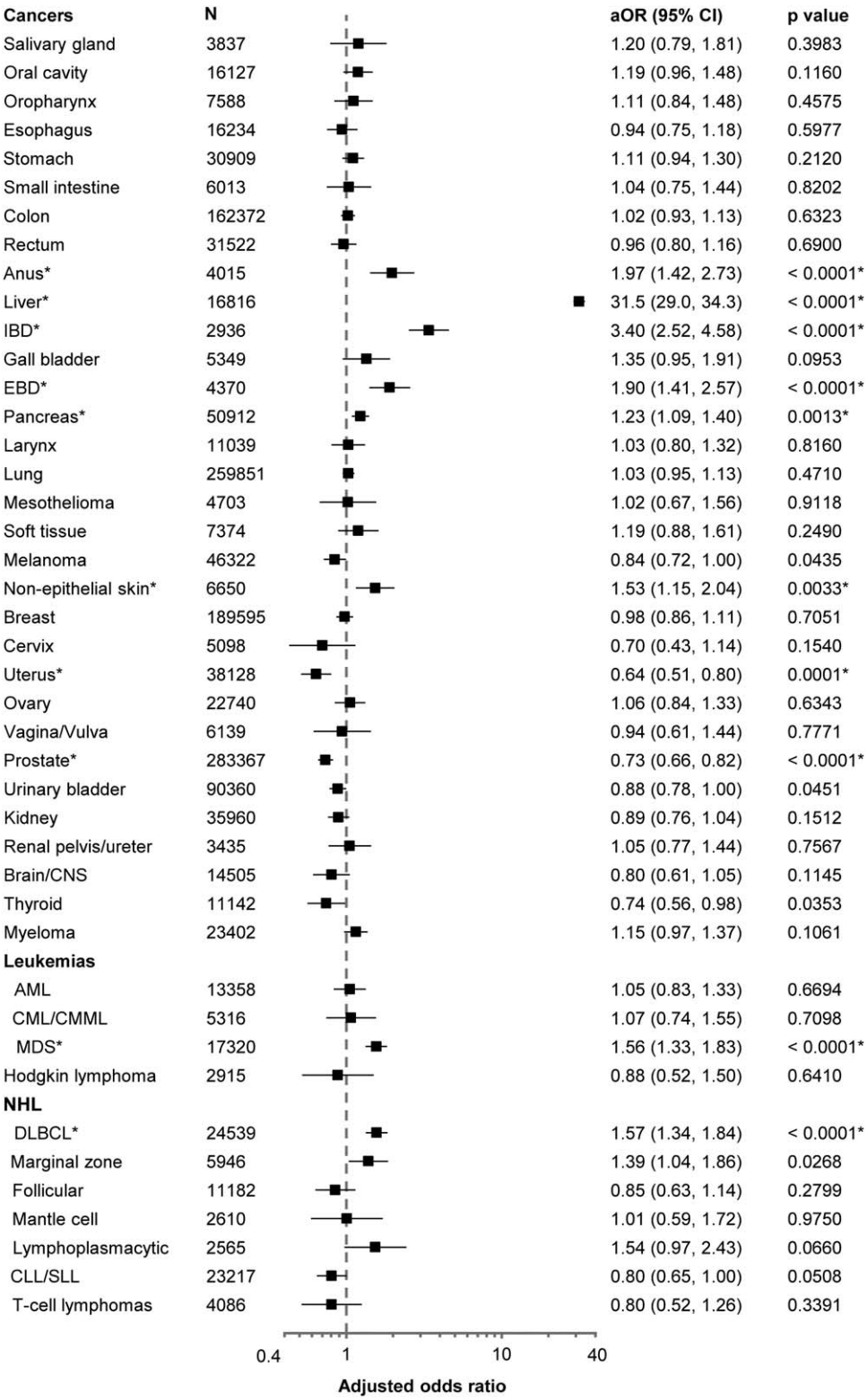

Figure 1. Associations between hepatitis C virus (HCV) infection and the risk of cancer are illustrated. The associations with HCV infection are presented for each cancer as an odds ratio and corresponding 95% confidence interval (horizontal axis, logarithmic scale). Odds ratios are adjusted for age categories (ages 65-69, 70-74, 75-79, 80-84, and ≥85 years), sex, race/ethnicity, calendar year of cancer diagnosis/control selection (1993-1999, 2000-2003, 2004-2007, and 2008-2011), number of physician claims per year (<2.56, 2.56 to < 5.57, 5.57 to < 10.07, and ≥10.07 physician claims per year), and smoking status (never/ever). AML indicates acute myeloid leukemia; aOR, adjusted odds ratio; CI, confidence intervals; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; EBD, extrahepatic bile ducts; IBD, intrahepatic bile ducts; MDS, myelodysplastic syndrome. Asterisks indicate cancers that had a significant association with hepatitis C virus infection after correction for multiple comparisons using the Benjamini-Hochberg method.

TABLE 2. Sensitivity Analyses Examining Associations of Hepatitis C Virus With Select Cancers

Cancer	Excluding Individuals Infected With HBV or HIV		Never Alcohol Abusers		Noncirrhotics		Additional Adjustment for Median Household Income	
	aOR (95% CI)[a]	*P*	aOR (95% CI)[a]	*P*	aOR (95% CI)[a]	*P*	aOR (95% CI)[a,b]	*P*
Anus	1.65 (1.09-2.50)	.0173	1.59 (1.05-2.40)	.0277	1.77 (1.22-2.56)	.0027	1.97 (1.42-2.73)	< .0001
Liver	32.20 (29.1-35.5)	< .0001	32.50 (29.5-35.7)	< .0001	23.80 (21.6-26.2)	< .0001	31.60 (29.0-34.3)	< .0001
