Common infection-related conditions and risk of lymphoid malignancies in older individuals

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Background: Chronic antigenic stimulation may initiate non-Hodgkin (NHL) and Hodgkin lymphoma (HL) development. Antecedent, infection-related conditions have been associated, but evidence by lymphoproliferative subtype is limited.

Methods: From the US SEER-Medicare database, 44 191 NHL, 1832 HL and 200 000 population-based controls, frequency-matched to all SEER cancer cases, were selected. Logistic regression models, adjusted for potential confounders, compared infection-related conditions in controls with HL and NHL patients and by the NHL subtypes diffuse large B-cell, T-cell, follicular and marginal zone lymphoma (MZL). Stratification by race was undertaken.

Results: Respiratory tract infections were broadly associated with NHL, particularly MZL. Skin infections were associated with a 15–28% increased risk of NHL and with most NHL subtypes, particularly cellulitis with T-cell lymphoma (OR 1.36, 95%CI 1.24–1.49). Only herpes zoster remained associated with HL following Bonferroni correction (OR 1.55, 95% CI 1.28–1.87). Gastrointestinal and urinary tract infections were not strongly associated with NHL or HL. In stratified analyses by race, sinusitis, pharyngitis, bronchitis and cellulitis showed stronger associations with total NHL in blacks than whites ($P < 0.001$).

Conclusions: Infections may contribute to the aetiologic pathway and/or be markers of underlying immune modulation. Precise elucidation of these mechanisms may provide important clues for understanding how immune disturbance contributes to lymphoma.

Chronic infections, including Epstein–Barr virus, human herpesvirus 8, human T lymphotropic virus type I, *Plasmodium falciparum*, hepatitis B virus, hepatitis C virus (HCV), *Helicobacter pylori*, *Campylobacter jejuni*, *Chlamydia psittaci*, *Borrelia burgdorferi* and human immunodeficiency virus, have been linked to the pathogenesis of non-Hodgkin lymphoma (NHL) (Hjalgrim and Engels, 2008), a heterogeneous group of disease entities characterised by the malignant transformation of B or T lymphocytes. Hodgkin lymphoma (HL), characterised by the presence of Reed–Sternberg cells, has been associated with Epstein–Barr virus, good hygiene and delayed exposure to infection (Serraino et al, 1991; Tavani et al, 2000).

Our immunological defence against pathogens utilises both the innate and adaptive immune systems. These systems working in synergy enable the host to clear infections. Genetic variation of genes involved in the innate immune response, including tumour necrosis factor receptor-associated factor, receptor-interacting serine-threonine kinase 3, BAT2, Toll-like receptor 6 (Cerhan et al, 2007) and Beta-Defensin 126 (Hu et al, 2013), have been associated with an increased risk of NHL and have a role in infection recognition and control. Chronic antigenic stimulation has been postulated as a potential mechanism for lymphomagenesis (Hjalgrim and Engels, 2008), with acute, community-acquired infections potentially playing a role (Cartwright et al, 1988;

La Vecchia *et al*, 1992; Tavani *et al*, 2000; Engels *et al*, 2004; Chang *et al*, 2005; Koshiol *et al*, 2011; Becker *et al*, 2012; Karunanayake *et al*, 2012; Liu *et al*, 2012).

Although one study of male US veterans reported associations with infections to be more profound in individuals aged ⩽ 50 years and those of black race (Koshiol *et al*, 2011); these results have not been replicated in other study populations. In addition, few studies have investigated infection-related conditions by NHL subtype (Anderson *et al*, 2009; Kristinsson *et al*, 2010). Using data from the Surveillance Epidemiology and End Results (SEER)-Medicare database, we previously reported an increased risk of chronic lymphocytic lymphoma (CLL), an NHL subtype, in patients with claims for respiratory and skin infections (Anderson *et al*, 2009). Similar associations have also been reported for lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia using the US Veterans Affairs database (Kristinsson *et al*, 2010). Given the heterogeneous nature of NHLs and their disparate clinical and prognostic characteristics, the objective of the study was to investigate the role of infection-related conditions by additional NHL subtypes and HL in SEER-Medicare.

