Original Article

Chronic Fatigue Syndrome and Subsequent Risk of Cancer Among Elderly US Adults

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BACKGROUND: The cause of chronic fatigue syndrome (CFS) is unknown but is thought to be associated with immune abnormalities or infection. Because cancer can arise from similar conditions, associations between CFS and cancer were examined in a population-based case-control study among the US elderly. **METHODS:** Using linked Surveillance, Epidemiology, and End Results (SEER)-Medicare registry data, approximately 1.2 million cancer cases and 100,000 controls (age range, 66-99 years; 1992-2005) were evaluated. CFS was identified in the period more than 1 year prior to selection, using linked Medicare claims. Unconditional logistic regression was used to estimate the odds ratios (ORs) comparing the CFS prevalence in cases and controls, adjusting for age, sex, and selection year. All statistical tests were 2-sided. **RESULTS:** CFS was present in 0.5% of cancer cases overall and 0.5% of controls. CFS was associated with an increased risk of non-Hodgkin lymphoma (NHL) (OR = 1.29, 95% confidence interval [CI] = 1.16-1.43, $P = 1.7 \times 10^{-6}$). Among NHL subtypes, CFS was associated with diffuse large B cell lymphoma (OR = 1.34, 95% CI = 1.12-1.61), marginal zone lymphoma (OR = 1.88, 95% CI = 1.38-2.57), and B cell NHL not otherwise specified (OR = 1.51, 95% CI = 1.03-2.23). CFS associations with NHL overall and NHL subtypes remained elevated after excluding patients with medical conditions related to CFS or NHL, such as autoimmune conditions. CFS was also associated, although not after multiple comparison adjustment, with cancers of the pancreas (OR = 1.25, 95% CI = 1.07-1.47), kidney (OR = 1.27, 95% CI = 1.07-1.49), breast (OR = 0.85, 95% CI = 0.74-0.98), and oral cavity and pharynx (OR = 0.70, 95% CI = 0.49-1.00). **CONCLUSIONS:** Chronic immune activation or an infection associated with CFS may play a role in explaining the increased risk of NHL. ***Cancer*** **2012;000:000–000.** © *2012 American Cancer Society.*

KEYWORDS: lymphoma, chronic fatigue, cancer, etiology.

Chronic fatigue syndrome (CFS) is a condition characterized by persistent, unexplained fatigue accompanied by neuropsychiatric and immunologic abnormalities. In 1994, the US Centers for Disease Control and Prevention presented a consensus definition for CFS, which, in summary, requires the presence of fatigue lasting for at least 6 months, reduction in the activities of daily life, and a constellation of persistent symptoms including impaired memory, sore throat, tender lymph nodes, muscle or joint pain, and/or headache.[1-3] The definition excludes people who have major depressive disorder, schizophrenia, anorexia nervosa, alcohol or substance abuse, or severe obesity. Also excluded by the Centers for Disease Control and Prevention, but not specified, are medical conditions that would explain the fatigue; these would likely include serious chronic health conditions such as cancer, autoimmune diseases, and cirrhosis.

The underlying cause of CFS is unknown, and may be heterogeneous, but in many cases it is thought to be triggered by an abnormal immune response to an agent, such as an infection, that results in chronic immune activation.[1,4-6] The prevalence of CFS in the United States was estimated at 0.2% to 0.4% in 2 population-based surveys in Chicago, Illinois (n = 18,668), and Wichita, Kansas (n = 7162).[7,8] In the 2 studies, the median duration of CFS symptoms was between 2.9 and 7.3 years. CFS was more common among women than men, and in middle-aged adults, although it occurred in all age groups.[7,8] In addition, nonwhites had a higher prevalence of CFS compared with whites, and middle income groups had a higher prevalence than those of lower or higher socioeconomic status.[7,8]

The immunologic changes in CFS and its possible relationship with infection have prompted investigators to consider whether CFS could also be associated with an elevated risk of cancer. Several ecological studies examining the incidence of non-Hodgkin lymphoma (NHL) and brain cancer in association with a CFS outbreak in Nevada were inconsistent but suggestive of a possible link with these cancers.[9-11] Of interest, Lombardi et al recently reported detecting DNA from xenotropic murine leukemia virus–related virus (XMRV), a retrovirus, in peripheral blood of 67% of US

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This study used the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the Applied Research Program, National Cancer Institute; the Office of Research, Development, and Information, Centers for Medicare and Medicaid Services; Information Management Services, Inc.; and the SEER Program tumor registries in the creation of the SEER-Medicare database. We thank Winnie Ricker (Information Management Services, Rockville, MD) for assistance with database management.