Intrahepatic bile duct	2.99 (2.05-4.34)	< .0001	3.11 (2.20-4.40)	< .0001	2.99 (2.12-4.20)	< .0001	3.38 (2.51-4.56)	< .0001
Extrahepatic bile duct	2.06 (1.46-2.90)	< .0001	1.99 (1.43-2.76)	< .0001	1.92 (1.39-2.64)	.0001	1.91 (1.41-2.58)	< .0001
Pancreas	1.28 (1.11-1.49)	.0009	1.24 (1.08-1.44)	.0030	1.27 (1.11-1.46)	.0005	1.23 (1.09-1.40)	.0012
Nonepithelial skin	1.78 (1.31-2.43)	.0002	1.67 (1.23-2.26)	.0010	1.59 (1.18-2.16)	.0027	1.54 (1.15-2.04)	.0033
Uterus	0.66 (0.51-0.86)	.0016	0.61 (0.48-0.77)	.0001	0.62 (0.48-0.79)	.0001	0.64 (0.51-0.80)	.0001
Prostate	0.73 (0.66-0.82)	< .0001	0.76 (0.67-0.87)	< .0001	0.77 (0.68-0.86)	< .0001	0.73 (0.66-0.82)	< .0001
MDS	1.56 (1.30-1.88)	< .0001	1.64 (1.37-1.96)	< .0001	1.43 (1.19-1.70)	.0001	1.56 (1.33-1.83)	< .0001
DLBCL	1.55 (1.29-1.87)	< .0001	1.74 (1.46-2.06)	< .0001	1.55 (1.30-1.84)	< .0001	1.57 (1.33-1.84)	< .0001

Abbreviations: aOR, adjusted odds ratio; CI, confidence intervals; DLBCL, diffuse large B-cell lymphoma; HBV, hepatitis B virus; HIV, human immunodeficiency virus; MDS, myelodysplastic syndrome.

[a] Odds ratios assess the association of hepatitis C virus with the specified cancer and were adjusted for age categories (ages 65-69, 70-74, 75-79, 80-84, ≥ 85 years), sex, race/ethnicity, calendar year of cancer diagnosis/control selection (1993-1999, 2000-2003, 2004-2007, and 2008-2011), number of physician claims per year (<2.56, 2.56 to < 5.57, 5.57 to < 10.07, and ≥10.07 physician claims per year), and smoking status (never/ever).

