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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. *Materials and methods*: Using the Surveillance, Epidemiology and End Result (SEER)-Medicare database, fourteen community-acquired infections were compared between myeloid malignancy patients [AML ($n$ = 8489), CML ($n$ = 3626) diagnosed 1992–2005; MDS ($n$ = 3072) and MPNs ($n$ = 2001) 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 (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.



## 1. 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

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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.

## 2. Materials 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 to 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.

## 3. Results

Comparisons between 8489 AML and 3626 CML cases and 200,000 controls and 3072 MDS and 2001 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