DOI: 10.1002/cncr.27612, **Received:** December 8, 2011; **Revised:** March 1, 2012; **Accepted:** March 14, 2012, **Published online** in Wiley Online Library (wileyonlinelibrary.com)

patients with CFS, compared with 4% of healthy controls.[12] In other studies, XMRV DNA and protein expression have been detected in prostate tumor tissues.[13,14] The possible role of XMRV might suggest that patients with CFS would have an elevated risk of prostate cancer. Notably, however, detection of XMRV in humans remains controversial,[15-17] and the study by Lombardi et al was fully retracted due to omission of relevant details and evidence of poor quality control (www.sciencemag.org).[18]

Despite the biological plausibility that CFS could cause cancer through immune abnormalities or infection, the association has not been previously examined in an epidemiologic study with individual-level data on both CFS and cancer. We therefore evaluated this association in a large case-control study among elderly adults in the United States, using linked data from cancer registries and Medicare claims files.

MATERIALS AND METHODS

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program comprises population-based state and metropolitan cancer registries that ascertain cancers occurring in approximately 26% of the US population.[19] Medicare is a federally-funded program that provides health insurance for 97% of the US population aged greater than 65 years. All Medicare beneficiaries are entitled to coverage for inpatient care (Part A), and most purchase additional coverage for physician and outpatient services (Part B).

The SEER-Medicare data set was created by electronically linking SEER and Medicare data.[19] The resulting match links 94% of SEER cancer cases aged 65 and older to Medicare data. In addition, data are available for a 5% random sample of Medicare beneficiaries living in SEER regions. The SEER-Medicare data set contains demographic and clinical information, and Medicare claims data (Part A beginning in 1986, Part B claims beginning in 1991) on these individuals.

The current study is a population-based case-control study based on the SEER-Medicare data, for which the design, strengths, and limitations have been previously described in detail.[20] Cases were people with first cancers identified in SEER, aged 66 to 99 years during 1992 to 2005. Cases identified solely at autopsy or by death certificate were excluded. We also required cases to have had at least 13 months Part A and Part B Medicare coverage prior to diagnosis. Patients enrolled in health maintenance organizations (HMOs) were excluded, because HMOs receive capitated payments and do not submit claims for specific conditions to Medicare.[20] Cancers were categorized based on the SEER program "site recode with Kaposi sarcoma and mesothelioma,"[21] which we modified to collapse some rare categories. NHL was classified based on the World Health Organization scheme and included chronic lymphocytic leukemia.[22]

Controls (N = 100,000) were selected from the 5% random sample of Medicare beneficiaries living in SEER areas and were frequency-matched to cases by sex, age category (66-69, 70-74, 75-79, 80-84, and 85-99 years), and calendar year of selection. As of July 1 of the calendar year of selection, controls were alive, cancer-free, and had at least 13 months of Part A, Part B, and non-HMO Medicare coverage. Controls could have been selected multiple times in different calendar years or could later have become a case.

The presence of CFS was assessed using Medicare claims. For CFS, the International Classification of Diseases, 9th revision (ICD-9) code 780.71 ("chronic fatigue syndrome") is most specific, but it was introduced only in 1998. The 300.5 code for "neurasthenia," an older and less precise clinical diagnosis, is available in claims going back to 1991. Given the differences in the years of coverage, we considered 2 definitions of CFS: either 300.5 or 780.71 beginning in 1991 (CFS1), or 780.71 beginning in 1998 (CFS2). In order to minimize the possibility of falsely diagnosed cases,[20] we required for both conditions that a CFS diagnosis was documented in 1 hospital claim or at least 2 physician or outpatient claims that were present 30 days apart. We also did not consider CFS diagnoses during the year prior to diagnosis of cases or control selection, to avoid reverse causation (ie, incipient cancer causing fatigue and misdiagnosis of CFS).[20]

Unconditional logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs), comparing the prevalence of CFS in cases and controls. All statistical tests were 2-sided. We accounted for the repeated sampling of controls and the fact that some controls later became cases in the variance calculation.[20] All analyses were adjusted for sex, age (67-69, 70-74, 75-79, 80-84, 85-89 years), and calendar year of diagnosis/selection (1992-1994, 1995-1998, 1999-2005). We also examined ORs relating CFS to cancer adjusted for race.

