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Increased incidence of cancer and cancer-related mortality among persons with chronic hepatitis C infection, 2006–2010

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Background & Aims: Persons chronically infected with the hepatitis C virus (HCV) may be at higher risk for developing and dying from non-liver cancers than the general population.
Methods: 12,126 chronic HCV-infected persons in the Chronic Hepatitis Cohort Study (CHeCS) contributed 39,984 person-years of follow-up from 2006 to 2010 and were compared to 133,795,010 records from 13 Surveillance, Epidemiology and End Results Program (SEER) cancer registries, and approximately 12 million U.S. death certificates from Multiple Cause of Death (MCOD) data. Measurements included standardized rate ratios (SRR) and relative risk (RR).
Results: The incidence of the following cancers was significantly higher among patients with chronic HCV infection: liver (SRR, 48.6 [95% CI, 44.4–52.7]), pancreas (2.5 [1.7–3.2]), rectum (2.1 [1.3–2.8]), kidney (1.7 [1.1–2.2]), non-Hodgkin lymphoma (NHL) (1.6 [1.2–2.1]), and lung (1.6 [1.3–1.9]). Age-adjusted mortality was significantly higher among patients with: liver (RR, 29.6 [95% CI, 29.1–30.1]), oral (5.2 [5.1–5.4]), rectum (2.6 [2.5–2.7]), NHL (2.3 [2.2–2.31]), and pancreatic (1.63 [1.6–1.7]) cancers. The mean ages of cancer diagnosis and cancer-related death were significantly younger among CHeCS HCV cohort patients compared to the general population for many cancers.
Conclusions: Incidence and mortality of many types of non-liver cancers were higher, and age at diagnosis and death younger, in patients with chronic HCV infection compared to the general population.
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Introduction

Over one hundred million persons are infected with the HCV worldwide, and in the United States an estimated three million persons are chronically infected [1,2]. HCV causes about 25% of all hepatocellular carcinoma (HCC), one of the most commonly diagnosed cancers and among the most common causes of cancer-related deaths both in the U.S. and worldwide [3–5]. Chronic HCV infection has also been associated with an increased risk of developing many other non-liver cancers, usually non-Hodgkin lymphoma, NHL (Supplementary material Table 1) [6–22]. An increase in mortality related to non-liver cancers has been observed in chronic HCV-infected persons in Taiwan [23], but has not been reported in the U.S. or Europe previously. To describe malignant cancer incidence and cancer-related mortality among persons with chronic HCV infection, data were analyzed from a large retrospective cohort study, the Chronic Hepatitis Cohort Study (CHeCS). Cancer incidence and mortality rates among CHeCS patients were compared with incidence and mortality in the general population, derived from Surveillance, Epidemiology, and End Results (SEER) cancer registry data and Multiple Causes of Death (MCOD) data, respectively, for the 5-year period from 2006 to 2010.

Patients and methods

Chronic hepatitis cohort study

CHeCS is a multi-center cohort of patients infected with chronic viral hepatitis created from electronic health records (EHR) and administrative data of adult patients who had a service provided between January 1, 2006 and December 31, 2010 at one of four U.S. healthcare systems: Geisinger Health System (GHS), Danville, PA; Henry Ford Health System (HFHS), Detroit, MI; Kaiser Permanente Northwest (KPNW), Portland, OR; and Kaiser Permanente Hawaii (KPH), Honolulu, HI. Criteria for inclusion and composition of the CHeCS cohort have been summarized in a previous report [24]. Briefly, patients were considered confirmed cases based upon measurable viral load by PCR and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) criteria. EHR and administrative data were collected for each cohort patient and supplemented with individual chart review by trained data abstractors. Trained data abstractors reviewed and verified chronic HCV infection from EHR data. Tumor registry data were collected and stored in each health system according to Surveillance, Epidemiology, and End Results (SEER) program standards [25,26], and included in the CHeCS database. Only incident primary cancers were used for calculation of cancer incidence in CHeCS. Additional data collected included patient demographics, medical encounters, laboratory results, and deaths from all causes that occurred or were reported to health system facilities during 2006–2010. Each health system compared cohort patient records to the

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U.S. National Death Index (NDI), Social Security Death Index (SSDI), or an electronic state death registry to enhance death ascertainment through 2010 (http://www.cdc.gov/nchs/data_access/ndi/about_ndi.htm; for SSDI see NTIS http://www.ntis.gov/products/ssa-dmf.aspx).

