Hematopoietic Malignancies Associated with Viral and Alcoholic Hepatitis

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Abstract

Hepatitis C virus (HCV) and hepatitis B virus (HBV) have been associated with hematopoietic malignancies, but data for many subtypes are limited. From the U.S. Surveillance, Epidemiology, and End Results-Medicare database, we selected 61,464 cases (≥67 years) with hematopoietic malignancies and 122,531 population-based controls, frequency-matched by gender, age, and year (1993-2002). Logistic regression was used to compare the prevalence of HCV, HBV, and alcoholic hepatitis in cases and controls, adjusted for matching factors, race, duration of Medicare coverage, and number of physician claims. HCV, HBV, and alcoholic hepatitis were reported in 195 (0.3%), 111 (0.2%), and 404 (0.7%) cases and 264 (0.2%), 242 (0.2%), and 798 (0.7%) controls, respectively. HCV was associated with increased risk of diffuse large B-cell lymphoma [odds ratio (OR) 1.52, 95% confidence interval (95% CI) 1.05-2.18], Burkitt lymphoma (OR 5.21, 95% CI 1.62-16.8), follicular lymphoma (OR 1.88, 95% CI 1.17-3.02), marginal zone lymphoma (OR 2.20, 95% CI 1.22-3.95), and acute myeloid leukemia (OR 1.54, 95% CI 1.00-2.37). In contrast, HBV was unrelated to any hematopoietic malignancies. Alcoholic hepatitis was associated with decreased risk of non–Hodgkin lymphoma overall, but increased risk of Burkitt lymphoma. In summary, HCV, but not other causes of hepatitis, was associated with the elevated risk of non–Hodgkin lymphoma and acute myeloid leukemia. HCV may induce lymphoproliferative malignancies through chronic immune stimulation. (Cancer Epidemiol Biomarkers Prev 2008;17(11):3069–75)

Introduction

Hematopoietic malignancies comprise a diverse group of neoplasms, likely with different etiologies. Infectious agents have been associated with some hematopoietic malignancies (1). In particular, hepatitis C virus (HCV) infection has consistently been associated with an increased risk of non–Hodgkin lymphoma (NHL) in epidemiologic studies (2, 3). In addition, HCV infection is strongly associated with type II mixed cryoglobulinemia, a lymphoproliferative disorder that can progress to B-cell NHL (4). Although many studies have investigated the association between HCV and NHL and some have included data on specific NHL subtypes (2, 3, 5-8), most have been limited in the small number of cases for individuals subtypes. Studies investigating HCV infection and risk of other lymphoproliferative (3, 6, 9, 10) and myeloproliferative (6, 10-13) malignancies are also limited.

Prior studies of HCV infection and NHL have raised interest in whether other types of hepatitis may also influence risk of hematopoietic malignancies. Recent studies, mainly in hepatitis B virus (HBV) endemic areas, have investigated the relationship between HBV infection and NHL, with most reporting significant associations (14-22). Alcohol abuse is also an important cause of hepatitis. However, as yet, no studies have investigated the association between alcoholic hepatitis and hematopoietic malignancies. Whereas HCV and HBV induce a chronic lymphocytic inflammatory response in the liver, alcoholic hepatitis is characterized by repeated toxic insults to the liver, associated with infiltration of neutrophils (23).

Additional data clarifying these associations may shed light on possible biological mechanisms involved in the development of hematologic malignancies. To date, research has been hindered by difficulty in obtaining information on a sufficiently large sample of study subjects, given the rarity of some hematopoietic malignancy subtypes and low prevalence of viral hepatitis in many populations, e.g., HCV prevalence is 1.8% (24) and HBV prevalence is 0.4% (25) in the general U.S. population. The Surveillance, Epidemiology, and End Results (SEER)-Medicare dataset includes information on >61,000 patients with hematopoietic malignancies (26). As part of the SEER-Medicare Assessment of Hematopoietic Malignancy Risk Traits (SMAHRT) Study, we used these data to investigate the role of infectious and alcoholic hepatitis in lymphoproliferative and myeloproliferative malignancies.