We also assessed medical conditions potentially related to CFS or NHL, because we found an association between CFS and NHL. These conditions included alcohol abuse (ICD-9: 303.X or 305.0), blood transfusion (ICD-9: 9904 or BLDPNTS>0),[23] human immunodeficiency virus (HIV) infection (ICD-9: 042, V08), hepatitis B virus (HBV) infection (ICD-9: 070.2X, 070.3X, or

Table 1. Characteristics of Cases and Controls in the SEER-Medicare Case-Control Study

Characteristic	Cases (N = 1,176,950)		Controls (N = 100,000)		*P*
	N	%	N	%	
Sex					
Male	624,464	53.1	53,056	53.1	–
Female	552,486	46.9	46,944	46.9	
Age, y					
66-69	193,397	16.4	16,431	16.4	–
70-74	300,368	25.5	25,520	25.5	
75-79	298,807	25.4	25,388	25.4	
80-84	217,667	18.5	18,496	18.5	
85+	166,711	14.2	14,165	14.2	
Median	76		76		
Selection year					
1991-1994	178,842	15.2	15,198	15.2	–
1995-1998	227,618	19.3	19,337	19.3	
1999-2005	770,490	65.5	65,465	65.5	
Race/ethnicity					
White	1,005,547	85.4	83,451	83.5	<.0001
Black	92,559	7.9	6,886	6.9	
Asian	30,384	2.6	4,135	4.1	
Hispanic	19,463	1.7	2,625	2.6	
Native American Indian	2,666	0.2	309	0.3	
Other/unknown	26,328	2.2	2,594	2.6	
Duration of Medicare coverage, mo					
13-60	309,407	26.3	27,300	27.3	<.0001
61-120	439,209	37.3	37,000	37.0	
121-180	289,863	24.6	24,093	24.1	
181-240	138,471	11.8	11,607	11.6	
Median	97		96		

V02.61),[24] hepatitis C virus (HCV) infection (ICD-9: 070.41, 070.44, 070.51, 070.54, 070.70, 070.71, or V02.61),[24] lupus (ICD-9: 710.0),[25] Sjögren's syndrome (ICD-9: 710.2),[25] and rheumatoid arthritis (ICD-9: 714.0, 714.1, 714.2, 714.3, 714.81, V82.1).[25] Specifically, we compared the prevalence of CFS among control subjects with or without these conditions, and we also repeated the logistic regression analyses for NHL after excluding subjects with these medical conditions. Finally, because depression can mimic CFS, we evaluated associations of NHL with depression (ICD-9: 296.2-296.3, 311).

RESULTS

The characteristics of cases and controls are presented in Table 1. Most subjects were white, male, and selected between 1999 and 2005. Cases and controls were well matched by sex, age, and calendar year of diagnosis/selection, and differed slightly by race and duration of Medicare coverage. The most inclusive definition of CFS (CFS1), based on either ICD-9 300.5 or ICD-9-CM 780.71 in any calendar year, had a prevalence of 0.5% among controls (498 of 100,000 controls selected in 1992-2002). CFS defined by ICD-9-CM 780.71 in 1998 and later (CFS2) had a similar prevalence of 0.7% among controls (444 of 65,465 controls selected in 1999-2002).

Neither CFS1 nor CFS2 was associated with cancer overall (both ORs = 0.99; Table 2). Using the broadest definition of exposure, CFS1 was most strongly associated with elevated risk of NHL (OR = 1.29, 95% CI = 1.16-1.43, $P = 1.7 \times 10^{-6}$), kidney cancer (OR = 1.27, 95% CI = 1.07-1.49, $P = .005$), and pancreatic cancer (OR = 1.25, 95% CI = 1.07-1.47, $P = .006$), and there was an inverse association with breast cancer (OR = 0.85, 95% CI = 0.74-0.98, $P = .025$) and cancers of the oral cavity and pharynx (OR = 0.70, 95% CI = 0.49-1.00, $P = .049$) (Table 1). CFS2 was similarly associated with elevated risk of NHL (OR = 1.22, 95% CI = 1.09-1.37, $P = 4.6 \times 10^{-4}$), kidney cancer (OR = 1.29, 95% CI = 1.09-1.53, $P = .004$), and pancreatic cancer (OR = 1.27, 95% CI = 1.07-1.50, $P = .006$), and reduced risk of breast cancer (OR = 0.85, 95% CI = 0.74-0.99, $P = .034$) and cancers of the oral cavity and pharynx (OR =

