Published in final edited form as:

J Hepatol. 2015 October ; 63(4): 822–828. doi:10.1016/j.jhep.2015.04.021.

Incidence of Cancer and Cancer-related Mortality Among Persons with Chronic Hepatitis C Infection, 2006–2010

Robert D. Allison, MD, MPH[1,2], **Xin Tong, MPH**[1], **Anne C. Moorman, BSN, MPH**[1], **Kathleen N. Ly, MPH**[1], **Loralee Rupp, MSE, MBA**[3], **Fujie Xu, MD, PhD**[1], **Stuart C. Gordon, MD**[3], and **Scott D. Holmberg, MD, MPH**[1] **for the Chronic Hepatitis Cohort Study (CHeCS) Investigators***

[1]Centers for Disease Control and Prevention, Atlanta, Georgia [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland [3]Henry Ford Health System, Detroit, Michigan, USA

Abstract

Persons chronically infected with hepatitis C (HCV) may be at higher risk for developing and dying from non-liver as well as liver cancers than the general population. We therefore assessed cancer incidence and mortality among HCV-infected patients in four large health systems in the United States serving over 1.6 million adults, and compared with rates for the general population during the five-year period from 2006 to 2010. 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 US death certificates from Multiple Cause of Death (MCOD) data. Standardized rate ratios (SRR) and relative risk (RR) were calculated for incidence and mortality, respectively. 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 (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]), non-Hodgkin lymphoma (2.3 [2.2–2.31]), and pancreatic (1.63 [1.6–1.7]) cancers. The mean age of cancer diagnosis and cancer-related death was significantly younger in 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.

Keywords

hepatitis C virus; SEER; cancer; incidence; mortality; cause of death

Please address correspondence to: Dr. Robert D. Allison, Johns Hopkins Bloomberg School of Public Health, 615 N Wolfe Street Room WB602, Baltimore, MD 21205. ralliso2@jhu.edu.

*See Appendix

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Background

In the United States, an estimated three million persons are chronically infected with the hepatitis C virus (HCV) and over one hundred million persons are infected with HCV worldwide.[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.[3,4,5] Chronic HCV infection has also been associated with an increased risk of developing many other non-liver cancers, usually non-Hodgkin lymphoma (Table 1). 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. 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.

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 laboratory 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. Validated tumor registry data were collected and stored in each health system according to SEER program standards, included in the CHeCS database, and used for calculation of cancer incidence in CHeCS.[25] 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 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.[26] 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.[27] 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.[28] 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 Appendix Table 1, Hepatology.com). 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. Prevalent and recurrent cancers were excluded. For comparison to CHeCS, malignant cancer incidence rates for the general population were calculated using SEER data. CHeCS and SEER data were directly standardized 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.[29] 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 dividing 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 Appendix Table

1, available at Hepatology.com). 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 standardized 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. Incidence and mortality rates were calculated for types of cancer that occurred at least five times during the study period. 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.

Financial Support

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 CDC Foundation, 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.

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. 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 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 6.6% 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 non-Hodgkin lymphoma 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 2 of 26 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 Appendix Table 1 available at Hepatology.com.

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 general population (Table 3); these included oral cavity, esophagus, stomach, colon, liver, pancreas, lung, and prostate cancers, non-Hodgkin lymphoma 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 3 of 7 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 4 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 non-Hodgkin lymphoma in the HCV group was more than two times higher (2.3 [2.2–2.31]). Only 1 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 Appendix Table 1 available at Hepatology.com.

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

There exists a large body of epidemiologic evidence linking HCV infection with the development of B-cell non-Hodgkin lymphoma (NHL) (Table 1), and NHL regression after HCV elimination with treatment supports a causal relationship.[30,31] 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. In addition to prior studies, we observed that NHL was diagnosed in CHeCS 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 thirteen 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 3 co-infected patients with NHL in our study did not affect the rate calculations. Of note, smoking and alcohol use have not been associated with an increased incidence or risk of death from NHL.