Materials and Methods

SEER-Medicare Dataset. The SEER program, a cancer surveillance program supported by the National Cancer Institute, commenced data collection on January 1, 1973, in seven U.S. sites, including Connecticut, Iowa, New

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Mexico, Utah, Hawaii, Detroit, and San Francisco-Oakland. In latter years, other sites were added, including Atlanta (1974-1975), the Seattle-Puget Sound area (1974-1975), 10 counties in Georgia (1978), Arizona (for American Indians only; 1980), New Orleans (2001), New Jersey (2001), Los Angeles County (2001), four counties in the San Jose-Monterey area of San Francisco (2001), Kentucky (2001), and Greater California (2001). In 2001, the SEER registries covered ~25% of the U.S. population (26).

Medicare, a federally funded program administered by the Centers for Medicare and Medicaid Services, provides health insurance for ~97% of persons (ages 65 years or older) in the United States. All beneficiaries are entitled to Part A coverage for hospital inpatient care, nursing facilities, and home health and hospice care. Approximately, 96% of participants also subscribe to Part B coverage, which covers physician and outpatient services.

The SEER-Medicare dataset has been described previously (26). Briefly, data from SEER cancer registries were linked to Medicare enrollment and claims files. The SEER-Medicare database contains demographic and clinical information on all newly diagnosed cancer patients through December 2002. Through the linkage, Medicare data (Part A claims, 1986-2002; Part B claims, 1991-2002) are available for all cancer patients residing in one of the SEER registry areas. In addition, Medicare data are available for a 5% random sample of Medicare beneficiaries residing in SEER areas.

Subject Selection. The SMAHRT Study is a population-based, nested case-control study of hematopoietic malignancies using SEER-Medicare data. All individuals diagnosed with a lymphoproliferative or myeloproliferative malignancy as a first cancer between 1993 and 2002 were identified using the third edition of the International Classification of Diseases for Oncology (ICD-O3) morphology codes 9590-9989 (27). Codes for lymphoproliferative malignancies were grouped into diagnostic entities according to a recently proposed hierarchical system (28) based on the WHO classification (29). Myeloproliferative malignancies were classified into the following categories: acute myeloid leukemia (ICD-O3: 9840, 9861, 9866, 9867, 9870-9874, 9891, 9895-9897, 9910, 9920, 9930, 9931), chronic myeloid leukemia (ICD-O3: 9863, 9875, 9876), myelodysplastic syndrome (ICD-O3: 9945, 9980, 9982, 9983, 9985, 9986, 9989), and chronic myeloproliferative disease (ICD-O3: 9741, 9742, 9750, 9754, 9755, 9756, 9757, 9950, 9960, 9961-9964, 9975).

Cases included in the present study were of ages 67 to 99 y at diagnosis of malignancy and had at least 12 mo of Part A, Part B, non–health maintenance organization Medicare coverage before diagnosis. Persons of ages 65 to 66 y were excluded so that included subjects had sufficient time to accrue exposure information. Individuals diagnosed before 1993 were also excluded because no claims for HCV were covered by the Medicare system before 1992 and Part B Medicare data were not available until 1991. Persons diagnosed only at autopsy or by death certificate were excluded.

For each included case, two controls were selected at random from the 5% random sample of Medicare beneficiaries who, as of July 1 in the calendar year of selection, were alive, free of any malignancy, and had at least 12 mo of prior Part A, Part B, non–health maintenance organization Medicare coverage. The controls were frequency matched to cases with a hematopoietic malignancy by individual calendar year of diagnosis, age in five categories (67-69, 70-74, 75-79, 80-84, 85-99 y), and gender. It was possible for a person to be selected as a control multiple times for cases in different calendar years. Cases and controls with a record of HIV infection (n = 87 and 163, respectively) were excluded after frequency matching, because coinfection with HCV and HIV can occur and HIV is a strong risk factor for lymphoma.

Ascertainment of Hepatitis Diagnoses. In assessing exposures, the 12-mo period before cancer diagnosis/control selection was excluded to avoid differential ascertainment of hepatitis in patients being evaluated for their malignancy-related illness. Subjects were then classified as having HCV infection if they had at least one hospital, physician, or outpatient claim in Medicare for HCV infection (ICD-9: 070.41, 070.44, 070.51, 070.54, 070.70, 070.71, or V02.62). Similarly, HBV infection (ICD-9: 070.2X, 070.3X, or V02.61) and alcoholic hepatitis (ICD-9: 571.1) status were based on the presence of a single Medicare claim. In a sensitivity analysis, we increased the stringency for these diagnoses by requiring subjects to have one hospital claim for the condition or at least two physicians or outpatient claims at least 30 d apart.

