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Changing incidence of myeloproliferative neoplasms in Australia, 2003-2014

To the Editor:

The Philadelphia-negative myeloproliferative neoplasms (MPNs) include three clinical entities commonly referred to as the "classic" MPNs: polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). In comparison to other cancer types, epidemiological data for these cancers are sparse. We report here the latest available statistics on incidence, prevalence, and survival of MPN in Australia.

Methodological details, including statistical methods, can be found in the online supplement. Data were sourced from the Australian Cancer Database, which incorporates each of the eight population-based cancer registries covering Australia.

Between 2003 and 2014, 8604 Australian residents were diagnosed with a classic MPN, representing an average age-standardized (2001 Australian population) incidence rate of 23.0 cases per million population (Table 1), which is at the lower end of incidence rates reported in recent publications covering the same time period from the US,[1] Norway,[2] and Korea.[3]

As at December 2014, there were 5016 Australians living after being diagnosed with MPN during the preceding 10 years. Of these, 1848 (36.8%) had been diagnosed with PV, 2448 (49%) with ET, and 720 (14.4%) with PMF. This 10-year prevalence likely under-estimates the true prevalence of MPN, as many MPN patients are likely to be alive more than 10 years after diagnosis. However, since registration of MPN only started in Australian for diagnoses from 2003 onwards, we are unable to report longer term prevalence estimates.

The incidence of all classic MPNs combined was generally higher among males than females (incidence rate ratio = 1.27, $P < 0.001$) (Table 1) including patients with PV or PMF in each age group. However, for ET there were more females than males overall, and up to the 50 to 69 year age group.

The burden of these diseases is heaviest among the elderly. Incidence increased with age (Table 1 and Supporting Information Figure S1), with the median age at diagnosis for all cases of MPN being 68 years, ranging from 66 years for ET, 67 years for PV to 72 years for PMF. The excess mortality relative to age-matched controls was also higher among older than younger patients (Supporting Information Table S1, Supporting Information Figure S3). For example, the excess hazard was nearly three times higher (EHR = 2.97 [2.3-3.9]) for Australians diagnosed when aged 50 to 69 years compared to those diagnosed when aged 15 to 49 years old, and seven times higher for those aged 70 to 89 years at diagnosis (EHR = 7.30 [5.6-9.5]). The age effect was particularly pronounced for people diagnosed with ET. Given that vascular complications account for a large proportion of MPN-associated mortality, it is possible that prevalent vascular risk factors in older individuals interact to amplify the disease-specific risk.[4,5] Determination of the specific causes of death was not possible within this study, but understanding the factors that contribute to excess mortality could help clinicians to address factors that may reduce this risk.

The incidence of classic MPNs overall in Australia between 2003 and 2014 decreased significantly by an average of −2.9% per year for males (95% CI = [−0.6, −5.1]), while the decrease among females (−1.7% per year, [−4.5, +1.2]) was not statistically significant (Supporting Information Figure S2). There was no evidence of a change in the magnitude or direction of the trend over this period. Most of this decreasing trend was driven by PV incidence, reducing by 8.8% per year among males [−11.1, −6.4] and 7.8% among females [−10.2, −5.3]. In contrast, incidence rates of ET have been increasing over the same period by 4.9% in males [+0.4, +9.6] and (non-significantly) 3.4% among females [−1.3, +8.4]. Neither of the slightly decreasing trends for PMF incidence rates among males (−2.0% [−4.2, +0.3]) or females (−3.5% [−7.4, +0.5]) were statistically significant.

Consistent with the Australian trends, rates of PV in Norway have been decreasing since 2007 to 2009 and in the US since 2004, while in Korea the peak incidence was in 2006. There are several possible explanations for these trends. The *JAK2* mutation was first identified in 2005 and was included in the WHO diagnostic criteria in 2008. It may be that some cases of secondary polycythemia were wrongly reported as PV prior to the widespread use of *JAK2* testing and that more specific diagnostic testing has reduced false positive reporting. Testing for the *JAK2* V617F mutation became available in most large centers within 1 to 2 years of the initial reports of the mutation, and some clinicians do not routinely perform bone marrow biopsies in patients with suspected PV who have a somatic *JAK2* mutation. Cancer registries usually obtain notifications from pathology laboratories based on bone marrow biopsy reports, so the absence of a biopsy may result in under-reporting. Conversely, for ET we found an increase in incidence of nearly 5% per year in males, and a smaller, statistically non-significant increase in women over the same time period. The availability of genetic tests for ET may have led to an increase in diagnostic procedures for this disease in which the symptom burden is lower and delays to diagnosis are commonly observed.[6] Further investigations and capture-recapture studies are needed to clarify the factors that may have led to these changes in reported incidence.