MATERIALS AND METHODS

Study design. The SEER-Medicare database links SEER and Medicare data (Anderson *et al*, 2008). Since 1973, the SEER program has collected demographic and clinical information on cancers diagnosed in multiple US sites and currently covers approximately 28% of the US population (SEER*Stat Databases (submitted November 2011)). Medicare provides federally funded health insurance for US citizens aged ⩾ 65 years, entitling them to Part A coverage for hospital inpatient care (Warren *et al*, 2002). Approximately 95% of beneficiaries subscribe to Part B coverage, including physician and outpatient services (Warren *et al*, 2002). Individuals may also subscribe to a health maintenance organisation (HMO) scheme providing capitated care; associated claims are not captured by Medicare (Engels *et al*, 2011).

We conducted a retrospective case–control study using SEER-Medicare data. Cases were defined as individuals with a SEER diagnosis of a primary lymphoid malignancy between 1992 and 2005. In addition to overall NHL, we evaluated the main NHL subtypes, including diffuse large B-cell lymphoma (DLBCL), T-cell lymphoma, follicular lymphoma (FL) and marginal zone lymphoma (MZL). Other rarer subtypes and CLL/SLL, which has been previously reported (Anderson *et al*, 2009), were not reported seperately. HL cases were investigated although data on extranodal HL are not presented owing to the small number of cases ($N = 83$). Cancer case definition was based on the InterLymph hierarchical classification of lymphoid neoplasms (Turner *et al*, 2010). Cases were required to be aged 66–99 years at diagnosis of malignancy and to have at least 13 months of Part A and Part B and no HMO Medicare coverage before diagnosis to ensure sufficient time to accrue exposure status. Patients diagnosed with malignancy only at autopsy or by death certificate were excluded. Controls ($N = 200\,000$) were previously selected from the 5% random sample of all Medicare beneficiaries without cancer residing in SEER areas (Engels *et al*, 2011) and were frequency matched to a larger group of all cancer types in the SEER data set by gender, age (66–69, 70–74, 75–79, 80–84, 85–99 years) and year of selection.

To ascertain exposure to common infection-related conditions, Medicare hospital, physician and outpatient files were searched for claims made by the attending physicians for infections of the respiratory tract (including acute nasopharyngitis (common cold), bronchitis, pharyngitis, laryngitis, sinusitis, pneumonia), skin (cellulitis, herpes zoster), gastrointestinal tract (gingivitis/periodonitis,

gastroenteritis) and urinary tract (acute pyelonephritis, cystitis, prostatitis). Infection-related conditions were selected if the prevalence in controls was > 0.5%. Cases and controls with at least one claim for an infection were considered exposed. Claims occurring during the 13-month period before case diagnosis/control selection were excluded to minimise the possibility that diagnoses were attributable to the disease process.

Statistical analysis. Polytomous logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to assess the association of each infectious disease and subsequent risk of lymphoid malignancy subtypes compared with controls. In the variance computation for the ORs, the fact that each case subtype was compared with the same control population, that some controls later served as cases and that individuals could be selected more than once as controls were accommodated (Anderson *et al*, 2008).

The combined NHL analyses were stratified by white and black race. The Wald *P*-value for the interaction term between race and an infection was used to evaluate homogeneity between associations in whites and blacks. Stratified results for NHL subtypes, HL and/or other racial groups are not presented given the small sample sizes.

All analyses were adjusted for gender, age and year of diagnosis/selection. No missing data were observed. As 112 main analyses were conducted to investigate the associations between each infectious disease and each lymphoid malignancy subtype, we used Bonferroni correction ($P < 0.00045$) to highlight associations (underlined) that remained significant after controlling for multiple comparisons.

To assess the time point at which infections may be important in the development of lymphoid malignancies, we investigated infections diagnosed at different time intervals preceding diagnosis (i.e., ⩽ 30 months, 31–48 months, 49–72 months, > 72 months) for those that remained significant following Bonferroni correction. Analyses were conducted with and without patients with human immunodeficiency virus ($n = 39$); as similar point estimates were observed (data not shown), results are presented for the full cohort of patients.

RESULTS

There were small differences in the distribution of characteristics between the case and control groups due to non-restricted matching (Table 1). Compared with controls, NHL cases overall were less likely to be male and more likely to be older, of white race, selected in more recent calendar years and to have longer Medicare coverage. Conversely, HL cases appeared younger and had shorter Medicare coverage than controls.

