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Community-acquired infections and their association with myeloid malignancies

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Abstract

Introduction—Antigenic stimulation is a proposed aetiologic mechanism for many haematological malignancies. Limited evidence suggests that community-acquired infections may increase the risk of acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS). However, associations with other myeloid malignancies including chronic myeloid leukaemia (CML) and myeloproliferative neoplasms (MPNs) are unknown.

Material and Methods—Using the Surveillance, Epidemiology and End Result (SEER)-Medicare database, fourteen community-acquired infections were compared between myeloid malignancy patients [AML (n=8,489), CML (n=3,626) diagnosed 1992–2005; MDS (n=3,072) and MPNs (n=2,001) diagnosed 2001–2005; and controls (200,000 for AML/CML and 97,681 for MDS/MPN]. Odds ratios (ORs) and 95% confidence intervals were adjusted for gender, age and year of selection excluding infections diagnosed in the 13 month period prior to selection to reduce reverse causality.

Results—Risk of AML and MDS respectively, were significantly associated with respiratory tract infections, bronchitis (ORs 1.20 [95% CI: 1.14–1.26], 1.25 [95% CI: 1.16–1.36]), influenza (ORs 1.16 [95% CI:1.07–1.25], 1.29 [95% CI: 1.16–1.44]), pharyngitis (ORs 1.13 [95% CI: 1.06–1.21], 1.22 [95% CI: 1.11–1.35]), pneumonia (ORs 1.28 [95% CI: 1.21–1.36], 1.52 [95% CI: 1.40–1.66]), sinusitis (ORs 1.23 [95% CI: 1.16–1.30], 1.25 [95% CI: 1.15–1.36]) as was cystitis (ORs 1.13 [95% CI: 1.07–1.18], 1.26 [95% CI: 1.17–1.36]). Cellulitis (OR 1.51 [95% CI: 1.39–1.64]), herpes zoster (OR 1.31 [95% CI: 1.14–1.50]) and gastroenteritis (OR 1.38 [95% CI: 1.17–1.64]) were more common in MDS patients than controls. For CML, associations were limited to bronchitis (OR 1.21 [95% CI: 1.12–1.31]), pneumonia (OR 1.49 [95% CI: 1.37–1.62]), sinusitis

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Conflict of interest

LAA was the principle investigator and takes primary responsibility for the paper; EAE provided access to the dataset and coordinated the research; GJT wrote the paper; EAE, LAA, MFMc, CMMc and MC contributed to the interpretation of the results and writing of the paper. All authors approved the final version of the article. The authors report no potential conflicts of interest.

(OR 1.19 [95% CI: 1.09–1.29]) and cellulitis (OR 1.43 [95% CI: 1.32–1.55]) following Bonferroni correction. Only cellulitis (OR 1.34 [95% CI: 1.21–1.49]) remained significant in MPN patients. Many infections remained elevated when more than 6 years of preceding claims data were excluded.

Discussion—Common community-acquired infections may be important in the malignant transformation of the myeloid lineage. Differences in the aetiology of classic MPNs and other myeloid malignancies require further exploration.

Keywords

Infection; Myeloid Malignancy; SEER-Medicare

Introduction

Myeloid malignancies are a heterogeneous group of diseases including acute myeloid leukaemia (AML), myelodysplastic syndrome (MDS), chronic myeloid leukaemia (CML) and myeloproliferative neoplasms (MPNs) that are characterised by overproduction of one or more myeloid lineages resulting in an excess of mature and immature blood cells. These malignant diseases have an incidence rate of 4.00, 4.98, 1.64 and 2.76 per 100,000 for AML, MDS, CML and MPNs, respectively[1], reflecting the rarity of these neoplasms in the general population. Incidence is higher in males than females[1]. Approximately 1,660,290 new cases of cancer will be diagnosed in the USA in 2013 with the proportion of AML, MDS, CML and MPNs accounting for 0.9%, 1.2%, 0.36% and 0.55%, respectively[1]. The aetiology of this group of neoplasms remains largely unknown. AML is preceded by MDS in approximately 30% of cases [2] and is characterised by an abnormal blast cell count in the bone marrow with atypical cell morphology[3]. CML and MPNs are genetically categorised by the presence or absence of the Philadelphia chromosome, respectively [3], with MPNs subdivided into the following disease entities: polycythaemia vera (PV), essential thrombocythaemia (ET) and primary myelofibrosis (PMF)[4].

Infectious diseases, both viral and bacterial in origin, are aetiologically associated with a number of haematological malignancies, especially those of the lymphoid lineage[5]. Chronic antigenic stimulation has been suggested as an underlying mechanism for myeloid malignancies [6] with allergies and autoimmune conditions associated with an increased risk[7–10]. Infectious pathogens possess numerous virulence mechanisms permitting the synthesise of pathogenic virulence factors including M proteins, fever inducing cytokines and super antigens to induce pathogenicity in immunocompromised individuals by inhibiting or impairing natural immune function through genetic adaptation and evolution[11–13]. Exposure to common community-acquired infections in childhood and seasonal influenza epidemics have been suggested as risk factors for the development of AML and CML[7,8,14].

