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JAMA. 2007;297(18):2010-2017 (doi:10.1001/jama.297.18.2010)

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Risk of Non-Hodgkin Lymphoma and Lymphoproliferative Precursor Diseases in US Veterans With Hepatitis C Virus

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Context Hepatitis C virus (HCV) infection causes liver cancer and cirrhosis and may also increase the risk of other tumors, particularly hematopoietic malignancies and thyroid cancer. Previous studies have been too small to adequately assess these risks.

Objective To test the hypothesis that HCV infection is associated with increased risk for hematological malignancies, related lymphoproliferative disorders, and thyroid cancer.

Design, Setting, and Patients A retrospective cohort study of users of US Veterans Affairs health care facilities from 1997-2004, which included 146 394 patients infected with HCV who had at least 2 visits with a diagnostic code for HCV infection, and 572 293 patients uninfected with HCV. To assemble the HCV-uninfected cohort, we randomly selected up to 4 patients per patient infected with HCV from all veterans who matched on age, sex, and baseline visit date and type (inpatient or outpatient). Individuals with human immunodeficiency virus were excluded.

Main Outcome Measures Risks of hematopoietic malignancies, related lymphoproliferative precursor diseases, and thyroid cancer, adjusting for selection factors, race, era of military service, and use of medical services.

Results The mean (SD) age of the patients was 52 (8) years, and 97% were men. Risks for non-Hodgkin lymphoma (n=1359), Waldenström macroglobulinemia (n=165), and cryoglobulinemia (n=551) were increased with HCV infection (adjusted hazard ratio [HR], 1.28; 95% confidence interval [CI], 1.12-1.45; adjusted HR, 2.76; 95% CI, 2.01-3.79; and adjusted HR, 3.98; 95% CI, 3.36-4.72; respectively). We found no significantly increased risk for other hematological malignancies. Although thyroiditis risk was slightly increased, risk for thyroid cancer (n=320) was not (adjusted HR, 0.72; 95% CI, 0.52-0.99). Adjusted *P* values for non-Hodgkin lymphoma, Waldenström macroglobulinemia, cryoglobulinemia, and thyroiditis were all $<.0038$, the Bonferroni threshold for statistical significance considering multiple comparisons.

Conclusions Hepatitis C virus infection confers a 20% to 30% increased risk of non-Hodgkin lymphoma overall, and a 3-fold higher risk of Waldenström macroglobulinemia, a low-grade lymphoma. Risks were also increased for cryoglobulinemia. These results support an etiological role for HCV in causing lymphoproliferation and causing non-Hodgkin lymphoma.

JAMA. 2007;297:2010-2017 www.jama.com

HEPATITIS C VIRUS (HCV) IS AN RNA virus that causes chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Hepatitis C virus is primarily acquired through parenteral exposures, including injection drug use and receipt of blood transfusions before the introduction of widespread donor screening in the early 1990s. The prevalence of HCV infection in the US general population is estimated to be 1.6%, with an estimated 4.1 million persons infected and living in the United States.[1] Hepatitis C virus infection is more common in US military veterans who use the Veterans Affairs (VA) medical system, in which approximately 5% of veterans are infected with HCV.[2]

There is emerging evidence that HCV plays a role in lymphoproliferation. Recently, it was found that treatment of HCV infection with an interferon alfa–based regimen in patients with splenic marginal zone non-Hodgkin lymphoma (NHL) or lymphoplasmacytic NHL impacts tumor activity and can lead

See also Patient Page.

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to NHL regression.[3,4] Well in line with these observations, case-control studies have found increased HCV prevalence among persons with NHL.[5,6] In addition, HCV infection is strongly associated with essential mixed cryoglobulinemia, a plasma-cell dyscrasia that is itself associated with increased risk of lymphoma, particularly lymphoplasmacytic lymphoma.[4,7] Hepatitis C virus has also been linked with increased risk for thyroid cancer,[8] possibly mediated by autoimmune thyroiditis.[9]

Despite this evidence that HCV may cause nonhepatic malignancies, there has been continued uncertainty. Case-control studies have been too small to provide information regarding the association of HCV with NHL subtypes, and by design they can provide no data on the temporal relationship between HCV infection and NHL or premalignant lymphoproliferative diseases, such as cryoglobulinemia or monoclonal gammopathy of undetermined significance (MGUS). Cohort studies of persons with HCV have not provided convincing evidence to support associations with NHL or thyroid cancer, but the statistical power of these studies was limited.[10-12]

Because of the possibility that HCV may be of importance in lymphomagenesis, we conducted a large population-based cohort study including 146 394 US veterans with HCV (to our knowledge, the largest cohort of HCV-infected individuals assembled to date) and, for comparison, a cohort of 572 293 US veterans uninfected with HCV, to test the hypothesis that HCV infection is associated with lymphoproliferative malignancies. To better understand underlying pathogenetic mechanisms, we also examined the effect of HCV infection on related precursor diseases (MGUS and cryoglobulinemia) that often precede lymphoproliferative tumors. The final goal of our study was to assess whether HCV infection is associated with thyroid cancer.

