**Incidence and patient survival of myeloproliferative neoplasms and myelodysplastic/myeloproliferative neoplasms in the United States, 2001-2012**

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Text word count: ; 4,327

Tables: 3; Figures: 3; Supplementary Tables: 3; Supplementary Figures: 1

References: 64

Short title: MPN and MDS/MPN incidence and patient survival

*Conflict of interest disclosure:* The authors declare no competing financial interests.

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**Summary**

Descriptive epidemiologic information on myeloproliferative neoplasms (MPNs) and myelodysplastic (MDS)/MPNs is largely derived from single institution and European population-based studies. Data since adoption of the WHO classification of hematopoietic neoplasms and *JAK2 V617F* mutation testing are sparse. Using population-based data, we comprehensively assessed subtype-specific MPN and MDS/MPN incidence rates (IRs), IR ratios (IRRs), and relative survival (RS) in the United States (2001-2012). IRs were highest for polycythemia vera (PV) (IR=10.9) and essential thrombocythemia (ET) (IR=9.6). Except for ET and mastocytosis, overall IRs were significantly higher among males (IRRs=1.4-2.3). All evaluable MPNs were associated with lower IRs among Hispanic whites than non-Hispanic whites (NHWs), with the exception of *BCR-ABL1*-positive chronic myelogenous leukaemia (CML), chronic eosinophilic leukaemia (CEL), and juvenile myelomonocytic leukaemia. Except for CEL, Asians/Pacific Islanders had significantly lower MPN IRs than NHWs. ET, MPN-unclassifiable, and CEL IRs were 18%, 19%, and 60% higher, respectively, among blacks than NHWs. Five-year RS was more favorable for younger (<60 years) than older individuals and for women compared with men, except for PV at older ages. RS was highest (>90%) for younger PV and ET patients and lowest (<20%) for older chronic myelomonocytic leukaemia and atypical *BCR-ABL1*-negative CML patients. Varying MPN and MDS/MPN incidence patterns by subtype support distinct etiologies and/or susceptible populations. Decreased survival rates as compared to that expected in the general population were associated with every MPN subtype, highlighting the need for new treatments, particularly among older individuals.

**Key Words:**

Myeloproliferative neoplasm, MPNs, epidemiology, incidence, survival.

**Introduction**

Myeloproliferative neoplasms (MPNs) are a group of stem cell disorders characterized by clonal myeloproliferation that is devoid of dyserythropoiesis, granulocytic dysplasia, or monocytosis ([Swerdlow](#_ENREF_58" \o "Swerdlow, 2008 #13)*[, et al](#_ENREF_58" \o "Swerdlow, 2008 #13)* [2008](#_ENREF_58" \o "Swerdlow, 2008 #13)). Closely related but distinct are the myelodysplastic (MDS)/myeloproliferative neoplasms (MDS/MPNs), which are clonal hematopoietic neoplasms that share clinical, morphologic and laboratory features not only with MPNs but also with myelodysplastic syndromes ([Jaffe](#_ENREF_25" \o "Jaffe, 2001 #51)*[, et al](#_ENREF_25" \o "Jaffe, 2001 #51)* [2001](#_ENREF_25" \o "Jaffe, 2001 #51), [Swerdlow](#_ENREF_58" \o "Swerdlow, 2008 #13)*[, et al](#_ENREF_58" \o "Swerdlow, 2008 #13)* [2008](#_ENREF_58" \o "Swerdlow, 2008 #13)).

Epidemiologic studies of MPNs and MDS/MPNs in the United States (US) have been hampered by evolving disease classifications and nonreporting to cancer registries. In 2001, the World Health Organization (WHO) Classification of Tumors of Haematopoietic and Lymphoid Tissues ([Jaffe](#_ENREF_25" \o "Jaffe, 2001 #51)*[, et al](#_ENREF_25" \o "Jaffe, 2001 #51)* [2001](#_ENREF_25" \o "Jaffe, 2001 #51)) built upon existing guidelines from the Polycythemia Vera Study Group ([Murphy](#_ENREF_39" \o "Murphy, 1997 #253)*[, et al](#_ENREF_39" \o "Murphy, 1997 #253)* [1997](#_ENREF_39" \o "Murphy, 1997 #253)) to define seven MPNs and four MDS/MPNs ([Jaffe](#_ENREF_25" \o "Jaffe, 2001 #51)*[, et al](#_ENREF_25" \o "Jaffe, 2001 #51)* [2001](#_ENREF_25" \o "Jaffe, 2001 #51)). While morphologic and clinical features remained integral to the diagnosis of each MPN and MDS/MPN in 2001, the WHO classification incorporated genetic information into the diagnostic criteria of select entities. Most notably, the presence of *BCR-ABL* “unequivocally” confirmed a diagnosis of chronic myelogenous leukaemia (CML), and one of the major diagnostic criteria for polycythemia vera (PV) included the presence of a clonal genetic marker other than *BCR-ABL1* gene rearrangement. However, in 2001 no chromosomal or molecular markers specific for the *BCR-ABL*-negative MPNs had been identified ([Jaffe](#_ENREF_25" \o "Jaffe, 2001 #51)*[, et al](#_ENREF_25" \o "Jaffe, 2001 #51)* [2001](#_ENREF_25" \o "Jaffe, 2001 #51)).

