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COMMON COMMUNITY ACQUIRED INFECTIONS AND SUBSEQUENT RISK OF CHRONIC LYMPHOCYTIC LEUKEMIA

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Abstract

Emerging evidence supports a role for immune-related factors in the causation of chronic lymphocytic leukemia (CLL). Using the population-based U.S. SEER-Medicare database, we identified 10,171 elderly CLL patients and 122,531 frequency-matched controls to evaluate several community acquired infections associated with subsequent CLL risk. Odds ratios (ORs) were adjusted for gender, age, race, calendar year, and number of physician claims. We found increased CLL risk following Medicare claims for sinusitis (OR=1.11; 95%CI=1.05–1.17), pharyngitis (OR=1.15; 1.08–1.22), bronchitis (OR=1.14; 1.08–1.19), pneumonia (OR=1.17; 1.11–1.24), influenza (OR=1.10; 1.01–1.19), cellulitis (OR=1.08; 1.02–1.14), and herpes zoster (OR=1.26; 1.15–1.37). Associations with pneumonia and cellulitis remained significant when the 5-year period before diagnosis/control was excluded. CLL risk increased with increasing severity/frequency of pneumonia ($p=0.005$), cellulitis ($p<0.001$), and herpes zoster ($p<0.001$). Our findings suggest that common infections may play a role in CLL etiology. Alternatively, the associations might reflect an underlying immune disturbance present several years prior to CLL diagnosis.

Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the U.S., with approximately 4.0 cases per 100,000 yearly (Ries *et al*, 2006), affecting mostly older adults. Although CLL was initially considered to be derived from naïve B-cells, recent studies support the derivation of CLL from activated, antigen-experienced B-cells (Chiorazzi *et al*, 2005, Chiorazzi & Ferrarini, 2003, Klein & Dalla-Favera, 2005, Stevenson & Caligaris-Cappio, 2004). The initiating genetic lesion of CLL likely occurs in an immature bone marrow B-cell. Subsequent repetitive antigenic stimulation probably leads to additional genetic lesions that result in neoplastic transformation to leukemia (Chiorazzi *et al*, 2005). Alternatively, the initiating lesion in CLL could occur in immature B-cells circulating in the peripheral blood.

Based on limited observations, circulating monoclonal immunoglobulin proteins and skewed ratios of kappa-lambda free light chains are present at an increased rate among CLL patients (Pratt *et al*, 2008). Also, hypogammaglobulinemia may arise before CLL diagnosis (Lenders

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et al, 1984). Furthermore, circulating clones without evidence of lymphocytosis, i.e., monoclonal B-cell lymphocytosis (MBL), can be detected in peripheral blood in asymptomatic people (Rawstron *et al*, 2008), and MBL is present in the vast majority of CLL patients several years prior to diagnosis (Landgren *et al*, 2009). Other immune abnormalities present in CLL patients include depressed-T cell function, neutrophil dysfunction, and complement deficiencies (Tsiodras *et al*, 2000).

These considerations suggest that immune disturbance might be common prior to CLL diagnosis. It has been postulated that infectious agents could trigger CLL development (Chiorazzi & Ferrarini, 2003, Hamblin, 2006, Ghiotto *et al*, 2004). Indeed, two recent studies describe an increased occurrence of pneumonia in CLL patients up to five years before diagnosis (Landgren *et al*, 2007a, Landgren *et al*, 2007b). Sinusitis and herpes zoster have also been associated with an increased risk of CLL in male U.S. veterans (Landgren *et al*, 2007a). Although these studies were large and comprehensive (Landgren *et al*, 2007a, Landgren *et al*, 2007b), they utilized hospital discharge records and only partly captured information on common community infectious typically seen in outpatient settings.

Based on these considerations, we used the U.S. Surveillance Epidemiology and End Results (SEER)-Medicare database to conduct a large population-based case-control study of CLL. Our aim was to evaluate a broad range of common community acquired infections in relation to subsequent risk of developing CLL.

Methods

Details of the SEER-Medicare Assessment of Hematopoietic Malignancy Risk Traits (SMAHRT) Study have been published elsewhere (Anderson *et al*, 2008). Briefly, the SMARHT Study is a case-control study of hematopoietic malignancies using the SEER-Medicare database. The SEER cancer registry program has collected information on cancers from multiple U.S. sites since 1973 and currently covers approximately 25% of the U.S. population (Warren *et al*, 2002). Medicare provides federally funded health insurance for U.S. citizens aged 65 years or older. The SEER-Medicare database has demographic and clinical information from SEER on cancer patients through December 2002, linked to their Medicare enrollment and claims data (part A claims [inpatient]: 1986–2002; part B claims [physician and outpatient services]: 1991–2002) (Warren *et al*, 2002). In addition, Medicare data are available for a 5% random sample of all Medicare beneficiaries without cancer residing in SEER areas.