Statistical Analysis. Unconditional logistic regression models were used to derive odds ratios (OR) and 95% confidence intervals (95% CI), comparing the prevalence of HCV, HBV, and alcoholic hepatitis in hematopoietic malignancy cases and controls. For analyses of subtypes, we fitted separate logistic models for the cases (defined by hematopoietic malignancy subtype) and used all controls in each analysis. We accommodated the repeated selection of individuals as controls in the variance computation, in addition to the selection of controls who later served as cases (see Appendix A). All analyses were adjusted for age (67-69, 70-74, 75-79, 80-84, 85-99 y), gender, year of cancer diagnosis/selection (1993-1996, 1997-1999, 2000-2001, 2002), race (White, other/unknown), duration of Part A, Part B, non–health maintenance organization Medicare coverage (quartiles: 13-57, 58-93, 94-136, and ≥137 mo), and, as a measure of overall health care utilization, the number of physician claims >1 year before cancer diagnosis/selection (quartiles: 0-20, 21-57, 58-127, ≥128). Analyses were repeated using the number of outpatient or hospitalization claims instead of the number of physician claims, which yielded similar results (not shown). We further adjusted analyses for each medical condition for the other medical conditions investigated. For comparison, analyses were also repeated using conditional logistic regression conditioned on the strata, defined by the matching variables (age in five strata, gender, and year of diagnosis/selection), and adjusted for race, duration of Medicare coverage, and number of physician claims. Conditional regression analyses yielded similar results to the primary analyses (data not shown).

Results

The study included 61,464 cases with a hematopoietic malignancy and 122,531 controls (due to repeated

sampling, this corresponds to 100,527 unique control individuals). Although the absolute differences in characteristics were small, cases were more likely than controls to be White, to have a longer duration of Part A, Part B, non–health maintenance organization Medicare coverage, and to have more physician, outpatient, and hospital claims (Table 1).

A physician, hospital, or outpatient claim for HCV was reported in 195 (0.32%) cases and 264 (0.22%) controls (OR 1.37, 95% CI 1.13-1.66; Table 2). More specifically, HCV was associated with lymphoid neoplasms (OR 1.37, 95% CI 1.08-1.74), NHL (OR 1.35, 95% CI 1.06-1.73), and with several NHL subtypes, including diffuse large B-cell lymphoma (OR 1.52, 95% CI 1.05-2.18), Burkitt lymphoma (OR 5.21, 95% CI 1.62-16.8), marginal zone lymphoma (OR 2.20, 95% CI 1.22-3.95), and follicular lymphoma (OR 1.88, 95% CI 1.17-3.02). HCV infection was not associated with other NHL subtypes, including T-cell NHL, lymphoplasmacytic lymphoma, and chronic lymphocytic leukemia, or with other lymphoid neoplasms, including plasma cell neoplasm and Hodgkin lymphoma (Table 2). Myeloid neoplasms were also associated with HCV infection (OR 1.38, 95% CI 1.00-1.89). Of these, HCV was associated with acute myeloid leukemia (OR 1.54, 95% CI 1.00-2.37), and there was an elevated risk for myelodysplastic syndrome (OR 1.60, 95% CI 0.98-2.60).

HCV remained associated with hematopoietic malignancies overall when the 5-year period before cancer diagnosis/control selection was excluded (OR 1.41, 95% CI 1.08-1.84). In a sensitivity analysis conducted to test the robustness of our findings, we defined HCV more stringently, requiring one hospital claim or at least two physician or outpatient claims at least 30 days apart. Only the associations between HCV and follicular

Table 1. Characteristics of cases with hematopoietic malignancy and controls in the SMAHRT Study (1993-2002)