Surveillance, epidemiology, and end results program

Thirteen tumor registries from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER13) Program database were used for comparisons of incidence rate, and age, grade and stage at cancer diagnosis with CHeCS. SEER13 is an active and passive surveillance system that has collected cancer incidence and survival data from 13 population-based cancer registries for all cases diagnosed from 1992 to the present and covers approximately 26% of the U.S. population [27]. These registries include Atlanta, Connecticut, Detroit, Hawaii, Iowa, Los Angeles, New Mexico, Rural Georgia, San Francisco-Oakland, San Jose-Monterey, Seattle-Puget Sound, and Utah. The Alaska Native registry is also part of SEER13 but was excluded from this analysis for a better approximation of U.S. national data for comparison to CHeCS.

Multiple causes of death

Our methods for calculating and comparing causes of death have been previously described [28]. Briefly, the U.S. Standard Certificate of Death, developed by the National Center for Health Statistics (NCHS), serves as the foundation for state death certificates and increases uniformity in data collection and processing by state vital registration systems [29]. Every year, NCHS processes state death records and creates a national data set that is accessible for public use. Death certificates record the immediate cause of death, underlying causes and contributing causes. For our analysis, if cancer was listed as an immediate, underlying or contributing cause of death, the death was considered cancer-related.

Statistical analysis

Incidence rates were calculated for persons 25 years of age or older as the number of newly diagnosed malignant cancer cases in CHeCS and SEER for the five-year analysis period from 1 January 2006 to 31 December 2010. No incident cancers were observed in CHeCS patients less than 25 years old. Cancer incidence in CHeCS and SEER were coded as International Classification of Disease for Oncology, 3rd Edition (ICD-O-3), codes (Supplementary material, Table 2). Incidence rates were expressed per 100,000 prospective person-years of observation. In CHeCS, person-years were calculated from first observation to cancer diagnosis, last date of follow-up or death. If cancer was known or detected at first observation (i.e. first encounter in the healthcare system) then that cancer was excluded from the analysis. Recurrent cancers were also excluded. For comparison to CHeCS, malignant cancer incidence rates for the general population were calculated using SEER data. CHeCS and SEER data were age-adjusted by directly standardizing to the 2000 U.S. Census population. Standardized rate ratios were determined for the entire observation period (2006 to 2010) to compare the incidence of malignant cancer in CHeCS with the incidence in the general population as previously described [30]. The statistical differences between CHeCS and SEER mean age and mean cancer grade at the time of diagnosis were computed using Student's *t* test. The statistical difference between the proportion of cases presenting at diagnosis with regional extension, a distant site or distant nodes involved (cancer stage) was computed using the Pearson Chi-Square test.

Cancer-related mortality rates were calculated for persons 40 years of age or older by counting the number of each cancer listed as an immediate, underlying or contributing cause of death on death certificates in CHeCS and MCOD for the five-year analysis period from 1 January 2006 to 31 December 2010. No cancer-related deaths were observed in CHeCS patients less than 40 years old. Cancer-related deaths in CHeCS were coded as International Classification of Disease, Tenth Revision (ICD-10) codes (Supplementary material, Table 2). U.S. national cancer-related mortality rates were calculated by dividing the number of each cancer listed as an immediate, underlying or contributing cause of death on death certificates by the total U.S. census population for each year. For the comparative analysis between CHeCS and MCOD rates, CHeCS rates were age-adjusted by standardizing to the age distribution of the U.S. Census population in 2008, since this was the median year of our study period. The statistical difference between CHeCS and MCOD cancer-related mortality rates was calculated using the Pearson Chi-Square test. To examine the likelihood of having a cancer-related death in CHeCS relative to the general U.S. population, the relative risk and 95% confidence intervals were calculated.

For incidence, mortality and age, grade and stage analyses, a p value of less than 0.05 was considered statistically significant. Rare cancer types (n <5 cases) were excluded from incidence and mortality rate calculations. Statistical analyses were performed with the SEER*Stat software version 8.1.2 (Surveillance Research Program, National Cancer Institute, seer.cancer.gov/seerstat), and with SAS software version 9.2 (SAS Institute, Cary, North Carolina).