Classification of MPNs and MDS/MPNs further evolved with the introduction of the 2008 WHO classification ([Swerdlow](#_ENREF_58" \o "Swerdlow, 2008 #13)*[, et al](#_ENREF_58" \o "Swerdlow, 2008 #13)* [2008](#_ENREF_58" \o "Swerdlow, 2008 #13)). Among the most important changes was the inclusion of the *JAK2 V617F* or other clonal genetic/molecular markers in the diagnostic criteria for the majority of *BCR-ABL1*-negative MPNs and MDS/MPNs ([Kralovics](#_ENREF_26" \o "Kralovics, 2005 #229)*[, et al](#_ENREF_26" \o "Kralovics, 2005 #229)* [2005](#_ENREF_26" \o "Kralovics, 2005 #229)). Other changes included decreasing the platelet count threshold for essential thrombocythemia (ET), and changing the naming convention from chronic myeloproliferative disorders to MPNs, to better reflect the malignant nature of these entities ([Swerdlow](#_ENREF_58" \o "Swerdlow, 2008 #13)*[, et al](#_ENREF_58" \o "Swerdlow, 2008 #13)* [2008](#_ENREF_58" \o "Swerdlow, 2008 #13)).

The International Classification of Diseases for Oncology (ICD-O) classification evolved in concert with the 2001 WHO classification. Prior to 2001 when the third edition of ICD-O (ICD-O-3) was adopted, several MPNs were not considered malignant and thus were not reportable to cancer registries in the US.

Population-based studies describing incidence of MPNs and MDS/MPNs limited to the current century are sparse ([Rollison](#_ENREF_51" \o "Rollison, 2008 #102)*[, et al](#_ENREF_51" \o "Rollison, 2008 #102)* [2008](#_ENREF_51" \o "Rollison, 2008 #102), [Sant](#_ENREF_53" \o "Sant, 2010 #96)*[, et al](#_ENREF_53" \o "Sant, 2010 #96)* [2010](#_ENREF_53" \o "Sant, 2010 #96), [Smith](#_ENREF_56" \o "Smith, 2011 #91)*[, et al](#_ENREF_56" \o "Smith, 2011 #91)* [2011](#_ENREF_56" \o "Smith, 2011 #91)) and few include data subsequent to 2005 ([Smith](#_ENREF_56" \o "Smith, 2011 #91)*[, et al](#_ENREF_56" \o "Smith, 2011 #91)* [2011](#_ENREF_56" \o "Smith, 2011 #91)) when *JAK2 V617F* mutation testing became available. To gain insight into the patterns of occurrence of MPNs and MDS/MPNs by age, sex, race/ethnicity, and calendar year; identify susceptible populations; and provide a population-based assessment of patient survival; we used data from the Surveillance, Epidemiology and End Results (SEER) Program to describe incidence of MPNs and MDS/MPNs and patient survival in the US during the early 21st century.

**Methods**

A summary of the evolution of the MPNs and MDS/MPNs according to the WHO and ICD-O-3 classifications is detailed in Table 1. We assessed all malignant cases of MPNs and MDS/MPNs diagnosed among residents of 18 cancer registry areas of the National Cancer Institute’s (NCI) Surveillance, Epidemiology and End Results (SEER-18) Program during 2001-2012. An in-depth description of the SEER Program, including data quality and reliability methods, can be found at [www.seer.cancer.gov](http://www.seer.cancer.gov). In brief,a SEER-18 represents approximately 27.8% of the US population and includes the registries in eight states (Connecticut, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, and Utah); six metropolitan areas (Atlanta, Georgia; Detroit, Michigan; Los Angeles, San Francisco-Oakland, and San Jose-Monterey, California; Seattle-Puget Sound, Washington); the areas of Greater California, Rural Georgia, Greater Georgia; and the Alaska Native Tumor Registry. For specified analyses by calendar year, we utilized SEER-17 (excluding Greater Georgia, which only officially entered the SEER program in 2010).

*Disease classification*

The SEER Program began utilizing the ICD-O-3 for coding information on tumor histology and topography in 2001 ([Fritz*, et al* 2000](#_ENREF_19)). We included all MPNs and MDS/MPNs with an ICD-O-3 behavior code of “/3” (malignant behavior), as specified in Table 1, and to the extent possible, categorized disease entities according to the 2008 WHO classification.

*Incidence*

We calculated incidence rates (IRs), IR ratios (IRRs) and associated 95% confidence intervals (CI) for each MPN and MDS/MPN entity using SEER\*Stat (version 8.2.1). All IRs were age-adjusted using the 2000 US population standard and expressed per one million person-years (PY). We assessed IRs overall and according to sex, race/ethnicity, calendar year of diagnosis, and method of diagnostic confirmation. Age-specific IRs were calculated and depicted (plotted at the midpoint of the age group and at 93 years for the oldest age group) on a log-linear scale, as previously described ([Devesa*, et al* 1995](#_ENREF_15)).