METHODS

Data Sources

Our study was conducted using VA administrative records. The patient treatment file contains inpatient records, including demographic data, date of admission and discharge, vital status at discharge, and up to 10 discharge diagnoses (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] codes) for all hospitalizations at any of the more than 150 VA hospitals in the United States. We used data in this file from VA fiscal years 1989 through 2004, which corresponds to between October 1, 1988, and September 30, 2004. The outpatient clinic file contains similar data for all outpatient encounters at any VA facility. We considered only outpatient visits coded to indicate that they likely included a physician visit or physician oversight. This restriction was to improve the accuracy of the diagnostic codes and to identify patients who used VA physicians in distinction to other services. We used data in the outpatient clinic file from fiscal year 1997 (when the outpatient clinic file was started) through fiscal year 2004. Finally, we used the Beneficiary Identification Records Locator System file, which records date of death. The patient treatment file and Beneficiary Identification Records Locator System files together capture 90% to 95% of deaths of VA users.[13,14]

The study was approved by the institutional review boards of Baylor College of Medicine and Affiliated Hospitals, and the National Cancer Institute. A waiver of informed consent and release of protected health information was obtained.

Study Patients Infected and Uninfected With HCV

We identified patients with HCV as individuals who had 2 or more VA visits during fiscal years 1997-2004 with *ICD-9-CM* diagnosis codes specifying HCV infection (070.41, 070.44, 070.51, 070.54, and V02.62). We required that at least 1 of these visits was an outpatient visit, to increase the likelihood that patients were receiving ongoing medical care in the VA. The date of the second visit with the HCV code was considered the baseline date for that patient. For each patient infected with HCV, we identified up to 4 patients uninfected with HCV who had no *ICD-9-CM* diagnosis of HCV infection on or before the baseline date of the patient infected with HCV, who had a VA visit within 30 days of the baseline date of the patient infected with HCV, and who matched the patient infected with HCV according to sex and age on the baseline date (within 365 days). In addition, we required that patients uninfected with HCV had at least 1 prior VA visit and that both visits (the baseline and the prior visit) were the same type (inpatient or outpatient) for the matched HCV-infected and HCV-uninfected pairs. We deleted patients uninfected with HCV who were selected for more than 1 patient infected with HCV in the same month.

Because human immunodeficiency virus (HIV) infection is associated with HCV infection and an increased risk of some of the evaluated cancers, we excluded any patient with a diagnosis of HIV infection on or before the baseline date. Diagnoses indicating HIV infection (and *ICD-9-CM* codes) included HIV with associated conditions (042.0, 042.1, 042.2, 042.9, 043.0, 043.1, 043.2, 043.3, 043.9, 044.0, 044.9), asymptomatic HIV (V08), and positive serological or viral culture findings for HIV (795.8).

Demographic information and data on utilization of VA medical services before baseline were abstracted from administrative databases. Because some of the outcomes studied can vary by race, we also abstracted that information from the administrative records. Race categories included white, black, other, and unknown. To validate our approach for cohort selection, we reviewed the medical records from 50 patients included in the HCV-infected cohort and 50 patients in the HCV-uninfected cohort from the Michael E. DeBakey VA Medical Center in Houston, Tex. The chart reviewers, who were blinded to the HCV cohort assignment, documented any laboratory studies (ie, HCV antibody and RNA test results) demonstrating infection on or before the baseline date.

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Cancer and Related Outcomes

Outcomes of interest were ascertained at the first diagnosis recorded in either the patient treatment file or the outpatient clinic file. Outcomes (and *ICD-9-CM* codes) were NHL (200, 202.0-202.2, 202.8), Waldenström macroglobulinemia (273.0, 273.3), Hodgkin lymphoma (201), multiple myeloma (203.0-203.1, 238.6), acute lymphocytic leukemia (204.0), chronic lymphocytic leukemia (204.1), acute nonlymphocytic leukemia (including acute myeloid leukemia [205.0] and acute monocytic leukemia [206.0]), chronic myeloid leukemia (205.1), other leukemia (204.2, 204.8-204.9, 205.2, 205.8-205.9, 206.1-206.2, 206.8-206.9, 207.8, 208.0-208.2, 208.8-208.9), MGUS (273.1), cryoglobulinemia (273.2), thyroiditis (including Graves disease, hypothyroidism not otherwise specified [242.0, 244.9, 245 {except 245.4}]), and thyroid cancer (193).

