ONLINE SUPPLEMENT:

Changing incidence of myeloproliferative neoplasms in Australia, 2003-2014

Methodology

Data sources

De-identified data on classic MPN incidence and survival were obtained from the Australian Cancer Database (ACD), which is a national population-based repository managed by the Australian Institute of Health and Welfare, and containing information collected by the eight State and Territory-based cancer registries across Australia. Notifications of all cancers (excluding keratinocyte cancers) to these population-based cancer registries are required by law. Approval for access to these data was provided separately by each State- and Territory-based Cancer Registry, along with the required ethics approvals from Human Research Ethics Committees. No external funding was obtained for this study.

All patients reported to the ACD as being diagnosed with MPN in Australia between 2003 and 2014 were included in the MPN cohort, with mortality follow-up to December 2014. Mortality status is obtained through routine annual linkage of cancer records with the Australian National Death Index. Subtypes of MPN included in this analysis were PV (9950), ET (ICD-O-3 morphology code 9962), and PMF (9961). Transformations of ET/PV to PMF are usually not captured by cancer registries.

Variables provided in the data extract included a unique identifier, month and year of diagnosis, month and year of death (if applicable), number of days between diagnosis and death or last follow-up date (whichever came first), sex, age at diagnosis, type of MPN, and basis of diagnosis. We included all ages, but for the age-specific analyses we present results only for patients aged 15 years and over, due to the small numbers of children with MPNs.[9]

Population data for Australia between 2003 and 2014[10] and information about all-cause mortality for the Australian population[11] were obtained from the Australian Bureau of Statistics to generate population life tables.

Statistical methods

Direct age-standardised (World 2000) incidence rates (per million) were calculated according to year, sex and subtype categories. We used Joinpoint software (version 4.2.0.1, National Cancer Institute, 2015) to assess the trends (measured by the annual percentage change, or APC), and specifically to determine whether there were any statistically significant changes in the magnitude or direction of the trends over the study period. Age-adjusted incidence rate ratios (IRR) by sex were calculated using negative binomial regression to model the incidence counts, including age group (5-year age groups) and sex as covariates, and the log of the age- and sex-specific estimated resident population as the offset variable.

Relative survival was used to estimate prognosis for people diagnosed with MPN. Relative survival compares the observed survival of people diagnosed with MPN against the expected survival of a comparable group from the general population, without requiring cause of death information. Survival estimates were restricted to patients aged 15-89 years at diagnosis, and people diagnosed only on the basis of death certificate were excluded. Patients who were still alive at 31st December 2014 were considered censored.

Relative survival estimates were produced using the period approach,[12] with an 'at risk' period of 2005-2014 (inclusive). The period approach is recognised as providing more up-to-date survival estimates when using cancer registry data [12]. Observed survival was calculated using the life table, or actuarial, method.[13] Expected survival was calculated using the Ederer II method,[14] based on Australian all-cause mortality data obtained from the Australian Bureau of Statistics.[11] Relative survival estimates were calculated using the strs command in Stata (v16.1, StataCorp, Texas USA).

Excess hazard ratios for males and females, and broad age groups (15-49, 50-69 and 70-89 years) were calculated using a generalised linear model with the outcome being the number of deaths (d_j) which follow a Poisson distribution with mean $\underline{u_j}$, a Poisson error structure using the link function $\ln(\mu_j - d_j)$ and an offset variable being the log of the person time.[15]

To complement the relative survival estimates, we also provide estimates of the crude probability of death, also known as the cumulative incidence function.[16] Crude probability of death uses the same calculation mechanism as relative survival. However, the crude probability of death due to cancer calculates the time-specific probability of death due to cancer in the real world considering the competing risk of death from other causes.[17] These

calculations do not require information about the cause of death, but instead use life tables to partition the survival expectations[16] to estimate the time-specific probability of dying from the diagnosed cancer, dying from other causes, or being alive. Crude probabilities were calculated using the strs command in Stata (v16.1, Statacorp, Texas USA).