Few studies have investigated community-acquired infections in adulthood and subsequent risk of the myeloid malignancies[6–8]. Recently, Kristinsson *et al*, using data from the linked Swedish inpatient registry found an overall 30% increased risk of developing both AML and MDS following investigation of eighteen infections including the common community-acquired infections pneumonia, influenza and herpes zoster[6]. Although antigenic stimulation could be a potential causal mechanism driving development of myeloid malignancies, the findings could indicate a compromised immune system at an early stage during the process of malignant transformation[15]. To our knowledge no studies have reported on the association between antecedent community-acquired infections in adulthood and the development of CML or MPNs.

Using the United States of America (USA) Surveillance, Epidemiology and End Results (SEER)-Medicare database we sought to clarify the relationship between common community-acquired infections and subsequent risk of myeloid malignancies.

Material and Methods

Data on myeloid malignancies was obtained from the SEER-Medicare database, which has been described previously[16]. Briefly, SEER was established in 1973 to collect information on cancers diagnosed in the USA from state and metropolitan cancer registries. Currently 20 cancer registries covering approximately 28% of the US population provide demographic and clinical information[17]. Medicare is a federally funded insurance provider for individuals aged 65 years and over, covering approximately 97% of the US population[18]. Medicare comprises part A coverage (free hospital inpatient care) and part B coverage (physician and outpatient services subscribed to by 96% of beneficiaries). So AML and CML cases were available from 1992–2005 whereas MDS and MPN data was only available from 2001 to 2005 when classification was modified by the World Health Organisation[19]. Cases were defined as an individual with a primary diagnosis of a myeloid neoplasm using the international classification of morphology codes (ICD-03): AML 9896/3, MDS 9989/3, CML 9875/3 and MPN (PV 9950/3, ET 9962/3, PMF 9961/3)[18]. Controls were obtained from a 5% random sample of Medicare recipients who were alive, had at least 13 months of part A, part B and non-health maintenance organisation (HMO) coverage, who were malignancy free and previously selected to be frequency matched to larger group of all cancer types in SEER by age, gender and year of diagnosis. Cases and controls were excluded if they had less than 13 months part A, part B or HMO coverage preceding diagnosis or were aged <66 years to allow sufficient time for exposure assessment. Persons with HMO coverage were excluded as claims for individual service submissions are not required by SEER-Medicare leading to missing clinical information[17]. To avoid ascertainment bias and reverse causality, Medicare claims in the 12 months before selection were excluded. Controls may have been selected more than once in different calendar years or later as a case if they developed a myeloid malignancy[17]. Exposure ascertainment was established from one Medicare claim for a common community-acquired infection (bronchitis, common cold, influenza, pharyngitis, laryngitis, pneumonia, sinusitis, cellulitis, herpes zoster, cystitis, prostatitis, pyelonephritis, gastroenteritis and gingivitis) using physician, outpatient and/or inpatient files. Infections were chosen having a prevalence of at least 0.5% in the control population ensuring adequate power to detect differences between cases and controls.

To enable comparison of antecedent common community-acquired infections between cases and controls, odds ratios (ORs) and associated 95% confidence intervals (CIs) were calculated using unconditional polytomous logistic regression adjusted for age (66–69, 70–74, 75–79, 80–84, and 85–99 years old), gender and year of selection. Due to multiple comparisons (14 infections across 4 myeloid malignancies) Bonferroni correction ($p<0.00089$) was used to reduce the possibility of a chance finding and to identify the most prominent associations. Accommodation for controls who later developed a malignancy or who were reselected as a control in different calendar years were considered in the variance computation [9]. Analyses were performed over four time periods with infection claims occurring 13–30, 31–48, 49–72 or >72 months before selection. Linearity of the relationship was tested using tests for trend (p_{trend}). Analyses excluding individuals with human immunodeficiency virus showed similar findings (data not shown) and hence these patients were included in this report. We investigated associations by gender but not by age as data were adjusted by age and due to a small sample size the categories utilised would be too small.

Results

Comparisons between 8,489 AML and 3,626 CML cases and 200,000 controls and 3,072 MDS and 2,001 MPN cases and 97,681 controls were made. As cases were compared to controls matched to all cancer cases, for all myeloid malignancy categories, cases were more likely than controls to be older, have longer duration of Medicare coverage and more likely to be of white race, Table 1.