Table 1. Baseline Characteristics of HCV-Infected and HCV-Uninfected Veterans*

Characteristics	HCV-Infected Cohort (n = 146 394)	HCV-Uninfected Cohort (n = 572 293)
Age, y		
Mean (SD)	51.9 (8.4)	52.0 (8.5)
<40	5160 (3.5)	20 416 (3.6)
40-44	18 476 (12.6)	71 740 (12.5)
45-49	41 161 (28.1)	157 787 (27.6)
50-54	45 243 (30.9)	177 085 (30.9)
55-59	18 213 (12.4)	72 750 (12.7)
60-64	6149 (4.2)	24 621 (4.3)
65-69	4795 (3.3)	19 064 (3.3)
70-74	3468 (2.4)	13 904 (2.4)
≥75	3729 (2.6)	14 926 (2.6)
Sex		
Female	4699 (3.2)	18 634 (3.3)
Male	141 695 (96.8)	553 659 (96.7)
Race†		
White	76 382 (52.2)	341 181 (59.6)
Black	35 625 (24.3)	117 998 (20.6)
Other	1221 (0.8)	6145 (1.1)
Unknown	33 166 (22.7)	106 969 (18.7)
Fiscal year of baseline date		
1997	6175 (4.2)	24 243 (4.2)
1998	7464 (5.1)	29 546 (5.2)
1999	11 427 (7.8)	45 010 (7.9)
2000	17 036 (11.6)	66 742 (11.7)
2001	23 144 (15.8)	90 084 (15.7)
2002	26 025 (17.8)	101 284 (17.7)
2003	27 305 (18.7)	106 431 (18.6)
2004	27 818 (19.0)	108 953 (19.0)
Era of military service‡		
Pre-Vietnam	15 908 (10.9)	58 272 (10.2)
Vietnam	97 332 (66.5)	358 023 (62.6)
Post-Vietnam and other	33 135 (22.6)	155 952 (27.3)
No. of VA visits before baseline date, mean (SD)		
Inpatient visits in previous 5 y	1.2 (2.8)	1.6 (3.5)
Outpatient visits in previous 1 y	10.8 (24.1)	19.6 (40.1)

Abbreviation: HCV, hepatitis C virus; VA, Veterans Affairs.
*Data are shown as No. (%) unless otherwise specified. Because of rounding, percentages may not all total 100.
†Race was determined from administrative data. "Other" race includes 2831 American Indian patients, 3921 Asian patients, and 614 patients whose race was listed as "other."
‡Data were missing for 19 veterans infected with HCV and 46 veterans uninfected with HCV. Pre-Vietnam era is before August 5, 1964; Vietnam era, August 5, 1964, through May 7, 1975; and post-Vietnam era, after May 7, 1975. "Other" includes 10 689 patients listed as active military or nonveterans.

To assist in determining the validity of the study results, we selected negative and positive control outcomes. Negative control outcomes were colon cancer (*ICD-9-CM* code 153), prostate cancer (*ICD-9-CM* code 185), and melanoma (*ICD-9-CM* code 172), which have no plausible association with HCV. Liver cancer (*ICD-9-CM* code 155.0 [not 155.1 or 155.2]) served as the positive control.

Statistical Analysis

To accommodate delays in diagnosis or reporting, and because the initial evaluation of HCV infection could have affected surveillance for the outcomes, we excluded from the analysis any outcomes occurring within 6 months after the baseline date. We thus calculated the incidence of each outcome for the period beginning 6 months after the baseline date, continuing until the last recorded visit in the VA, death, or September 30, 2004, if the patient had a visit in fiscal year 2005. In addition, patients uninfected with HCV were censored when a first diagnosis of HCV infection was noted. Patients in either cohort were censored when a first diagnosis of HIV infection was noted.

We derived Kaplan-Meier method curves to depict cumulative incidence for outcomes in the HCV-infected and HCV-uninfected cohorts for the period subsequent to 6 months after baseline. A Cox proportional hazards regression model was used to compare the risk in the 2 cohorts, adjusting for the matching factors. In other analyses, we further adjusted for race, era of military service, and number of inpatient and outpatient visits before baseline (a measure of usage of VA medical services) as potential confounders. We used a 2-sided Bonferroni P value of .05 divided by 13 (.0038) to test for significance of the adjusted models because of the possibility that some associations with the 13 malignancies and nonmalignant conditions of interest would have arisen due to chance.