Basis of diagnosis

Of the 8,604 MPNs included in the study cohort, nearly half were diagnosed based on histology of primary (24.5%) or unknown histology (18.6%), one third (32.4%) on the basis of cytology (which includes laboratory techniques such as needle aspiration, without biopsy), and one fifth (19.8%) based on clinical investigations. Three percent of MPN cases were diagnosed based on death certificate only. There were no consistent trends in the basis of diagnosis over the 12 year period, with percentages generally fluctuating around the overall average for each category.

ONLINE TABLE 1: Relative survival and excess hazard ratios for myeloproliferative neoplasms, overall and according to sex and age group. Australia, Diagnosed between 2003-2014, at risk between 2005-2014, 15-89 years at diagnosis.

MPN type	N at risk	Relative survival (%) with 95% confidence intervals		Excess Hazard Ratios (with 95% confidence intervals)		
15-89 years at diagnosis		5-year	10-year	Males: Females	50-69: 15-49 years	70-89: 15-49 years
Myeloproliferative neoplasms	7,931	80.8 [79.5-82.0]	67.7 [65.6-69.9]	1.51 [1.3 - 1.7]	2.97 [2.3-3.9]	7.30 [5.6-9.5]
Polycythaemia vera	3,083	86.1 [84.1-87.9]	72.7 [69.5-75.8]	1.36 [1.1 - 1.7]	1.92 [1.3-2.9]	5.07 [3.4-7.5]
Essential thrombocythaemia	3,241	91.1 [89.3-92.9]	82.6 [79.0-86.1]	1.42 [1.0 - 2.0]	7.25 [2.6-20.5]	20.88 [7.5-58.2]
Primary myelofibrosis	1,607	50.1 [46.9-53.4]	29.6 [25.2-34.3]	1.14 [1.0 - 1.4]	2.46 [1.6-3.8]	4.83 [3.2-7.3]

N at risk: number at risk between 2005 and 2014

Myeloproliferative neoplasms (ICD-O-3 9950, 9961, 9962), Polycythaemia vera (9950), Essential thrombocythaemia (9962), Primary myelofibrosis (9961).