Four of the five non-liver malignancies that had significantly increased incidence rates among HCV-infected patients 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% versus 20.2% (JA Boscarino, manuscript in preparation). 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.[32] 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 eleven years younger. Smoking appears to be generally more common among HCV-infected persons in the U.S. (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.[33,34] Oral lichen planus is a chronic inflammatory condition, an extrahepatic manifestation of hepatitis C, and carries an increased risk for development of oral cancer.[35,36] Positive and negative HCV RNA strands have been detected in oral lichen planus and oral cancer tissues from patients with HCV infection.[37]

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 the National Health and Nutrition Survey (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 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 American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) 2014 recommendations.[38] 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.[39] 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Summary of Studies Reporting a Significant Association Between Non-liver Cancers and HCV-infection

Study, Year (Reference No.)	Non-liver cancers associated with HCV-infection (P<0.05)	Location	Study Type	No. Persons with HCV	No. Cases of Cancer	Period
El-Serag et al., 2002 (6)	Non-Hodgkin lymphoma	United States: Veterans	Case-Control	34,204	513	1992–1999
Giordano et al., 2007 (7)	Non-Hodgkin lymphoma	United States: Veterans	Cohort	146,394	3,953	1997–2004
Gordon et al., 2010 (8)	Kidney	United States: Detroit, MI	Cohort	3,057	17	1997–2008
Nobles et al., 2004 (9)	Head and neck	United States: Veterans	Case-Control	21	99	1991–2002
Zuckerman et al., 1997 (10)	Non-Hodgkin lymphoma	United States: Los Angeles, CA	Case-Control	26	120	1994–1996
Sanjose et al., 2008 (11)	Non-Hodgkin lymphoma	North America, Europe and Australia[†]	Case-Control	172	4,784	1998–2004
Duberg et al., 2005 (12)	Non-Hodgkin lymphoma, multiple myeloma	Sweden	Cohort	27,150	97	1990–2000
Montella et al., 2003 (13)	Thyroid	Italy	Case-Control	16	130	1997–1999
Nagao et al., 1995 (14)	Oral cavity	Japan	Case-Control	24	100	1989–1993
Nieters et al., 2006 (15)	Non-Hodgkin lymphoma	Europe[‡]	Case-Control	53	1,807	1998–2004
Omland et al., 2010 (16)	Lung (men), pancreas	Denmark	Cohort	4,204	100	1994–2003
Sanjose et al., 2004 (17)	Non-Hodgkin lymphoma	Spain	Case-Control	40	529	1998–2002
Spinelli et al., 2008 (18)	Non-Hodgkin lymphoma	Canada	Case-Control	19	776	2000–2004
Su et al., 2011 (19)	Breast (age <50 years)	Taiwan	Case-Control	56	1,958	2000–2008
Su et al., 2012 (20)	Oral cavity	Taiwan	Cohort	5,311	21	2000–2008
Swart et al., 2012 (21)	Cervix, mouth, pancreas, tonsil, trachea bronchus and lung (grouped together), unknown primary	Australia	Cohort	14, 892	240	1985–2007
Woo et al., 2013 (22)	Pancreas	Korea	Case-Control	21	753	2001–2011

Table 2

Age-adjusted Malignant Cancer Incidence and Standardized Rate Ratios (SRR) Among Chronic HCV-infected Persons (CHeCS) Compared to SEER,* 2006–2010

		Age-adjusted incidence per 100,000 person-years		
Cancers	**No. (%)†**	**CHeCS**	**SEER‡**	**SRR SEER (95% CI)**
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	ND	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	0.12	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

Cancer site	Mean age at cancer diagnosis*			Mean grade at cancer diagnosis†			Proportion of cancers with regional extension or distal involvement‡		
	CHeCS	SEER§	P Value	CHeCS	SEER§	P Value	CHeCS	SEER§	P Value
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)

ND, no or insufficient data; N/A, not applicable

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

§ Alcohol-related cancer

‖ Tobacco-related cancer