	Patients with a hematopoietic malignancy (n = 61,464)	Controls (n = 122,531)	P*
Gender †			0.699
Male	30,304 (49.3%)	60,295 (49.2%)	
Female	31,160 (50.7%)	62,236 (50.8%)	
Age, y †			0.483
67-69	7,018 (11.4%)	13,635 (11.1%)	
70-74	15,099 (24.6%)	30,217 (24.7%)	
75-79	16,277 (26.5%)	32,550 (26.6%)	
80-84	12,612 (20.5%)	25,227 (20.6%)	
85-99	10,458 (17.0%)	20,902 (17.1%)	
Selection year †			0.979
1993-1996	17,030 (27.7%)	33,841 (27.6%)	
1997-1999	13,482 (21.9%)	26,946 (22.0%)	
2000-2001	20,436 (33.3%)	40,750 (33.3%)	
2002	10,516 (17.1%)	20,994 (17.1%)	
Race/ethnicity			<0.001
White	53,716 (87.4%)	102,520 (83.7%)	
Black	3,840 (6.3%)	8,439 (6.9%)	
Asian	1,417 (2.3%)	4,973 (4.1%)	
Hispanic	1,039 (1.7%)	3,122 (2.6%)	
Native American Indian	117 (0.2%)	343 (0.3%)	
Other/unknown	1,335 (2.2%)	3,134 (2.6%)	
Duration of Medicare coverage ‡, mo			<0.001
12-57	14,457 (23.5%)	30,747 (25.1%)	
58-93	14,920 (24.3%)	30,804 (25.1%)	
94-136	16,706 (27.2%)	30,696 (25.1%)	
≥137	15,381 (25.0%)	30,284 (24.7%)	
No. physician claims§			<0.001
0-20	13,302 (21.6%)	31,568 (25.8%)	
21-57	14,222 (23.1%)	29,802 (24.3%)	
58-127	15,863 (25.8%)	30,699 (25.1%)	
≥128	18,077 (29.4%)	30,462 (24.9%)	
Median	68	57	
No. outpatient claims§			<0.001
0	11,502 (18.7%)	27,545 (22.5%)	
1-3	14,292 (23.3%)	29,975 (24.5%)	
4-7	10,629 (17.3%)	20,930 (17.1%)	
8-15	10,824 (17.6%)	20,637 (16.8%)	
≥16	14,217 (23.1%)	23,444 (19.1%)	
Median	5	4	
No. hospital claims§			<0.001
0	27,861 (45.3%)	60,548 (49.4%)	
1	11,910 (19.4%)	22,545 (18.4%)	
2-3	11,953 (19.5%)	21,574 (17.6%)	
≥4	9,740 (15.9%)	17,864 (14.6%)	
Median	1	1	

*P values were derived using the χ^2 test.
†Gender, age, and selection year were matching factors.
‡Duration of coverage refers to simultaneous coverage by Part A and Part B while the subject was not enrolled in a health maintenance organization.
§The number of claims excludes the 12 mo before hematopoietic malignancy diagnosis (cases) or selection (controls).

Table 2. Associations of hematopoietic malignancy subtypes with HCV infection, HBV infection, and alcoholic hepatitis

