ORIGINAL REPORT

Racial Differences in Chronic Immune Stimulatory Conditions and Risk of Non-Hodgkin's Lymphoma in Veterans From the United States

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A B S T R A C T

Purpose
To examine underlying etiologic factors that may explain the racial disparity in non-Hodgkin's lymphoma (NHL) incidence patterns.

Patients and Methods
We assessed immune-related conditions and risk of developing NHL among more than 4 million hospitalized US veterans including 9,496 patients with NHL (7,999 white patients and 1,497 black patients) with up to 26 years of follow-up. We used time-dependent Poisson regression to estimate rate ratios (RRs) and 95% CIs for NHL risk among patients with a history of specific autoimmune diseases, infections, and allergies compared with patients without such history, adjusting for attained age, calendar year, race, number of hospital visits, and time between study entry and exit.

Results
Patients with infectious conditions had an increased risk of developing NHL (RR, 1.2; 95% CI, 1.1 to 1.2), particularly for gastrohepatic, genital, and systemic infectious conditions. Patients with autoimmune disease were generally more likely to develop NHL than patients without autoimmune disease, especially for conditions that typically present with detectable autoantibodies with systemic involvement (RR, 2.0; 95% CI, 1.8 to 2.2). Allergies were also associated with increased risk (RR, 1.4; 95% CI, 1.3 to 1.5). Although the risk of NHL was lower for blacks than whites (RR, 0.87; 95% CI, 0.82 to 0.92), blacks had a slightly higher risk of NHL associated with infections than whites (likelihood ratio test, $P = .002$) and a tendency toward higher risk associated with allergies (likelihood ratio test, $P = .05$). Risks associated with autoimmune conditions were similar by race (likelihood ratio test, $P = .5$).

Conclusion
The observed difference in NHL risk by race supports a role for race-related differences in genes regulating immune/inflammatory response.

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INTRODUCTION

In 2010, non-Hodgkin's lymphoma (NHL) will account for an estimated 65,540 new cancer cases and 20,210 deaths in the United States.[1] NHL has been associated with broadly categorized immune-related conditions,[2,3] including immunodeficiency,[4] autoimmune diseases,[5,6] infections,[7] and allergies.[8,9] We previously found that the association of infectious conditions with risk of Waldenström macroglobulinemia, a rare B-cell subtype of NHL, was consistently higher for blacks than whites.[10]

Although the incidence of NHL is somewhat lower among blacks compared with whites,[2] blacks have higher rates of the extranodal NHL subtypes peripheral T-cell lymphoma and mycosis fun-goides.[11] These disparities, coupled with findings that associations between immune system–related gene polymorphisms and NHL vary by race,[12] suggest that genetic predisposition may play a role in immune-related NHL. Immune status has been associated with race, with blacks having higher levels of immunoglobulin A and CD8 cell counts than whites.[13] Furthermore, several studies observed that whites and blacks living in the same geographical region had different levels of γ-globulin, a marker of immune disruption.[14,15]

Previous epidemiologic studies on NHL generally have not included many blacks or were limited by small sample size. These studies often adjusted for race in their analyses[3] and rarely compared results across racial/ethnic groups. To further examine the

role of immune-related conditions in lymphomagenesis and potential differences by race, we investigated the relation between immune-related conditions and risk of developing NHL among a large cohort of more than 4 million adult male military veterans, including more than 800,000 black veterans, admitted to the US Veterans Affairs (VA) hospitals.

PATIENTS AND METHODS

Patients, Outcome, and Exposures

With more than 150 hospitals, the VA medical care system has been used to create a database of inpatient records from more than 4 million US veterans hospitalized between July 1, 1969, and September 30, 1996.[16,17] These patients originated from approximately 30 million US veterans eligible for admission to VA hospitals during the study period.[18] White or black men age 18 to 100 years who were hospitalized at least once during the study period were included if they were cancer free during the first year of follow-up and survived at least 1 year after the initial visit. Females and males of other ethnicities and ages were excluded because they formed a small proportion of hospitalized veterans. This study was exempt from institutional review board review and informed consent as per the National Institutes of Health Office of Human Subjects Research because it analyzed existing data stripped of personal identifiers and there was no patient contact.

NHL diagnoses were identified using the eighth and ninth revisions of the International Classification of Diseases codes (200, 202) as were the specific autoimmune, infectious, and allergic conditions listed in Tables 2 through 4. Combined categories of bacterial, viral, parasitic, organ site–specific, and total infections also were analyzed, as were autoimmune diseases that typically present with detectable autoantibodies (with either systemic involvement or organ-specific involvement) and those that do not have detectable autoantibodies.