In sensitivity analyses, we repeated the regression analyses after removing

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patients uninfected with HCV who ever developed an HCV diagnosis, rather than censoring them at the time of HCV diagnosis. We conducted another sensitivity analysis in which patients who ever developed HIV infection during follow-up were removed from consideration. Finally, we performed analyses that included all events in follow-up rather than just those events that occurred after the first 6 months. Statistics were analyzed using SAS version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

The HCV-infected cohort included 146 394 patients, and the HCV-uninfected cohort included 572 293 patients. Baseline characteristics of the cohorts are shown in TABLE 1. Nearly all the patients (97%) were men. The mean (SD) age was 52 (8) years in both cohorts. Although the majority of both cohorts was white, and the racial distributions were somewhat similar, there were more racial minorities and patients of unknown race in the HCV-infected group. Patients infected with HCV were slightly more likely to have served during the Vietnam era (1964-1975) than were patients uninfected with HCV. The HCV-uninfected group had greater use of VA inpatient and outpatient services before the baseline date.

We validated baseline HCV-infected status and HCV-uninfected status for a subset of cohort patients treated at the Michael E. DeBakey VA Medical Center. Among 50 patients included in the HCV-infected cohort, 47 (94%) had laboratory-confirmed HCV infection on or before their baseline visit, and the remaining 3 patients had clinic notes that indicated HCV infection. Among 50 patients included in the HCV-uninfected cohort, 5 (10%) had laboratory-confirmed HCV infection. Therefore, based on laboratory confirmation of HCV infection as the reference test, the selection procedure that we used had a positive predictive value of 94% (exact 95% confidence interval [CI], 83%-99%) for baseline HCV infection and a negative predictive value of 90% (exact 95% CI, 78%-97%) for the baseline absence of HCV infection.

During follow-up, 35 696 patients (6.2%) uninfected with HCV had 1 or more recorded HCV diagnoses, and HIV infection codes were noted in 813 patients (0.5%) in the HCV-infected cohort and 1539 patients (0.3%) in the HCV-uninfected cohort. Deaths were recorded in 16 120 patients (11.0%) infected with HCV and 48 309 patients (8.4%) uninfected with HCV. Beginning 6 months after baseline, patients in both cohorts were followed up for a mean 2.3 years, with a total follow-up time of 280 676 person-years in the HCV-infected cohort and 1 095 911 person-years in the HCV-uninfected cohort.

The incidence of each outcome and hazard ratios (HRs) comparing incidence in both cohorts are shown in TABLE 2, and incidence is shown graphically for selected outcomes in the FIGURE. We also examined the prevalence of possible precursor conditions among patients with hematological malignancies. Among NHL cases overall, 20 patients (1.5%) had a preceding diagnosis of cryoglobulinemia (prior to 3 months before NHL diagnosis). Likewise, among all Waldenström macroglobulinemia cases, 18 patients (10.9%) had a preceding diagnosis of cryoglobulinemia and 9 patients (5.5%) had a preceding diagnosis of MGUS. Among multiple myeloma cases, 43 patients (8.2%) had a preceding diagnosis of MGUS. A preceding diagnosis of thyroiditis was observed in 100 patients (31.3%) with thyroid cancer.

Risks for NHL (HR, 1.21; 95% CI, 1.07-1.37) and Waldenström macroglobulinemia (HR, 2.72; 95% CI, 2.00-3.72) were significantly higher in the HCV-infected cohort than in the HCV-uninfected cohort (Table 2 and Figure, A and B). Risks for plasma cell disorders including cryglobulinemia (HR, 3.93; 95% CI, 3.32-4.64) and the premalignant condition MGUS (HR, 1.30; 95% CI, 1.01-1.67) were also increased (Figure, C and D). The risk for acute lymphocytic leukemia was decreased (HR, 0.57; 95% CI, 0.38-0.85), while the risks for the other hematological malignancies were not significantly increased in the HCV-infected cohort (eg, multiple myeloma: HR, 0.88; 95% CI, 0.70-1.10) (Figure, E). Risk for thyroid cancer was significantly decreased in the HCV-infected cohort (HR, 0.66; 95% CI, 0.49-0.91) (Figure, F), although thyroiditis was slightly increased (HR, 1.06; 95% CI, 1.01-1.11). As expected, risk for liver cancer was greatly increased with HCV infection (HR, 24.15; 95% CI, 20.92-27.88). Risks for the negative control cancers were not increased, and risks for prostate cancer and melanoma were decreased.

After further adjustment for race, era of military service, and use of VA services before baseline, the point estimate of the HRs for the hematological malignancies generally came closer to 1 and the CIs all overlapped 1. The notable exceptions were NHL and Waldenström macroglobulinemia, which moved further from unity to an HR of 1.28 (95% CI, 1.12-1.45) and an HR of 2.76 (95% CI, 2.01-3.79), respectively. The HRs for the nonmalignant hematological conditions did not change substantially and remained increased, although the association with MGUS was no longer significant after adjustment (HR, 1.28; 95% CI, 0.99-1.65). The HR for thyroid cancer approached 1 (HR, 0.72; 95% CI, 0.52-0.99), and thyroiditis increased from an HR of 1.06 to 1.13 (95% CI, 1.08-1.18). Finally, the HRs for the control cancers did not change substantially, with the exception of melanoma, which moved closer to unity. Among the malignancies and conditions of interest, NHL, Waldenström macroglobulinemia, cryoglobulinemia, and thyroiditis had *P* values for adjusted HRs of less than .0038, the Bonferroni threshold for statistical significance (Table 2).