As shown in Table 2, NHL patients were 10–17% more likely than controls to have had claims for respiratory tract infections, except common cold, > 13 months before diagnosis (ORs 1.10–1.17). Skin infection claims, including those for cellulitis (OR 1.15, 95% CI 1.12–1.18) and herpes zoster (OR 1.28, 95% CI 1.22–1.35), and claims for prostatitis (OR 1.12, 95% CI 1.07–1.17) were also more common in NHL cases overall than controls. MZL was most strongly associated with respiratory tract infections, including sinusitis, bronchitis, influenza and pneumonia, Table 2. Following adjustment for multiple comparisons, DLBCL, the most common NHL subtype, remained associated with sinusitis, bronchitis, influenza, cellulitis and herpes zoster, Table 2. FL was associated with claims for sinusitis, laryngitis and herpes zoster while T-cell lymphoma remained associated with pharyngitis and cellulitis only, Table 2. Herpes zoster was the only infection to remain significantly associated with HL following multiple comparison adjustment (OR 1.55; Table 2).

		Non-Hodgkin lymphoma					Hodgkin lymphoma (n = 1832)
Table 1. characteristics of controls and patients with non-Hodgkin lymphoma (overall and by subtype) and Hodgkin lymphoma							
	Controls (n = 200 000)	Overall (n = 44 191)	Diffuse large B-cell lymphoma (n = 15 883)	T-cell non-Hodgkin lymphoma (n = 2813)	Follicular lymphoma (n = 4491)	Marginal zone lymphoma (n = 3223)	Hodgkin lymphoma (n = 1832)
Gender							
Male	106 172 (53.0%)	20 475 (46.3%)	7184 (45.2%)	1544 (54.9%)	3122 (43.0%)	1334 (41.4%)	874 (47.7%)
Female	93 828 (47.0%)	23 716 (53.7%)	8699 (54.8%)	1269 (45.1%)	4142 (57.0%)	1889 (58.6%)	958 (52.3%)
Age (years)							
66–69	33 780 (16.9%)	6542 (14.8)	2110 (13.3%)	442 (15.7%)	1390 (19.1%)	489 (15.2%)	337 (18.4%)
70–74	52 008 (26.0%)	10 594 (24.0%)	3679 (23.2%)	770 (27.4%)	1941 (26.7%)	776 (24.1%)	486 (26.5%)
75–79	50 440 (25.2%)	11 233 (25.4%)	4099 (25.8%)	724 (25.7%)	1819 (25.0%)	788 (24.5%)	469 (25.6%)
80–84	36 097 (18.0%)	8855 (20.4%)	3297 (20.8%)	512 (18.2%)	1309 (18.0%)	676 (21.0%)	318 (17.4%)
85–99	27 675 (13.8%)	6967 (15.8%)	2698 (17.0%)	365 (13.0%)	805 (11.1%)	494 (15.3%)	222 (12.1%)
Race							
White	166 827 (83.3%)	39 300 (88.9%)	14 042 (88.4%)	2345 (83.4%)	6681 (92.0%)	2800 (86.9%)	1632 (89%)
Black	13 949 (7.0%)	1823 (4.1%)	536 (3.4%)	207 (7.4%)	221 (3.0%)	172 (5.3%)	76 (4.2%)
Asian	8097 (4.0%)	1146 (2.6%)	457 (2.9%)	117 (4.2%)	120 (1.7%)	108 (3.4%)	28 (1.5%)
Hispanic	5199 (2.6%)	774 (1.8%)	349 (2.2%)	46 (1.6%)	102 (1.4%)	65 (2.0%)	50 (2.7%)
Other/unknown	5927 (3.0%)	1148 (2.6%)	499 (3.1%)	98 (3.5%)	140 (1.9%)	78 (2.4%)	46 (2.5%)
Year of selection							
1992–1994	31 364 (15.7%)	5930 (13.4%)	2063 (13.0%)	323 (11.5%)	962 (13.2%)	37 (1.15%)	275 (15%)
1995–1998	39 843 (19.9%)	8665 (19.6%)	3044 (19.2%)	589 (20.9%)	1351 (18.6%)	519 (16.1%)	330 (18%)
1999–2005	128 793 (64.4%)	29 596 (67.0%)	10 776 (67.9%)	1901 (67.6%)	4951 (68.2%)	2667 (82.8%)	1227 (67%)
Duration of Medicare coverage (months)							
13–60	57 440 (28.7%)	11 330 (25.6%)	3815 (24.0%)	775 (27.6%)	2159 (29.7%)	893 (27.7%)	555 (30.3%)
61–120	97 485 (48.7%)	21 798 (49.3%)	7951 (50.1%)	1376 (48.9%)	3503 (48.2%)	1514 (47.0%)	911 (49.7%)
121–180	35 805 (17.9%)	8699 (19.7%)	3212 (20.2%)	534 (19.0%)	1276 (17.6%)	612 (19.0%)	296 (16.2%)
181–240	9270 (4.6%)	2364 (5.4%)	905 (5.7%)	128 (4.6%)	326 (4.5%)	204 (6.3%)	70 (3.8%)
Percentages may not total to 100% due to rounding.							