Statistical Analysis

Person-time at risk began 1 year after the first hospital discharge and ended at diagnosis of NHL. Individuals not diagnosed with NHL were censored at first malignancy, death, or the end of follow-up (September 30, 1996), whichever came first. Records were linked to Social Security Administration Death Master File Records to determine dates of death.[19] Exposed person-time was calculated for chronic immune stimulatory conditions (autoimmunity, infections, and allergies) by subtracting the date of the first hospital discharge diagnosis for an immune stimulatory condition from the date of first hospital admission for NHL.

Time-dependent Poisson regression[20] (AMFIT module in Epicure version 1.4; HiroSoft International, Seattle, WA) was used to calculate rate ratios (RRs) and two-sided 95% CIs for the risk of NHL associated with race and with immune-related conditions in black and white patients. RRs were adjusted for attained age ($<$ 40, 40 to 49, 50 to 59, 60 to 69, 70 to 79, or $\geq$ 80 years), attained calendar year (1969 to 1974, 1975 to 1979, 1980 to 1984, 1985 to 1989, or 1990 to 1996), race (black or white), number of hospital visits (one to two, three to four, or $\geq$ five visits), and latency between study entry and exit (2 to 3, 4 to 5, 6 to 9, 10 to 14, or $\geq$ 15 years). Because estimates based on small numbers are unstable, we present RRs when there are five or more patients with NHL. The likelihood ratio test (LRT) for multiplicative interaction was used to formally test whether race modified the RRs for these conditions.

To assess whether undetected NHL might cause the immune-related conditions (ie, reverse causality), models for infectious, autoimmune, and allergic conditions were stratified by latency (time in the cohort) of 2 to 5 years and more than 5 years. To evaluate whether changes in the definition of NHL over time might affect the results, models were stratified by median calendar time ($<$ 1980 and $\geq$ 1980 at first visit). We also stratified by age at first visit ($<$ and $\geq$ 50 years).

RESULTS

We identified 9,496 patients with NHL (7,999 white patients and 1,497 black patients) with a mean follow-up time of 7.9 years (range, 1 to 26 years; Table 1). Overall, blacks had a lower risk of NHL than whites (RR, 0.87; 95% CI, 0.82 to 0.92). Patients with NHL tended to be older at study entry and to have slightly more hospital visits than patients without NHL, and blacks were younger than whites (Table 1).

Infections and Risk of NHL

Patients with infectious conditions had an increased risk of developing NHL (RR, 1.2; 95% CI, 1.1 to 1.2; Table 2). The risk was somewhat higher for viral (RR, 1.6; 95% CI, 1.5 to 1.8) and parasitic infections (RR, 1.7; 95% CI, 1.5 to 1.8) than for bacterial infections (RR, 1.2; 95% CI, 1.1 to 1.3). Gastrohepatic, genital, systemic, and arthropod-borne infectious conditions were particularly likely to increase risk. Among the conditions in the other category, herpes simplex, herpes zoster, infectious mononucleosis, and toxoplasmosis were associated with two- to eight-fold increased risk. Both blacks and whites had an increased risk of NHL associated with infections, but the risk was slightly higher for blacks than whites (Fig 1). This pattern was similar for systemic, reproductive, and lower airway infections (RR, 4.0; 95% CI, 3.3 to 4.9; RR, 1.7; 95% CI, 1.2 to 2.3; and RR, 1.3; 95% CI, 1.2 to 1.6, respectively, in blacks and RR, 2.7; 95% CI, 2.4 to 3.0; RR, 1.1; 95% CI, 0.89 to 1.3; and RR, 1.1; 95% CI, 1.0 to 1.2, respectively, in whites; LRT, $P \leq$ .001, .01, and .03, respectively). In contrast to other systemic infections, the RR for HIV was higher in whites (RR, 46.2; 95% CI, 38.8 to 55.0) than blacks (RR, 22.3; 95% CI, 17.1 to 29.0).

Table 1. Demographics and Clinical Characteristics of the Study Cohort: White and Black Male US Veterans With at Least One Hospital Admission Between July 1, 1969, and September 30, 1996, Who Were Observed More Than 1 Year

Characteristic	Whites		Blacks	
	No NHL	NHL	No NHL	NHL
No. of persons	3661,245	7,999	830,837	1,497
Mean age at study entry, years*	52.1	55.8	47.7	49.6
Mean years of follow-up†	11.7	7.8	11.9	8.6
Person-years at risk†	42,702,434	62,254	9876,557	12,935
Median No. of hospital visits	3	4‡	3	4‡

Abbreviation: NHL, non-Hodgkin's lymphoma.
*Age at first discharge record for inpatient hospitalization at Veterans Affairs hospitals between July 1, 1969, and September 30, 1996.
†Follow-up started 1 year after the first hospital visit.
‡Includes visits up to the exit date.