Overall, the 5-year relative survival for MPN was 80.8% (Supporting Information Table S1), reducing to 67.7% by 10 years after diagnosis. This varied by type of MPN, with 5-year survival for ET (86.1%) and PV (91.1%) being substantially higher than for PMF (50.1%). After adjusting for age group at diagnosis, survival for all classic MPNs was about 50% worse among males (Excess Hazard Ratio = 1.51, 95% confidence interval = [1.3-1.7]) than females (Supporting Information Table S1, Supporting Information Figure S3). This significantly worse prognosis for males was observed for PV (1.36, [1.1-1.7]) and ET (1.42, [1.0-2.0]), but did not reach statistical significance for PMF (1.14 [1.0,1.4]).

The crude probability of death from MPN was calculated using functions of the expected mortality rates, the excess mortality rate and the all-cause mortality rates. Of 100 Australians diagnosed with

TABLE 1 Age-adjusted incidence rates (per million population) and incidence rate ratios of myeloproliferative neoplasms, overall and according to sex and age group. Australia, 2003-2014

Name	N	M:F incidence ratio	Incidence rate (/million population)			M:F incidence rate ratio	
			Persons	Males	Females	IRR (95% CI)	*P*-value
All ages							
Myeloproliferative neoplasms	8604	1.13	23.0 [22.5-23.5]	25.8 [25.1-26.6]	20.4 [19.8-21.1]	1.14 (1.1-1.2)	<0.001
Polycythemia vera	3371	1.37	9.0 [8.7-9.4]	11.2 [10.7-11.8]	6.9 [6.5-7.3]	1.39 (1.3-1.5)	<0.001
Essential thrombocythemia	3434	0.78	9.5 [9.2-9.8]	8.6 [8.2-9.1]	10.4 [8.2-9.1]	0.78 (0.7-0.8)	<0.001
Primary myelofibrosis	1799	1.64	4.5 [4.2-4.7]	6.0 [5.6-6.3]	3.2 [2.9-3.4]	1.66 (1.5-1.8)	<0.001
15–49 years							
Myeloproliferative neoplasms	1365	0.99	9.8 [9.3-10.3]	9.7 [9.0-10.4]	9.9 [9.2-10.7]	0.98 (0.9-1.1)	0.697
Polycythemia vera	512	1.75	3.6 [3.3-4.0]	4.7 [4.2-5.2]	2.6 [2.3-3.1]	1.74 (1.5-2.1)	<0.001
Essential thrombocythemia	718	0.61	5.2 [4.8-5.6]	3.9 [3.5-4.4]	6.5 [5.9-7.1]	0.61 (0.5-0.7)	<0.001
Primary myelofibrosis	135	1.50	0.9 [0.8-1.1]	1.1 [0.9-1.4]	0.8 [0.6-1.0]	1.45 (1.0–2.0)	0.033
50–69 years							
Myeloproliferative neoplasms	3249	1.37	56.9 [54.9-58.9]	66.1 [63.1-69.1]	47.7 [45.2-50.3]	1.38 (1.3–1.5)	<0.001
Polycythemia vera	1379	1.77	24.1 [22.9-25.4]	31.1 [29.1-33.2]	17.3 [15.8-18.1]	1.79 (1.6-2.0)	<0.001
Essential thrombocythemia	1234	0.88	21.7 [20.5-22.9]	20.4 [18.7-22.1]	22.9 [21.2-24.8]	0.89 (0.8-1.0)	0.033
Primary myelofibrosis	636	1.93	11.1 [10.2-12.0]	14.6 [13.3-16.1]	7.5 [6.6-8.6]	1.95 (1.7-2.3)	<0.001
70 years and over							
Myeloproliferative neoplasms	3939	1.01	156.5 [152-162]	182.8 [175-191]	135.5 [129-142]	1.30 (1.2-1.4)	<0.001
Polycythemia vera	1466	1.00	58.3 [55.3-61.5]	68.3 [63.4-73.4]	49.7 [46.0-53.6]	1.28 (1.2–1.4)	<0.001
Essential thrombocythemia	1447	0.78	57.5 [54.5-60.6]	58.2 [53.7-62.9]	57.4 [53.3-61.6]	1.00 (0.9–1.1)	0.988
Primary myelofibrosis	1026	1.51	40.6 [38.1-43.2]	56.4 [52.0-61.0]	28.4 [25.6-31.4]	1.94 (1.7-2.2)	<0.001

N: number of cases diagnosed. IR: age-standardized incidence rate (2000 US Population).
IRR: incidence rate ratio, adjusted by 5-y age group, with 95% confidence interval. *P*-value tests whether the IRR is significantly different to 1.
Myeloproliferative neoplasms (ICD-O-3 9950, 9961, 9962), Polycythemia vera (9950), Essential thrombocythemia (9962), Primary myelofibrosis (9961).

MPN, we would expect about 29 to have died from the disease within 10 years of diagnosis, 19 to have died from other causes and 52 to remain alive (Supporting Information Table S2). Of Australians diagnosed with ET, 16% would be expected to have died from their MPN within 10 years, compared with 24% diagnosed with PV, and 64% diagnosed with PMF. The mortality burden increases as age increases, both for the number of deaths due to MPN and number of deaths due to other causes (Supporting Information Figure S4).