Following Bonferroni correction, risk of AML was increased in patients with a claim for respiratory tract infections including bronchitis (OR 1.20 [95% CI: 1.14–1.26]), influenza (OR 1.16 [95% CI: 1.07–1.25]), pharyngitis (OR 1.13 [95% CI: 1.06–1.21]), pneumonia (OR 1.28 [95% CI: 1.21–1.36]), sinusitis (OR 1.23 [95% CI: 1.16–1.30]) and cystitis (OR 1.13 [95% CI: 1.07–1.18]) when compared to controls, Table 2. Similarly, MDS was significantly associated with claims for bronchitis (OR 1.25 [95% CI: 1.16–1.36]), influenza (OR 1.29 [95% CI: 1.16–1.44]), pharyngitis (OR 1.22 [95% CI: 1.11–1.35]), pneumonia (OR 1.52 [95% CI: 1.40–1.66]), sinusitis (OR 1.25 [95% CI: 1.15–1.36]) and cystitis (OR 1.26 [95% CI: 1.17–1.36]), as well as cellulitis (OR 1.51 [95% CI: 1.39–1.64]), herpes zoster (OR 1.31 [95% CI: 1.14–1.50]) and gastroenteritis (OR 1.38 [95% CI: 1.17–1.64]), Table 2.

For CML, bronchitis (OR 1.21 [95% CI: 1.12–1.31]), pneumonia (OR 1.49 [95% CI: 1.37–1.62]), sinusitis (OR 1.19 [95% CI: 1.09–1.29]) and cellulitis (OR 1.43 [95% CI: 1.32–1.55]) were significantly associated with an increased risk compared to controls following Bonferroni correction, Table 2. Cellulitis (OR 1.34 [95% CI: 1.21–1.49]) was the only infection to remain associated with MPNs, Table 2.

Many associations remained significant when longer latency periods preceding selection were utilised, Table 3. Pneumonia was the only infection to remain significantly associated with AML, MDS and CML across all time points, Table 3. Similarly, sinusitis remained associated with AML across all time points, Table 3. Additionally, bronchitis and cystitis claims were more common in AML cases compared to controls >72 months (6 years) before selection, Table 3. This time frame was also emphasised for MDS patients with cystitis and cellulitis claims which remained elevated in cases compared to controls >6 years before diagnosis. For CML, sinusitis and cellulitis were associated with longer latency periods but no clear trends were demonstrated across time periods, Table 3. Infection associations investigated by gender revealed no statistical significance between males and females.

Discussion

Evidence to suggest an association between AML, MDS and antecedent community-acquired infections is lacking[8,20]. Our findings however, similar to a recent report from Sweden[6], suggest that several infections, particularly those affecting the respiratory tract, are significantly associated with AML and MDS even when they occur many years before diagnosis. Likewise, in both studies an excess risk of AML and MDS was observed with urinary tract and skin infections[6]. We report for the first time on a range of common community-acquired infections potentially associated with the development of CML and highlight the lack of association for most infections (except for cellulitis) with MPNs including PV, ET and PMF.

Consistent with the findings from the Swedish study, laryngitis, cellulitis, herpes zoster, pyelonephritis and gastroenteritis were significantly associated with AML however significance did not remain following adjustment for multiple comparisons[6]. These infections were also more common in MDS patients compared to controls, mirroring the reported association between cellulitis and MDS[6]. Although slightly fewer AML cases

were included in this study compared to the Swedish investigation we report on double the number of MDS cases providing greater statistical power. Additionally, utilisation of both inpatient and outpatient data is likely to have enabled enhanced acquisition of diagnoses commonly made in primary care settings reducing selection and information biases associated with hospital-based studies.

There are numerous potential explanations for these reported findings. They could reflect a compromised immune system many years before diagnosis making patients more susceptible to transient infections[21,22]. Alternatively, pathological mechanisms of these infections could influence the development of myeloid malignancies in patients by altering both genetic regulation and immune function[10]. The white cells of the myeloid lineage are components of the innate immune system, the first line of defence against infectious pathogens, and could be susceptible to genetic alteration in myeloblast precursor cells causing clonal expansion[23].

As MDS often precedes AML[2] infections could drive this transformation. However, our results suggest that these infections affect earlier in the disease process as most were similarly associated with both MDS and AML. Population-based studies investigating factors affecting progression from MDS to AML in relation to infectious agents are warranted.

To our knowledge the role of community-acquired infections in the development of CML or MPN has not previously been investigated in population-based datasets. We found that CML, and to a much larger extent MPNs, were associated with fewer infections than AML or MDS mirroring the differing associations reported with autoimmune conditions[8,10]. Pneumonia, sinusitis and cellulitis remained significantly associated with CML following the exclusion of >6 years of claims data. Reflective of their commonality within the community these infections are frequently seen in patients with haematological malignancies[24,25] with sinusitis suggested as an underlying disease [26,27]. The slow progression of CML is often asymptomatic in the early stages of disease progression. The gradual increase in the number of peripheral myeloid cells could be stimulated by infection, in turn encouraging disease progression many years before diagnosis. Infections were not associated with CML closer to diagnosis suggesting that further investigation is warranted. Likewise further investigation of the interrelationship between cellulitis and MPNs is warranted.