To assess the robustness of these results, we conducted a number of sensitivity analyses as described in the Methods section. None of these analyses produced substantially different results than those presented (data not shown).

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COMMENT

Our cohort study of 718 687 veterans with more than 1.37 million person-years of follow-up is the largest study conducted to our knowledge on the risk conferred by HCV infection for hematopoietic malignancies, related lymphoproliferative disorders, and thyroid cancer. We found a small but significant 20% to 30% increase in the risk of NHL, including all subtypes, and an almost 3-fold increased risk of the low-grade lymphoma subtype Waldenström macroglobulinemia in persons with HCV infection. HCV infection was also associated with an increased risk of nonmalignant plasma cell disorders, including cryoglobulinemia and the precursor condition MGUS, although the association with MGUS was not significant in adjusted regression models. We demonstrated that infection precedes development of these outcomes, and that the risk in individuals infected with HCV is consistently increased, with over 5 years of follow-up. In contrast, we found no evidence that HCV infection increases the risk of thyroid cancer.

To our knowledge, our study is the first to show an increased risk of Waldenström macroglobulinemia associated with HCV. Several groups have reported series of patients with Waldenström macroglobulinemia with widely varying HCV prevalence estimates (7%-100%), but the series were small and uncontrolled.[15-17] Waldenström macroglobulinemia is characterized by the presence of a malignant lymphoplasmacytic infiltrate in the bone marrow along with a circulating IgM monoclonal gammopathy. Likewise, essential mixed cryoglobulinemia, in which HCV infection is almost universally present, is also characterized by the presence of an IgM monoclonal gammopathy.[7] Finally, MGUS can be divided into cases with circulating monoclonal IgG (the majority of cases), and more rarely IgM, IgA, IgD, or biclonal MGUS.[18] Although we did not have data on the immunoglobulin subtype of MGUS, we hypothesize that the modest increase in MGUS incidence associated with HCV infection may reflect an increase in incidence for the subset of IgM MGUS. Our results therefore suggest the intriguing possibility that chronic immune stimulation by HCV infection can result in progression along a spectrum of IgM monoclonal gammopathy from asymptomatic MGUS to symptomatic cryoglobulinemia to the malignant Waldenström macroglobulinemia. In contrast, HCV infection was not associated with an increased risk for multiple myeloma, which is present following IgG or IgA MGUS, and very infrequently after IgD MGUS.

Lymphoproliferation induced by HCV may occur due to binding of the virion to receptors on the surface of B lymphocytes, which might lower their threshold for antigen response or induce DNA

Table 2. Incidence and Adjusted HRs of Malignancies and Precursor Conditions Among HCV-Infected and HCV-Uninfected Veterans

Outcome	No. of Events (Incidence/100 000 Person-Years)		Comparing HCV-Infected vs HCV-Uninfected Cohorts		
	HCV-Infected Cohort (n = 146 394)	HCV-Uninfected Cohort (n = 572 293)	HR (95% CI)*	Adjusted HR (95% CI)†	*P* Value‡
Malignancies of interest					
Non-Hodgkin lymphoma	319 (114.5)	1040 (95.8)	1.21 (1.07-1.37)	1.28 (1.12-1.45)	<.001§
Waldenström macroglobulinemia	67 (23.9)	98 (8.9)	2.72 (2.00-3.72)	2.76 (2.01-3.79)	<.001§
Hodgkin lymphoma	65 (23.2)	295 (27.0)	0.87 (0.66-1.13)	0.97 (0.74-1.27)	.81
Multiple myeloma	95 (33.9)	431 (39.4)	0.88 (0.70-1.10)	0.95 (0.76-1.19)	.63
Chronic lymphocytic leukemia	69 (24.6)	343 (31.4)	0.81 (0.62-1.04)	0.89 (0.68-1.15)	.37
Acute lymphocytic leukemia	27 (9.6)	184 (16.8)	0.57 (0.38-0.85)	0.75 (0.50-1.13)	.16
Chronic myeloid leukemia	30 (10.7)	163 (14.9)	0.73 (0.49-1.08)	0.84 (0.56-1.24)	.38
Acute nonlymphocytic leukemia	56 (20.0)	243 (22.2)	0.92 (0.68-1.22)	1.04 (0.78-1.40)	.79
Other leukemias	104 (37.1)	479 (43.9)	0.85 (0.69-1.06)	0.96 (0.78-1.19)	.73
Thyroid cancer	46 (16.4)	274 (25.1)	0.66 (0.49-0.91)	0.72 (0.52-0.99)	.04
Nonmalignant conditions					
MGUS	80 (28.6)	248 (22.7)	1.30 (1.01-1.67)	1.28 (0.99-1.65)	.06
Cryoglobulinemia	273 (97.7)	278 (25.4)	3.93 (3.32-4.64)	3.98 (3.36-4.72)	<.001§
Thyroiditis	2252 (841.8)	8265 (805.4)	1.06 (1.01-1.11)	1.13 (1.08-1.18)	<.001§
Control malignancies					
Liver cancer	1300 (466.1)	218 (19.9)	24.15 (20.92-27.88)	23.57 (20.39-27.24)	<.001§
Colon cancer	442 (158.9)	1735 (160.2)	1.02 (0.92-1.13)	1.03 (0.93-1.15)	.55
Prostate cancer	1072 (391.9)	4848 (458.6)	0.88 (0.82-0.94)	0.85 (0.80-0.91)	<.001§
Melanoma cancer	261 (93.5)	1412 (130.1)	0.73 (0.64-0.84)	0.82 (0.71-0.93)	.003§