In stratified analyses by race, associations among whites were similar to those all subjects combined for most infection-related conditions, due to the majority of the cohort being of white race (Tables 2 and 3). For blacks, the only infection-related conditions to reach statistical significance following Bonferroni correction were sinusitis, pharyngitis and cellulitis. However, several infections, including sinusitis, pharyngitis, bronchitis and cellulitis, were more commonly associated with NHL in blacks than in whites, $P < 0.001$.

Most infections highly significant in Table 2 remained associated with NHL even when the 6-year period preceding diagnosis was excluded (Table 4). Sinusitis, bronchitis, cellulitis and herpes zoster remained associated with DLBCL while cellulitis was associated with T-cell NHL across all time periods investigated (Table 4). For FL, sinusitis, laryngitis and herpes zoster were significant at longer latencies. Sinusitis was associated with MZL across all time periods investigated (Table 4). Claims for herpes zoster > 30 months before diagnosis were associated with HL (Table 4).

DISCUSSION

In the largest population-based study to date, we identified respiratory and skin infections to be associated with an increased risk of NHL in individuals aged $\geqslant 66$ years, paralleling our previous findings for CLL (Anderson et al, 2009). MZLs were associated with the broadest range of infection-related conditions and T-cell lymphomas the fewest. Interestingly, only herpes zoster infection was associated with HL, an association which remained even when initial claims were made > 6 years before cancer diagnosis.

Consistent with the observed association between respiratory infections and NHL, Koshiol et al (2011) reported an increased risk of NHL among male US Veterans with upper and lower airway infections, including sinusitis and pneumonia, but did not report by NHL subtype. They identified stronger associations close to NHL diagnosis and postulated that this may have been due to reverse causality due to an underlying, undetected NHL (Koshiol et al, 2011; Richardson et al, 2011). In the current investigation, most associations occurring close to diagnosis were for MZL, an indolent, slow growing lymphoma, potentially supporting this hypothesis. Koshiol et al (2011) also suggested that undetected lymphoma would not fully explain why several infection-related conditions, including lower airway infections, occurred more frequently in cases > 5 years before diagnosis. This observation was also apparent in the current study and was particularly evident for DLBCL and FL. Most FL cases have t(14;18)-positive B cells, which are thought to be transformed by exogenous antigen stimulation, such as from a viral infection (Roulland et al, 2006). Antigenic

Table 2. Associations between common infection-related conditions and non-Hodgkin lymphoma (combined and by main subtypes) and Hodgkin lymphoma