	Total	HCV		HBV		Alcoholic hepatitis	
	n	*n* (%)	OR (95% CI)*	*n* (%)	OR (95% CI)*	*n* (%)	OR (95% CI)*
Controls	122,531	264 (0.2)	Reference	242 (0.2)	Reference	798 (0.7)	Reference
Hematopoietic malignancy	61,464	195 (0.3)	*1.37 (1.13-1.66)*	111 (0.2)	0.88 (0.70-1.12)	404 (0.7)	0.93 (0.82-1.06)
Lymphoid neoplasm†	48,173	147 (0.3)	*1.37 (1.08-1.74)*	91 (0.2)	0.96 (0.75-1.23)	285 (0.6)	*0.84 (0.72-1.00)*
NHL (overall)†	33,940	103 (0.3)	*1.35 (1.06-1.73)*	62 (0.2)	0.97 (0.72-1.29)	197 (0.6)	*0.85 (0.72-1.00)*
Diffuse large B-cell lymphoma	10,144	34 (0.3)	*1.52 (1.05-2.18)*	17 (0.2)	0.89 (0.54-1.47)	56 (0.6)	0.83 (0.63-1.09)
Burkitt lymphoma	197	<5 (1.5)	*5.21 (1.62-16.8)*	<5 (0.5)	1.95 (0.27-14.31)	<5 (2.0)	*2.86 (1.05-7.75)*
Marginal zone lymphoma	1,908	12 (0.6)	*2.20 (1.22-3.95)*	7 (0.4)	1.51 (0.71-3.22)	8 (0.4)	0.57 (0.29-1.16)
Follicular lymphoma	4,491	19 (0.4)	*1.88 (1.17-3.02)*	12 (0.3)	1.47 (0.82-2.63)	19 (0.4)	0.65 (0.41-1.02)
Chronic lymphocytic leukemia‡	10,170	23 (0.2)	1.08 (0.70-1.67)	12 (0.1)	0.66 (0.37-1.19)	59 (0.6)	0.84 (0.64-1.10)
Lymphoplasmacytic lymphoma	1,148	<5 (0.2)	0.74 (0.18-3.00)	<5 (0.4)	1.76 (0.65-4.76)	6 (0.5)	0.69 (0.30-1.54)
NHL B-cell, not otherwise specified	1,667	5 (0.3)	1.16 (0.48-2.84)	<5 (0.2)	0.84 (0.27-2.64)	17 (1.0)	1.41 (0.87-2.29)
NHL T-cell	1,870	<5 (0.1)	0.42 (0.10-1.69)	<5 (0.2)	0.90 (0.33-2.42)	11 (0.6)	0.76 (0.42-1.39)
NHL, unknown lineage	1,809	<5 (0.2)	1.11 (0.35-3.51)	<5 (0.1)	0.75 (0.18-3.03)	13 (0.7)	1.19 (0.68-2.06)
Plasma cell neoplasm	9,995	31 (0.3)	1.34 (0.92-1.95)	20 (0.2)	0.89 (0.56-1.41)	56 (0.6)	0.79 (0.60-1.04)
Hodgkin lymphoma	1,155	<5 (0.3)	1.18 (0.38-3.70)	<5 (0.2)	0.91 (0.23-3.68)	7 (0.6)	0.92 (0.44-1.95)
Lymphoid neoplasm, not otherwise specified	3,083	10 (0.3)	1.72 (0.91-3.26)	7 (0.2)	1.29 (0.61-2.75)	25 (0.8)	1.25 (0.83-1.87)
Myeloid neoplasm§	11,945	47 (0.4)	*1.38 (1.00-1.89)*	18 (0.2)	0.63 (0.39-1.02)	109 (0.9)	1.16 (0.94-1.42)
Acute myeloid leukemia	6,068	23 (0.4)	*1.54 (1.00-2.37)*	6 (0.1)	0.45 (0.20-1.02)	48 (0.8)	1.04 (0.77-1.40)
Chronic myeloid leukemia	1,528	<5 (0.1)	0.58 (0.14-2.36)	<5 (0.3)	1.26 (0.47-3.41)	12 (0.8)	1.08 (0.61-1.93)
Myelodysplastic syndrome	3,084	18 (0.6)	1.60 (0.98-2.60)	5 (0.2)	0.57 (0.24-1.37)	37 (1.2)	1.33 (0.94-1.86)
Chronic myeloproliferative disease	1,038	<5 (0.4)	1.02 (0.38-2.74)	<5 (0.3)	1.26 (0.47-3.41)	10 (1.0)	1.25 (0.66-2.35)
Hematopoietic malignancy, not otherwise specified	1,346	<5 (0.1)	0.36 (0.05-2.61)	<5 (0.2)	0.75 (0.18-3.04)	10 (0.7)	1.00 (0.53-1.88)

NOTE: Observations wherein the number of exposed cancer cases or controls is between 1 and 4 are listed as ''<5'' to preserve subjects' anonymity, in accordance with the SEER-Medicare data use agreement. Significant findings ($P < 0.05$) are in italics.

*OR and 95% CI are adjusted for age (67-69, 70-74, 75-79, 80-84, and 85-99 y), gender, selection year (1993-1996, 1997-1999, 2000-2001, 2002), race (White, non-White), duration of Medicare benefits (13-57, 58-93, 94-136, and ≥137 mo), and number of physician claims (0-20, 21-57, 58-127, ≥128).

†The categories of lymphoid neoplasm and NHL (overall) also include cases with hairy cell leukaemia ($n = 317$) and precursor B-cell NHL ($n = 219$).

‡The category of chronic lymphocytic leukemia includes cases with small lymphocytic lymphoma, prolymphocytic lymphoma, and mantle cell lymphoma.

§The category of myeloid neoplasm also includes cases with myeloid neoplasm, not otherwise specified ($n = 227$).

lymphoma (OR 1.83, 95% CI 1.01-3.33) and acute myeloid leukemia (OR 1.70, 95% CI 1.03-2.83) remained significant, whereas the associations were attenuated for lymphoid neoplasms (OR 1.24, 95% CI 0.94-1.62), NHL overall (OR 1.21, 95% CI 0.89-1.64), diffuse large B-cell lymphoma (OR 1.43, 95% CI 0.90-2.26), Burkitt lymphoma (OR 2.61, 95% CI 0.35-19.26), marginal zone lymphoma (OR 1.68, 95% CI 0.74-3.78), and myelodysplastic syndrome (OR 1.11, 95% CI 0.54-2.31).