The main strengths of this study were the large population-based sample of patients with AML, MDS, CML and MPNs which were available from the SEER cancer registries covering approximately 28% of the US population[18]. However, the under reporting of myeloid malignancies, particularly MDS and MPNs, could reduce case ascertainment[28]. Some studies have reported a lower age of diagnosis for CML[29,30] which may have an impact on the generalisability of these findings to CML patients as a whole. Only data on people aged 66 years and over were available which limited any extrapolation of the association between infections and myeloid malignancies to the elderly population of the USA. Reliance on Medicare claims means that there may be misclassification of exposure status or an under reporting of infections not commonly requiring interaction with health care professionals. However in comparison to other population based studies observing a higher frequency of infection, notably pneumonia[31] and those limited to hospital diagnoses[6], our study should reflect a more accurate ascertainment of exposure. In addition, the non-significant associations with conditions such as the common cold suggest against differences in health seeking behaviour of cases and controls. Due to the multiple comparisons undertaken some associations may have resulted from chance. However, we crudely adjusted for this by using Bonferroni correction with many associations remaining

highly significant. Although the Medicare dataset did not facilitate adjustment of potential confounders such as diet, socioeconomic status and smoking habits, it is unlikely that these would have exerted a strong effect as these factors are not strongly associated with disease outcome[32–35].

In conclusion, we found that common community-acquired infections were more common in AML, MDS and to a lesser extent CML patients compared to controls adding strength to the recently reported association between infectious diseases and AML and MDS[7]. This suggests that infections may instigate chronic antigenic stimulation and immune disruption which could be a trigger for chronic development of myeloid malignancies or that underlying immune disturbances may alter genetic regulation of the myeloid lineage driving malignant transformation. Further investigations are needed to improve our understanding of infectious disease mechanisms and the risk of myeloid malignancies. In addition, exploration of the differences in aetiology of classic MPNs and other myeloid malignancies are warranted.

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References

1. Seer.cancer.gov. SEER Cancer Statistics. 2013. seer.cancer.gov
2. Wang L-L, Gao C, Chen B-A. Research progress on mechanism of MDS transformation into AML. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2011 Feb; 19(1):254–9. [PubMed: 21362264]
3. Hoffbrand, AV.; Moss, PAH.; Pettit, JE. Essential Haematology. 5. Oxford: Blackwell Publishing; 2006. p. 378
4. Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. Blood. 2002 Oct 1; 100(7):2292–302. [PubMed: 12239137]
5. Hjalgrim H, Engels Ea. Infectious aetiology of Hodgkin and non-Hodgkin lymphomas: a review of the epidemiological evidence. JIM. 2008 Dec; 264(6):537–48.
6. Kristinsson SY, Björkholm M, Hultcrantz M, Derolf ÅR, Landgren O, Goldin LR. Chronic immune stimulation might act as a trigger for the development of acute myeloid leukemia or myelodysplastic syndromes. JCO. 2011 Jul 20; 29(21):2897–903.
7. Doody MM, Linet MS, Glass AG, Friedman GD, Pottern LM, Boice JD, et al. Leukemia, lymphoma, and multiple myeloma following selected medical conditions. CCC. 1992 Sep; 3(5): 449–56. [PubMed: 1525326]
8. Cooper GS, Kamel F, Sandler DP, Cooper S, Davey R, Bloomfield D. Risk of adult acute leukemia in relation to prior immune-related conditions. Cancer Epidemiol Biomarkers Prev. 1996; 5:867–72. [PubMed: 8922293]
9. Anderson, LA.; Pfeiffer, RM.; Landgren, O.; Gadalla, S.; Berndt, SI.; Engels, EA. BJC. Vol. 100. Centre for Public Health, Queen's University Belfast; Northern Ireland, UK: 2009 Mar 10. Risks of myeloid malignancies in patients with autoimmune conditions; p. 822-8.l.anderson@qub.ac.uk
10. Kristinsson, SY.; Landgren, O.; Samuelsson, J.; Bjorkholm, M.; Goldin, LR. Haematologica. Vol. 95. Department of Medicine, Division of Hematology, Karolinska University Hospital Solna;

SE-171 76 Stockholm, Sweden: 2010 Jul. Autoimmunity and the risk of myeloproliferative neoplasms; p. 1216-20.