Table 2. Associations Between Chronic Fatigue Syndrome and Cancer[a]

Cancer Type	CFS1: ICD-9 300.5 or ICD-9-CM 780.71 (1992-2005)				CFS2: ICD-9-CM 780.71 (1999 or later)			
	Total	% with CFS1	OR (95% CI)[b]	*P*	Total	% with CFS2	OR (95% CI)[b]	*P*
Controls	100,000	0.5	1.0 (reference)		65,465	0.7	1.0 (reference)	
All cancers	1,176,950	0.5	0.99 (0.89, 1.09)	.788	770,490	0.7	0.99 (0.89, 1.09)	.776
Lip	2,432	–	0.40 (0.15, 1.07)	.069	1,414	–	0.44 (0.16, 1.17)	.099
Tongue	4,619	0.5	1.03 (0.68, 1.58)	.875	3,111	0.7	1.05 (0.68, 1.64)	.813
Salivary gland	2,593	0.6	1.13 (0.67, 1.90)	.646	1,763	0.7	1.10 (0.63, 1.92)	.736
Oral cavity and pharynx	9,750	0.3	0.70 (0.49, 1.00)	.049	5,997	0.4	0.65 (0.44, 0.97)	.033
Esophagus	11,829	0.4	0.84 (0.62, 1.14)	.258	8,002	0.5	0.85 (0.62, 1.18)	.338
Stomach	23,604	0.6	1.15 (0.94, 1.40)	.165	14,973	0.8	1.12 (0.91, 1.38)	.281
Small intestine	3,825	0.5	0.94 (0.60, 1.48)	.793	2,686	0.6	0.80 (0.48, 1.34)	.400
Colorectum	154,984	0.5	0.89 (0.79, 1.00)	.050	100,198	0.7	0.89 (0.79, 1.01)	.080
Anus	2,717	0.5	0.90 (0.53, 1.54)	.704	1,829	0.6	0.80 (0.44, 1.47)	.476
Liver	10,662	0.6	1.16 (0.89, 1.52)	.265	7,512	0.7	1.09 (0.81, 1.45)	.582
Gall bladder and bile duct	11,045	0.4	0.79 (0.59, 1.04)	.097	7,245	0.5	0.71 (0.51, 0.97)	.032
Pancreas	34,402	0.7	1.25 (1.07, 1.47)	.006	22,929	0.9	1.27 (1.07, 1.50)	.006
Larynx	8,447	0.4	1.15 (0.82, 1.62)	.423	5,320	0.6	1.06 (0.73, 1.54)	.751
Lung	185,853	0.5	0.94 (0.84, 1.05)	.282	125,379	0.6	0.95 (0.84, 1.07)	.419
Soft tissue including heart	4,909	0.4	0.82 (0.53, 1.26)	.362	3,397	0.5	0.76 (0.47, 1.22)	.252
Melanoma	28,364	0.6	1.17 (0.98, 1.40)	.074	20,615	0.8	1.20 (1.00, 1.44)	.056
Other nonepithelial skin	4,253	0.4	0.72 (0.44, 1.17)	.182	2,977	0.5	0.76 (0.46, 1.26)	.284
Breast	138,041	0.5	0.85 (0.74, 0.98)	.025	88,705	0.7	0.85 (0.74, 0.99)	.034
Cervix	4,131	0.5	0.78 (0.49, 1.25)	.306	2,516	0.7	0.85 (0.53, 1.38)	.523
Uterus	27,530	0.5	0.88 (0.72, 1.09)	.240	16,853	0.7	0.88 (0.70, 1.09)	.236
Ovary	16,621	0.5	0.86 (0.68, 1.10)	.231	10,621	0.8	0.87 (0.67, 1.12)	.283
Vulva	3,404	0.5	0.68 (0.41, 1.13)	.142	2,182	0.7	0.74 (0.44, 1.26)	.268
Prostate	221,389	0.3	0.99 (0.84, 1.18)	.945	135,448	0.5	0.99 (0.83, 1.19)	.929
Urinary bladder	63,951	0.5	1.07 (0.92, 1.23)	.380	43,309	0.7	1.04 (0.89, 1.21)	.626
Kidney	22890	0.6	1.27 (1.07, 1.49)	.005	16,179	0.8	1.29 (1.09, 1.53)	.004
Renal pelvis	2594	0.7	1.42 (0.90, 2.23)	.131	1,701	0.8	1.10 (0.63, 1.89)	.744
Brain	9,860	0.4	0.75 (0.54, 1.06)	.102	6,467	0.5	0.77 (0.54, 1.10)	.156
Thyroid	6,082	0.7	1.21 (0.88, 1.66)	.230	4,478	0.9	1.24 (0.89, 1.73)	.205
Hodgkin lymphoma	1,989	0.6	1.08 (0.59, 1.95)	.809	1,359	–	0.76 (0.36, 1.61)	.480
Non-Hodgkin lymphoma	57,632	0.7	1.29 (1.16, 1.43)	1.7E-06	39,142	0.8	1.22 (1.09, 1.37)	4.6E-04
Myeloma	15,993	0.5	0.97 (0.76, 1.24)	.823	10,480	0.7	0.99 (0.77, 1.28)	.943
Acute lymphocytic leukemia	758	–	0.51 (0.13, 2.06)	.348	479	–	0.58 (0.14, 2.32)	.439
Other lymphocytic leukemia	919	–	0.91 (0.34, 2.46)	.857	587	–	0.76 (0.24, 2.38)	.638
Acute myeloid leukemia	8,786	0.6	1.17 (0.88, 1.56)	.273	5,969	0.8	1.17 (0.87, 1.58)	.294
Chronic myeloid leukemia	3,788	0.6	1.13 (0.74, 1.75)	.568	2,442	0.9	1.23 (0.79, 1.91)	.359
Other myeloid monocytic leukemia	445	–	0.80 (0.20, 3.26)	.760	302	–	0.92 (0.23, 3.74)	.909
Acute monocytic leukemia	538	–	1.33 (0.49, 3.59)	.572	384	–	1.50 (0.55, 4.04)	.426
Other acute leukemia	1,228	–	0.94 (0.42, 2.11)	.885	716	–	0.71 (0.26, 1.90)	.494
Aleukemic, subleukemic, and NOS leukemias	985	–	1.49 (0.73, 3.02)	.273	635	–	1.70 (0.83, 3.45)	.144
Mesothelioma	3,460	0.5	1.14 (0.70, 1.84)	.604	2,408	0.7	1.10 (0.66, 1.83)	.704
Miscellaneous	16,480	0.6	1.20 (0.98, 1.46)	.073	10,985	0.8	1.22 (0.99, 1.50)	.060