Ethical considerations

The investigation followed the guidelines of the U.S. Department of Health and Human Services regarding protection of human subjects. The study protocol was approved and renewed annually by each participating institution's institutional review board.

Results

Of 2,143,369 adult patients who had a service provided from 2006 to 2010 at one of four participating U.S. healthcare systems, 12,126 (0.57%) were diagnosed with chronic HCV infection and contributed 39,984 person-years of follow-up time. Demographics are summarized in Table 1. Seventeen percent of the patients with chronic HCV infection came from Geisinger Health System in Danville, PA; 44.3% from the Henry Ford Health System in Detroit, MI; 28.1% from Kaiser Permanente Northwest in Portland, OR; and 10.3% from Kaiser Permanente

Table 1. Characteristics of chronic HCV-infected patients (CHeCS), 2006–2010.

Characteristic	No. (%)
Total No. HCV-infected patients	12,126
Age at diagnosis by birth year	
Born before 1945	1213 (10)
Born from 1945-1965	9337 (77)
Born after 1965	1576 (13)
Sex	
Male	7397 (61)
Female	4729 (39)
Race	
Non-hispanic white	7276 (60)
Non-hispanic black	2910 (24)
Hispanic	437 (3.6)
Asian	400 (3.3)
Hawaiian/PI	182 (1.5)
American indian	158 (1.3)
Other or unknown	763 (6.3)
Co-morbid infections	
Hepatitis B virus, DNA positive	99 (0.8)
HIV, RNA positive	367 (3.0)
CHeCS cohort site	
Geisinger Health System, Danville, PA	2061 (17.0)
Henry Ford Health System, Detroit, MI	5371 (44.3)
Kaiser Permanente, Honolulu, HI	3407 (28.1)
Kaiser Permanente Northwest, Portland, OR	1249 (10.3)
Insurance status (data available for n = 11,792)	
Medicaid	1474 (12.5)
Medicare	3137 (26.6)
Private	6816 (57.8)
Other	365 (3.0)

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Hawaii. Seventy-seven percent of the patients with HCV infection were born between 1945 and 1965; 10% were born before 1945 and 13% were born after 1965. Sixty-one percent were male, 60% white, 24% black, 3.6% Hispanic, 3.3% Asian, 1.5% Hawaiian or Pacific Islander, 1.3% American Indian and 6.3% of unknown or other race. Of 11,792 (97%) patients with chronic HCV infection for whom health insurance data were available, 97% were insured, including 12.5% on Medicaid, 26.6% on Medicare and 57.8% with private insurance coverage. Ninety-nine (0.8%) were HCV/hepatitis B co-infected and 367 (3%) were HCV/HIV co-infected.

Cancer incidence in chronic HCV-infected persons compared to SEER

Five hundred and ninety-five persons ages 25 or older were diagnosed with 612 incident malignant neoplasms during the five-year period from 2006 to the end of 2010. Of 612 cancers, 565 (92.3%) met the inclusion criteria for analysis. Detailed results of age-adjusted cancer incidence in HCV-infected persons compared to SEER are provided in Table 2. We examined rates of several cancers related to alcohol use and particularly to smoking, a leading cause of cancer and death from cancer. Compared with the general population, patients with chronic HCV infection had a higher incidence of four of eight smoking-related cancers analyzed including: pancreas (standardized rate ratio [SRR], 2.5 [95% CI, 1.7–3.2]), rectum (2.1 [1.3–2.8]), lung (1.6 [1.3–1.9]), and kidney (1.7 [1.1–2.2]). Cancers of the esophagus, stomach and colon were not more frequent among HCV-infected patients compared with the general population. Oral cavity cancers were of borderline significance. Colon cancer incidence was lower among HCV-infected persons (0.4 [0.3–0.6]). Rectal cancer, also a smoking-related cancer, was the only one of four alcohol-related cancers (excluding liver) that had a higher incidence in the HCV-infected group. Breast cancer incidence among 150 females with chronic HCV infection was lower than the rate among the general population (0.7 [0.6–0.8]). The incidence of NHL was higher in the HCV-infected group (1.6 [1.2–2.1]), a cancer that is not associated with smoking or alcohol use, but has been associated with HIV. Only two of twenty-six patients with incident NHL had HIV/HCV co-infection. Twenty of twenty-six (77%) of incident NHL were B-cell type and the remainder were labeled not otherwise specified (NOS). ICD-O-3 morphology (histology) codes of all analyzed malignancies are given in Supplementary material, Table 2.