Table 2. Infection-Related Conditions and Risk of NHL in US Male Veterans

Category	No. of Veterans Exposed		RR	95% CI
	No NHL	NHL		
Total infection-related conditions	1,536,589	3,832	1.2*	1.1 to 1.2
Upper airway	223,750	573	1.1*	1.0 to 1.2
Acute bronchitis/bronchiolitis	89,435	191	0.94	0.81 to 1.1
Chronic sinusitis	74,701	243	1.3*	1.2 to 1.5
Laryngitis	9,890	27	1.1	0.77 to 1.6
Nasopharyngitis/pharyngitis	54,430	125	1.0	0.86 to 1.2
Otitis media/mastoiditis	12,190	39	1.1	0.78 to 1.5
Lower airway	442,063	1,088	1.2*	1.1 to 1.2
Influenza	22,172	69	1.2	0.94 to 1.6
Pneumonia	361,834	867	1.2*	1.1 to 1.3
Tuberculosis	82,151	225	1.1	0.92 to 1.2
Gastrohepatic	145,366	415	1.4*	1.2 to 1.5
Cholangitis/cholecystitis	32,844	86	0.98	0.78 to 1.2
Hepatitis virus	45,826	115	1.9*	1.5 to 2.3
Hepatitis A virus	2,911	9	1.9	0.89 to 3.9
Hepatitis B virus	14,678	52	2.6*	1.9 to 3.5
Hepatitis C virus	16,610	21	1.2	0.68 to 2.2
Intestinal	70,392	228	1.4*	1.2 to 1.6
Genital	76,399	250	1.6*	1.4 to 1.8
Condyloma acuminatum	11,436	30	1.5*	1.0 to 2.1
Genital herpes	3,234	34	6.9*	4.7 to 10.1
Gonorrhea	9,387	33	1.7*	1.2 to 2.4
Syphilis	49,161	156	1.5*	1.2 to 1.7
Trichomoniasis	4,851	9	0.95	0.49 to 1.8
Reproductive	66,319	204	1.2*	1.0 to 1.4
Orchitis and epididymitis	48,829	155	1.2*	1.0 to 1.4
Chronic prostatitis	18,620	51	0.98	0.73 to 1.3
Urinary	27,583	72	1.2	0.91 to 1.5
Chronic cystitis	4,049	8	0.98	0.49 to 2.0
Chronic pyelonephritis	10,317	30	1.3	0.88 to 1.9
Urethritis	13,726	34	1.1	0.76 to 1.5
Cardiovascular†	111,164	233	1.0	0.89 to 1.2
Acute pericarditis	6,714	15	1.1	0.68 to 1.9
Endocarditis	104,554	216	1.0	0.87 to 1.2
Systemic	96,770	508	2.9*	2.7 to 3.3
HIV	14,410	329	35.8*	30.9 to 41.5
Meningitis	13,827	74	2.4*	1.9 to 3.1
Septicemia	72,643	193	1.3*	1.1 to 1.6
Arthropod-borne diseases‡	20,720	55	1.5*	1.1 to 1.9
Acariasis	7,522	17	1.2	0.73 to 1.9
Malaria	4,656	7	1.2	0.54 to 2.7
Pediculosis and *Phthirus* infestation	6,157	14	1.2	0.72 to 2.1
Rickettsia	815	7	3.7*	1.7 to 8.2
Viral arthropod-borne diseases	1,147	6	2.2*	1.0 to 5.0
Other				
Conjunctivitis	16,790	42	0.96	0.70 to 1.3
Gingivitis and periodontitis	478,113	1,142	0.93*	0.87 to 0.99
Helminthiases	4,251	17	1.6	0.98 to 2.7
Herpes simplex	13,441	110	3.8*	3.0 to 4.7
Herpes zoster	18,913	106	2.2*	1.8 to 2.7
Infectious mononucleosis	2,330	11	2.7*	1.4 to 5.5
Infective arthritis	8,079	28	1.8*	1.2 to 2.7
Mycoses	174,953	599	1.7*	1.5 to 1.8
Osteomyelitis	57,655	112	0.86	0.71 to 1.1
Skin and soft tissue infections	296,539	757	1.2*	1.1 to 1.3
Toxoplasmosis	1,509	40	7.8*	4.8 to 12.7
Zoonoses	1,630	5	1.5	0.61 to 3.5