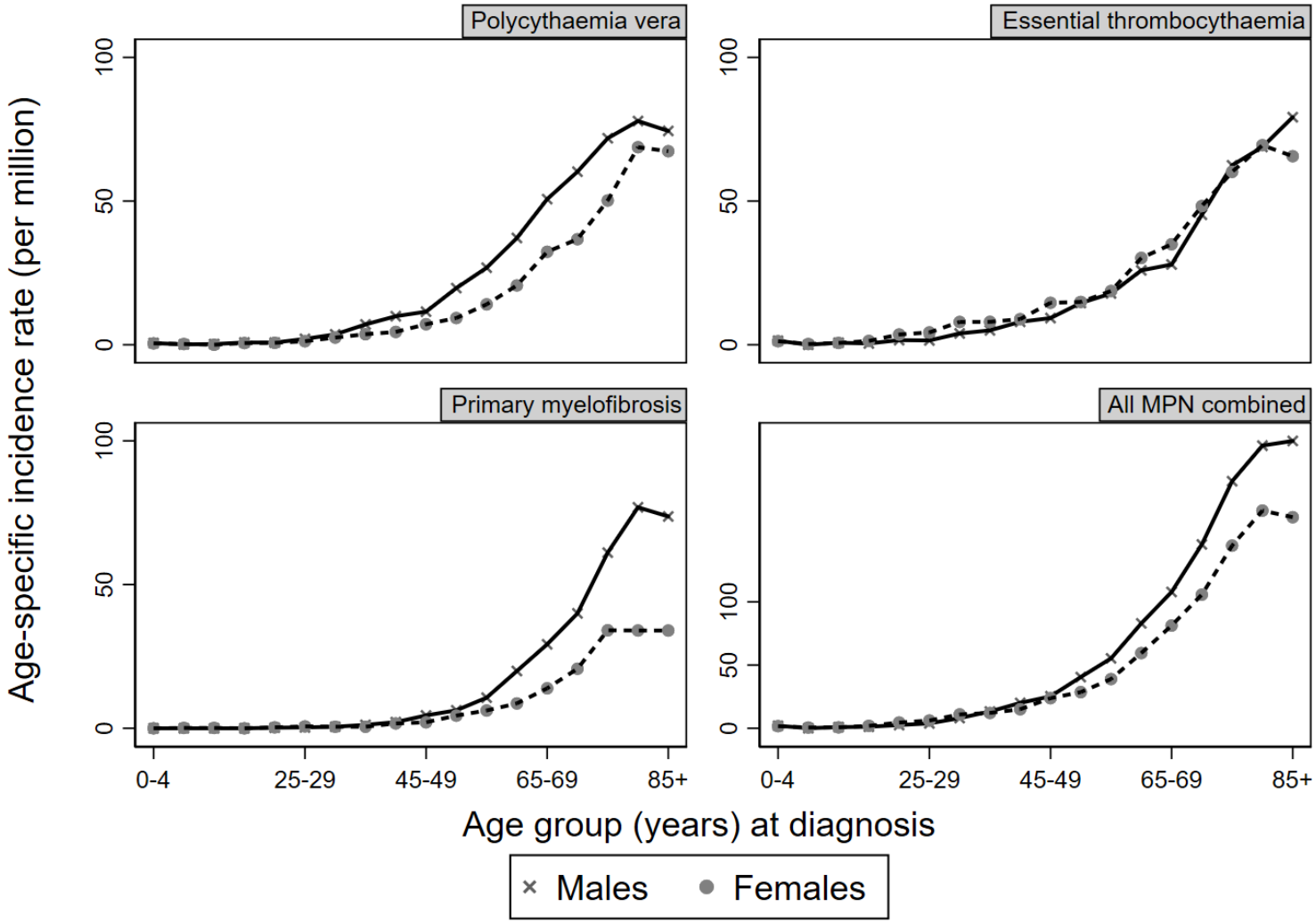
ONLINE TABLE 2: Crude probability of death due to MPN and other causes: Australia, Diagnosed between 2003-2014, at risk between 2005-2014, 15-89 years at diagnosis.

MPN type	N at risk	Within 5 years of diagnosis			Within 10 years of diagnosis		
15-89 years at diagnosis		Death due to MPN (%)	Death due to other causes (%)	Alive (%)	Death due to MPN (%)	Death due to other causes(%)	Alive (%)
Myeloproliferative neoplasms	7,931	18.2 [17.0-19.5]	10.2 [10.1-10.3]	71.6 [70.4-72.7]	29.0 [27.2-30.9]	18.8 [18.6-19.0]	52.2 [50.5-53.8]
Polycythaemia vera	3,083	13.3 [11.5-15.1]	10.2 [10.1-10.4]	76.5 [74.8-78.2]	24.4 [21.7-27.1]	19.4 [19.1-19.8]	56.2 [53.8-58.6]
Essential thrombocythaemia	3,241	8.4 [6.8-10.2]	10.5 [10.4-10.6]	81.1 [79.5-82.7]	15.5 [12.6-18.7]	20.6 [20.2-20.9]	63.9 [61.2-66.6]
Primary myelofibrosis	1,607	46.9 [43.9-49.9]	9.5 [9.2-9.7]	43.6 [40.8-46.4]	63.6 [59.7-67.3]	14.2 [13.6-14.8]	22.2 [18.9-25.4]