Age, grade and severity of stage of cancer in HCV-infected persons compared to SEER

For ten of sixteen cancers, mean age at diagnosis was 7.4 years younger among HCV-infected patients compared with the

Table 2. Age-adjusted malignant cancer incidence and standardized rate ratios (SRR) among 543 chronic HCV-infected persons (CHeCS) compared to SEER,* 2006–2010.

Cancers	No. (%)†	Age-adjusted incidence per 100,000 person-years		SRR SEER	(95% CI)
		CHeCS	SEER‡		
Oral cavity and pharynx					
Lip, gum and mouth§	7 (1.2)	9.3	3.7	2.5	(0.9, 4.1)
Digestive system					
Esophagus§‖	9 (1.6)	12.9	6.2	2.1	(0.9, 3.2)
Stomach§	8 (1.4)	12.2	11.6	1.1	(0.5, 1.6)
Colon§‖	13 (2.3)	20.1	45.0	0.4	(0.3, 0.6)
Rectum§‖	12 (2.1)	27.4	13.3	2.1	(1.3, 2.8)
Liver‖	277 (49.0)	525.8	10.8	48.6	(44.4, 52.7)
Pancreas§	19 (3.4)	44.1	17.9	2.5	(1.7, 3.2)
Respiratory system					
Lung and bronchus§	67 (11.9)	124.7	78.9	1.6	(1.3, 1.9)
Melanoma	10 (1.8)	23.9	28.9	0.8	(0.5, 1.2)
Breast among female‖ (n = 150)	19 (12.7)	132.2	188.5	0.7	(0.6, 0.8)
Prostate (n = 393)	46 (11.7)	131.7	209.1	0.6	(0.5, 0.7)
Urinary system					
Kidney and renal pelvis§	17 (3.0)	33.1	19.8	1.7	(1.1, 2.2)
Brain and other nervous system	5 (0.9)	9.0	7.9	1.1	(0.4, 1.9)
Thyroid	6 (1.0)	18.8	17.3	1.1	(0.6, 1.6)
Lymphoid and related tissue					
Non-Hodgkin lymphoma	26 (4.6)	46.8	28.5	1.6	(1.2, 2.1)
Leukemia	10 (1.8)	17.0	16.9	1.0	(0.5, 1.5)
Unknown primary and unspecified	14 (2.5)	25.2	12.3	2.1	(1.3, 2.9)

*Includes persons from CHeCS and SEER ages 25 and older.
†Includes 565 incident cancers in 543 patients; 22 second cancers were histologically distinct from first.
‡Includes all SEER 13 registries except Alaska Natives.
§Tobacco-related cancer.
‖Alcohol-related cancer.

Table 3. Age, grade and severity of stage of malignant cancer at time of diagnosis among chronic HCV-infected persons (CHeCS) compared to SEER, 2006–2010.