NOTE. All analyses were adjusted for age, calendar time, race, latency, and number of hospital visits.
Abbreviations: NHL, non-Hodgkin's lymphoma; RR, rate ratio.
*Significant result.
†Includes acute myocarditis, for which only two veterans had NHL.
‡Includes Lyme disease and babesiosis, for which no veterans had NHL, and other bacterial and protozoan arthropod-borne disease, for which only four veterans had NHL.
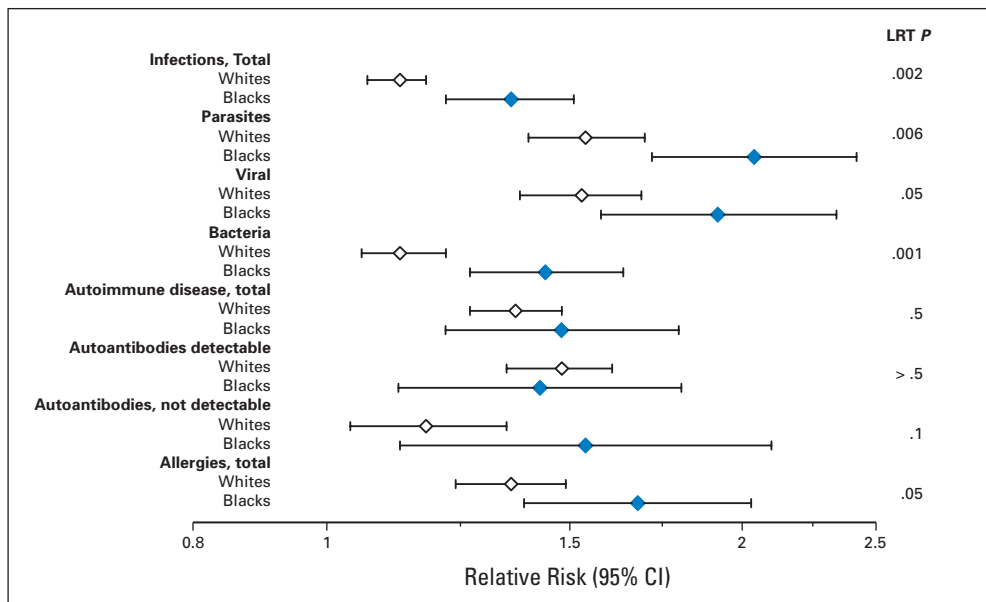
Fig 1. Forest plots of the rate ratios (RRs) and 95% CIs for infectious, autoimmune, and allergic conditions (left) and subsequent non-Hodgkin's lymphoma among blacks and whites. The likelihood ratio test (LRT) provides a formal evaluation of the difference in RRs by race. All analyses were adjusted for age, calendar time, latency, and number of hospital visits.

Additional RRs for individual infection-related conditions with ≥ five exposed black and white patients are listed in Appendix Table A1 (online only). To ensure that the observed differences by race were not a result of HIV infection, we conducted analyses adjusting broad categories of infections for HIV; differences by race remained for all categories (LRT, $P = .02$ for total, bacterial, and parasitic infections) except viral infections (LRT, $P = .2$).

Autoimmune Disease and Risk of NHL

Patients with autoimmune disease had a 1.4-fold increased risk of NHL (95% CI, 1.3- to 1.5-fold), although there was considerable variability across individual conditions (Table 3). The strongest associations tended to be for autoimmune diseases in which autoantibodies are detectable (RR, 1.5; 95% CI, 1.3 to 1.6), especially for those with systemic involvement (RR, 2.0; 95% CI, 1.8 to 2.2). Autoimmune diseases with organ involvement had a much lower increased risk (RR, 1.2; 95% CI, 1.1 to 1.4), although some conditions, such as autoimmune hemolytic anemia (RR, 5.0; 95% CI, 3.4 to 7.3), immune thrombocytopenic purpura (RR, 3.7; 95% CI, 2.2 to 6.4), discoid lupus erythematosus (RR, 2.2; 95% CI, 1.5 to 3.4), and celiac disease (RR, 2.6; 95% CI, 1.5 to 4.5), showed notable elevations. Interestingly, risk of NHL was decreased in patients with multiple sclerosis (RR, 0.66; 95% CI, 0.45 to 0.96). Patients with autoimmune conditions that generally do not have detectable autoantibodies had a slightly increased risk of NHL (RR, 1.2; 95% CI, 1.1 to 1.4), especially for sarcoidosis (RR, 1.6; 95% CI, 1.0 to 2.4), Crohn's disease (RR, 1.5; 95% CI, 1.0 to 2.1), psoriasis (RR, 1.3; 95% CI, 1.1 to 1.6), and Wegener's granulomatosis (RR, 3.8; 95% CI, 1.4 to 10.3). Risks associated with autoimmune conditions were similar for black and white patients (Fig 1). Appendix Table A2 (online only) provides the distribution of individual autoimmune conditions by race.