Cases were defined as individuals with a first primary diagnosis of CLL or the equivalent diagnosis small lymphocytic lymphoma (ICD-O-2 codes 9823 and 9670), between 1993 and 2002. Cases were aged 67–99 years at diagnosis and had at least 12 months of Part A, Part B Medicare coverage (without enrollment in a health maintenance organization) before diagnosis. In the SMAHRT Study, two controls per hematopoietic malignancy case (n=61,464) were selected from the 5% random sample of Medicare beneficiaries who were alive, free of any malignancy, and had at least 12 months Medicare coverage as of July 1 in the calendar year of selection. Controls were frequency matched to the entire group of hematopoietic malignancy cases by calendar year of diagnosis, age in five categories (67–69, 70–74, 75–79, 80–84, 85–99 years) and gender.

We considered common community acquired infections (Table 2) to be present if a subject had at least one Medicare claim before CLL diagnosis/control selection. The 12-month period before case diagnosis/control selection was excluded to reduce the possibility that, among the cases, the infection resulted from undiagnosed CLL. For significant associations, we further extended the exclusion period to 2 and 5 years. For infections that might commonly be treated

in a hospital setting, including pneumonia, cellulitis, and herpes zoster, we categorized subjects according to severity/frequency of infection, i.e., outpatient or physician claim only, 1 hospital claim, and 2 or more hospital claims.

Unconditional logistic regression was used to calculate odds ratios (ORs) comparing infections in cases and controls. The variance computation accommodated that some controls later served as cases and the repeated selection of some individuals as controls (Anderson *et al*, 2008). Analyses were adjusted for age, gender, year of diagnosis/selection, race, and, as a measure of overall healthcare utilization, the number of prior physician claims.

Results

There were 10,171 CLL cases and 122,531 controls (Table 1). Differences were present between CLL cases and controls because controls were matched to all hematopoietic malignancy cases. Thus, cases were more likely than controls to be male and had slightly longer duration of Medicare coverage than controls (Table 1). CLL cases also were more likely to be of white race and had more physician, outpatient, and hospital claims, although differences were small.

As shown in Table 2, CLL risk was significantly elevated following diagnoses of sinusitis (adjusted OR 1.11), pharyngitis (1.15), bronchitis (1.14), pneumonia (1.17), influenza (1.10), cellulitis (1.08), and herpes zoster (1.26). Most associations remained significant when the 2-year period prior to diagnosis/ selection was excluded. Associations with pneumonia and cellulitis remained significant when a 5-year period was excluded. Significant associations with laryngitis, gastroenteritis, and urinary tract infections (cystitis, pyelonephritis, prostatitis) were not observed.

CLL risk increased with increasing severity/frequency of Medicare claims for pneumonia ($p=0.005$), cellulitis ($p<0.001$), and herpes zoster ($p<0.001$). For herpes zoster, this trend test corresponded to a steady increase in risk with each level of severity/frequency (i.e., adjusted ORs increasing from 1.23 with only outpatient/physician claims, to 1.43 with one hospital claim, to 2.46 with two or more hospital claims). This pattern was less clear-cut for pneumonia and cellulitis (Table 2).

Discussion

In this large population-based case-control study, we found several common community acquired infections to be associated with subsequently increased risk of CLL. Our results extend upon those from recent hospital registry-based studies in Denmark and among U.S military veterans, which also demonstrated associations between pneumonia and CLL (Landgren *et al*, 2007a, Landgren *et al*, 2007b). As in our study, both prior studies found somewhat modest increases in the overall magnitude of CLL risk (ORs 1.3–1.6), although in one study risk increased substantially in persons with 3 or more infections (Landgren *et al*, 2007a, Landgren *et al*, 2007b). In both previous studies, the elevated risk of CLL appeared limited to the 5-year period following pneumonia diagnosis. In contrast, we found that pneumonia remained marginally associated with increased risk of CLL for more than a 5-year period after the pneumonia episode (OR 1.09, 95%CI 1.00–1.17). The presence of a long latency period extending over several years argues against reverse causality, i.e. that undiagnosed CLL caused the pneumonia. We observed a significant trend in CLL risk with increasing severity/frequency of pneumonia, although the association between pneumonia and CLL was not significant in patients with 2 or more hospital claims, possibly due to small numbers.