*Delayed reporting*

The SEER Program allows 22 months between the end of the diagnosis year and the time cancers are reported to NCI ([Howlader](#_ENREF_23" \o "Howlader, 2015 #237)*[, et al](#_ENREF_23" \o "Howlader, 2015 #237)* [2015](#_ENREF_23" \o "Howlader, 2015 #237)). If case information becomes available after this period, the data are collected by the registries and reported to NCI in a subsequent data submission. The addition of cases after the standard 22-month delay is termed “reporting delay,” which may lead to initial underestimation of incidence rates ([Clegg](#_ENREF_11" \o "Clegg, 2002 #100)*[, et al](#_ENREF_11" \o "Clegg, 2002 #100)* [2002](#_ENREF_11" \o "Clegg, 2002 #100)). We speculated that new cancer registry reporting requirements in the U.S. for some MPNs and MDS/MPNs in 2001 might be associated with delayed case ascertainment. Reporting delays related to changes in outpatient practice patterns also have been reported for melanoma ([Clegg](#_ENREF_11" \o "Clegg, 2002 #100)*[, et al](#_ENREF_11" \o "Clegg, 2002 #100)* [2002](#_ENREF_11" \o "Clegg, 2002 #100)) and chronic lymphocytic leukaemia (CLL) ([Dores](#_ENREF_16" \o "Dores, 2007 #99)*[, et al](#_ENREF_16" \o "Dores, 2007 #99)* [2007](#_ENREF_16" \o "Dores, 2007 #99)). Similar to CLL, MPNs are often diagnosed in the outpatient setting and may not require histologic confirmation to establish a diagnosis ([Jaffe](#_ENREF_25" \o "Jaffe, 2001 #51)*[, et al](#_ENREF_25" \o "Jaffe, 2001 #51)* [2001](#_ENREF_25" \o "Jaffe, 2001 #51), [Swerdlow](#_ENREF_58" \o "Swerdlow, 2008 #13)*[, et al](#_ENREF_58" \o "Swerdlow, 2008 #13)* [2008](#_ENREF_58" \o "Swerdlow, 2008 #13)). Additionally, because features of MPNs and MDS/MPNs overlap and evolve, precise disease classification may be difficult initially but may become apparent over time. To evaluate whether IRs of MPNs were affected by reporting delays, using SEER-17 we calculated IRs for cases diagnosed during 2001-2002, 2003-2004, 2005-2006, 2007-2008, 2009-2010, and 2011-2012 using data from the November 2014 submission file and compared these IRs to those based on cases diagnosed during these time periods as reported in the November 2012, November 2010, and November 2008 data submission files.

*Survival*

We utilized the SEER\*Stat Survival Session to estimate 5-year relative survival (RS) and 95% CIs. RS provides a measure of the likelihood of survival from MPN or MDS/MPN in the absence of other causes of death by comparing the observed survival proportion among individuals with MPN or MDS/MPN with the survival of a similar (same sex, age, and race) hypothetical “cancer-free” U.S. population ([Howlader](#_ENREF_23" \o "Howlader, 2015 #237)*[, et al](#_ENREF_23" \o "Howlader, 2015 #237)* [2015](#_ENREF_23" \o "Howlader, 2015 #237)). The actuarial or life table method is used to calculate the observed survival rate, with the assumption that cancer deaths represent a negligible proportion of all deaths. Therefore, RS represents the proportion of observed MPN and MDS/MPN survivors compared to the proportion of expected survivors in the population expressed as a percentage. We included all cases of MPNs and MDS/MPNs diagnosed in SEER-18 during 2001-2011 and actively followed for vital status through 2012. Among 40 810 individuals with MPNs and MDS/MPNs, we excluded individuals diagnosed by death certificate only (n=394), with unknown age or age not included in the expected survival table (n=26), alive with unknown survival time (n=124), or excluded from the Research Database (n=88). To minimize bias in survival estimates, we included patients with multiple primary cancers. Four individuals were excluded due to having had a prior diagnosis of MPN or MDS/MPN. Thus, the survival analysis was based on 40 174 individuals with MPNs or MDS/MPNs. We calculated RS for each disease entity overall and according to sex and age at diagnosis.

**Results**

*Overall incidence*

During 2001-2012, there were 31 904 cases of MPNs and 4 102 cases of MDS/MPNs diagnosed among residents of the 18 SEER registries (Table 2). Age-adjusted IRs for MPNs were highest for PV (IR=10.9 per one million person-years) and ET (IR=9.6); intermediate for MPN-unclassifiable (IR=4.8), *BCR-ABL1*-positive CML (IR=3.3), and PMF (IR=3.1); and lowest for chronic neutrophilic leukaemia, chronic eosinophilic leukaemia, and mastocytosis (IRs 0.1-0.4). Among the MDS/MPNs, rates were highest for chronic myelomonocytic leukaemia (CMML, IR=4.1) and very low for *BCR-ABL1*-negative CML and juvenile myelomonocytic leukaemia (IRs=0.1).