11. Smeesters PR, McMillan DJ, Sriprakash KS. The streptococcal M protein: a highly versatile molecule. TRENDS MICROBIOL. 2010 Jun; 18(6):275–82. [PubMed: 20347595]
12. Netea MG, Kullberg BJ, Van der Meer JW. Circulating cytokines as mediators of fever. CID. 2000 Oct; 31(Suppl 5):S178–84.
13. Van der Woude MW, Bäumler AJ. Phase and antigenic variation in bacteria. CMR. 2004 Jul; 17(3):581–611. table of contents.
14. Timonen TT. A hypothesis concerning deficiency of sunlight, cold temperature, and influenza epidemics associated with the onset of acute lymphoblastic leukemia in northern Finland. Ann Hematol. 1999 Sep; 78(9):408–14. [PubMed: 10525828]
15. Rapp F, Cory JM. Viral oncogenesis and the immune system. CANCER Detect PREV. 1990 Jan; 14(4):437–44. [PubMed: 2224909]
16. Anderson LA, Pfeiffer R, Warren JL, Landgren O, Gadalla S, Berndt SI, et al. Hematopoietic malignancies associated with viral and alcoholic hepatitis. Cancer Epidemiol Biomarkers Prev. 2008; 17(11):3069–75. [PubMed: 18957521]
17. Engels, Ea; Pfeiffer, RM.; Ricker, W.; Wheeler, W.; Parsons, R.; Warren, JL. Use of surveillance, epidemiology, and end results-medicare data to conduct case-control studies of cancer among the US elderly. AJE. 2011 Oct 1; 174(7):860–70.
18. Ries, Lag, et al. SEER Cancer Stat. Rev. 1975–2003. Natl. Cancer Institute; Bethesda, MD: 2006. SEER Cancer Statistics Review. http//seer.cancer.gov/csr/1975_2003/, based Novemb. 2005 SEER data submission, posted to SEER web site, 2006
19. Fukuhara, T.; Kakinoki, Y. Clinical features of a new category, myelodysplastic/myeloproliferative diseases, defined by WHO classification. Byori, Rinsho, editor. Vol. 54. Department of Medicine; Asahikawa City Hospital, Asahikawa 070–8610: 2006 Mar. p. 243-9.
20. Zheng W, Linet MS, Shu XO, Pan RP, Gao YT, Fraumeni JF. Prior medical conditions and the risk of adult leukemia in Shanghai, People's Republic of China. CCC. 1993 Jul; 4(4):361–8. [PubMed: 8347786]
21. Camous X, Pera A, Solana R, Larbi A. NK cells in healthy aging and age-associated diseases. J Biomed Biotechnol. 2012 Jan.2012:195956. [PubMed: 23251076]
22. Gazit R, Weissman IL, Rossi DJ. Hematopoietic stem cells and the aging hematopoietic system. Semin Hematol. 2008 Oct; 45(4):218–24. [PubMed: 18809091]
23. Marley SB, Gordon MY. Chronic myeloid leukaemia: stem cell derived but progenitor cell driven. ClinSci (London, Engl 1979). 2005 Jul; 109(1):13–25.
24. Scott JD, Englund Ja, Myerson D, Geballe AP. Influenza A pneumonia presenting as progressive focal infiltrates in a stem cell transplant recipient. JCV. 2004 Oct; 31(2):96–9. [PubMed: 15364264]
25. Sakamoto S, Oiso N, Emoto M, Uchida S, Hirao A, Tatsumi Y, et al. Cellulitis with Leukocytopenia as an Initial Sign of Acute Promyelocytic Leukemia. Case Rep Dermatol. 2012; 4(1):47–9. [PubMed: 22529802]
26. Pomeroy C, Oken MM, Rydell RE, Filice GA. Infection in the myelodysplastic syndromes. AJM. 1991 Mar; 90(3):338–44.
27. Chen, C-Y.; Sheng, W-H.; Cheng, A.; Chen, Y-C.; Tsay, W.; Tang, J-L., et al. BMC Infect Dis. Vol. 11. BioMed Central Ltd; 2011 Jan. Invasive fungal sinusitis in patients with hematological malignancy: 15 years experience in a single university hospital in Taiwan; p. 250
28. Craig BM, Rollison DE, List AF, Cogle CR. Underreporting of myeloid malignancies by United States cancer registries. Cancer Epidemiol Biomarkers Prev. 2012 Mar; 21(3):474–81. [PubMed: 22237987]
29. Jonte F, Fernández-Fuertes F, Cecchini C, Luño E, Ordóñez A, Fernández C, et al. Cause of death, survival, and prognostic factors in a series of 98 patients with chronic myeloid leukemia. Sangre (Barc). 1992 Oct; 37(5):351–4. [PubMed: 1293774]
30. Jonte F, Barez A, Soto I, Rayón C, Carrera D, Coma A, et al. Features of chronic myeloid leukemia at diagnosis. Study of a series of 134 cases. Sangre (Barc). 1992 Oct; 37(5):345–50. [PubMed: 1293773]

31. Millett ERC, Quint JK, Smeeth L, Daniel RM, Thomas SL. Incidence of Community-Acquired Lower Respiratory Tract Infections and Pneumonia among Older Adults in the United Kingdom: A Population-Based Study. PLoS One [Internet]. 2013 Jan.8(9):e75131. cited 2013 Oct 22. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3770598&tool=pmcentrez&rendertype=abstract.

32. Kroll ME, Murphy F, Pirie K, Reeves GK, Green J, Beral V. Alcohol drinking, tobacco smoking and subtypes of haematological malignancy in the UK Million Women Study. BJC. 2012 Aug 21; 107(5):879–87. [PubMed: 22878373]

33. Strom SS, Oum R, Elhor Gbito KY, Garcia-Manero G, Yamamura Y. De novo acute myeloid leukemia risk factors: a Texas case-control study. Cancer. 2012 Sep 15; 118(18):4589–96. [PubMed: 22297571]

34. Ma X, Park Y, Mayne ST, Wang R, Sinha R, Hollenbeck AR, et al. Diet, lifestyle, and acute myeloid leukemia in the NIH-AARP cohort. AJE. 2010 Feb 1; 171(3):312–22.