HBV infection was identified in 111 (0.18%) cases and 242 (0.20%) controls. HBV was not associated with hematopoietic malignancies overall (OR 0.88, 95% CI 0.70-1.12) nor with any of the lymphoid or myeloid subtypes investigated (Table 2). Findings were similar in the sensitivity analysis (data not shown). Alcoholic hepatitis was identified in 404 (0.66%) cases and 798 (0.65%) controls. Alcoholic hepatitis was not associated with hematopoietic malignancies overall (OR 0.93, 95% CI 0.82-1.06; Table 2). However, alcoholic hepatitis was inversely associated with lymphoid neoplasms (OR 0.84, 95% CI 0.72-1.00) and NHL overall (OR 0.85, 95% CI 0.72-1.00), and there seemed to be decreased risks in several NHL subtypes, including the two major subtypes, diffuse large B-cell lymphoma (OR 0.83, 95% CI 0.63-1.09) and follicular lymphoma (OR 0.65, 95% CI 0.41-1.02). In contrast, Burkitt lymphoma was positively associated with alcoholic hepatitis (OR 2.86, 95% CI 1.05-7.75). In the sensitivity analyses requiring one hospital claim or two physician or outpatient claims for alcoholic hepatitis, the associations with lymphoid neoplasms (OR 0.80, 95% CI 0.66-0.97), NHL (OR 0.78, 95% CI 0.63-0.98), and Burkitt lymphoma (OR 3.82, 95% CI 1.21-12.03) remained.

More than one type of hepatitis were recorded in Medicare for 52 (0.08%) cases and 83 (0.07%) controls. Of those with HCV infection, 24 (12.3%) cases and 32 (12.1%) controls had HBV infection, and 23 (11.8%) cases and 43 (16.3%) controls had alcoholic hepatitis. Of those with HBV infection, 11 (9.9%) cases and 20 (8.3%) controls had alcoholic hepatitis. The association between HCV and hematopoietic malignancy overall was not affected by adjustment for HBV infection and alcoholic hepatitis (OR 1.41, 95% CI 1.16-1.72). In addition, our findings by hematopoietic malignancy subtype were similar in the adjusted analyses (not shown). Likewise, adjusting for HCV and alcoholic hepatitis in the HBV analyses and for HCV and HBV in the alcoholic hepatitis analyses did not alter our findings (not shown).

Discussion

In this U.S. population–based study, including >61,000 elderly patients with hematopoietic malignancy, we found HCV to be associated with 1.5-fold to 5-fold increased risks of diffuse large B-cell, Burkitt, marginal zone, and follicular lymphomas. We also found HCV to be associated with 1.5-fold increased risks of acute myeloid leukemia and its related precursor state myelodysplastic syndrome. In contrast, HBV infection was not associated with any lymphoid or myeloid malignancies.

Alcoholic hepatitis was inversely associated with NHL overall but, in particular, was positively associated with Burkitt lymphoma.

In accord with our study, a recent meta-analysis reported an association between HCV and NHL, with pooled ORs of 2.5 (95% CI 2.1-3.1) and 2.0 (95% CI 1.8-2.2) for case-control and cohort studies, respectively (3). These results were also confirmed in a pooled analysis of case-control studies from the Interlymph Consortium (7). The associations with HCV observed for diffuse large B-cell, follicular, and marginal zone lymphomas are also in keeping with the results of these studies, which had large enough sample sizes to produce stable estimates for the major NHL subtypes (3, 7). To our knowledge, our study is the first to report an association between HCV infection and Burkitt lymphoma, although some case reports exist (30, 31). Other lymphoma subtypes of B-cell origin, including chronic lymphocytic leukemia and lymphoplasmacytic lymphoma, were not associated with HCV, although the low prevalence of HCV in the present study precludes us from excluding associations reported previously (3, 6). Prior studies have produced mixed results for T-cell lymphoma, Hodgkin lymphoma, and plasma cell neoplasms (including multiple myeloma; refs. 3, 6, 7, 10, 11, 13, 32), but these were not associated with HCV in our study.

The specificity of our associations to lymphoma subtypes of B-cell origin is consistent with the proposed mechanism of HCV-driven B-cell lymphomagenesis. HCV is an RNA virus that cannot integrate into the host genome. The HCV envelope protein E2 binds to the extracellular CD81 receptor (33, 34), which can facilitate B-cell proliferation (33). Continual stimulation of the immune system by HCV may lead to genetic mutations in lymphocytes, such as translocation of the *bcl2* oncogene frequently present in patients with B-cell NHLs (35, 36). Further supporting an etiologic role, treatment of HCV-infected NHL patients with antiviral therapy can result in clearance of HCV infection and simultaneous remission of NHL (37). This process of chronic antigenic stimulation is analogous to the role of *Helicobacter pylori* in gastric mucosa-associated lymphoid tissue lymphoma (38).