*Incidence rates by age and sex*

The overall IR of each MPN and MDS/MPN subtype generally was significantly higher among males than females, with IRs ranging from >14% to >100% higher among males (Table 2). ET was the only entity with significantly lower IR among males than females, (male-to-female IRR=0.80; 95% CI 0.77-0.83). Among the more common entities, *BCR-ABL1*-positive CML (IRR=1.40; 95% CI 1.30-1.50), PV (IRR=1.64; 95% CI 1.57-1.70), and CML-not otherwise specified (NOS) (IRR=1.56; 95% CI 1.49-1.63) predominated among males across nearly the entire age spectrum (Figure 1). PMF, MPN-unclassifiable, and CMML occurred rarely among the youngest age groups, and the male predominance was most apparent only after mid to later life. The female predominance for ET was most notable at ages <60 years. Among males and females, rates increased exponentially with increasing age until the oldest age group for most entities shown, with the pace most rapid for CMML and least rapid for *BCR-ABL1*-positive CML.

*Incidence rates by race/ethnicity*

All specified MPNs, MDS/MPNs, and CML-NOS rates were lower among Hispanic whites than non-Hispanic whites (Table 3). With the exception of chronic eosinophilic leukaemia having a similar incidence among non-Hispanic whites (IRR=0.75; 95% CI 0.51-1.07) and Asians/Pacific Islanders (APIs) (IRR=1.12; 95% CI 0.77-1.60), all other MPN IRs were significantly lower among APIs. In contrast, IRs of ET, chronic eosinophilic leukaemia, MPN-unclassifiable, and CML-NOS were 18%, 60%, 19%, and 8% higher among blacks than non-Hispanic whites; *BCR-ABL1*-positive CML occurred approximately equally (IRR=0.91; 95% CI 0.81-1.03); and only PV (IRR 0.61; 95% CI 0.57-0.66), PMF (IRR 0.73; 95% CI 0.63-0.84), mastocytosis, and CMML IRs were significantly lower among blacks than non-Hispanic whites.

*Delayed reporting*

While the follow-up interval was short and limited to 2001-2012, some findings were notable. The incidence of PV peaked in 2003-2004 and progressively decreased thereafter (Figure 2). In contrast, IRs for ET markedly increased after 2003-2004, with a suggestion of decrease after 2008. *BCR-ABL1*-positive CML IRs increased progressively over the study period, while, CML-NOS rates decreased. PMF, CMML, and MPN-unclassifiable IRs remained relatively stable over time, although rising IRs are suggested beginning in 2011-2012 and additional follow-up will be needed to clarify this observation. Delayed reporting was most evident for PV, ET, and PMF (Figure 2, Supplementary Table 1). In contrast, *BCR-ABL1*-positive CML and CMML rates did not show any significant delayed reporting effects.

*Method of diagnosis according to time period*

In the 2001 and 2008 WHO classifications, the presence of a clonal marker was a major diagnostic criteria for PV, and bone marrow biopsy became nonessential if other criteria were fulfilled ([Jaffe](#_ENREF_25" \o "Jaffe, 2001 #51)*[, et al](#_ENREF_25" \o "Jaffe, 2001 #51)* [2001](#_ENREF_25" \o "Jaffe, 2001 #51), [Swerdlow](#_ENREF_58" \o "Swerdlow, 2008 #13)*[, et al](#_ENREF_58" \o "Swerdlow, 2008 #13)* [2008](#_ENREF_58" \o "Swerdlow, 2008 #13)). In contrast, while clonal markers were incorporated into the diagnostic algorithms of other MPNs, bone marrow biopsy remained an essential component of diagnosis. To assess the effect of *JAK2 V617F* mutation testing introduced in 2005, we evaluated the method of diagnostic confirmation for each entity prior to 2005, early use of *JAK2 V617F* testing during 2005-2008, and broader use of *JAK2 V617F* mutation testing in 2009-2012 (Supplementary Figure and Supplementary Table 2). Because information on *JAK2 V617F* mutation testing is not available in the SEER Program prior to 2010, we utilized calendar year as a surrogate. The percent of cases microscopically confirmed over the three time periods decreased not only for PV, from 61.2% to 54.0% to 50.3%, but also for ET, from 83.2% to 70.9% to 60.1%, during 2001-2004 to 2005-2008 to 2009-2012, respectively. There was a notable rise in the fraction of chronic neutrophilic leukaemia, PV, and ET cases diagnosed by laboratory test/marker study or clinical means over time with an associated decrease in percent of cases diagnosed by microscopic confirmation. Of note, however, is the limited number of cases of chronic neutrophilic leukaemia available for this analysis.