	Mean age at cancer diagnosis*			Mean grade at cancer diagnosis†			Proportion of cancers with regional extension or distal involvement‡		
Cancer site	CHeCS	SEER§	*p* value	CHeCS	SEER§	*p* value	CHeCS	SEER§	*p* value
Oral cavity and pharynx									
Lip, gum and mouth	55.1	63.7	0.001	2.0	1.9	0.73	0.40	0.44	1.00
Digestive system									
Esophagus	57.9	66.0	0.02	2.6	2.5	0.85	0.88	0.76	0.69
Stomach	56.3	65.2	0.049	2.1	2.7	0.03	0.57	0.70	0.43
Colon	55.8	66.2	<0.001	2.1	2.1	0.73	0.38	0.60	0.28
Rectum	56.3	61.6	0.15	1.7	2.1	0.09	0.45	0.50	1.00
Liver	58.3	62.8	<0.001	1.8	2.0	0.002	0.34	0.50	<0.001
Pancreas	61.2	67.4	0.02	n.d.	2.3	n.a.	1.00	0.90	0.25
Respiratory system									
Lung and bronchus	59.7	68.1	<0.001	2.3	2.6	0.11	0.73	0.82	0.06
Melanoma	56.6	58.6	0.42	n.a.	n.a.	n.a.	1.00	0.96	1.00
Breast among females	58.3	59.6	0.64	2.0	2.1	0.48	0.41	0.36	0.80
Prostate	61.5	65.7	<0.001	2.7	2.6	0.04	0.29	0.17	0.047
Urinary system									
Kidney and renal pelvis	56.9	62.3	0.07	2.0	2.4	0.09	0.06	0.33	0.02
Brain and other nervous system	61.8	58.0	0.57	0.60‖	0.85‖	0.16	0.33	0.20	0.48
Thyroid	52.3	50.5	0.74	n.a.	n.a.	n.a.	0.33	0.32	1.00
Lymphoid and related tissue									
Non-Hodgkin lymphoma	58.3	62.9	0.01	0.60¶	0.44¶	0.18	0.73	0.70	1.00
Leukemia	53.9	64.0	0.03	n.a.	n.a.	n.a.	1.00	0.998	1.00
Unknown primary and unspecified	58.0	67.3	0.004	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

*Mean age calculated for persons 25–84 years old.
†Mean grade from SEER Summary Staging 2000 (SS2000) (Young *et al.*, 2001), calculated for persons 25 and older.
‡Proportion of cancers with regional extension, distant site or distant node(s) involved (SEER SS2000 Stage 2, 3, 4, 5 or 7), calculated for persons aged 25 and older.
§Includes all SEER 13 registries except Alaska Natives.
‖Proportion of brain and other nervous system tumors that were WHO grade IV at diagnosis (Tatter *et al.*, 1995).
¶Proportion of non-Hodgkin lymphomas that were high grade at diagnosis (Wilson *et al.* 2008).
n.d., no or insufficient data; n.a., not applicable.

general population (Table 3); these included oral cavity, esophagus, stomach, colon, liver, pancreas, lung, and prostate cancers, NHL and leukemia. For six of the eight cancers diagnosed at a younger age among patients with HCV that had available tumor grade data, tumor grade at diagnosis was either higher or not significantly different for patients with chronic HCV infection compared with the general population. Similarly for cancer stage, of ten cancers diagnosed at a younger age among patients with HCV severity was higher or not significantly different for patients with chronic HCV infection compared with the general population. In other words, these ten types of cancer were not simply diagnosed at an earlier stage of development among these HCV-infected patients who were on average younger at diagnosis, but were as or more advanced as similar tumors among persons in the general population who were on average more than seven years older.

Cancer-related mortality in chronic HCV-infected persons compared to MCOD

Three hundred and thirty-five deaths in persons aged 40 years or older were related to 380 histologically distinct, primary malignancies during the five-year period from 2006 to the end of 2010. Detailed results of age-adjusted annual cancer-related mortality in patients with chronic HCV infection compared with the general population are provided in Table 4. Persons with chronic HCV infection had an increased cancer-related mortality from three of seven smoking-related cancers including: oral (relative risk [RR], 5.2 [95% CI, 5.1–5.4]), rectum (2.6 [2.5–2.7]), and pancreas (1.63 [1.6–1.7]). The mortality from the other four smoking-related cancers was significantly lower in the HCV group including: esophagus, colon, lung and kidney. Rectal cancer is the only one of four alcohol-related cancers (excluding liver) that had increased mortality in HCV-infected persons, but is also smoking-related. Breast cancer mortality among 87 females was lower than the general population (0.42 [0.41–0.43]). The mortality related to NHL in the HCV group was more than two times higher (2.3 [2.2–2.31]). Only one of 18 patients who died from NHL had HIV/HCV co-infection. ICD-10 codes of all malignancies analyzed for mortality comparisons are given in Supplementary material, Table 2.