Abbreviations: CI, confidence interval; HCV, hepatitis C virus, HR, hazard ratio; MGUS, monoclonal gammopathy of undetermined significance.
*Adjusted for matching variables (age, sex, baseline visit date, and type of visit [inpatient or outpatient] for the baseline visit and a preceding visit).
†Adjusted for matching variables, race, era of military service, and previous Veterans Affairs use. Sixty-five patients with missing data on era of military service were excluded.
‡For adjusted HR (95% CI).
§Considered statistically significant (*P*<.0038) after a Bonferroni adjustment for multiple comparisons.

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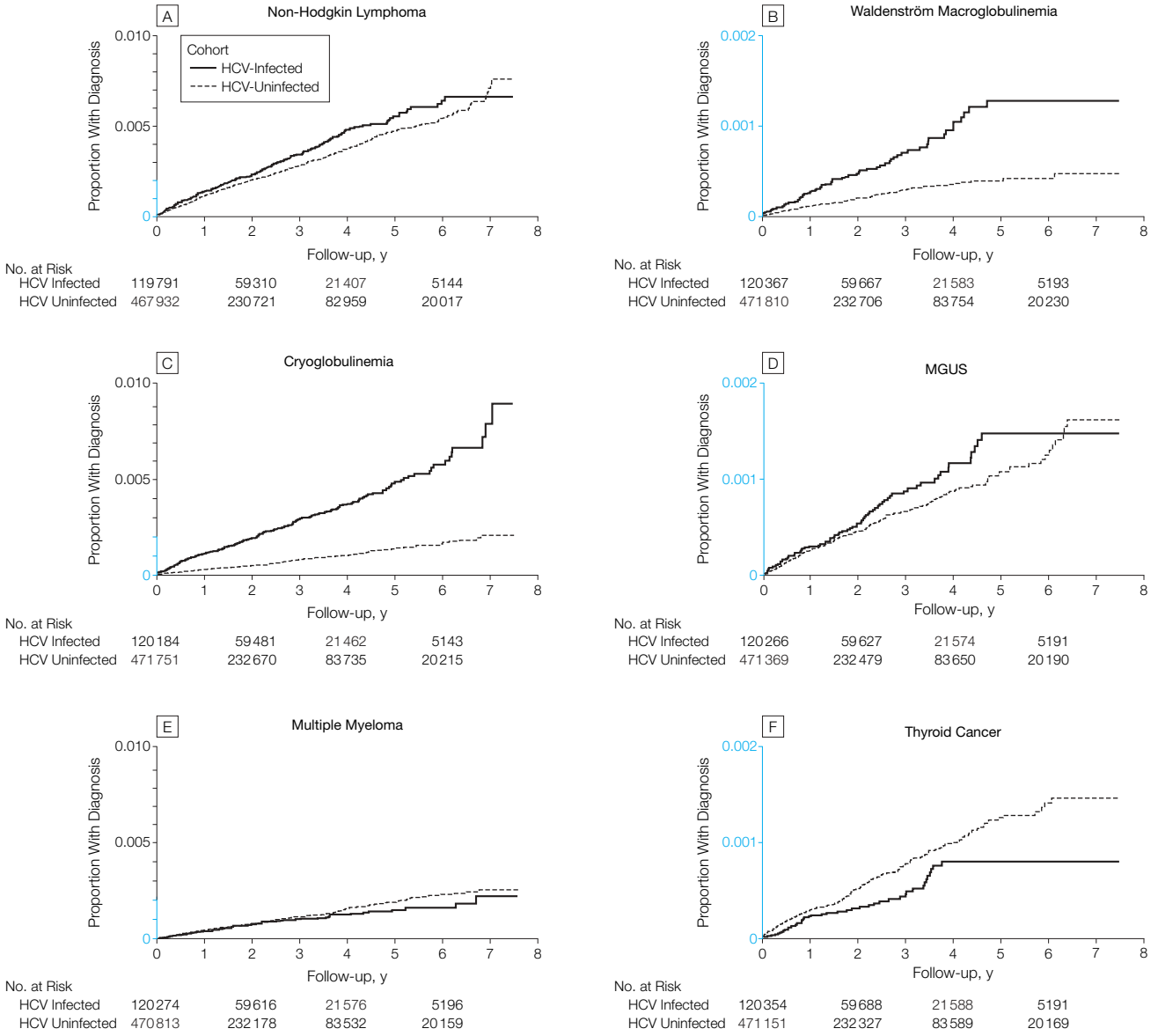
mutations.[19,20] Among patients infected with HCV with splenic marginal zone NHL or lymphoplasmacytic NHL, treatment of HCV infection with interferon alfa–based regimens can lead to regression of NHL.[3,4] These observations support the hypothesis that by directly driving lymphoproliferation HCV infection could be causal in at least a subset of lymphoproliferative disorders, such as low-grade NHLs.