*Relative survival*

Among males and females, for all evaluable MPNs, 5-year RS was more favorable for those <60 years of age at diagnosis than for those diagnosed at older ages (>60 years) (Figure 3, Supplementary Table 3). Patients with PV or ET had the most favorable RS among both sexes and age groups, generally 92.0%-96.7% among those <60 years and 79.1%-87.9% among those >60 years. Survival among the younger age group with PV was similar for males and females (IRR 1.00) and only slightly, but significantly better, for older males than females (male-to-female IRR=1.08, 95% CI 1.03-1.13). Generally, 5-year RS was significantly better for females than males at all ages, except for PV, *BCR-ABL1-*positive CML, and CML-NOS among males >60 years. Based on small numbers, patients with chronic neutrophilic leukaemia, CMML, or *BCR-ABL1*-negative atypical CML had the least favorable 5-year RS (<35%).

**Discussion**

This is the largest population-based study of MPNs and MDS/MPNs in the US that comprehensively describes incidence patterns and patient survival by disease subtypes, and one of the few to include more than five years of data from the *JAK2 V617F* diagnostic era. Disease heterogeneity across MPNs and MDS/MPNs was evident based on distinct age, sex, and racial/ethnic incidence patterns, as has similarly been described for other myeloid and lymphoproliferative neoplasms ([Dores](#_ENREF_17" \o "Dores, 2012 #125)*[, et al](#_ENREF_17" \o "Dores, 2012 #125)* [2012](#_ENREF_17" \o "Dores, 2012 #125), [Morton](#_ENREF_36" \o "Morton, 2006 #190)*[, et al](#_ENREF_36" \o "Morton, 2006 #190)* [2006](#_ENREF_36" \o "Morton, 2006 #190)). In this first assessment of delayed reporting, we found significant delayed reporting for PV, ET, and PMF, entities with new cancer registry reporting requirements in the U.S. in 2001, demonstrating that IRs were previously underestimated. The decrease in microscopic confirmation for PV and ET cases over time suggests that diagnoses are increasingly reliant on clonal markers/clinical diagnosis, and for ET, that fewer cases are diagnosed utilizing WHO criteria. Further, the decline in PV incidence after 2004 may have been influenced by the availability of *JAK2 V617F* mutation testing facilitating the exclusion of cases of secondary erythrocytosis. Lastly, we found that 5-year RS varied considerably by MPN subtype, with poorer survival among males, with a few exceptions, and among those diagnosed at older ages.

*Population-based studies in the 21st century*

Population-based studies describing incidence of MPNs and MDS/MPNs limited to the current century are sparse ([Rollison](#_ENREF_51" \o "Rollison, 2008 #102)*[, et al](#_ENREF_51" \o "Rollison, 2008 #102)* [2008](#_ENREF_51" \o "Rollison, 2008 #102), [Sant](#_ENREF_53" \o "Sant, 2010 #96)*[, et al](#_ENREF_53" \o "Sant, 2010 #96)* [2010](#_ENREF_53" \o "Sant, 2010 #96), [Smith](#_ENREF_56" \o "Smith, 2011 #91)*[, et al](#_ENREF_56" \o "Smith, 2011 #91)* [2011](#_ENREF_56" \o "Smith, 2011 #91)) and few include data subsequent to 2005 ([Smith](#_ENREF_56" \o "Smith, 2011 #91)*[, et al](#_ENREF_56" \o "Smith, 2011 #91)* [2011](#_ENREF_56" \o "Smith, 2011 #91)). Smith and colleagues described incidence for CML, PMF, chronic MPNs, and CMML during 2004-2009 in the Haematologic Malignancy Research Network and found age and gender to be determinants of these and other haematologic diseases ([Smith](#_ENREF_56" \o "Smith, 2011 #91)*[, et al](#_ENREF_56" \o "Smith, 2011 #91)* [2011](#_ENREF_56" \o "Smith, 2011 #91)). While they noted a male predominance across most myeloid neoplasms, chronic MPNs were associated with a significant female excess. Given the differences in disease groupings in prior studies, as described by others ([Moulard](#_ENREF_37" \o "Moulard, 2014 #37)*[, et al](#_ENREF_37" \o "Moulard, 2014 #37)* [2014](#_ENREF_37" \o "Moulard, 2014 #37), [Titmarsh](#_ENREF_62" \o "Titmarsh, 2014 #218)*[, et al](#_ENREF_62" \o "Titmarsh, 2014 #218)* [2014](#_ENREF_62" \o "Titmarsh, 2014 #218)), comparison with our findings is limited. In the European HAEMACARE project (2000-2002), a clear male predominance was noted for CML, whereas incidence was nearly equal for other MPNs considered as a group ([Sant](#_ENREF_53" \o "Sant, 2010 #96)*[, et al](#_ENREF_53" \o "Sant, 2010 #96)* [2010](#_ENREF_53" \o "Sant, 2010 #96)). The authors also found less geographic variation across Europe for CML than other MPNs, citing more stable diagnostic and classification criteria over time for the former, similar to the disease classification changes we describe in the US. Using data from SEER and the North American Association of Central Cancer Registries, Rollison *et al* described incidence and 3-year RS of chronic myeloproliferative disorders (MPNs, excluding CML, considered in aggregate) diagnosed 2001-2004 in the US, with information by MPN subtypes limited to overall IRs ([Rollison](#_ENREF_51" \o "Rollison, 2008 #102)*[, et al](#_ENREF_51" \o "Rollison, 2008 #102)* [2008](#_ENREF_51" \o "Rollison, 2008 #102)). Increasing age, male sex, and white race were noted to be risk factors for these chronic myeloproliferative disorders ([Rollison](#_ENREF_51" \o "Rollison, 2008 #102)*[, et al](#_ENREF_51" \o "Rollison, 2008 #102)* [2008](#_ENREF_51" \o "Rollison, 2008 #102)). We were able to assess MPNs and MDS/MPNs by subtype, and found age-, sex-, and racial/ethnic differences in IRs and reported 5-year patient survival by gender and age. Our findings suggest important etiologic, susceptibility, and/or biologic differences across subtypes that are obscured when disease categories are considered in aggregate.