We also found significantly increased CLL risk following other respiratory tract infections, and CLL risk was elevated for more than 5 years following a sinusitis diagnosis. Likewise, Landgren *et al*. reported that sinusitis was associated with an increased risk of CLL (OR 1.13) (Landgren *et al*, 2007a). Many of the same infectious agents are involved in all of these respiratory tract infections, including the encapsulated bacteria *Streptococcus pneumoniae* and *Haemophilus influenzae*. B-cell immunity is thought to be important in protection against these encapsulated bacteria.

Two skin infections, cellulitis and herpes zoster, were each associated with an increased risk of CLL. Risk of CLL increased with severity/frequency for both infections. This trend was clearest for herpes zoster, with a particularly high risk of CLL in those with 2 or more hospital claims (OR 2.46). Landgren *et al.* also found a significant association between herpes zoster and CLL (OR 1.98) (Landgren *et al*, 2007a). We are not aware of previous studies associating cellulitis to CLL. Cellulitis is typically caused by *Staphylococcus aureus* or *Streptococcus pyogenes*, while herpes zoster is caused by reactivation of varicella zoster virus. Herpes zoster risk is also elevated in immunocompromised individuals (e.g., with acquired immunodeficiency syndrome (Engels *et al*, 1999)) and in patients with other hematologic malignancies (e.g. Hodgkin lymphoma) (Wareham & Breuer, 2007). However, we did not replicate the association between prostatitis and CLL reported by Landgren *et al.* (Landgren *et al*, 2007a).

There are a few potential explanations for the associations observed between common community acquired infections and subsequent risk of CLL. Firstly, common community acquired infections, such as pneumonia, could trigger the development of CLL, perhaps acting to promote the transition from MBL to CLL. CLL tumor cells exhibit clonal V_H gene mutations, suggesting that antigenic stimulation is important (Kienle *et al*, 2006). In particular, it has been hypothesized that respiratory tract infections with encapsulated bacteria may play a role in development of CLL (Landgren *et al*, 2007b). Secondly, the frequent presence of community acquired infections could reflect an underlying immune disruption in patients before diagnosis of CLL. CLL patients manifest B-cell deficits and experience infectious complications of the respiratory tract subsequent to diagnosis (Tsiodras *et al*, 2000, Bartik *et al*, 1998). Both MBL and hypogammaglobulinemia commonly occur before CLL diagnosis (Lenders *et al*, 1984, Landgren *et al*, 2009), and such immune disturbances could predispose to bacterial and viral infections. Thirdly, the observed association between certain infections and subsequent CLL risk might arise due to the influence of undetected early-stage CLL. However, given the presence of associations between infections and CLL extending for more than 5 years, we feel that this explanation is unlikely. Since a complete blood count would be a standard diagnostic study in subjects being evaluated and followed for infection, early-stage CLL would likely be detected shortly after the onset of infection. Nonetheless, it cannot be entirely ruled out that early-stage CLL diagnosis was missed in certain cases, perhaps partially accounting for associations at shorter latency intervals. Finally, because most associations were modest in magnitude, our results should be cautiously interpreted with respect to causality. If a causal relationship between infections and CLL does exist, then it is likely to explain only a minority of cases.

The main strengths of this study were its large size and the population-based sampling of CLL patients from the SEER registries (Warren *et al*, 2002), and the random selection of population-based controls. Our study sample is thus representative of the elderly U.S. population. In addition, the availability of Medicare outpatient, inpatient, and physician claims allowed us to build upon previous investigations to include several community acquired infections commonly detected and treated in outpatient settings. In addition, the use of Medicare claims meant that the associations between community acquired infections and CLL could be investigated without recall bias (i.e., the possibility that cases and controls would differentially