CFS indicates chronic fatigue syndrome; CI, confidence interval; ICD-9-CM, International Classification of Diseases, 9th revision, Clinical Modification; NOS, not otherwise specified; OR, odds ratio. Underlined values indicate that these associations are significant at a p-value cutoff of 0.05.

[a] Numbers of exposed cancer cases between 1 and 10 were suppressed in accordance with the SEER-Medicare data use agreement.

[b] Odds ratios were adjusted for age, sex, and selection year.

0.65, 95% CI = 0.44-0.97, $P = .033$). In addition, CFS2 was associated with reduced risk of gallbladder and bile duct cancers (OR = 0.71, 95% CI = 0.51-0.97, $P = .032$).

Among NHL subtypes (Table 3), CFS1 was significantly associated with diffuse large B cell lymphoma (DLBCL) (OR = 1.34, 95% CI = 1.12-1.61, $P = .002$); marginal zone lymphoma (MZL) (OR = 1.88, 95% CI = 1.38-2.57, $P = 6.5 \times 10^{-5}$); and B cell NHL, not otherwise specified (NOS) (OR = 1.51, 95% CI = 1.03-2.23, $P = .037$). The significant associations for CFS1 were also significant or borderline for CFS2. We repeated the analysis to exclude an additional year of Medicare claims for subjects, so that cases must have developed NHL at least 2 years after a CFS diagnosis, and results were similar. Specifically, associations remained apparent for

Table 3. Associations Between Chronic Fatigue Syndrome and NHL Subtypes[a]