*Race-ethnicity*

Population-based data describing incidence of MPN and MDS/MPN subtypes among different racial/ethnic groups has not been previously reported. We report lower IRs of all evaluable MPNs and MDS/MPNs among Hispanic whites compared to non-Hispanic whites. Similarly, with the exception of chronic eosinophilic leukaemia, APIs had significantly lower incidence of MPNs and MDS/MPNs compared to non-Hispanic whites. Although subtype-specific incidence data by racial/ethnic subgroups were not previously available, it is notable that *JAK2 V617F* mutations have been reported with generally similar frequencies among Asian populations with MPNs as in other populations ([Ha](#_ENREF_21" \o "Ha, 2012 #157)*[, et al](#_ENREF_21" \o "Ha, 2012 #157)* [2012](#_ENREF_21" \o "Ha, 2012 #157), [Xu](#_ENREF_64" \o "Xu, 2012 #103)*[, et al](#_ENREF_64" \o "Xu, 2012 #103)* [2012](#_ENREF_64" \o "Xu, 2012 #103)). We observed greater variation in IRs across MPN and MDS/MPN subtypes among blacks than other racial/ethnic groups when compared to non-Hispanic whites. Interestingly, ET was associated with a female predominance among non-Hispanic whites, white Hispanics, blacks, and APIs, suggesting shared gender-specific risk factor(s) across these racial/ethnic groups. The diverse incidence patterns we observed for MPNs and MDS/MPNs support inherent differences in susceptibility.

*Sex*

Excluding ET, which predominated among females, and mastocytosis, which occurred approximately equally among males and females, all other MPNs and MDS/MPNs were associated with significantly higher overall IRs among males. The gender disparities for PV, ET, and PMF are similar to those reported in a recent systematic review and meta-analysis of MPNs ([Titmarsh](#_ENREF_62" \o "Titmarsh, 2014 #218)*[, et al](#_ENREF_62" \o "Titmarsh, 2014 #218)* [2014](#_ENREF_62" \o "Titmarsh, 2014 #218)) and a review of European studies ([Moulard](#_ENREF_37" \o "Moulard, 2014 #37)*[, et al](#_ENREF_37" \o "Moulard, 2014 #37)* [2014](#_ENREF_37" \o "Moulard, 2014 #37)), but differ from the higher PV rates reported among women than men in Malmo City, Sweden between 1980-1984 ([Berglund and Zettervall 1992](#_ENREF_6)). Among the European studies, ET was noted to predominate among women in most, but not all studies ([Maynadie](#_ENREF_33" \o "Maynadie, 2011 #97)*[, et al](#_ENREF_33" \o "Maynadie, 2011 #97)* [2011](#_ENREF_33" \o "Maynadie, 2011 #97)). With the exception of ET and cancers of the anus, gallbladder, breast, and thyroid, few hematopoietic ([Dores](#_ENREF_17" \o "Dores, 2012 #125)*[, et al](#_ENREF_17" \o "Dores, 2012 #125)* [2012](#_ENREF_17" \o "Dores, 2012 #125), [Morton](#_ENREF_36" \o "Morton, 2006 #190)*[, et al](#_ENREF_36" \o "Morton, 2006 #190)* [2006](#_ENREF_36" \o "Morton, 2006 #190), [Smith](#_ENREF_56" \o "Smith, 2011 #91)*[, et al](#_ENREF_56" \o "Smith, 2011 #91)* [2011](#_ENREF_56" \o "Smith, 2011 #91)) and solid tumors ([Cook*, et al* 2009](#_ENREF_12)) demonstrate a female proclivity. Possible explanations for the gender differences include hormonal influences, occupational exposures, lifestyle factors, or other health conditions ([Cook*, et al* 2009](#_ENREF_12), [Smith](#_ENREF_56" \o "Smith, 2011 #91)*[, et al](#_ENREF_56" \o "Smith, 2011 #91)* [2011](#_ENREF_56" \o "Smith, 2011 #91)). The gender disparity for ET was most prominent in young adulthood and midlife supporting a potential role for hormonal influences in disease initiation/progression. As recently reviewed, some male predominant occupations including agricultural workers and other rural sector workers have been found to have increased risk of MPNs, whereas no association has been found for professional, administrative, and clerical occupations ([Anderson](#_ENREF_3" \o "Anderson, 2012 #120)*[, et al](#_ENREF_3" \o "Anderson, 2012 #120)* [2012](#_ENREF_3" \o "Anderson, 2012 #120)). Distinct etiologies for MPN subtypes are supported by the association of ET, but not PV, with body mass index, physical activity, and adult onset diabetes; whereas PV, but not ET, has been linked with smoking ([Leal](#_ENREF_30" \o "Leal, 2013 #175)*[, et al](#_ENREF_30" \o "Leal, 2013 #175)* [2013](#_ENREF_30" \o "Leal, 2013 #175)). Although these entities are rare, subtype-specific analytical studies are needed to clarify subtype-specific risk factors ([Kroll](#_ENREF_28" \o "Kroll, 2012 #171)*[, et al](#_ENREF_28" \o "Kroll, 2012 #171)* [2012](#_ENREF_28" \o "Kroll, 2012 #171), [Murphy](#_ENREF_38" \o "Murphy, 2013 #192)*[, et al](#_ENREF_38" \o "Murphy, 2013 #192)* [2013](#_ENREF_38" \o "Murphy, 2013 #192)).