[b] Odds ratios assess the association of hepatitis C virus with the specified cancer and also were adjusted for the zip code median household income categories (<$35,097, $35,097-$45,537, $45,538-$59,164, and ≥$59,165 [US dollars]). Models were separately adjusted for the education and poverty variables listed in Table 1 instead of median household income, with a resulting change in point estimates by <10% for all cancers (results not shown).

TABLE 3. Population-Attributable Fractions for Hepatitis C Virus and Selected Cancers

Cancer	aOR	Proportion of Cases with HCV Infection (Pd)	Population-Attributable Fraction, %[a]
Liver	31.50	0.1667	16.14
Intrahepatic bile duct	3.40	0.0163	1.15
Extrahepatic bile duct	1.90	0.0105	0.50
Pancreas	1.23	0.0067	0.13
Myelodysplastic syndrome	1.56	0.0114	0.41
Diffuse large B cell lymphoma	1.57	0.0076	0.28

Abbreviations: aOR, adjusted odds ratio; HCV, hepatitis C virus.

[a] Population-attributable fractions were calculated using the following formula:

$$P_d \times \left(\frac{aOR-1}{aOR}\right),$$

where P_d is the proportion of patients exposed to HCV infection, and aOR is the adjusted odds ratio from the logistic regression model.

(aOR, 0.73; 95% CI, 0.66-0.82). Associations between HCV and marginal zone lymphoma (MZL) (aOR, 1.39; 95% CI, 1.04-1.86), and lymphoplasmacytic lymphoma (LPL) (aOR, 1.54; 95% CI, 0.97-2.43) were of borderline significance. With the Bonferroni method, associations remained significant for most cancers, except for pancreatic and nonepithelial skin cancers.

Additional analyses were directed to assess specific subtypes of nonmelanoma nonepithelial skin cancer. We observed associations between HCV and Merkel cell carcinoma (aOR, 1.92; 95% CI, 1.30-2.85; N = 2669 cases) and appendageal skin cancers (aOR, 2.02; 95% CI, 1.29-3.16; N = 1969 cases); we did not detect an association with skin sarcomas, although the number of cases that could be assessed was small (data not shown). The associations between HCV and DLBCL were similar in magnitude for those with nodal (aOR, 1.54; 95% CI, 1.26-1.88; N = 9544 cases) and extranodal (aOR, 1.62; 95% CI, 1.28-2.06; N = 14,995 cases) disease.

In a sensitivity analyses, we excluded HBV-infected or HIV-infected individuals. Because the prevalence of these 2 infections was low, there were no discernible differences in the aORs (Table 2). The associations were

maintained when we conducted analyses among individuals without documented alcohol abuse or cirrhosis (Table 2). Additional adjustment for SES variables such as median household income did not affect the associations (Table 2). The association between HCV infection and liver cancer was attenuated among individuals with diabetes (aOR, 18.9; 95% CI, 16.7-21.4) versus those without diabetes (aOR, 48.2; 95% CI, 43.0-53.9). The associations did not differ according to diabetes status for bile duct or pancreatic cancers (Supporting Table 2; see online supporting information). When we used the more stringent criterion for HCV diagnosis, the associations for most cancers were maintained; however, the associations for pancreatic cancer and nonmelanoma nonepithelial skin cancer were attenuated and no longer statistically significant (Supporting Table 3; see online supporting information).

The population-attributable fractions for most cancers were very low, except for liver cancer (Table 3). Assuming that HCV infection is causally associated with the cancers, elimination of HCV infection would reduce the risk of the cancers of liver, intrahepatic bile ducts, extrahepatic bile ducts, and pancreas; MDS; and DLBCL by 16.14%, 1.15%, 0.50%, 0.13%, 0.41%, and 0.28%, respectively.

DISCUSSION

Persistent HCV infection leads to liver fibrosis and eventually cirrhosis, which increases the risk for HCC.[2] Chronic HCV infection also has important biologic effects beyond the liver. In accordance with 2 previous studies,[14,15] our analyses of a large, population-based data set of elderly individuals demonstrate that, along with HCC, several additional cancers are associated with HCV infection.