recall their medical histories). In comparison to our study, the Danish study also included inpatient and outpatient records to investigate the association between infections and CLL but was limited to respiratory tract infections. Unlike our investigation it included patients of all ages (Landgren *et al*, 2007b). Despite investigating a wider range of infections than the Danish study, the U.S. military veterans study was limited to hospital discharge records of male veterans age 18 years and over (Landgren *et al*, 2007a). Our study also had limitations. Firstly, our reliance upon Medicare claims may have led us to miss some infections or inaccurately diagnose others. However, because it is likely that these inaccuracies did not differ between CLL cases and controls, this bias would have been conservative and shifted observed odds ratios towards the null value. Secondly, cases and controls differed according to duration of Medicare coverage and the number of Medicare claims, which could have led to differential ascertainment of the community acquired infections. However, the absolute differences were small, and we adjusted for the number of physician claims in the statistical models. Thirdly, since we investigated the relationship between numerous community acquired infections and CLL, some associations may have resulted due to chance. However, most associations exhibited very low p-values (Table 2), arguing against this possibility. Finally, we were unable to obtain specific information about the infectious agents involved in the conditions investigated, and we had no information about immune disturbance or the presence of MBL prior to CLL diagnosis.

In conclusion, common respiratory tract infections, cellulitis, and herpes zoster are associated with an increased risk of CLL. These results point to the existence of disturbed immune function preceding the onset of CLL, or the possible role of these infections as a trigger in the late development of CLL. Further investigation of the involvement of infections in the development of CLL should be targeted to better understand the sequence of events preceding CLL diagnosis.

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Table 1

Characteristics of chronic lymphocytic leukemia cases and controls.

	Controls (n=122,531)	CLL casesp-value (n=10,171)
Gender		<0.001
Male	60,295 (49.2%)	5,488 (54.0%)
Female	62,236 (50.8%)	4,683 (46.0%)
Age, years		0.106
67–69	13,635 (11.1%)	1,203 (11.8%)
70–74	30,217 (24.7%)	2,509 (24.7%)
75–79	32,550 (26.6%)	2,684 (26.4%)
80–84	25,227 (20.6%)	2,012 (19.8%)
85–99	20,902 (17.1%)	1,763 (17.3%)
Median age	77.4	77.5
Selection year		<0.001
1993–1996	33,841 (27.6%)	3,064 (30.1%)
1997–1999	26,946 (22.0%)	2,294 (22.6%)
2000–2001	40,750 (33.3%)	3,272 (32.2%)
2002	20,994 (17.1%)	1,541 (15.2%)
Race/ethnicity		<0.001
Non-Hispanic white	102,520 (83.7%)	8,296 (91.4%)
Non-Hispanic black	8,439 (6.9%)	575 (5.7%)
Asian	4,973 (4.1%)	103 (1.0%)
Hispanic	3,122 (2.6%)	95 (0.9%)
Native American Indian	343 (0.3%)	10 (0.1%)
Other/unknown	3,134 (2.6%)	92 (0.9%)
Duration of Medicare coverage, months *		<0.001
12–57	30,746 (25.1%)	2,364 (23.2%)
58–93	30,804 (25.1%)	2,476 (24.3%)
94–136	30,696 (25.1%)	2,844 (28.0%)
≥137	30,285 (24.7%)	2,487 (24.5%)
Number of physician claims †		<0.001
0–20	31,319 (25.6%)	2,325 (22.9%)
21–57	29,810 (24.3%)	2,481 (24.4%)
58–127	30,815 (25.3%)	2,628 (25.8%)
≥128	30,587 (25.0%)	2,737 (26.9%)
Number of outpatient claims †		<0.001
0	27,401 (22.4%)	2,028 (19.9%)
1–3	29,939 (24.4%)	2,375 (23.4%)
4–7	20,972 (17.1%)	1,842 (18.1%)
8–15	20,677 (16.9%)	1,741 (17.1%)
≥16	23,542 (19.2%)	2,185 (21.5%)
Number of hospital claims †		<0.001
0	60,328 (49.2%)	4,728 (46.5%)
1	22,668 (18.5%)	2,027 (19.9%)
2–3	21,628 (17.7%)	1,924 (18.9%)
≥4	17,907 (14.6%)	1,492 (14.7%)

Abbreviation: CLL chronic lymphocytic leuekemia

* Duration of Medicare coverage refers to simultaneous coverage by Part A and Part B while the subject was not enrolled in a health maintenance organization.

† The number of claims excludes the 12 months prior to chronic lymphocytic leukemia diagnosis (cases) or selection (controls).

Table 2

Associations between common community acquired infections and subsequent risk of chronic lymphocytic leukemia.

