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 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 diagnoses 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.

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 prostatis (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).
commonly associated with NHL in blacks than in whites, including sinusitis, pharyngitis, bronchitis and cellulitis, were more sinusitis, pharyngitis and cellulitis. However, several infections, reach statistical significance following Bonferroni correction were (Tables 2 and 3). For blacks, the only infection-related conditions to conditions, due to the majority of the cohort being of white race similar to those all subjects combined for most 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 NHL diagnosis and postulated that this may have been due to infections, including sinusitis and pneumonia, but did not report 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). For FL, sinusitis, laryngitis and herpes zoster were significant at later latencies. Sinusitis was associated with MZL across all time periods investigated (Table 4). For FL, sinusitis, laryngitis and herpes zoster were associated with DLBCL while cellulitis 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
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 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., 2007; Jia and Sun, 2004; Falagas et al., 2007).

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). However, the long latency period between infection and diagnosis is suggested that misdiagnosis of T-cell lymphoma is unlikely.

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

| Infection-related conditions by site | 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) |
|------------------------------------|--------------------------|------------------------------------------|----------------------|--------------------------------|--------------------------------|-------------------------------|
| 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 (0.99–1.19)              | 544                            | 1.04 (0.94–1.14)              | 1560                           | 1.16 (1.01–1.24)              | 853                            | 1.32 (1.21–1.43)              | 380                            | 1.15 (1.02–1.29)              |
| Lingngyitis                        | 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                        | 22 427                   | 5695                                     | 1.11 (1.07–1.15)     | 1595                           | 1.03 (0.98–1.09)              | 396                            | 1.25 (1.12–1.39)              | 915                            | 1.09 (1.01–1.17)              | 476                            | 1.14 (0.93–1.35)              | 240                            | 1.17 (1.02–1.34)              |
| Bronchitis                         | 45 215                   | 11 458                                   | 1.11 (1.06–1.15)     | 4123                           | 1.11 (1.06–1.15)              | 704                            | 1.10 (1.01–1.21)              | 17 79                         | 1.08 (1.02–1.15)              | 939                            | 1.15 (1.07–1.25)              | 446                            | 1.09 (0.98–1.22)              |
| Influenza                          | 14 726                   | 3892                                     | 1.11 (1.07–1.15)     | 1389                           | 1.11 (1.05–1.18)              | 255                            | 1.21 (1.06–1.38)              | 628                            | 1.16 (1.06–1.26)              | 370                            | 1.13 (1.17–1.49)              | 157                            | 1.17 (0.99–1.38)              |
| Pneumonia                          | 30 201                   | 7556                                     | 1.10 (0.97–1.14)     | 2679                           | 1.05 (0.91–1.10)              | 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 (0.95–1.14)              | 627                            | 1.36 (1.24–1.49)              | 1352                           | 1.10 (0.94–1.18)              | 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 (1.04–1.42)              | 118                            | 1.55 (1.28–1.87)              |
| Gastrointestinal tract             |                          |                                          |                      |                                |                                |                               |                                |                                |                                |                                |                                |                                |                                |
| Gingivitis                         | 917                      | 209                                     | 0.98 (0.84–1.14)     | 89                             | 1.14 (0.92–1.42)              | <11                             | 0.67 (0.35–1.30)              | 24                             | 0.70 (0.46–1.05)              | 89                             | 1.14 (0.92–1.42)              | <11                             | 0.94 (0.47–1.89)              |
| Gastroenteritis                    | 5312                     | 1299                                     | 1.03 (0.96–1.10)     | 488                            | 1.04 (0.95–1.15)              | 179                            | 1.03 (0.82–1.30)              | 175                            | 1.01 (0.75–1.25)              | 207                            | 1.04 (0.85–1.26)              | <11                             | 1.27 (0.99–1.65)              |
| Urinary tract                      |                          |                                          |                      |                                |                                |                               |                                |                                |                                |                                |                                |                                |                                |
| Cystitis                           | 35 283                   | 13 876                                   | 1.04 (1.02–1.07)     | 3410                           | 1.01 (0.94–1.06)              | 494                            | 1.05 (0.93–1.18)              | 1536                           | 1.02 (0.91–1.09)              | 794                            | 1.05 (0.94–1.16)              | 565                            | 1.11 (1.00–1.23)              |
| Prostatitis                        | 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 (0.98–1.31)              | 246                            | 1.05 (0.91–1.21)              | 128                            | 0.96 (0.79–1.16)              |
| Pyelonephritis                     | 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.

*Ors and 95% Cls were adjusted for age (64–69, 70–74, 75–79, 80–84 and 85–99 years), gender and diagnosis/selection year.

**Males only.
Table 3. Main associations for non-Hodgkin lymphoma (combined) stratified by race

| Infection-related conditions by site | Whites* | | Blacks* |
|------------------------------------|---------|---------|
| Respiratory-related conditions      |         |         |
| Common cold                        | 1510    | 1.09 (1.03–1.16) | 67 | 1.18 (0.90–1.15) |
| Sinusitis                          | 8699    | 1.13 (1.10–1.17) | 347 | 1.35 (1.18–1.55) |
| Laryngitis                         | 1630    | 1.18 (1.11–1.25) | 50 | 1.28 (0.94–1.75) |
| Pharyngitis                        | 5004    | 1.11 (1.08–1.15) | 206 | 1.42 (1.21–1.68) |
| Bronchitis                         | 10190   | 1.13 (1.10–1.17) | 385 | 1.22 (1.07–1.38) |
| Influenza                          | 3460    | 1.17 (1.13–1.22) | 134 | 1.13 (0.93–1.37) |
| Pneumonia                          | 6745    | 1.11 (1.07–1.14) | 304 | 1.17 (1.02–1.35) |
| Skin                               |         |         |
| Cellulitis                         | 8077    | 1.13 (1.09–1.16) | 359 | 1.27 (1.12–1.45) |
| Herpes zoster                      | 2346    | 1.26 (1.20–1.33) | 55 | 1.32 (0.98–1.78) |
| Gastrointestinal tract             |         |         |
| Gingivitis                         | 159     | 1.09 (0.91–1.31) | 12  | 0.74 (0.41–1.35) |
| Gastroenteritis                    | 1152    | 1.04 (0.97–1.12) | 32  | 0.83 (0.57–1.21) |
| Urinary tract                      |         |         |
| Cystitis                           | 12317   | 1.03 (1.00–1.06) | 618 | 1.16 (1.03–1.29) |
| Prostatitis                        | 3244    | 1.10 (1.05–1.15) | 133 | 1.18 (0.96–1.44) |
| Pyelonephritis                     | 703     | 0.96 (0.88–1.05) | 37  | 0.98 (0.69–1.40) |

Abbreviations: CI = confidence interval; OR = odds ratio. Associations significant following Bonferroni correct (P<0.00045) are underlined.

*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.

Males only.

Females only.

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, overdiasgnosis 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.
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 host’s 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.

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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)* | 31–48 months OR (95% CI)* | 49–72 months OR (95% CI)* | >72 months OR (95% CI)* |
|------------------------------------|---------------------------|---------------------------|---------------------------|-------------------------|
| **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 (0.96–1.20)          | 1.00 (0.92–1.0)           | 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 (1.11–1.48)          | 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.

*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.
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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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