Our study adds to a body of data from multiple countries with different mixes of race and ethnicity showing an apparent change in incidence patterns of MPN. These changes, particularly the declining rate of PV diagnosis, are still unexplained, but may reflect changes in investigation and reporting rather than a true change in incidence. As is the case for most population-based registries, cancer registries in Australia do not routinely collect information about genetic testing, and so this precludes the opportunity to investigate how diagnosis and prognosis varies according to somatic driver mutations in different age and sex cohorts. Accurate enumeration of the MPNs is reliant on cancer registries having appropriate notification processes for these cancers. Accurate population-based reporting, including the collection of genetic information, is needed to facilitate future studies of MPN etiology and to assess whether changes in practice alter survival.

CONFLICT OF INTEREST

Nothing to report.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Early-onset severe infections in allogeneic hematopoietic stem cell transplantation recipients with graft failure

To the Editor:

Graft failure (GF) is a rare but severe event after allogeneic hematopoietic stem cell transplantation (HSCT), leading to increased mortality through infections, disease relapse and drawbacks of marrow aplasia.[1] Retrospective studies have estimated the overall incidence of GF around 5.5%.[1,2] Hematological risk factors such as non-malignant underlying diseases, partial remission at transplant, HLA mismatch, use of a cord blood source and low graft cellularity are consistently associated with GF.[1–3] In most studies, infections are cited as circumstantial events but to date, no study has specifically documented early-onset severe infections (ESIs) associated with GF. The present study focuses on the incidence, the chronology, the type and the outcome of ESIs during the expected engraftment period in the setting of GF after allogeneic HSCT.

We conducted a retrospective, observational, multicentric matched case-control (1:2) study among adult allogeneic HSCT recipients transplanted at three French tertiary-care Hematology departments (Saint-Louis, Paris; Lyon-Sud, Lyon; Oncopôle, Toulouse) between January 2008 and December 2017. GF recipients were identified by cross-referencing the databases of the Hematology departments and by additional chart reviews. Eligible GF recipients matched the following criteria[1–3]: (i) primary GF was failure to achieve donor-derived ANC ≥0.5 G/L for more than three consecutive days by day 42 post-HSCT, including neutropenic GF with persisting aplasia and non-neutropenic GF with autologous recovery, without evidence of disease relapse; (ii) early secondary GF was the loss by day 42 post-HSCT of a previously functioning graft (donor-derived sustained ANC ≥0.5 G/L for more than 3 days) associated with loss of full donor chimerism without evidence of disease relapse. Each case was matched with two controls according to stem cell source, underlying hematological disease, temporal proximity of HSCT (±5 years), age (±10 years) and gender. Death before day 20 after HSCT was an exclusion criterion. Ethics Committees of each hospital approved the study.

ESIs were defined as life-threatening fungal, viral, parasitic or bacterial infection occurring upon conditioning (day 7 before HSCT) until day 42 post-HSCT using the most recent consensus definitions from international groups provided in Supporting Information Table S1.

Cumulative incidence and survivals were calculated using the Fine and Gray competing risk regression model. Competing events were death from all causes for the cumulative incidence of ESIs, and infection-free death for the cumulative survival rate of infection-related death. Analyses were based on two-sided *P*-values, with statistical significance defined by $P < 0.05$ and conducted with R software version 3.4.3.

Over the study period, 2094 allogeneic HSCT were performed. Forty-nine GF were ultimately selected, including 45 (91.8%) primary GF and 4 (8.2%) early secondary GF. Full baseline characteristics are provided in Supporting Information Table S2.

In univariate analysis, ESIs were strongly associated with GF (OR 11.04; 95%CI [3.86-31.61]; $P < 0.0001$). Infections associated with ESIs were toxoplasmosis (OR 29.44; 95%CI [1.29-671.65]; $P = 0.034$), prolonged undocumented sepsis-like syndrome (OR 24.35; 95%CI [1-592.07]; $P = 0.050$), invasive fungal infection (IFI) (OR 11.13; 95%CI [2.49-49.72]; $P = 0.002$), bacterial blood stream infections (BSIs) (OR 8.29; 95%CI [1.78-38.69]; $P = 0.007$) and viral infections (OR 2.84; 95%CI [1.28-6.27]; $P = 0.010$) with the subset including BK virus, adenovirus and influenza A infections significantly associated with GF (OR 11.02; 95%CI [1.251-97.16]; $P = 0.031$). Significantly higher frequency of CMV serodiscordance (both positive recipient (R+) with negative donor (D-) and R−/D+) was observed among cases (OR 2.17; 95% CI [1.06-4.42]; $P = 0.033$) with a prominence of R+/D- (31.3%) vs R−/D+ (18.8%).

Median delay to first ESI episode was 12 (IQR, 7-22) vs 19.5 (IQR, 8.8-26.8) days for cases and controls, respectively ($P = 0.201$). The delay according to the graft source was shorter in cases than in controls (CB, 9.5 [IQR, 7.3-17.3] vs 14 [IQR, 10-20.3], PB 9.5 [IQR, 2.5-20.5] vs 25 [IQR, 9.3-33], BM 20 [IQR, 13-25] vs 29 [IQR, 19-32]