Allergies and Risk of NHL

Overall, risk of NHL was increased with previous diagnosis of an allergic condition (RR, 1.4; 95% CI, 1.3 to 1.5), but the association was not consistent across individual conditions (Table 4). Allergic alveoli-

tis, dermatitis, and erythema were associated with approximately two- to four-fold increased risk (although the RR for allergic alveolitis was based on only five exposed patients with NHL), whereas prior asthma, rhinitis, and urticaria were not associated with NHL. The risk of NHL associated with allergies seemed slightly higher for blacks than whites (LRT, $P = .05$; Fig 1). Appendix Table A3 (online only) provides the distribution of individual allergic conditions by race.

Sensitivity Analyses

For all but infections of the reproductive system, the risk of NHL was more strongly elevated for infections that occurred 2 to 4 years before NHL than ≥ 5 years before NHL (Table 5). Infections also tended to be more strongly associated with NHL when they occurred after 1980. Nearly all of the increased risk associated with infections occurred among patients who were younger than 50 years old at their first visit. In contrast, we saw few differences for autoimmune conditions across latency, calendar year, or age (Table 5). Although the association between autoimmune conditions and NHL seemed somewhat stronger for diagnoses before 1980 versus 1980 or later, the RRs were fairly similar across calendar year for subgroups of autoimmune conditions. Autoimmune conditions with organ involvement had slightly stronger associations with NHL diagnosed before age 50 years (RR, 1.4; 95% CI, 1.2 to 1.7) than NHL diagnosed at or after age 50 years (RR, 1.2; 95% CI, 1.0 to 1.3; LRT, $P = .03$), but the RRs for total autoimmune diseases were the same across age groups. Allergies were more strongly associated when diagnosed 2 to 4 years before NHL than ≥ 5 years before NHL (LRT, $P = .02$), but the association did not vary by calendar year or age (Table 5).

DISCUSSION

In this large study of more than 4 million US veterans, infectious, autoimmune, and allergic conditions were all associated with increased risk of NHL, but the risk of NHL associated with infections was slightly higher in blacks compared with whites. A notable exception

Table 3. Autoimmune Conditions and Risk of NHL in US Male Veterans

Category	No. of Veterans Exposed			
	No NHL	NHL	RR	95% CI
Total autoimmune conditions	288,874	918	1.4*	1.3 to 1.5
Autoantibodies detectable	199,426	667	1.5*	1.3 to 1.6
Systemic involvement	66,005	317	2.0*	1.8 to 2.2
Rheumatoid arthritis	59,208	280	1.9*	1.7 to 2.2
Sjögren's syndrome	1,875	18	3.3*	2.0 to 5.5
Systemic sclerosis	2,667	7	1.5	0.70 to 3.1
Systemic lupus	3,798	24	3.0*	1.9 to 4.6
Organ involvement†	139,475	382	1.2*	1.1 to 1.4
Addison's disease	4,192	9	0.84	0.38 to 1.9
Amyotrophic lateral sclerosis	7,269	11	0.80	0.41 to 1.5
Autoimmune hemolytic anemia	3,046	32	5.0*	3.4 to 7.3
Celiac disease	2,019	13	2.6*	1.5 to 4.5
Chronic rheumatic heart disease	64,839	151	1.1	0.90 to 1.3
Discoid lupus erythematosus	5,076	27	2.2*	1.5 to 3.4
Graves' disease	6,391	9	0.55	0.27 to 1.1
Hashimoto's thyroiditis	1,185	5	1.4	0.54 to 3.8
Immune thrombocytopenic purpura	9,160	47	2.8*	2.1 to 3.8
Multiple sclerosis	19,341	27	0.66*	0.45 to 0.96
Myasthenia gravis	2,429	8	1.2	0.59 to 2.6
Pernicious anemia	9,220	30	1.1	0.71 to 1.6
Primary biliary cirrhosis	7,807	15	0.98	0.59 to 1.6
Autoantibodies not detectable‡	106,340	317	1.2*	1.1 to 1.4
Ankylosing spondylitis	10,468	30	1.2	0.81 to 1.7
Crohn's disease	9,313	31	1.5*	1.0 to 2.1
Hemorrhagic proctitis	19,896	40	0.84	0.59 to 1.2
Polymyalgia rheumatica	9,488	8	1.2	0.44 to 3.1
Psoriasis	40,540	133	1.3*	1.1 to 1.6
Reiter's disease	3,628	12	1.5	0.80 to 2.8
Rheumatic fever	4,677	14	1.3	0.70 to 2.3
Sarcoidosis	8,264	26	1.6*	1.0 to 2.4
Ulcerative colitis	11,464	24	0.82	0.54 to 1.3
Wegener's granulomatosis	9,488	8	3.8*	1.4 to 10.3

NOTE. All analyses were adjusted for age, calendar time, race, latency, and number of hospital visits.
Abbreviations: NHL, non-Hodgkin's lymphoma; RR, rate ratio.
*Significant result.
†Includes polyarteritis and localized scleroderma, for which only two and four veterans had NHL, respectively.
‡Includes Behçet's syndrome, for which no veterans had NHL, and rheumatic chorea, for which only one veteran had NHL.