	Controls	Overall NHL (n = 44 191)		Diffuse large B- cell lymphoma (n = 15 883)		T-cell NHL (n = 2813)		Follicular lymphoma (n = 4491)		Marginal zone lymphoma (n = 3223)		Hodgkin lymphoma (n = 1832)	
Infection-related conditions by site	No.	No.	OR (95% CI)[a]	No.	OR (95% CI)[a]	No.	OR (95% CI)[a]	No.	OR (95% CI)[a]	No.	OR (95% CI)[a]	No.	OR (95% CI)[a]
Respiratory tract													
Common cold	7322	1801	1.06 (1.00–1.12)	624	1.00 (0.92–1.09)	119	1.12 (0.93–1.35)	279	1.02 (0.91–1.16)	171	1.24 (1.06–1.45)	66	0.97 (0.76–1.25)
Sinusitis	36 249	9464	1.17 (1.13–1.20)	3389	1.14 (1.09–1.19)	544	1.04 (0.94–1.14)	1560	1.16 (1.10–1.24)	853	1.32 (1.21–1.43)	380	1.15 (1.02–1.29)
Laryngitis	6584	1810	1.17 (1.11–1.24)	652	1.15 (1.06–1.25)	119	1.26 (1.04–1.51)	310	1.25 (1.11–1.41)	157	1.23 (1.05–1.45)	75	1.23 (0.97–1.55)
Pharyngitis	22 472	5695	1.11 (1.07–1.15)	1959	1.03 (0.98–1.09)	396	1.25 (1.12–1.39)	915	1.09 (1.01–1.17)	476	1.14 (1.03–1.26)	240	1.17 (1.02–1.34)
Bronchitis	45 215	11 458	1.13 (1.10–1.16)	4123	1.11 (1.06–1.15)	704	1.10 (1.01–1.21)	1779	1.08 (1.02–1.15)	939	1.15 (1.07–1.25)	446	1.09 (0.98–1.22)
Influenza	14 726	3892	1.15 (1.11–1.19)	1389	1.11 (1.05–1.18)	255	1.21 (1.06–1.38)	628	1.16 (1.06–1.26)	370	1.33 (1.19–1.49)	157	1.17 (0.99–1.38)
Pneumonia	30 201	7556	1.10 (1.07–1.14)	2679	1.05 (1.01–1.10)	448	1.04 (0.94–1.16)	1093	1.03 (0.96–1.10)	633	1.22 (1.11–1.34)	280	1.05 (0.92–1.19)
Skin													
Cellulitis	34 426	8939	1.15 (1.12–1.18)	3176	1.09 (1.05–1.14)	627	1.36 (1.24–1.49)	1352	1.10 (1.04–1.18)	751	1.23 (1.13–1.34)	345	1.13 (1.00–1.28)
Herpes zoster	8557	2553	1.28 (1.22–1.35)	889	1.20 (1.12–1.30)	153	1.25 (1.06–1.48)	386	1.24 (1.11–1.38)	200	1.22 (1.06–1.42)	118	1.55 (1.28–1.87)
Gastrointestinal tract													
Gingivitis	917	209	0.98 (0.84–1.14)	89	1.14 (0.92–1.43)	<11	0.67 (0.35–1.30)	24	0.70 (0.46–1.05)	89	1.14 (0.92–1.43)	<11	0.94 (0.47–1.89)
Gastroenteritis	5312	1299	1.03 (0.96–1.10)	488	1.04 (0.95–1.15)	79	1.03 (0.82–1.30)	175	0.88 (0.75–1.02)	107	1.04 (0.85–1.26)	62	1.27 (0.99–1.65)
Urinary tract													
Cystitis[b]	35 283	13 876	1.04 (1.02–1.07)	3410	1.01 (0.96–1.06)	494	1.05 (0.93–1.18)	1536	1.02 (0.96–1.09)	794	1.05 (0.96–1.16)	565	1.11 (1.00–1.23)
Prostatitis[c]	16 203	3620	1.12 (1.07–1.17)	1194	1.02 (0.96–1.09)	256	1.05 (0.91–1.20)	555	1.19 (1.08–1.31)	246	1.05 (0.91–1.21)	128	0.96 (0.79–1.16)
Pyelonephritis[b]	2184	799	0.95 (0.88–1.03)	214	1.01 (0.88–1.17)	34	1.14 (0.81–1.61)	74	0.79 (0.62–0.99)	37	0.77 (0.55–1.07)	20	0.91 (0.58–1.42)

Abbreviations: CI = confidence interval; NHL = non-Hodgkin lymphoma; OR = odds ratio. Associations significant following Bonferroni correct (P<0.00045) are underlined. Observations, in which the number of exposed patients is between 1 and 10, are listed as '<11' to preserve subjects' anonymity, in accordance with the SEER-Medicare data use agreement.
[a] ORs and 95% CIs were adjusted for age (66–69, 70–74, 75–79, 80–84 and 85–99 years), gender and diagnosis/selection year.
[b] Females only.
[c] Males only.

stimulation and/or subclinical immune deficiency, predisposing patients to both infections and lymphoma, may therefore explain the associations identified between infection-related conditions and lymphoma.

Interestingly, in the US Veterans study, associations between infections and NHL were most noticeable in those aged < 50 years (Koshiol *et al*, 2011). Unfortunately, we were unable to assess these associations in a similar age group but have demonstrated, in a non-selected, population-based study, that similar associations are observed in individuals aged ⩾ 66 years. In stratified analyses, we substantiated the observation that associations with infection-related conditions, particularly sinusitis, pharyngitis, bronchitis and cellulitis, were significantly stronger in black than in white individuals (Koshiol *et al*, 2011). Further analysis by NHL subtypes was hindered by small numbers. Differences in immune-associated polymorphisms by race have been reported (Skibola *et al*, 2010) and could explain the differential effects observed.

Herpes zoster, commonly known as shingles, has previously been reported to precede HL (Tavani *et al*, 2000) and other haematological malignancies (Gramenzi *et al*, 1991; Landgren *et al*, 2007; Brown *et al*, 2008; Anderson *et al*, 2009; Kristinsson *et al*, 2010; Liu *et al*, 2012). Shingles is a skin rash caused by reactivation of the varicella-zoster virus, which commonly occurs in immuno-suppressed individuals (Kennedy, 2002; Grulich *et al*, 2007).