Subtype	CFS1: ICD-9 300.5 or ICD-9-CM 780.71 (1992-2005)				CFS2: ICD-9-CM 780.71 (1999 or later)			
	Total	% with CFS1	OR (95% CI)[b,c]	*P*	Total	% with CFS2	OR (95% CI)[b,c]	*P*
Controls	100,000	0.5	1.0 (reference)		65,465	0.7	1.0 (reference)	
Overall NHL	57,632	0.7	1.29 (1.16, 1.43)	1.7E-06	39,142	0.8	1.22 (1.09, 1.37)	.0005
Burkitt	273	–	0.59 (0.08, 4.17)	.594	224	–	0.66 (0.09, 4.66)	.673
CLL/SLL/PLL	15,456	0.6	1.22 (1.00, 1.49)	.054	10,360	0.8	1.16 (0.93, 1.44)	.183
Mantle cell	1,619	0.7	1.27 (0.70, 2.30)	.428	1,225	–	1.30 (0.70, 2.42)	.412
DLBCL	16,470	0.7	1.34 (1.12, 1.61)	.002	11,354	0.9	1.21 (0.99, 1.47)	.070
Follicular	7,493	0.6	1.17 (0.88, 1.57)	.283	5,175	0.8	1.23 (0.91, 1.67)	.174
LPL/Waldenstrom	727	–	1.00 (0.37, 2.68)	1.000	509	–	1.11 (0.42, 2.98)	.831
Marginal zone	3,358	1.2	1.88 (1.38, 2.57)	6.5E-05	2,799	1.3	1.89 (1.36, 2.62)	1.3E-04
NHL, NOS	2,097	–	1.45 (0.78, 2.70)	.244	830	–	1.16 (0.55, 2.45)	.688
B cell NHL, NOS	2,930	0.9	1.51 (1.03, 2.23)	.037	2,184	1.1	1.48 (0.98, 2.24)	.062
T cell NHL	2,933	0.4	0.80 (0.45, 1.41)	.437	2,014	–	0.59 (0.29, 1.18)	.138
LN, NOS	4,238	0.4	0.92 (0.59, 1.44)	.716	2,446	0.7	0.94 (0.58, 1.51)	.785

CFS indicates chronic fatigue syndrome; CI, confidence interval, CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B cell lymphoma; ICD-9-CM, International Classification of Disease, 9th revision, Clinical Modification; LN, lymphoid neoplasm; LPL, lymphoplasmacytic lymphoma; NHL, non-Hodgkin lymphoma; NHL NOS, NHL of unknown lineage; NOS, not otherwise specified; OR, odds ratio; PLL, prolymphocytic leukemia; SLL, small lymphocytic lymphoma. Underlined values indicate that these associations are significant at a p-value cutoff of 0.05.

[a] Numbers of exposed cancer cases between 1 and 10 were suppressed in accordance with the SEER-Medicare data use agreement.

[b] Odds ratios were adjusted for age, sex, and selection year.

[c] Odds ratios for precursor lymphoblastic leukemia/lymphoma, B cell were not estimable.

Table 4. Associations of Chronic Fatigue Syndrome[a] (N = 498) With Medical Conditions Among Controls (N = 100,000)

Characteristics	Total with Characteristic	OR (95% CI) Associated with CFS)	Chi-Squared *P*
Alcohol abuse	1,798	1.24 (0.68, 2.25)	.489
Transfusion	5,252	1.98 (1.47, 2.66)	<.0001
HIV infection	143	1.41 (0.20, 10.08)	.732
Hepatitis B virus infection	225	2.71 (0.86, 8.50)	.075
Hepatitis C virus infection	291	2.80 (1.04, 7.54)	.033
Lupus	214	1.89 (0.47, 7.62)	.364
Sjögren's syndrome	197	4.17 (1.54, 11.26)	.002
Rheumatoid arthritis	2,514	3.05 (2.17, 4.29)	<.0001

CFS indicates chronic fatigue syndrome; CI, confidence interval; HIV, human immunodeficiency virus; ICD-9 = International Classification of Diseases, 9th revision, Clinical Modification; OR, odds ratio.

[a] CFS1, ICD-9 300.5 or ICD-9-CM 780.71 (1992-2005).