In contrast to published studies (6, 10-13), we observed an association between HCV and both acute myeloid leukemia and its related precursor state myelodysplastic syndrome. Myelodysplastic syndrome is a heterogeneous group of disorders originating from abnormal multipotent progenitor cells in the bone marrow (39) and can progress to acute myeloid leukemia. At this time, it is unknown whether all cases of acute myeloid leukemia are preceded by a myelodysplastic phase. HCV has been shown to infect CD34(+) hematopoietic progenitor cells (40), and it is possible that such infection could lead to progressive abnormalities and, ultimately, leukemia.

In contrast to HCV, HBV was not associated with NHL in our study, which could suggest that chronic immune stimulation by itself may not be sufficient to cause NHL. For example, engagement of the CD81 receptor, specific to HCV, may be required for B-cell proliferation. Whereas most prior studies investigating the association between HBV and NHL have reported significant associations (14-22), the majority determined HBV status after NHL diagnosis (14-19, 21, 41). Because HBV infection can be reactivated in patients undergoing treatment for NHL (42-44), some of the observed associations may be artifactual. Only two studies have investigated this association using a cohort study design in areas with low HBV seroprevalence (20, 22). The most recent study, a U.S. study using data from two health care delivery systems, reported a significant association between chronic HBV infection and NHL (OR 2.3, 95% CI 1.0-5.2; ref. 20). In the other study, HBV infection was associated with an increased risk of Burkitt lymphoma only (22). Further investigation of the effect of HBV on lymphomagenesis is required to resolve these discrepant findings.

In the present study, alcoholic hepatitis was inversely associated with lymphoid neoplasms, particularly NHL. Alcohol intake has been reported to reduce the risk of NHL in other studies (45, 46). Although the mechanism for these associations has not been identified, moderate alcohol consumption can have beneficial immunomodulatory effects (47). The difference between the effects of HCV and alcoholic hepatitis on the risk of developing lymphoid neoplasms may relate to the type of liver inflammation (23) associated with these conditions (chronic lymphocytic infiltration versus neutrophilic infiltration, respectively). Unexpectedly, we found that alcoholic hepatitis increased risk of Burkitt lymphoma. One possibility is that this finding is a false positive result due to the large number of comparisons made. Alternatively, the result could be attributed to inadequate control for confounding by HIV infection. In the United States, Burkitt lymphoma is highly associated with HIV infection (48). Although we eliminated HIV-infected cases from the analyses, we relied on diagnostic information from Medicare claims, which could have been incomplete.

Our study has several important strengths, including its large size and the representativeness of the hematopoietic malignancy cases. The SEER registries cover ~25% of the U.S. population and are representative of the general population with respect to age and gender (26). Although the SMAHRT Study only included individuals of ages 67 or older, the incidence of most hematopoietic malignancies increases with age, with ~52% of all hematopoietic malignancies in the United States occurring in the elderly population (49). Characterization of hematopoietic malignancy subtypes was provided by comprehensive information collected by the SEER registries.

Several limitations should also be mentioned. Because numerous comparisons were undertaken and we did not formally adjust for multiple comparisons, some of the observed associations may have occurred by chance. Nonetheless, the patterns observed, especially for HCV, were similar to previously reported associations. Even with the large sample size, small increases in risk for rarer malignancy subtypes may not have been detected. HCV infection (0.22%) was lower in our controls than the HCV seroprevalence reported by Alter et al. (1.0% for persons of ages ≥70 years or older in the United States; ref. 24). Although no data are available on HBV prevalence in the elderly U.S. population, HBV seroprevalence in the general U.S. population is 0.4% (25) higher than in our study (0.20%). We included both inpatient and outpatient claims in our study to increase