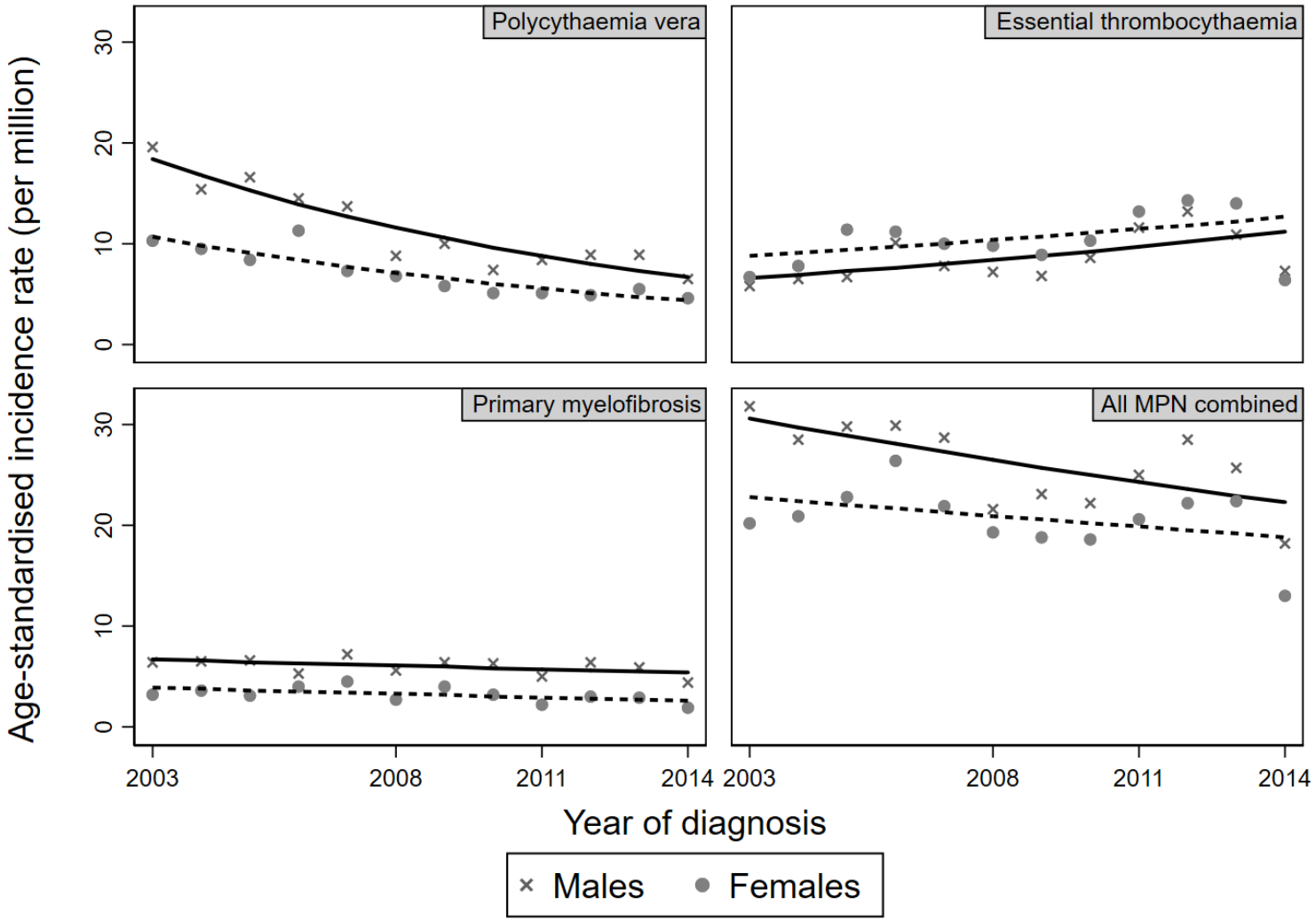
N at risk: number at risk between 2005 and 2014

Myeloproliferative neoplasms (ICD-O-3 9950, 9961, 9962), Polycythaemia vera (9950), Essential thrombocythaemia (9962), Primary myelofibrosis (9961).