CFS1 with NHL overall (OR = 1.33, 95% CI = 1.17-1.63, $P = 1.2 \times 10^{-5}$), DLBCL (OR = 1.44, 95% CI = 1.16-1.79, $P = .001$), and MZL (OR = 2.16, 95% CI = 1.47-3.18, $P = 9.8 \times 10^{-5}$), and for CFS2 with NHL overall (OR = 1.21, 95% CI = 1.05-1.39, $P = .009$), DLBCL (OR = 1.18, 95% CI = 0.92-1.53, $P = .190$), and MZL (OR = 1.83, 95% CI = 1.21-2.77, $P = .004$).

In analyses adjusted for race, associations between CFS and NHL overall, DLBCL, and MZL remained the same (results not shown). Associations of CFS1 with various demographic characteristics and medical conditions are shown in Table 4 for control subjects. CFS was more common among individuals who had a blood transfusion, or had HCV infection, Sjögren's syndrome, or rheumatoid arthritis. Nonetheless, after excluding subjects with a history of transfusion, HIV, HBV, HCV, lupus, Sjögren's syndrome, or rheumatoid arthritis, the associations with CFS1 were still significant for NHL overall (OR = 1.33, 95% CI = 1.19-1.49, $P = 8.5 \times 10^{-7}$) as well as for DLBCL (OR = 1.35, 95% CI = 1.10-1.65, $P = .003$) and MZL (OR = 2.04, 95% CI = 1.46-2.85, $P = 3.3 \times 10^{-5}$).

Because depression and CFS can be confused with each other, we examined associations of NHL with depression. Depression was not associated with NHL overall (OR = 0.99, 95% CI = 0.96-1.03), DLBCL (OR = 0.94, 95% CI = 0.88-1.01), or MZL (OR = 0.96, 95% CI = 0.84-1.11).

DISCUSSION

Although the underlying etiology of CFS remains unclear, immune abnormalities and chronic manifestations of

infections have been reported.[5] Because some cancers, particularly lymphomas, can arise from similar conditions, we examined associations between CFS and subsequent risk of cancer in a population-based case-control study among elderly individuals in the United States. In this study, we observed that CFS was significantly associated with an increased risk of NHL, particularly for 2 specified NHL subtypes, DLBCL and MZL. The association we found with B cell NHL not otherwise specified may be due to the fact that this category includes cases of DLBCL (one of the most common NHL subtypes). Our findings for NHL support the link with CFS suggested in the prior ecological studies,[10] although the present study is the first to evaluate NHL subtypes.

Several findings add support to the associations between CFS and NHL. First, the associations with DLBCL and MZL risk were among the strongest we observed across multiple cancer sites and had a high degree of statistical significance. Second, the associations remained apparent even after we excluded 2 years of Medicare data prior to cancer diagnosis or control selection. Thus, the association is unlikely to be due to undiagnosed lymphoma causing fatigue. Third, we evaluated associations with depression, which may mimic CFS, but did not find similarities in the direction or magnitude of the ORs that we observed for CFS. Finally, the associations with DLBCL and MZL persisted after adjustment for race, and after we excluded subjects with other medical conditions or procedures associated with CFS or NHL.

Patients with CFS have been reported to manifest reduced T cell response to antigens, suppressed natural killer T cell (NKT) activity, alterations in inflammatory marker levels, and the presence of autoantibodies.[5] Landay et al observed a reduced number of CD8+ suppressor T cells and increased number of CD8+ cytotoxic T cells in blood samples of patients with CFS, indicating immune activation.[26] Other studies have observed an increased CD4+/CD8+ lymphocyte ratio (ie, increased helper, decreased suppressor T cells) in patients with CFS,[27,28] which is associated with immune activation and has been observed in patients with autoimmune diseases such as multiple sclerosis and autoimmune hemolytic anemia.[29] At least 2 studies reported elevated circulating levels of inflammatory markers, including C-reactive protein, in patients with CFS.[30,31] Reduced NKT activity has been repeatedly observed and has been proposed as a biomarker for CFS.[32-34] Because NKT cells may play a role in suppressing autoimmunity, a disturbance in NKT activity could lead to increased immune activation.[3]