ascertainment but we, likely, still underestimated the prevalence of HCV, HBV, and alcoholic hepatitis in the elderly due to patients not receiving medical care that resulted in a Medicare claim, underreporting by physicians treating other medical conditions or because the disease was asymptomatic. The limited time period to gather information on these conditions may have further resulted in underascertainment, particularly if the initial diagnosis was some time in the past. Nondifferential misclassification of exposures would have biased comparisons between cases and controls toward the null and reduced statistical power, perhaps explaining the null findings for HBV infection. Another potential limitation is that cases may have been more likely than controls to seek medical care for symptoms, especially during the period leading to the diagnosis of their hematopoietic malignancy. For this reason, we excluded 1 year before diagnosis/selection. Although cases still had a higher number of hospital, physician, and outpatient claims in the earlier period when we ascertained exposure status, the absolute differences were quite small, and we adjusted for these differences in the statistical analyses. It is also possible that some claims for HCV, HBV, or alcoholic hepatitis could represent incorrect diagnoses. We, therefore, conducted a sensitivity analysis classifying subjects as exposed if they had a hospital claim, which has been shown to be highly accurate (26), or two physician or outpatient claims at least 30 days apart. This stringent approach decreased the number of subjects considered exposed. Although the only associations with HCV that remained significant were follicular lymphoma and acute myeloid leukemia, ORs for the other conditions remained elevated.

In conclusion, the present study confirmed associations between HCV infection and NHL, including the major subtypes, among elderly adults in the United States. We did not find HBV infection or alcoholic hepatitis to be associated with similarly increased risk for hematopoietic malignancies. The observation of increased risk for myelodysplastic syndrome and acute myeloid leukemia, in association with HCV infection, was novel and suggests the need for further mechanistic investigations.

Appendix A. Statistical Appendix

Let Y denote the outcome variable in a nested case-control study comprised of one control group, denoted by $Y = 0$, and K case groups, denoted by $Y = 1, \ldots, K$. We used K separate unconditional logistic regression models to compare the respective case group to the common controls. In the calculation of the variances of the estimates, two issues need to be considered: first, we used the same control group for each disease subtype comparison, and second, due to constraints in the cohort, a substantial number of individuals were sampled multiple times as controls. We accommodate both issues using the following approach.

For the jth logistic model, we obtained the log OR estimates $\theta_j = [\theta_{j1}, \theta_{j2}, \ldots, \theta_{jm}]$, $j = 1, \ldots, K$, for the covariate vector $X = [1, X_1, \ldots, X_m]$, which includes a 1 for the intercept term, and the covariance matrix Σ_i. For each study subject, we also obtained the scores from the jth logistic regression, given by

$$S_{j1} = \sum_n X_{\ln}[Y_{\ln}(1 - p(X_{\ln}, \theta_{j1})) - (1 - Y_{\ln})p(X_{\ln}, \theta_{j1})],$$

where the summation is over all controls and cases in the jth disease subgroup, and $p(X,\theta_j) = \exp(X'\theta_j)/\{1 + \exp(X'\theta_j)\}$. Letting $S_j = (S_{1j}, \ldots, S_{jm})$, we define the matrix of scores for n subjects as

$$S = \begin{pmatrix} S_{11} & S_{12} & \ldots & S_{1K} \\ S_{21} & S_{22} & \ldots & S_{2K} \\ S_{(n-1)1} & \ldots & S_{(n-1)(K-1)} & S_{(n-1)K} \\ S_{n1} & S_{n2} & S_{n(K-1)} & S_{nK} \end{pmatrix}$$

Control subjects have entries in every column of the score matrix, as they contribute to all logistic models. Some individuals served as controls before they were selected as cases and, thus, also contribute to several logistic models. If there is no overlap between cases and controls, S amplifies to

$$S = \begin{pmatrix} S_1 & 0 & \ldots & 0 \\ 0 & S_2 & \ldots & 0 \\ 0 & \ldots & S_{K-1} & 0 \\ S_1 & S_2 & S_{K-1} & S_K \end{pmatrix}$$

The covariance matrices for all K disease subtypes are summarized in

$$\Sigma = \begin{pmatrix} \Sigma_l & 0 & \ldots & 0 \\ 0 & \Sigma_2 & \ldots & 0 \\ 0 & \ldots & \Sigma_{K-1} & 0 \\ 0 & \ldots & \ldots & \Sigma_K \end{pmatrix}$$

Using the above notation, the asymptotic variance of the estimates $(\theta_1, \ldots, \theta_K)$ is given by $\Sigma B \Sigma$. B is estimated by

$$\hat{B} = \sum_i (\Sigma S_{ik})(\Sigma S_{ik})'$$

where i denotes the sum over individuals and the second sum inside the parentheses refers to the repeated measurements on the same person.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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