Infection	Controls No. (%)	CLL cases No. (%)	OR (95% CI)*	p-value
Sinusitis	24,066 (19.6)	2,224 (21.9)	1.11 (1.05–1.17)	<0.001
Excluded time interval				
2 years	20,831 (17.0)	1,872 (18.4)	1.07 (1.01–1.13)	0.009
5 years	11,526 (9.4)	988 (9.7)	1.03 (0.96–1.11)	0.189
Pharyngitis	15,805 (12.9)	1,473 (14.5)	1.15 (1.08–1.22)	<0.001
Excluded time interval				
2 years	13,697 (11.2)	1,233 (12.1)	1.10 (1.03–1.18)	0.002
5 years	7,708 (6.3)	646 (6.4)	1.03 (0.95–1.13)	0.232
Laryngitis	4,592 (3.8)	407 (4.0)	1.05 (0.94–1.17)	0.188
Bronchitis	30,634 (25.0)	2,815 (27.7)	1.14 (1.08–1.19)	<0.001
Excluded time interval				
2 years	26,237 (21.4)	2,377 (23.4)	1.11 (1.05–1.17)	<0.001
5 years	14,190 (11.6)	1,202 (11.8)	1.04 (0.97–1.11)	0.150
Pneumonia	21,025 (17.2)	2,027 (19.9)	1.17 (1.11–1.24)	<0.001
Excluded time interval				
2 years	17,523 (14.3)	1,668 (16.4)	1.15 (1.08–1.22)	<0.001
5 years	8.861 (7.2)	796 (7.8)	1.09 (1.00–1.17)	0.022
Severity/frequency				
Outpatient/physician claim(s) only	1,762 (1.4)	172 (1.7)	1.18 (1.01–1.39)	
1 hospital claim	763 (0.6)	86 (0.9)	1.31 (1.05–1.64)	
2+ hospital claims	335 (0.3)	30 (0.3)	1.06 (0.73–1.54)	
p trend for severity/frequency				0.005
Influenza	7,611 (6.2)	686 (6.7)	1.10 (1.01–1.19)	0.017
Excluded time interval				0.147
2 years	6,487 (5.3)	560 (5.5)	1.05 (0.96–1.15)	
5 years	3,488 (2.9)	278 (2.7)	0.99 (0.87–1.12)	0.429
Gastroenteritis	3,758 (3.1)	339 (3.3)	1.07 (0.96–1.21)	0.470
Cellulitis	24,066 (19.6)	2,224 (21.9)	1.08 (1.02–1.14)	0.003
Excluded time interval				
2 years	19,611 (16.0)	1,770 (17.4)	1.07 (1.01–1.13)	0.014
5 years	9,946 (8.1)	891 (8.8)	1.08 (1.00–1.17)	0.024
Severity/frequency				
Outpatient/physician claim(s) only	20,538 (16.8)	1,832 (18.0)	1.06 (1.00–1.12)	
1 hospital claim	2,149 (1.8)	232 (2.3)	1.27 (1.10–1.46)	
2+ hospital claims	724 (0.6)	70 (0.7)	1.13 (0.88–1.45)	
p trend for severity/frequency				<0.001
Herpes zoster	6,294 (5.1)	661 (6.5)	1.26 (1.15–1.37)	<0.001
Excluded time interval				
2 years	5,249 (4.3)	513 (5.0)	1.16 (1.06–1.28)	0.001
5 years	2,657 (2.2)	226 (2.2)	1.02 (0.89–1.18)	0.386
Severity/frequency				
Outpatient/physician claim(s) only	5,855 (4.8)	602 (5.9)	1.23 (1.13–1.34)	
1 hospital claim	373 (0.3)	45 (0.4)	1.43 (1.05–1.95)	
2+ hospital claims	66 (0.1)	14 (0.1)	2.46 (1.38–4.40)	
p trend for severity/frequency				<0.001
Cystitis†	24,890 (40.0)	1,945 (41.5)	1.00 (0.93–1.07)	0.452
Pyelonephritis†	1,667 (2.7)	129 (2.8)	0.99 (0.82–1.19)	0.453
Prostatitis†	10,760 (17.9)	1,062 (19.4)	1.05 (0.98–1.14)	0.082

Abbreviations: CLL chronic lymphocytic leukemia, OR odds ratio, CI confidence interval.

Overall associations that were significant at p<0.05 are underlined.

*Odds ratios were adjusted for age (67–69, 70–74, 75–79, 80–84 and 85–99 years), gender, selection year (1993–1996, 1997–1999, 2000–2001, 2002), race (white, non-white), and number of physician claims (0–20, 21–57, 58–127, ≥128).

†Analyses for cystitis and pyelonephritis were restricted to females. Analyses for prostatitis were restricted to males. The percentages reflect these restrictions.