Herpes zoster infection remained significantly associated with HL even when claims were made > 6 years previously. Because of limited sample size, we were unable to investigate infection claims in a longer time frame preceding lymphoma diagnosis, but it has been suggested that lymphoma risk is restricted to the first 10 years since infection onset (Tavani *et al*, 2000). We observed similar associations between herpes zoster and DLBCL and FL, supporting previous reports in some (Karunanayake *et al*, 2012; Liu *et al*, 2012) but not all studies (Cartwright *et al*, 1988; Becker *et al*, 2012). Given the timing of these associations, it is possible that herpes zoster infection is a marker of an immunocompromised state many years before diagnosis or that it instigates a decline in cell-mediated immunity (Liu *et al*, 2012).

Cellulitis, a skin infection generally caused by staphylococcus or streptococcus bacteria, was associated with all NHL subtypes, particularly T-cell lymphoma. T-cell lymphomas are a heterogeneous group of lymphomas that can present with extensive skin and soft tissue necrosis, resembling an infectious process (Serra *et al*, 1998; Jia and Sun, 2004; Falagas *et al*, 2007). Misdiagnosis of T-cell lymphomas could explain the observed associations particularly as some cutaneous T-cell lymphomas are often difficult to diagnose in the early stages of disease (Serra *et al*, 1998; Falagas *et al*, 2007; Soo *et al*, 2011). However, the long latency period between infection and diagnosis suggests that misdiagnosis of T-cell lymphoma is unlikely

Table 3. Main associations for non-Hodgkin lymphoma (combined) stratified by race					
	Whites[a]		**Blacks**[a]		
Infection-related conditions by site	No.	OR (95% CI)	No.	OR (95% CI)	Wald *P*-value
Respiratory tract					
Common cold	1510	1.09 (1.03–1.16)	67	1.18 (0.90–1.55)	0.325
Sinusitis	8699	1.13 (1.10–1.17)	347	1.35 (1.18–1.55)	<0.001
Laryngitis	1630	1.18 (1.11–1.25)	50	1.28 (0.94–1.75)	0.178
Pharyngitis	5004	1.11 (1.08–1.15)	206	1.42 (1.21–1.68)	<0.001
Bronchitis	10190	1.13 (1.10–1.17)	385	1.22 (1.07–1.38)	<0.001
Influenza	3460	1.17 (1.13–1.22)	134	1.13 (0.93–1.37)	0.254
Pneumonia	6745	1.11 (1.07–1.14)	304	1.17 (1.02–1.35)	0.051
Skin					
Cellulitis	8077	1.13 (1.09–1.16)	359	1.27 (1.12–1.45)	<0.001
Herpes zoster	2346	1.26 (1.20–1.33)	55	1.32 (0.98–1.78)	0.128
Gastrointestinal tract					
Gingivitis	159	1.09 (0.91–1.31)	12	0.74 (0.41–1.35)	0.349
Gastroenteritis	1152	1.04 (0.97–1.12)	32	0.83 (0.57–1.21)	0.302
Urinary tract					
Cystitis[b]	12317	1.03 (1.00–1.06)	618	1.16 (1.03–1.29)	0.076
Prostatitis[c]	3244	1.10 (1.05–1.15)	133	1.18 (0.96–1.44)	0.054
Pyelonephritis[b]	703	0.96 (0.88–1.05)	37	0.98 (0.69–1.40)	0.821

Abbreviations: CI = confidence interval; OR = odds ratio. Associations significant following Bonferroni correct (*P* < 0.00045) are underlined.
[a]OR and 95% CIs were adjusted for age (66–69, 70–74, 75–79, 80–84 and 85–99 years), gender and diagnosis/selection year.
[b]Females only.
[c]Males only.

to fully explain the observed associations, and further investigation by T-cell subtype may provide further insight.

We did not observe any strong associations between pyelonephritis (or cystitis or prostatitis, which generally precede pyelonephritis) and NHL or associated NHL subtypes despite previous reports (La Vecchia *et al*, 1992; Tavani *et al*, 2000). However, these studies have been limited by the number of exposed cases and relied on self-reported diagnoses, potentially explaining the disparate findings (La Vecchia *et al*, 1992; Tavani *et al*, 2000). Similarly we did not find any associations between gastrointestinal infections and lymphoma.