*Age*

Age at relevant exposure, duration of exposure, and disease latency influence age-specific patterns. Accumulating DNA damage, immune senescence, autoimmunity, and chronic inflammation have been suggested as causes for increasing cancer incidence with aging ([Boren and Gershwin 2004](#_ENREF_8), [Coussens and Werb 2002](#_ENREF_13)). The rate of rise in incidence of *BCR-ABL1*-positive CML with advancing age was less prominent than in other MPNs, and the flattening IR pattern is reminiscent of that observed for AML subtypes with associated cytogenetic abnormalities (e.g., t(8:21), inv(16), t(15;17)) ([Dores](#_ENREF_17" \o "Dores, 2012 #125)*[, et al](#_ENREF_17" \o "Dores, 2012 #125)* [2012](#_ENREF_17" \o "Dores, 2012 #125)). The slowing in IRs with aging may reflect a change in disease susceptibility or less intensive testing among older individuals. PMF, CMML, and MPN-unclassifiable occurred rarely prior to age 25 years, in contrast to PV, ET, and CML. While the majority of MPNs occur in a sporadic fashion, childhood MPNs have been reported ([Niemeyer](#_ENREF_40" \o "Niemeyer, 1997 #193)*[, et al](#_ENREF_40" \o "Niemeyer, 1997 #193)* [1997](#_ENREF_40" \o "Niemeyer, 1997 #193), [Teofili](#_ENREF_61" \o "Teofili, 2007 #216)*[, et al](#_ENREF_61" \o "Teofili, 2007 #216)* [2007](#_ENREF_61" \o "Teofili, 2007 #216)), and studies have suggested a role for shared susceptibility genes and familial inheritance patterns for some ([Landgren](#_ENREF_29" \o "Landgren, 2008 #94)*[, et al](#_ENREF_29" \o "Landgren, 2008 #94)* [2008](#_ENREF_29" \o "Landgren, 2008 #94), [Ranjan](#_ENREF_50" \o "Ranjan, 2013 #205)*[, et al](#_ENREF_50" \o "Ranjan, 2013 #205)* [2013](#_ENREF_50" \o "Ranjan, 2013 #205)), but not all MPNs ([Bjorkholm*, et al* 2013](#_ENREF_7)). As postulated for other infant leukaemias ([Linet](#_ENREF_31" \o "Linet, 2013 #231)*[, et al](#_ENREF_31" \o "Linet, 2013 #231)* [2013](#_ENREF_31" \o "Linet, 2013 #231)), in utero exposures and/or maternal/paternal factors may be most relevant for juvenile myelomoncytic leukaemia given the early age at onset (median age <1 year).