HCV infection has previously been linked to hematologic malignancies, including some subtypes of B-cell NHLs (such as DLBCL, MZL, and LPL) and MDS.[24,25] It is believed that HCV causes NHL through chronic antigenic stimulation. We observed a significant association of HCV with DLBCL. The associations with MZL and LPL were of borderline significance, perhaps because of a lack of statistical power related to the low HCV prevalence in our study. Notably, HIV infection also causes NHLs, especially DLBCL.[26] The association with DLBCL persisted in our study in individuals who lacked claims for HIV infection, although it is possible that some HIV-infected individuals were missed using this approach. A previous study conducted using the SEER-Medicare database also indicated an elevated risk of MDS in HCV-infected individuals.[24] MDS is a heterogeneous group of malignant disorders characterized by ineffective blood cell production, and patients with MDS have an increased risk of progression to acute myeloid leukemia.[27] HCV can infect and replicate inside pluripotent hematopoietic stem cells, and HCV proteins and RNA have been isolated from these cells.[12] Furthermore, a recent case report described the resolution of MDS in an HCV-infected individual after viral clearance with antiviral therapy.[28]

Prior epidemiological studies have demonstrated that HCV is associated with intrahepatic cholangiocarcinoma, with ORs ranging from 3.4 to 4.8.[29-31] The detection of HCV RNA in bile duct epithelial cells[32] and of HCV core proteins and RNA in cholangiocarcinoma specimens[33] and the demonstration of increased cellular proliferation and decreased apoptosis in HCV-positive cholangiocarcinoma specimens[34] suggest that HCV may play a direct role in the development of cholangiocarcinoma. We also observed an association between HCV and extrahepatic cholangiocarcinoma. Although this was not observed in some previous studies, a recent meta-analysis indicated that the pooled estimate was of borderline significance (OR, 1.75; 95% CI, 1.00-3.05).[29] We observed a moderate association between HCV infection and pancreatic cancer that was not affected by adjustment for diabetes mellitus and was similar in strength to the results from a meta-analysis of 8 observational studies (OR, 1.26; 95% CI, 1.03-1.50).[35] However, the association with pancreatic cancer became attenuated when we used a more stringent definition of HCV infection. The results from the sensitivity analysis suggest that the association with pancreatic cancer may reflect nonspecific coding for HCV infection.

The associations we observed for HCV with anal cancer and nonepithelial skin cancers may be explained as confounding by shared risk factors. A high prevalence of HCV infection is observed in men who have sex with men (MSM) and injection drug users,[1,36] and MSM also have a high prevalence of anal human papillomavirus infection,[37] the cause of anal cancer. MSM and injection drug users have an elevated prevalence of HIV infection, which increases the risk of anal cancer.[38] Similarly, the risk of nonepithelial skin cancers, including Merkel cell carcinoma and appendageal carcinomas, is increased in individuals with HIV infection.[39] The associations with HCV in our study persisted in a sensitivity analysis in which we excluded individuals with documented HIV infection, but the Medicare claims may have missed some HIV infections.

The negative associations of HCV infection with uterine and prostate cancers are intriguing. A potential explanation for the negative association with uterine cancer is that some women included in our study could have undergone a hysterectomy, which is the most common nonobstetric abdominal surgery in women. An estimated 33% women eligible for our study would have had a hysterectomy before age 60 years,[40] which would not have been captured in Medicare claims. According to the age structure of our study population, most of these women would have undergone open abdominal hysterectomies in the 1970s and 1980s, because laparoscopic techniques were developed only in the 1990s.[41] Total abdominal hysterectomy is associated with a risk of hemorrhage requiring blood transfusion, and blood transfusions before 1992 conveyed a risk of HCV infection.[1] Obviously, none of the patients with uterine cancer had previously undergone hysterectomy, but prior hysterectomies among control women would have contributed to a relatively high HCV prevalence. In the United States, a large fraction of prostate cancers are detected through screening.[42] We believe that the deficit in prostate cancer cases may be because of lower rates of prostate cancer screening in HCV-infected individuals, because they often come from lower SES groups.[43]

We did not observe associations between HCV infection and cancers of the oral cavity, oropharynx, kidney, and thyroid, which were detected in other studies.[6,7,10,14,44] Variation across studies may be because of differences in the populations or in the methods of exposure and outcome ascertainment. Alternatively, some prior studies were retrospective or used hospital-based controls, which may have biased their results. We observed that the presence of diabetes attenuated the association between HCV infection and liver cancer. A similar negative interaction between HCV and diabetes has been previously reported.[45] Although HCV infection and diabetes both contribute to the development of HCC, the biologic mechanisms responsible for the negative interaction between the 2 conditions are unclear.