35. Corman LC. The relationship between nutrition, infection, and immunity. Med Clin North Am. 1985 May; 69(3):519–31. [PubMed: 3892189]

Table 1

Characteristics of Cases and Controls.

	Controls 1992–2005	Controls 2001–2005	AML 1992–2005	MDS 2001–2005	CML 1992–2005	MPN 2001–2005
Sex						
Males	106172 (53%)	51591 (52%)	4525 (53%)	1642 (53%)	1968 (54%)	918 (46%)
Females	93828 (47%)	46090 (48%)	3964 (47%)	1430 (47%)	1658 (46%)	1083 (54%)
Age (Years)						
67–69	33780 (16.9%)	16211 (15.8%)	1078 (12.7%)	277 (7.4%)	478 (13.2%)	308 (15.4%)
70–74	52008 (26.0%)	23878 (23.2%)	1941 (22.9%)	500 (16.3%)	758 (21.0%)	438 (21.9%)
75–79	50440 (25.2%)	24691 (24.0%)	2146 (25.3%)	783 (25.5%)	885 (24.4%)	544 (27.2%)
80–84	36097 (18.1%)	18671 (18.2%)	1839 (21.7%)	784 (25.5%)	791 (21.8%)	405 (20.2%)
85–99	27675 (13.8%)	14230 (13.9%)	1485 (17.5%)	778 (25.3%)	714 (19.7%)	306 (15.3%)
Race						
White	166827 (83.4%)	81434 (79.3%)	7433 (87.6%)	2692 (87.6%)	3200 (88.3%)	1723 (86.1%)
Black	13949 (7.0%)	6788 (6.6%)	453 (5.3%)	184 (6.0%)	220 (6.1%)	145 (7.3%)
Asian	8097 (4.1%)	4042 (4%)	227 (2.7%)	91 (3.0%)	79 (2.5%)	57 (2.9%)
Hispanic	5199 (2.6%)	2697 (2.6%)	127 (1.5%)	46 (1.5%)	53 (1.5%)	29 (1.5%)
Other/Unknown	5927 (2.9%)	2720 (2.6%)	249 (2.9%)	59 (1.9%)	74 (1.6%)	47 (2.2%)
Diagnosis (selection Year)						
1992–1994	31364 (15.7%)	NA	1130 (13.3%)	NA	570 (15.7%)	NA
1995–1998	39843 (19.9%)	NA	1685 (19.9%)	NA	772 (21.3%)	NA
1999–2005	128793 (64.4%)	97681 (100.0%)	5674 (66.8%)	3072 (100.0%)	2284 (63.0%)	2001 (100.0%)
Duration of Medicare (Months)						
13–60	57440 (28.7%)	29730 (28.9%)	1970 (23.2%)	631 (20.5%)	873 (24.1%)	599 (30.0%)
61–120	97485 (48.7%)	49247 (47.9%)	4199 (49.5%)	1788 (58.2%)	1794 (50.0%)	1025 (51.2%)
121–180	35805 (17.9%)	9434 (9.2%)	1808 (21.3%)	270 (8.8%)	757 (20.1%)	199 (10.0%)
181–240	9270 (4.6%)	9270 (9%)	512 (6.0%)	383 (12.5%)	202 (5.6%)	178 (8.8%)

Abbreviations: AML= Acute myeloid leukaemia, MDS = Myelodysplastic Syndrome, CML= Chronic myeloid leukaemia, MPN = Myeloproliferative neoplasms, OR = Odds Ratio.

Table 2

Common community-acquired infections and their associations with AML. MDS, CML and MPNs.