Our finding of a significant association between HCV and NHL overall supports prior observations, although the association was notably weaker than reported in case-control studies (adjusted HR was 1.28 in our study vs odds ratios reported to range from 2 to 10).[21] The reason for this difference is unknown, but it could reflect differences in the study population or methods. Our study was similar in design to a recent registry-based cohort study in Sweden, which included 26 000 individuals infected with HCV.[11] In that study, Duberg et al[11] reported a significantly increased risk for NHL in the HCV-infected cohort (standardized incidence ratio, 2.0; 95% CI, 1.2-3.1), but the increase was attenuated and no longer significant after exclusion of HIV-infected NHL cases (standardized incidence ratio, 1.6; 95% CI, 0.9-2.6). In contrast, we found an

Figure. Kaplan-Meier Estimates of the Cumulative Incidence of 6 Outcomes Among Veterans Infected and Uninfected With HCV



HCV indicates hepatitis C virus; MGUS, monoclonal gammopathy of uncertain significance. Follow-up began 6 months after baseline date. Y-axis intervals shown in blue indicate range from 0 to 0.002.

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HCV-NHL association when we censored or excluded individuals at an HIV diagnosis, suggesting that the association with HCV that we observed is not due to the confounding effects of HIV infection.

On the other hand, our results do not support an association between HCV infection and thyroid cancer. Two previous studies from Italy suggested an increased risk of thyroid cancer in persons infected with HCV,[8,22] and a study in Japan found an increased risk among individuals with a history of transfusion or liver disease.[10] However, only a modest nonsignificant association with HCV infection was observed in Sweden,[11] and no association was observed in an Australian study.[12] The biological mechanism by which HCV infection could cause thyroid cancer has not been fully articulated. Others have also observed that HCV infection is associated with thyroiditis, as did we, especially during treatment with interferon alfa–based regimens.[23] Although thyroiditis is associated with development of thyroid NHL, an association with thyroid carcinoma has not been demonstrated.[24] Still, it is of interest that a substantial fraction (31.3%) of thyroid cancer cases in this study had a preceding diagnosis of thyroiditis. If HCV-induced thyroiditis increases thyroid cancer risk, the effect may have been too small for us to detect.

Our results are similar to those in a smaller study of extrahepatic manifestations of HCV in US veterans by El-Serag et al.[25] That study included 34 200 veterans infected with HCV and 136 800 veterans uninfected with HCV who were hospitalized between 1992 and 1999; therefore, there is some overlap with the data from our study. Similar to our study, the previous study found an adjusted odds ratio for NHL of 1.22 (95% CI, 1.01-1.39), and a strong association between HCV and cryoglobulinemia, but an association with thyroiditis was not observed (adjusted odds ratio, 0.94; 95% CI, 0.67-1.30). Our study extends those findings by including more than 4 times as many veterans from a largely different study period, and by examining additional outcomes.