Koshiol *et al* (2011) reported that viral (RR 1.6, 95% CI 1.5–1.8) and parasitic (RR 1.7, 95% CI 1.5–1.8) infections were more strongly associated with NHL than bacterial infections (RR 1.2, 95% CI 1.1–1.3). Although our study did not include these broad categorisations, the vast majority of conditions associated with NHL were of viral origin, including sinusitis, influenza, bronchitis and herpes zoster.

Although we were able, for the first time, to extensively study infection-related conditions by NHL subtype, the heterogeneous nature of NHLs may mean that some associations were masked by incorporating them into these broad categories. We have previously reported associations between infection-related conditions and CLL in the SEER-Medicare data set (Anderson *et al*, 2009), but despite being the largest study to date, we had limited sample sizes to investigate rare or more specific NHL subtypes. The population-based sampling of cases and controls means that these findings are more representative than those from hospital-based case–control studies (La Vecchia *et al*, 1992; Tavani *et al*, 2000) or specialised registers (Doody *et al*, 1992; Koshiol *et al*, 2011) but are limited to the elderly population and by lack of lifetime exposure information to chronic or repeated infection exposure.

Exposure status was not limited by recall bias inherent in case–control studies (Cartwright *et al*, 1988; La Vecchia *et al*, 1992; Tavani *et al*, 2000; Chang *et al*, 2005; Becker *et al*, 2012; Karunanayake *et al*, 2012; Liu *et al*, 2012), although the use of claims data, instead of diagnostically confirmed infections, means that misclassification of exposure status is possible. This misclassification would be unlikely to be differential in nature, especially for claims many years before lymphoma diagnosis; however, overdiagnosis of infections, such as cellulitis, is possible. As both inpatient and outpatient claims were incorporated into the study, we were able to investigate a broader range of common infection-related conditions than previous studies (Cartwright *et al*, 1988; Doody *et al*, 1992; La Vecchia *et al*, 1992; Tavani *et al*, 2000; Chang *et al*, 2005; Koshiol *et al*, 2011; Karunanayake *et al*, 2012; Liu *et al*, 2012). Despite this strength, infections requiring few physician visits, such as the common cold, are likely to be underestimated. As we observed no associations between these infections and lymphoma risk, it supports the contention that we did not have differential diagnosis between cases and controls due to early prediagnostic symptoms. As diagnosis of infections were based on the attending physician claiming compensation, it was not possible to examine characteristics of infections more closely (e.g., whether herpes zoster and varicella-zoster virus-positive patients had the characteristic rash or were only antibody positive). Additionally, we were not able to differentiate the cause of the infection-related conditions and unable to comment on the severity of the infections encountered. Our models were adjusted for limited confounding variables, and hence residual confounding effects by other factors, such as comorbidities, could not be captured. Comorbidities with immune disturbance, such as autoimmune conditions which have been linked with lymphoma (Brown *et al*, 2008), could increase the susceptibility to infection.

Table 4. Association between common infection-related conditions and risk of non-Hodgkin lymphoma/Hodgkin lymphoma by the time of claim before diagnosis