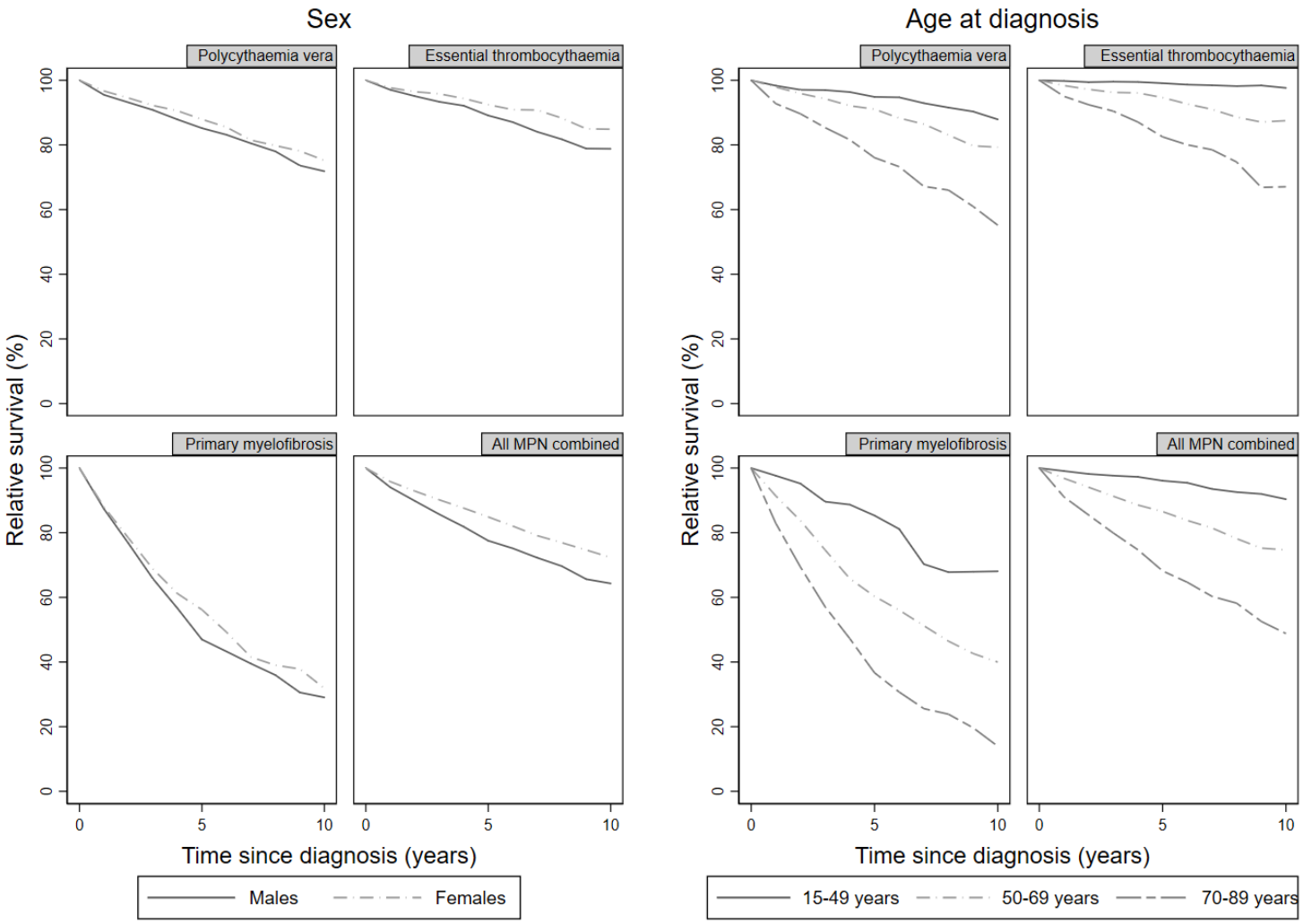
ONLINE FIGURE 1: Age-specific incidence of myeloproliferative neoplasms (MPN) in Australia, 2003-2014, 15 years and over at diagnosis



ONLINE FIGURE 2: Incidence rate trends for myeloproliferative neoplasms (MPN) in Australia, 2003-2014, 15 years and over at diagnosis



ONLINE FIGURE 3: Relative survival for myeloproliferative neoplasms (MPN) in Australia by sex and age (period method; diagnosed 2003-2014, at risk period of 2005-2014), 15-89 years at diagnosis



ONLINE FIGURE 4: Crude probability of death for myeloproliferative neoplasms (MPN) in Australia by age group (period method; diagnosed 2003-2014, at risk period of 2005-2014), 15-89 years at diagnosis