The incidence of cancer in US military veterans is higher than in the general population,[26,27] and the rates in our study were increased as well (data not shown). This increase may reflect the high prevalence among veterans of chronic medical conditions, poverty, or use of tobacco or alcohol. In addition, in our study, we evaluated veterans infected with HCV who were in active medical care in the VA and who were therefore especially likely to have comorbid medical conditions. To account for these unique characteristics, we compared the HCV-infected group to a similar group of veterans without HCV infection rather than comparing them to the general US population. Interestingly, the risks of the negative control cancers were actually lower, to a small but noticeable degree, in the HCV-infected cohort than in the HCV-uninfected cohort. We do not believe that HCV infection is protective of these cancers; rather, there may have been differential ascertainment of outcomes in the 2 cohorts. Because the probability of being selected for the HCV-uninfected cohort was higher for persons who had more visits to the VA, patients were more likely to be selected for the HCV-uninfected cohort if they used the VA more regularly. Indeed, this pattern of usage was apparent in our baseline characteristics. Higher usage of VA services (including, for example, cancer screening) would lead patients uninfected with HCV to be more likely to be diagnosed subsequently with cancer in the VA system. Although we attempted to adjust for VA usage, residual confounding may have been present. Because this type of confounding would likewise bias the HRs for other outcomes downward, our results probably provide slightly conservative estimates of risk conferred by HCV infection.

Laboratory data are not systematically collected nationwide, so we relied on *ICD-9-CM* codes recorded in large administrative databases to identify HCV infection. The results of our validation study indicate that the cohort assignment was very accurate, in that the majority of patients infected with HCV, but only a minority of patients uninfected with HCV, had documented laboratory evidence of HCV infection. Nonetheless, because the validation study was small, the estimates of positive and negative predictive values in our approach were somewhat uncertain, and we were unable to adjust the results of our main study for possible misclassification. During follow-up, we observed that 6.2% of the HCV-uninfected cohort developed a new *ICD-9-CM* diagnosis of HCV infection. These new diagnoses likely represent delayed diagnoses and/or delayed coding by physicians for prior conditions, rather than new infections. Indeed, in our validation study, 4 of 5 patients with HCV infection whom we initially misclassified as being uninfected with HCV later had an *ICD-9-CM* diagnosis of HCV infection in the patient treatment file or outpatient clinic file. In a sensitivity analysis, we deleted individuals from the HCV-uninfected cohort who subsequently had documented HCV diagnoses, and the results were unchanged, indicating that this misclassification had little effect.

Other limitations should be mentioned. First, we did not validate the cancer diagnoses through a separate chart review, and our reliance on diagnoses coded in the patient treatment file and outpatient clinic file could have introduced inaccuracies. Also, the *ICD-9-CM* codes for NHL did not allow us to distinguish the various pathological subtypes, which should be a goal of future research. Nonetheless, there is no reason to suspect that the overall accuracy or reliability of the diagnostic recording for the outcomes would differ by HCV infection status. Second, because the study was conducted with VA data, very few women were included. Third, we did not have data on some known or postulated risk factors for NHL, such as family history and pesticide exposure.

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However, those factors are unlikely to explain our findings because they should not differ substantially by HCV status. Finally, we did not have access to data from non-VA sources, so differential loss to follow-up or use of non-VA health care resources could have affected the results.

In conclusion, among military veterans infected with HCV, we found a 20% to 30% increased risk of NHL overall and, for the first time, we found an almost 3-fold increased risk of the low-grade lymphoma subtype Waldenström macroglobulinemia. Furthermore, HCV infection was associated with an increased risk of cryoglobulinemia, supporting the hypothesis that chronic HCV infection serves as an immunological stimulus for progression to hematological malignancy. Although the clinical significance of these findings is unknown, it is possible that screening of individuals infected with HCV could identify early-stage lymphoproliferative conditions suitable for early intervention strategies, including chemoprevention trials on premalignant disease. Future epidemiological and pathophysiological studies are needed to further explore the relationship between HCV and NHL.

Author Contributions: Dr Giordano had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Giordano, Henderson, Landgren, Chiao, Kramer, El-Serag, Engels.
Acquisition of data: Giordano, Henderson, Chiao, El-Serag.
Analysis and interpretation of data: Giordano, Henderson, Landgren, Chiao, Kramer, El-Serag, Engels.
Drafting of the manuscript: Giordano, Henderson, Landgren, Engels.
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Statistical analysis: Giordano, Henderson, Engels.
Obtained funding: Giordano, El-Serag, Engels.
Administrative, technical, or material support: Giordano, El-Serag, Engels.
Study supervision: Giordano, Engels.
Financial Disclosures: None reported.
Funding/Support: This work was supported by the Intramural Program of the National Cancer Institute, National Institutes of Health, and the facilities and resources of the Michael E. DeBakey Veterans Affairs Medical Center, Department of Veterans Affairs, Houston, Tex. Dr Giordano received support (grant K23MH67505) from the National Institute of Mental Health, National Institutes of Health. Dr Chiao received support (grant K23CA124318) from the National Cancer Institute, National Institutes of Health.
Role of the Sponsors: The funding sources had no involvement in the study design, in the collection, analysis, or interpretation of data, in the writing of the manuscript, or in the decision to submit the manuscript for publication. Before submission, the manuscript received routine administrative review by scientific staff in the Division of Cancer Epidemiology and Genetics of the National Cancer Institute.

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