Infection-related conditions by site	13–30 months OR (95% CI)[a]	31–48 months OR (95% CI)[a]	49–72 months OR (95% CI)[a]	>72 months OR (95% CI)[a]
Non-Hodgkin lymphoma				
Sinusitis	1.11 (1.05–1.16)	1.30 (1.23–1.37)	1.18 (1.12–1.23)	1.12 (1.07–1.17)
Laryngitis	1.10 (0.99–1.22)	1.34 (1.20–1.49)	1.16 (1.05–1.29)	1.13 (1.01–1.26)
Pharyngitis	1.04 (0.97–1.10)	1.21 (1.13–1.29)	1.12 (1.06–1.19)	1.09 (1.03–1.16)
Bronchitis	1.05 (1.00–1.10)	1.25 (1.19–1.31)	1.15 (1.10–1.19)	1.12 (1.08–1.17)
Influenza	1.26 (1.20–1.32)	1.08 (0.98–1.20)	1.00 (0.92–1.10)	1.07 (0.99–1.17)
Pneumonia	1.05 1.00–1.10)	1.18 (1.12–1.25)	1.08 (1.02–1.14)	1.14 (1.08–1.20)
Cellulitis	1.11 (1.06–1.16)	1.14 (1.09–1.20)	1.17 (1.11–1.23)	1.18 (1.12–1.24)
Herpes zoster	1.29 (1.19–1.40)	1.36 (1.24–1.49)	1.24 (1.13–1.36)	1.24 (1.13–1.37)
Prostatitis	1.07 (1.00–1.16)	1.12 (1.03–1.21)	1.11 (1.03–1.20)	1.17 (1.09–1.25)
Diffuse large B-cell lymphoma				
Sinusitis	1.09 (1.01–1.18)	1.28 (1.19–1.39)	1.15 (1.07–1.23)	1.08 (1.00–1.15)
Bronchitis	1.04 (0.97–1.11)	1.15 (1.07–1.24)	1.11 (1.04–1.19)	1.13 (1.06–1.21)
Influenza	1.21 (1.11–1.31)	0.98 (0.84–1.14)	1.04 (0.91–1.18)	1.07 (0.94–1.21)
Cellulitis	1.05 (0.98–1.13)	1.08 (1.00–1.17)	1.13 (1.05–1.22)	1.12 (1.03–1.21)
Herpes zoster	1.13 (0.99–1.29)	1.26 (1.09–1.46)	1.28 (1.11–1.46)	1.16 (1.00–1.35)
T-cell NHL				
Pharyngitis	1.24 (1.01–1.52)	1.26 (1.00–1.57)	1.34 (1.10–1.62)	1.17 (0.96–1.43)
Cellulitis	1.33 (1.14–1.56)	1.42 (1.20–1.67)	1.41 (1.20–1.66)	1.29 (1.08–1.54)
Follicular lymphoma				
Sinusitis	1.10 (0.99–1.22)	1.35 (1.21–1.51)	1.10 (0.99–1.22)	1.16 (1.05–1.29)
Laryngitis	1.14 (0.90–1.43)	1.25 (0.97–1.60)	1.30 (1.04–1.63)	1.33 (1.06–1.67)
Herpes zoster	1.40 (1.18–1.68)	1.24 (1.00–1.53)	1.02 (0.81–1.28)	1.25 (1.00–1.55)
Marginal zone lymphoma				
Sinusitis	1.50 (1.30–1.72)	1.34 (1.14–1.57)	1.32 (1.15–1.51)	1.16 (1.01–1.33)
Bronchitis	1.13 (0.98–1.30)	1.23 (1.06–1.43)	1.21 (1.07–1.38)	1.07 (0.94–1.23)
Influenza	1.37 (1.18–1.60)	1.53 (1.17–2.01)	1.18 (0.91–1.52)	1.25 (0.99–1.59)
Pneumonia	1.25 (1.07–1.46)	1.32 (1.11–1.57)	1.05 (0.88–1.25)	1.27 (1.08–1.49)
Cellulitis	1.29 (1.12–1.50)	1.23 (1.05–1.44)	1.24 (1.07–1.44)	1.16 (0.99–1.35)
Hodgkin lymphoma				
Herpes zoster	1.36 (0.95–1.94)	1.48 (1.00–2.19)	1.93 (1.38–2.70)	1.49 (1.00–2.22)

Abbreviations: CI = confidence interval; NHL = non-Hodgkin lymphoma; OR = odds ratio.
[a]ORs and 95% CIs were adjusted for age (66–69, 70–74, 75–79, 80–84 and 85–99 years), gender and diagnosis/selection year.

Similarly, we did not have data on characteristics and behaviours like smoking, drinking and obesity and therefore could not adjust for these factors. Finally, as we investigated numerous associations between infection-related conditions and lymphomas, some of the associations may have occurred by chance. We therefore focussed our discussion on those associations that remained after crude adjustment for multiple comparisons.

It is possible that an infection or other antigen could lead to different clinical manifestations depending on the hosts immune systems. For example, EBV is an extremely common infection that does not lead to cancer in most people. In a small subset, EBV may contribute to DLBCL (Kinch *et al*, 2013; Ozsan *et al*, 2013), whereas in most people it does not. Similarly, not all DLBCL cases are EBV-positive, reflecting heterogeneity in the aetiology even of the same NHL subtype. Immune differences resulting in different clinical outcomes could, for example, be driven by differences in HLA polymorphisms, which can affect antigen presentation.

In conclusion, several common infection-related conditions were associated with NHLs but not with HL, where only herpes zoster was more common in cases than in controls after adjustment for multiple comparisons. Herpes zoster showed the strongest associations for both NHL and HL. Most respiratory tract infections were associated with NHL, particularly MZL. Several infection-related conditions were more strongly associated with NHL in blacks than in whites. Precise elucidation of the mechanisms underlying lympho-proliferations may provide important clues for understanding how immune disturbance contributes to the development of both NHL and HL.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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