Table 4. Allergic Conditions and Risk of NHL in US Male Veterans

Category	No. of Veterans Exposed			
	Non-NHL	NHL	RR	95% CI
Total allergic conditions	223,529	718	1.4*	1.3 to 1.5
Asthma	86,099	175	0.90	0.77 to 1.1
Allergic alveolitis	633	5	4.2*	1.8 to 10.1
Dermatitis	92,651	367	1.6*	1.5 to 1.8
Erythema	29,202	189	2.7*	2.3 to 3.2
Rhinitis	16,800	29	0.81	0.56 to 1.2
Urticaria	10,895	33	1.2	0.85 to 1.7

NOTE. All analyses were adjusted for age, calendar time, race, latency, and number of hospital visits.
Abbreviations: NHL, non-Hodgkin's lymphoma; RR, rate ratio.
*Significant result.

carcinogenesis.[26-31] Previous studies have largely included white participants, preventing stratification by race.[21] With more than 800,000 black patients, our study demonstrates that autoimmune conditions are associated with increased risk of NHL in both blacks and whites.

Results from previous studies of allergies and NHL are inconsistent. Many previous studies have found an inverse association with NHL,[2,32] but prospective cohort studies tend to suggest that allergies are associated with an increased risk of NHL.[33] Part of this inconsistency may be a result of the reliance on self-report of allergies,[2] which is less objective than assessment based on discharge diagnoses. In addition, because NHL may reduce immunoglobulin reactivity, an apparent inverse association between allergies and NHL may be a result of reverse causality (ie, patients with undetected NHL may have an impaired immune response and thus reduced allergic responses).[9,34] To our knowledge, only one previous study has evaluated allergies and risk of NHL by race and found some variation by race/ethnicity.[35]

Previous studies have fairly consistently reported an increased risk of NHL for a number of individual infectious agents, such as HIV, Epstein-Barr virus, human herpesvirus 8, and human T-cell lymphotropic virus.[2] Similarly, we found that patients with infection-related conditions had an increased risk of NHL, most notably for systemic, genital, or arthropod-borne diseases. Although one recent study found no associations between genital infectious or sexual behavior and NHL,[36] it had few exposed patients and controls and thus limited power.

Few studies have examined the association between infections and NHL by race. One case-only study found that Chinese patients with NHL were three times more likely to have Epstein-Barr virus–associated B-cell lymphoma than Malay patients with NHL.[37] In a black South African population, HIV was associated with a six-fold increased risk of NHL, which is an order of magnitude lower than that observed in developed countries[38] and implicates a racial disparity. In our study, the RR of NHL associated with HIV in blacks was approximately half as high as the RR in whites. Such racial differences in the incidence of HIV-associated NHL might be a result of racial/ethnic variation in stromal cell–derived factor 1-3′A chemokine allele frequency.[39]

The patterns of NHL and immune response in different ethnic groups also implicate genetic dissimilarities. For instance, the risk of

was the risk associated with HIV, which was two-fold higher in whites. Allergies also tended to be more strongly associated with risk of NHL in blacks than in whites, whereas the risks associated with autoimmune conditions were generally similar by race.

Similar to previous studies,[2,21] we found an increased risk of NHL in patients with autoimmune conditions such as rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, autoimmune hemolytic anemia, and celiac disease. We found that patients with multiple sclerosis had a reduced risk of NHL, in accord with previous studies,[22,23] although the literature is mixed.[21,24,25] Patients with multiple sclerosis have an innate immune profile skewed toward T helper 1–type immune activation, which may inhibit