Discussion

In this study, we measured the incidence of malignant cancers and cancer-related mortality among 12,126 chronic HCV-infected patients in the Chronic Hepatitis Cohort Study

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Table 4. Cancer-related, age-adjusted annual mortality in Chronic HCV-infected persons (CHeCS) compared with United States national data (MCOD),* 2006–2010.

		Mean age at death			Age-adjusted mortality per 100,000 persons		
Cancer causes of death	Deaths, No. (%)†	CHeCS	MCOD	*p* value	CHeCS	MCOD	Relative risk (95% CI)
Oral cavity§	9 (2.4)	55.6	68.2	<0.001	18.5	3.5	5.22 (5.06, 5.38)
Digestive system							
Esophagus§‖	7 (1.8)	59.1	69.4	0.02	10.3	10.7	0.96 (0.94, 0.98)
Colon§‖	6 (1.6)	60.3	74.5	0.01	12.1	35.5	0.34 (0.33, 0.35)
Rectum§‖	6 (1.6)	60.2	71.4	0.04	13.7	5.3	2.60 (2.53, 2.67)
Liver‖	174 (45.8)	60.7	67.5	<0.001	323.2	11.0	29.6 (29.1, 30.1)
Pancreas§	19 (5.0)	63.1	72.0	0.001	42.6	26.1	1.63 (1.61, 1.65)
Other digestive organs‡	16 (4.2)	59.2	71.8	<0.001	30.0	15.6	1.93 (1.90, 1.96)
Lung and bronchus§	61 (16.0)	60.7	71.1	<0.001	117.8	120.6	0.98 (0.97, 0.98)
Breast among females‖ (n = 87)	5 (5.7)	55.8	70.9	0.02	28.1	67.2	0.42 (0.41, 0.43)
Prostate (n = 293)	9 (3.1)	68.8	79.7	<0.001	38.6	62.2	0.62 (0.61, 0.63)
Urinary system							
Urinary bladder	5 (1.3)	64.4	77.7	0.01	11.3	13.0	0.87 (0.85, 0.89)
Kidney and renal pelvis§	5 (1.3)	61.8	71.6	0.08	10.2	10.6	0.46 (0.44, 0.47)
Lymphoid and related tissue							
Non-Hodgkin lymphoma	18 (4.7)	62.0	74.6	<0.001	33.7	14.8	2.27 (2.23, 2.31)
Leukemia	5 (1.3)	56.4	72.8	<0.001	7.5	11.1	0.68 (0.66, 0.70)
Unknown primary and unspecified	35 (9.2)	61.1	71.7	<0.001	60.0	43.9	1.37 (1.35, 1.38)

*Includes persons from CHeCS and MCOD ages 40 and older (no deaths were observed in CHeCS patients <40).
†Includes 335 deaths related to 380 cancers.
‡Other digestive organs included the combination of digestive malignancies with <5 cases related to death: stomach, gallbladder, extra and intrahepatic bile ducts, intestine (not otherwise specified, NOS), peritoneum (NOS) and anus.
§Tobacco-related cancer.
‖Alcohol-related cancer.

(CHeCS) and compared them to the general population during the five-year period from 2006 to 2010.

Similar to prior studies, we found that persons with chronic HCV infection in CHeCS had a significantly increased risk of NHL [SRR, 1.6 (CI, 1.2–2.1)] with a predominantly B-cell type (Supplementary material, Table 1). There exists a large body of epidemiologic evidence linking HCV infection with the development of B-cell NHL and regression of NHL after HCV elimination with treatment supports a causal relationship [6–22,31,32]. In addition, we observed that NHL was diagnosed in CHeCS patients nearly five years earlier than the general population. Were they diagnosed earlier because they were already linked to the healthcare system by their HCV diagnosis? If that was the case, one might expect a lower NHL mortality rate. Instead, we observed an age-adjusted death rate that was more than double for NHL in the HCV group. In addition, HCV-infected persons died from NHL nearly 13 years earlier. Further, the NHL grade and stage in CHeCS patients were higher, though not statistically different, than the general population despite the significantly earlier diagnosis. NHL is associated with HIV infection, but the three co-infected patients with NHL in our study did not affect the rate calculations. Of note, smoking and alcohol use have generally not been associated with an increased incidence or risk of death from NHL. In contrast, a mixed group of leukemia diagnoses (not B-cell predominant) had an incidence similar to the general population. A younger age at diagnosis may be related to earlier linkage to the healthcare system and might also account for a lower mortality rate observed among HCV-infected patients with leukemia compared to the general population.