In concert with these immune abnormalities, viruses and bacteria, such as Epstein-Barr virus (EBV), cytomegalovirus, parvovirus B19, HCV, and *Chlamydia pneumoniae*, have been implicated in CFS.[4] Although the link between CFS and these infections is disputed,[6] it is noteworthy that some of these infections and other immune-related medical conditions are associated with DLBCL and MZL in other contexts. In a pooled analysis of 7 case-control studies, HCV infection was associated with both DLBCL (OR = 2.24, 95% CI = 1.68-2.99) and MZL (OR = 2.47, 95% CI = 1.44-4.23).[35] HCV is thought to increase risk of NHL through chronic immune stimulation.[35] In our study, CFS was associated with HCV, but HCV was too rare to explain the association between CFS and NHL, and the association persisted after we excluded subjects with known HCV infection. Transfusion, which could increase risk of NHL through transmission of a virus or immune modulation, has been associated with both DLBCL and MZL in a number of case-control studies,[36,37] most recently in the SEER-Medicare population.[23] EBV has been detected in DLBCL tumors among individuals with an HIV infection and the elderly, in the setting of immunosuppression or immunosenescence, respectively, and is thought to directly drive lymphoproliferation.[38,39] In cytotoxicity assays, lymphocytes from patients with CFS were shown to lack the ability to lyse EBV-infected B cells.[40] DLBCL and MZL are also observed in association with autoimmune conditions, including rheumatoid arthritis, lupus, and Sjögren's syndrome.[25,41] The findings of altered immune function in CFS, along with data from other contexts that implicate immune disturbances or viral infections in the etiology of DLBCL and MZL, suggest that an etiologic relationship underlies the observed associations in our study.

There were also significant associations between CFS1 and a few other cancers, including cancers of the pancreas, kidney, and breast. However, because the *P* values for these other associations were higher (*P* values from .006 to .049, according to the broader definition) than that for NHL ($P = 1.7 \times 10^{-6}$), and because we had no a priori hypotheses for these other associations, we would tend to discount these as chance findings. Indeed, using a Bonferroni *P* value cutoff of .001 (ie, 0.05 divided by 40 cancer types), only the association with NHL would remain significant after correction for multiple comparisons. Initial reports described detection of XMRV in blood samples from patients with CFS, and prostate cancer tissue,[12,42] but the CFS study[18] was retracted, and recent studies have called into question a role of XMRV in

either disease.[15-17] We found no association between CFS and prostate cancer (OR = 0.99, 95% CI = 0.84-1.18, P = .95), which would argue against a role of XMRV in either CFS or prostate cancer. Of interest, in a recent study in the United Kingdom,[43] XMRV was not detected in tumor tissue from patients with NHL, including cases of DLBCL. Finally, we did not find an association between CFS and risk of brain tumors, and thus we failed to support findings from prior ecological studies.[9,10]

The study has a number of strengths. The large number of cancer cases and controls gave us ample power to detect associations for an exposure as rare as CFS. The availability of subtype information for NHL allowed us to assess NHL subtype-specific associations with CFS. Our study was based on data obtained from population-based sources (Medicare and SEER), giving a representative sampling of elderly US adults. In addition, CFS was documented in Medicare hospital and provider claims using the same procedure for cases and controls, eliminating recall bias.

This study also has limitations. We were unable to assess whether CFS was correctly diagnosed by physicians and reported in Medicare claims. However, our prevalence estimate (0.5% among controls) falls within the estimated range of uncertainty in CFS prevalence among those aged 60 and older in a population-based survey (0.35%; 95% CI = 0.19%-0.52%).[7] CFS is a heterogeneous syndrome and is often subdivided by presenting or chronic symptoms, but we were unable to do this subdividing with our data.[26,28,44,45] Despite the detailed diagnostic criteria, diagnosis can be challenging due to the lack of standard disease biomarkers. In addition, we could not assess CFS before subjects had Medicare benefits and claims in the SEER-Medicare database (prior to age 65 years or before 1992). Finally, because our study was limited to people aged 66 years and older, our results may not be generalizable to younger (nonelderly) populations. We would also caution further against any direct interpretation or application of our results in a clinical setting. We could not estimate the absolute risk of NHL associated with CFS, but the risk is likely too small to affect the clinical management of patients with CFS.

In conclusion, we observed an elevated risk of NHL overall and for 2 defined NHL subtypes, DLBCL and MZL, following a CFS diagnosis. These findings should be confirmed in another epidemiologic study. Chronic immune activation or an infection may play a role in explaining the observed association between CFS and NHL. Our study results support continued efforts to understand the biology of CFS.

FUNDING SOURCES

This work was supported by the Intramural Research Program of the National Cancer Institute at the US National Institutes of Health.

CONFLICT OF INTEREST DISCLOSURE

The authors made no disclosure.

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