	AML (1992 – 2005) (n=8,489)				(MDS 2001 – 2005) (n=3,072)				CML (1992 – 2005) (n=3,626)				MPN (2001 – 2005) (n=2,001)			
INFECTION	**No. of Controls with infection (%)**	**No. of Cases with infection (%)**	**OR (95%CI)[3]**	**p-value**	**No. of Controls with infection (%)**	**No. of Cases with infection (%)**	**OR (95%CI)[3]**	**p-value**	**No. of Controls with infection (%)**	**No. of Cases with infection (%)**	**OR (95%CI)[3]**	**p-value**	**No. of Controls with infection (%)**	**No. of Cases with infection (%)**	**OR (95%CI)[3]**	**p-value**
Respiratory Tract																
Bronchitis	45215 (22.6%)	2308 (27.2%)	1.20 (1.14–1.26)	<0.001*	26332 (27.0%)	1051 (34.2%)	1.25 (1.16–1.36)	<0.001*	45215 (22.6%)	970 (26.8%)	1.21 (1.12–1.31)	<0.001*	26332 (27.0%)	572 (28.6%)	1.05 (0.95–1.16)	0.349
Common cold	7322 (3.7%)	362 (4.3%)	1.10 (0.99–1.23)	0.075	4188 (4.3%)	157 (5.1%)	1.09 (0.93–1.29)	0.300	7322 (3.7%)	159 (4.4%)	1.17 (1.00–1.38)	0.056	4188 (4.3%)	106 (5.3%)	1.21 (0.99–1.48)	0.062
Influenza	14726 (7.4%)	760 (9.0%)	1.16 (1.07–1.25)	<0.001*	9991 (10.2%)	427 (13.9%)	1.29 (1.16–1.44)	<0.001*	14726 (7.4%)	322 (8.9%)	1.19 (1.06–1.34)	0.003	9991 (10.2%)	241 (12.0%)	1.17 (1.02–1.35)	0.022
Laryngitis	6584 (3.3%)	330 (3.9%)	1.12 (1.00–1.25)	0.054	3838 (3.9%)	167 (5.4%)	1.27 (1.08–1.50)	0.003	6584 (3.3%)	124 (3.4%)	1.01 (0.84–1.21)	0.908	3838 (3.9%)	76 (3.8%)	0.92 (0.73–1.16)	0.495
Pharyngitis	22472 (11.2%)	1107 (13.0%)	1.13 (1.06–1.21)	<0.001*	12732 (13.0%)	501 (16.3%)	1.22 (1.11–1.35)	<0.001*	22472 (11.2%)	420 (11.6%)	1.0 3 (0.92–1.14)	0.634	12732 (13.0%)	291 (14.5%)	1.09 (0.96–1.24)	0.162
Pneumonia	30201 (15.1%)	1684 (19.8%)	1.28 (1.21–1.36)	<0.001*	16201 (16.6%)	815 (26.5%)	1.52 (1.40–1.66)	<0.001*	30201 (15.1%)	806 (22.2%)	1.49 (1.37–1.62)	<0.001*	16201 (16.6%)	378 (18.9%)	1.15 (1.03–1.30)	0.016
Sinusitis	36249 (18.1%)	1867 (22.0%)	1.23 (1.16–1.30)	<0.001*	21513 (22.0%)	828 (27.0%)	1.25 (1.15–1.36)	<0.001*	36249 (18.1%)	748 (20.6%)	1.19 (1.09–1.29)	<0.001*	21513 (22.0%)	463 (23.1%)	1.03 (0.92–1.14)	0.628
Skin																
Cellulitis	34426 (17.2%)	1927 (22.7%)	1.31 (1.24–1.38)	<0.001	19513 (20.0%)	943 (30.7%)	1.51 (1.39–1.64)	<0.001*	34426 (17.2%)	871 (24.0%)	1.43 (1.32–1.55)	<0.001*	19513 (20.0%)	510 (25.5%)	1.34 (1.21–1.49)	<0.001*
Herpes Zoster	8857 (4.3%)	459 (5.4%)	1.18 (1.07–1.30)	<0.001	5047 (5.2%)	233 (7.6%)	1.31 (1.14–1.50)	<0.001*	8857 (4.3%)	171 (4.7%)	1.04 (0.89–1.22)	0.631	5047 (5.2%)	109 (5.4%)	1.02 (0.83–1.24)	0.872
Urinary Tract																
Cystitis[1]	56813 (28.4%)	2764 (32.6%)	1.13 (1.07–1.18)	<0.001*	31594 (32.3%)	1270 (41.3%)	1.26 (1.17–1.36)	<0.001*	56813 (28.4%)	1146 (31.6%)	1.09 (1.01–1.18)	0.019	31594 (32.3%)	699 (34.9%)	1.04 (0.94–1.15)	0.405
Prostatitis[2]	16408 (8.2%)	766 (9.0%)	1.04 (0.96–1.12)	0.379	9185 (9.4%)	337 (11.0%)	1.05 (0.93–1.19)	0.428	16408 (8.2%)	358 (9.9%)	1.16 (1.04– 1.31)	0.012	9185 (9.4%)	172 (8.6%)	1.04 (0.88–1.23)	0.648
Pyelonephritis[1]	3529 (1.8%)	184 (2.2%)	1.16 (0.99–1.35)	0.060	1851 (1.9%)	86 (2.8%)	1.32 (1.06–1.64)	0.014	3529 (1.8%)	93 (2.6%)	1.39 (1.13–1.71)	0.002	1851 (1.9%)	41 (2.0%)	1.02 (0.74–1.39)	0.908
Gastrointestinal																
Gastroenteritis	5312 (2.7%)	272 (3.2%)	1.13 (0.99–1.28)	0.065	3027 (3.1%)	148 (4.8%)	1.38 (1.17–1.64)	<0.001*	5312 (2.7%)	127 (3.5%)	1.26 (1.05–1.51)	0.013	3027 (3.1%)	70 (3.5%)	1.08 (0.85–1.38)	0.517
Gingivitis	917 (0.5%)	58 (0.7%)	1.42 (1.09–1.86)	0.010	525 (0.5%)	22 (0.7%)	1.25 (081–1.93)	0.307	917 (0.5%)	24 (0.7%)	1.42 (0.94–2.14)	0.092	525 (0.5%)	<11‡ (0.4%)	0.80 (0.42–1.56)	0.519

Abbreviations: AML= Acute myeloid leukaemia, MDS = Myelodysplastic Syndrome, CML= Chronic myeloid leukaemia, MPN = Myeloproliferative neoplasms, OR = Odds Ratio, CI = Confidence Intervals.