Four of the five non-liver malignancies that had significantly increased incidence rates among HCV-infected patients in CHeCS are also smoking-related, including cancers of the kidney, lung, pancreas and rectum. Smoking rates in CHeCS participants are higher than in the general population 33.7% *vs.* 20.2% [33]. Because we were unable to control for tobacco use, it remains unclear whether this difference in smoking rates could account for the differences in incidence rates [34]. Regardless of smoking rate differences, the severity of these cancers appeared to be worse in HCV-infected patients. Despite having their cancer diagnosis made about eight and a half years earlier, the grade and stage of CHeCS patients' cancers were not remarkably different from the general population. Additionally, HCV-infected patients had significantly higher mortality rates for cancers of the oral cavity, pancreas and rectum, and died from their smoking-related cancers an average 11 years younger. Smoking appears to be generally more common among HCV-infected persons (U.S. National Health and Nutrition Examination Survey, NHANES, unpublished). Therefore, increased rates of smoking-related cancers observed in CHeCS may be generalizable to HCV-infected persons in the U.S., regardless of the risk attributable to hepatitis C, smoking or both HCV and smoking combined.

There is evidence to support a biological basis for the increased risk observed for kidney and oral cavity cancers in persons with hepatitis C. HCV-induced chronic renal disease is a known extrahepatic manifestation of hepatitis C, and HCV RNA and core protein have been detected in glomeruli and renal tubules of HCV-infected patients [35,36]. Oral lichen planus is a chronic inflammatory condition, an extrahepatic manifestation of hepatitis C, and carries an increased risk for development of oral cancer [37,38]. Positive and negative HCV RNA strands have been detected in oral lichen planus and oral cancer tissues from patients with HCV infection [39].

Our study has several limitations. In addition to smoking, we could not control for alcohol use or other important behavioral risk factors related to cancer incidence and mortality due to lack of these data in SEER and MCOD datasets. Rectal cancer was the only alcohol-related cancer with increased incidence or mortality among HCV-infected patients in our study, and is also smoking-related. Our data are derived from four U.S. healthcare systems that may not be representative of the population at large, though CHeCS is the largest cohort of non-veteran HCV-infected persons in the United States to date and represents a wide age, racial, demographic and geographic range [24]. Another problem is that HCV infection status is not available in SEER or MCOD and some SEER cancers and MCOD deaths include HCV-related incident cancers and deaths in HCV-infected persons, respectively. According to recent data from NHANES, approximately 2.7 million persons, or 1.0% of the U.S. population, have chronic HCV infection [1]. However, the inclusion of HCV-related morbidity and mortality in SEER and MCOD data would be a bias against finding a difference between CHeCS and general population incidence and mortality rates.

In conclusion, our findings indicate that HCV-infected persons had a higher incidence and mortality and a younger age at diagnosis and death than the general U.S. population for many types of non-liver cancers. Both primary care physicians and hepatitis C specialists should be aware of these elevated risks and take preventive actions such as encouraging tobacco and alcohol cessation and curing HCV infection with new oral directly acting antivirals per European Association for the Study of the Liver (EASL), American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) 2014 recommendations [40,41]. Currently, it is estimated that one-half of persons with chronic hepatitis C are unaware of their infection and even persons diagnosed may not seek or receive therapy [42]. Thus, they are at increased risk for liver and non-liver cancers and death from these cancers at an earlier age if they are not screened, linked to care and treated earlier.

Disclosure

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Conflict of interest

Dr. Allison was hired as a Guest Researcher from the Johns Hopkins Bloomberg School of Public Health and funded by the CDC Foundation (CDCF) to complete this study. CHeCS was funded by the CDCF, which currently receives grants from AbbVie, Gilead Sciences, Janssen Pharmaceuticals, Inc., and Vertex Pharmaceuticals. Past funders include Genentech, a member of the Roche Group. Current and past partial funders include Bristol-Myers Squibb. Granting corporations do not have access to CHeCS data and do not contribute to data analysis or writing of manuscripts.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2015.04.021.

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