Table 5. Risk of NHL for Selected Conditions by Years of Follow-Up (latency), Year of First Visit, and Age at First Visit in US Male Veterans

| | Follow-Up (Latency) | | | | | Year of First Visit | | | | | Age at First Visit | | | | |
| | 2-4 Years | | ≥ 5 Years | | | < 1980 | | ≥ 1980 | | | < 50 Years | | ≥ 50 Years | | |
Condition	RR	95% CI	RR	95% CI	LRT P	RR	95% CI	RR	95% CI	LRT P	RR	95% CI	RR	95% CI	LRT P
Total infectious diseases	1.4	1.3 to 1.5	1.1	1.0 to 1.1	< .001*	1.1	1.1 to 1.2	1.2	1.1 to 1.3	.2	1.5	1.4 to 1.6	1.0	0.98 to 1.1	< .001*
Upper airway	1.3	1.1 to 1.5	1.1	0.95 to 1.2	.1	1.1	0.99 to 1.2	1.1	0.93 to 1.3	> .5	1.1	0.98 to 1.3	1.1	0.96 to 1.2	> .5
Lower airway	1.4	1.2 to 1.6	1.1	1.0 to 1.2	.003*	1.1	1.0 to 1.2	1.3	1.2 to 1.5	.02*	1.6	1.4 to 1.8	1.0	0.91 to 1.1	< .001*
Gastrohepatic	1.7	1.4 to 2.1	1.3	1.1 to 1.5	.3	1.3	1.1 to 1.5	1.6	1.4 to 2.0	.03*	1.9	1.7 to 2.2	1.0	0.88 to 1.2	< .001*
Genital	1.8	1.4 to 2.4	1.5	1.3 to 1.8	.07	1.4	1.2 to 1.7	2.1	1.7 to 2.7	.004*	2.2	1.8 to 2.6	1.1	0.87 to 1.4	< .001*
Reproductive	0.9	0.58 to 1.3	1.2	1.1 to 1.5	.04*	1.3	1.1 to 1.5	1.0	0.72 to 1.3	.07	1.3	1.0 to 1.7	1.1	0.91 to 1.3	.2
Urinary	1.8	1.2 to 2.8	1.0	0.76 to 1.3	.04*	1.2	0.88 to 1.5	1.2	0.69 to 1.9	> .5	0.9	0.6 to 1.4	1.3	0.99 to 1.8	.2
Cardiovascular	1.1	0.88 to 1.5	1.0	0.76 to 1.3	.3	0.9	0.76 to 1.2	1.1	0.90 to 1.3	.4	1.1	0.8 to 1.4	1.0	0.85 to 1.2	> .5
Systemic	5.6	4.8 to 6.5	2.1	1.9 to 2.4	< .001*	1.7	1.5 to 2.1	4.3	3.8 to 4.9	< .001*	6.5	5.7 to 7.4	1.3	1.1 to 1.5	< .001*
Arthropod-borne diseases	1.8	0.98 to 3.2	1.4	1.0 to 1.9	.5	1.2	0.84 to 1.8	2.0	1.3 to 3.1	.08	1.5	1.0 to 2.1	1.4	0.93 to 2.3	> .5
Total autoimmune diseases	1.5	1.3 to 1.7	1.4	1.3 to 1.5	.4	1.5	1.4 to 1.6	1.2	1.1 to 1.4	.01*	1.4	1.2 to 1.5	1.4	1.3 to 1.5	> .5
Autoantibodies detectable	1.5	1.3 to 1.8	1.4	1.3 to 1.6	> .5	1.5	1.4 to 1.7	1.3	1.1 to 1.5	.08	1.5	1.3 to 1.8	1.5	1.3 to 1.6	> .5
Systemic involvement	1.8	1.4 to 2.3	2.0	1.7 to 2.3	.1	2.1	1.8 to 2.4	1.7	1.4 to 2.1	.1	2.1	1.7 to 2.7	2.0	1.7 to 2.2	.3
Organ involvement	1.5	1.2 to 1.8	1.1	0.99 to 1.3	.3	1.3	1.1 to 1.4	1.1	0.93 to 1.4	> .5	1.4	1.2 to 1.7	1.2	1.0 to 1.3	.03*
Autoantibodies not detectable	1.3	1.0 to 1.6	1.2	1.1 to 1.4	> .5	1.3	1.2 to 1.5	1.1	0.88 to 1.3	.2	1.2	0.99 to 1.5	1.2	1.1 to 1.4	> .5
Total allergies	1.7	1.5 to 2.0	1.3	1.2 to 1.4	.02*	1.5	1.3 to 1.6	1.4	1.2 to 1.6	> .5	1.4	1.2 to 1.6	1.5	1.3 to 1.6	.4

Abbreviations: NHL, non-Hodgkin's lymphoma; RR, rate ratio; LRT, likelihood ratio test.
*Significant result.