[1] Females only.

[2] Males only.

[3] Odds ratios (OR) and 95% confidence intervals (CI) were adjusted for age (66–69, 70–74, 75–79, 80–84 and 85+ years), gender and calendar year of selection.

* Statistically significant p-value <0.00089 (Bonferroni corrected).

‡ Observations, in which the number of exposed patients is between one and ten, are listed as '<11' to preserve subjects' anonymity, in accordance with the SEER-Medicare data use agreement.

Table 3

Latency analysis of statistically significant community-acquired infections.

INFECTION	13–30 Months OR (95% CI)[2]	31–48 Months OR (95% CI)[2]	49–72 Months OR (95% CI)[2]	>72 Months OR (95% CI)[2]	p-value for trend
AML 1991–2005					
Bronchitis	1.06 (0.97, 1.16)	1.43 (1.31, 1.57)	1.24 (1.14, 1.35)	1.14 (1.04, 1.24)	0.732
Influenza	1.23 (1.11, 1.37)	1.15 (0.95, 1.40)	1.12 (0.94, 1.33)	1.04 (0.87, 1.24)	0.090
Pharyngitis	1.02 (0.90, 1.17)	1.27 (1.11, 1.45)	1.19 (1.05, 1.34)	1.09 (0.97, 1.23)	0.611
Pneumonia	1.30 (1.18, 1.43)	1.39 (1.25, 1.54)	1.26 (1.13, 1.40)	1.19 (1.07, 1.33)	0.153
Sinusitis	1.21 (1.10, 1.34)	1.32 (1.19, 1.47)	1.23 (1.12, 1.35)	1.18 (1.08, 1.30)	0.566
Cystitis[1]	1.04 (0.95, 1.13)	1.15 (1.06, 1.26)	1.14 (1.05, 1.24)	1.17 (1.08, 1.27)	0.033
MDS 2001–2005					
Bronchitis	1.22 (1.05, 1.41)	1.50 (1.30, 1.73)	1.32 (1.17, 1.49)	1.08 (0.95, 1.22)	0.002
Influenza	1.45 (1.27, 1.65)	1.31 (0.96, 1.79)	1.14 (0.88, 1.47)	1.01 (0.79, 1.29)	0.004
Pharyngitis	1.21 (0.99, 1.50)	1.63 (1.35, 1.98)	1.32 (1.11, 1.57)	0.96 (0.80, 1.14)	0.006
Pneumonia	1.44 (1.24, 1.67)	1.77 (1.52, 2.07)	1.72 (1.50, 1.97)	1.22 (1.05, 1.43)	0.130
Sinusitis	1.10 (0.92, 1.31)	1.56 (1.33, 1.82)	1.38 (1.21, 1.57)	1.08 (0.94, 1.23)	0.226
Cystitis[1]	1.22 (1.06, 1.40)	1.22 (1.06, 1.40)	1.42 (1.26, 1.59)	1.18 (1.05, 1.32)	0.885
Cellulitis	1.64 (1.43, 1.88)	1.52 (1.31, 1.76)	1.64 (1.44, 1.87)	1.26 (1.09, 1.45)	0.016
Herpes zoster	1.45 (1.13, 1.86)	1.46 (1.12, 1.92)	1.24 (0.95, 1.63)	1.11 (0.84, 1.46)	0.101
Gastroenteritis	1.50 (1.08, 2.06)	1.76 (1.26, 2.46)	1.36 (0.97, 1.89)	1.04 (0.73, 1.49)	0.080
CML 1991–2005					
Bronchitis	1.06 (0.92, 1.22)	1.43 (1.24, 1.64)	1.34 (1.18, 1.51)	1.08 (0.95, 1.24)	0.942
Pneumonia	1.41 (1.23, 1.61)	1.83 (1.58, 2.11)	1.49 (1.29, 1.73)	1.28 (1.09, 1.51)	0.230
Sinusitis	1.01 (0.86, 1.19)	1.29 (1.10, 1.52)	1.24 (1.07, 1.43)	1.22 (1.06, 1.41)	0.122
Cellulitis	1.49 (1.31, 1.70)	1.47 (1.27, 1.70)	1.38 (1.20, 1.60)	1.36 (1.17, 1.59)	0.281
MPN 2001–2005					
Cellulitis	1.32 (1.10, 1.59)	1.39 (1.15, 1.67)	1.54 (1.30, 1.83)	1.11 (0.91, 1.36)	0.369

Abbreviations: AML= Acute myeloid leukaemia, MDS = Myelodysplastic Syndrome, CML= Chronic myeloid leukaemia, MPN = Myeloproliferative neoplasms, OR = Odds Ratio, CI = Confidence Intervals

[1] Females only.

[2] Odds ratios (OR) and 95% confidence intervals (CI) were adjusted for age (66–69, 70–74, 75–79, 80–84 and 85+ years), gender and year of diagnosis selection.

p-value to 3 decimal places.