Despite a high prevalence of HCV infection in baby boomers, less than 50% of infected individuals are aware of their infection, and even fewer get treated for HCV.[46] The first members of this birth cohort became eligible for Medicare (by virtue of attaining an age of 65 years) in 2010; and, in 15 years, approximately 90% of Medicare beneficiaries will belong to the baby-boomer generation.[47] This ageing population is already contributing to high resource use and health care costs in the United States.[48] On the basis of our calculations, HCV infection is responsible for approximately 16% of liver cancers in elderly adults, but it is likely that this burden will continue to rise. Although the introduction of direct-acting antivirals has dramatically improved cure rates, HCC risk still remains relatively high in infected individuals who have cleared the virus—particularly elderly individuals.[49] Whether effective antiviral therapy reduces the risk of cancers other than HCC is not known. Hence, physicians who manage HCV-infected individuals need to be aware of a potential risk of non-HCC cancers.

A strength of our study is the systematic assessment of a large, nationally representative population of elderly individuals. Previous large US studies used data either from 4 urban health centers[14] or from a large HMO organization[15] and compared cancer incidence in HCV-infected individuals with cancer incidence in SEER areas. SEER registries have strict quality-control measures for cancer ascertainment, which improved the reliability of our outcomes compared with other large studies that relied on administrative claims data for the identification of cancer outcomes. Given the size of our study, we also were able to assess the associations of HCV with a large number of cancer types and subtypes, many of which are uncommon.

We also acknowledge some limitations. First, because our study focused on elderly individuals, the results are not directly generalizable to a younger population. Second, the study is limited by the inability to accurately assess smoking, alcohol use, coinfections, obesity, and other cancer risk factors, which may have caused confounding. Third, because HCV infection was identified using administrative claims, under-ascertainment of HCV diagnosis is likely, eg, if physicians did not test patients for infection. Conversely, some misreporting of ICD-9 codes for HCV infection by physicians also likely occurred. In addition, some patients may have had HCV antibodies but no detectable HCV RNA in serum, indicating resolved infection. To improve the specificity of HCV diagnosis, we conducted an analysis using a stricter claims definition for HCV infection, which produced mostly similar results. We expect that both biases (ie, under-ascertainment and false-positive diagnoses) were nondifferential between cases and controls and would have driven associations that we measured toward the null. Fourth, we were unable to account for the effect of antiviral therapy. New interferon-free antiviral regimens have improved viral clearance rates, but the calendar period covered by our study suggests that individuals were unlikely to have received these therapies. Finally, because we made multiple comparisons, some associations could be

because of chance. We used a statistical procedure to minimize this possibility and emphasized the most significant associations.

In summary, we observed significant associations between HCV infection and several cancers other than liver cancer, notably intrahepatic and extrahepatic cholangiocarcinomas and DLBCL. Studies are needed to strengthen the evidence linking HCV infection to these cancers and to further elucidate biologic mechanisms.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Parag Mahle: Study conception and design, data analysis and interpretation, writing, and approval of the final article. **Harrys A. Torres**: Data interpretation, writing, and approval of the final article. **Jennifer R. Kramer**: Data interpretation, writing, and approval of the final article. **Lu-Yu Hwang**: Data interpretation, writing, and approval of the final article. **Ruosha Li**: Data interpretation, writing, and approval of the final article. **Eric L. Brown**: Data interpretation, writing, and approval of the final article. **Eric A. Engels**: Study conception and design, data analysis and interpretation, writing, and approval of the final article.

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