NHL varies by ethnicity among second-generation immigrants to Sweden, and γ-globulin levels remain high in indigenous people who have migrated from tropical to temperate regions even several centuries after their migration.[40-42] In addition, some evidence suggests that immune response to infections, such as Epstein-Barr virus, is depressed in African children compared with Chinese, Indian, and white children.[43]

A recent pooled analysis from the International Lymphoma Epidemiology Consortium found evidence for ethnic variability in the risk of NHL associated with polymorphisms in two immune system–related genes, tumor necrosis factor (TNF) and interleukin-10 (IL10).[12] For example, the TNF-308A allele increased the risk of diffuse large B-cell lymphoma by 2.7-fold (95% CI, 1.3- to 5.6-fold) in blacks but only 1.3-fold (95% CI, 1.2- to 1.4-fold) in whites. Similarly, the IL10-1082G allele was associated with a 1.7-fold (95% CI, 1.1- to 2.6-fold) increased risk of NHL in Hispanic whites but no increased risk (odds ratio, 1.1; 95% CI, 0.98 to 1.2) in non-Hispanic whites. Thus, the differential distribution of immune gene polymorphisms by race might explain why infections, and possibly allergies, are more strongly associated with NHL in blacks than whites. At this time, we have no clear explanation for the observed similar associations for blacks and whites regarding autoimmune diseases and subsequent NHL risk.

Given that the development of NHL can alter immunity in and of itself,[8] the potential for reverse causality (ie, that the observed associations are a result of developing disease, rather than a cause of the disease) is of concern. However, our cohort design allowed us to evaluate associations with NHL over time. The stability of RRs for autoimmune diseases across latency categories suggests that they are not explained by reverse causality. Although associations with infection-related conditions were generally stronger when they occurred closer to the diagnosis of NHL, many of the site-specific categories remained elevated with a latency of ≥ 5 years, suggesting that the observed associations are not entirely a result of undetected NHL.

In addition, nearly all the increased risk of NHL occurred in patients younger than 50 years old, which is consistent with infection-related lymphomagenesis because infection-related cancer tends to occur at younger ages.[44,45] Alternatively, this pattern could reflect minor immunologic defects, as suggested by the observation that children hospitalized for infection in the first year of life are at increased risk of developing NHL later in life.[46] Allergies also were associated more strongly with NHL when diagnosed within 2 to 4 years of disease. Because the development of NHL is inversely associated with immunoglobulin reactivity,[9,34] reverse causality would be expected to produce an inverse association. Instead, we observed a positive association, similar to other prospective studies.[33,35]

NHL was more strongly associated with several categories of infection-related conditions at or after 1980, possibly as a result of the discovery, and therefore increased diagnosis, of cancer-related infections. For example, the relation between human papillomavirus (HPV) and cervical cancer was not clearly elucidated until the development of sensitive polymerase chain reaction assays in the late 1980s to early 1990s.[47] This improved understanding of cervical carcinogenesis may also have led to increased reporting of the HPV-associated condition condyloma acuminatum, even though genital warts are caused by noncarcinogenic HPV. Similarly, the discovery of hepatitis C virus in 1989 and HIV in 1983 might have influenced associations with gastrohepatic and systemic infections over time.

Our study included only hospitalized male US veterans, limiting generalizability. Also, less severe immune-related conditions, typically diagnosed in outpatient settings, may be under-represented. Clinical data, laboratory data, and medical records were not available to verify diagnoses. However, we expect any potential exposure misclassification to be nondifferential because immune-related conditions were identified similarly for patient cases and non–patient cases. Another limitation is the large number of tested immune-related conditions, which implies that one has to interpret detected associations with caution as a result of multiple comparisons. Some diagnoses may have

been missed because veterans may choose either VA or civilian health care, although this potential bias may be limited because many patients who choose VA care lack other health insurance.[48] In addition, we do not have data on potential confounders such as organ transplantation; chemotherapy/radiation; chemical exposure to benzene, solvents, herbicides, or pesticides; family history; or socioeconomic status. Within this study population, the potential for confounding by socioeconomic status may be limited because patients within the VA system typically have low socioeconomic status,[48] and previous VA studies found similar health care utilization and outcomes for blacks and whites.[49,50]

This study has several strengths. First, the large sample size of more than 4 million veterans permitted us to evaluate risk of NHL separately in blacks and whites for infectious, autoimmune, and allergic conditions. These patients had access to standardized medical care without regard to socioeconomic status. The follow-up time was extensive. In addition, immune-related conditions were identified before the development of NHL using discharge diagnoses, thus eliminating recall bias.

In summary, we found that risk of NHL is associated with infectious, autoimmune, and allergic conditions. The increased risk of NHL associated with infection-related conditions, and possibly allergies, seemed to be stronger in blacks than in whites, whereas the risk related to autoimmune conditions was similar for both. These patterns could reflect underlying race-related genetic differences in immune response. Additional studies are needed to explore the pathologic mechanisms underlying these associations.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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