*Survival*

With the exception of CML ([Brunner*, et al* 2013](#_ENREF_9), [Pulte](#_ENREF_49" \o "Pulte, 2013 #202)*[, et al](#_ENREF_49" \o "Pulte, 2013 #202)* [2013](#_ENREF_49" \o "Pulte, 2013 #202)), population-based studies describing survival of MPNs in the US are sparse ([Price](#_ENREF_48" \o "Price, 2014 #114)*[, et al](#_ENREF_48" \o "Price, 2014 #114)* [2014](#_ENREF_48" \o "Price, 2014 #114), [Rollison](#_ENREF_51" \o "Rollison, 2008 #102)*[, et al](#_ENREF_51" \o "Rollison, 2008 #102)* [2008](#_ENREF_51" \o "Rollison, 2008 #102)), in contrast to reports emanating from European countries ([Barbui*, et al* 2011](#_ENREF_5), [Cervantes*, et al* 2012](#_ENREF_10), [Hultcrantz](#_ENREF_24" \o "Hultcrantz, 2012 #95)*[, et al](#_ENREF_24" \o "Hultcrantz, 2012 #95)* [2012](#_ENREF_24" \o "Hultcrantz, 2012 #95), [Maynadie](#_ENREF_32" \o "Maynadie, 2013 #93)*[, et al](#_ENREF_32" \o "Maynadie, 2013 #93)* [2013](#_ENREF_32" \o "Maynadie, 2013 #93), [Maynadie](#_ENREF_33" \o "Maynadie, 2011 #97)*[, et al](#_ENREF_33" \o "Maynadie, 2011 #97)* [2011](#_ENREF_33" \o "Maynadie, 2011 #97), [Osca-Gelis](#_ENREF_41" \o "Osca-Gelis, 2014 #194)*[, et al](#_ENREF_41" \o "Osca-Gelis, 2014 #194)* [2014](#_ENREF_41" \o "Osca-Gelis, 2014 #194), [Phekoo](#_ENREF_46" \o "Phekoo, 2006 #103)*[, et al](#_ENREF_46" \o "Phekoo, 2006 #103)* [2006](#_ENREF_46" \o "Phekoo, 2006 #103), [Sant](#_ENREF_54" \o "Sant, 2014 #209)*[, et al](#_ENREF_54" \o "Sant, 2014 #209)* [2014](#_ENREF_54" \o "Sant, 2014 #209)). This is the first US population-based study to describe 5-year RS of MPN and MDS/MPN by individual subtype, sex, and age for cases diagnosed in the modern diagnostic and treatment era. We found the most favorable 5-year RS for PV and ET, as also noted by others ([Hultcrantz](#_ENREF_24" \o "Hultcrantz, 2012 #95)*[, et al](#_ENREF_24" \o "Hultcrantz, 2012 #95)* [2012](#_ENREF_24" \o "Hultcrantz, 2012 #95), [Maynadie](#_ENREF_32" \o "Maynadie, 2013 #93)*[, et al](#_ENREF_32" \o "Maynadie, 2013 #93)* [2013](#_ENREF_32" \o "Maynadie, 2013 #93), [Mesa](#_ENREF_35" \o "Mesa, 1999 #107)*[, et al](#_ENREF_35" \o "Mesa, 1999 #107)* [1999](#_ENREF_35" \o "Mesa, 1999 #107), [Phekoo](#_ENREF_46" \o "Phekoo, 2006 #103)*[, et al](#_ENREF_46" \o "Phekoo, 2006 #103)* [2006](#_ENREF_46" \o "Phekoo, 2006 #103), [Rollison](#_ENREF_51" \o "Rollison, 2008 #102)*[, et al](#_ENREF_51" \o "Rollison, 2008 #102)* [2008](#_ENREF_51" \o "Rollison, 2008 #102)). While some studies have reported normal life expectancy with ET ([Abdulkarim](#_ENREF_1" \o "Abdulkarim, 2010 #118)*[, et al](#_ENREF_1" \o "Abdulkarim, 2010 #118)* [2010](#_ENREF_1" \o "Abdulkarim, 2010 #118), [Passamonti](#_ENREF_43" \o "Passamonti, 2008 #196)*[, et al](#_ENREF_43" \o "Passamonti, 2008 #196)* [2008](#_ENREF_43" \o "Passamonti, 2008 #196), [Passamonti](#_ENREF_44" \o "Passamonti, 2004 #197)*[, et al](#_ENREF_44" \o "Passamonti, 2004 #197)* [2004](#_ENREF_44" \o "Passamonti, 2004 #197), [Rozman](#_ENREF_52" \o "Rozman, 1991 #232)*[, et al](#_ENREF_52" \o "Rozman, 1991 #232)* [1991](#_ENREF_52" \o "Rozman, 1991 #232)), our findings of decreased 5-year RS for ET and PV, confirm clinical and population-based reports from Europe ([Gruppo Italiano Studio Policitemia 1995](#_ENREF_20" \o "Gruppo Italiano Studio Policitemia, 1995 #34), [Hultcrantz](#_ENREF_24" \o "Hultcrantz, 2012 #95)*[, et al](#_ENREF_24" \o "Hultcrantz, 2012 #95)* [2012](#_ENREF_24" \o "Hultcrantz, 2012 #95), [Passamonti](#_ENREF_44" \o "Passamonti, 2004 #197)*[, et al](#_ENREF_44" \o "Passamonti, 2004 #197)* [2004](#_ENREF_44" \o "Passamonti, 2004 #197)) and the US ([Price](#_ENREF_48" \o "Price, 2014 #114)*[, et al](#_ENREF_48" \o "Price, 2014 #114)* [2014](#_ENREF_48" \o "Price, 2014 #114), [Wolanskyj](#_ENREF_63" \o "Wolanskyj, 2006 #233)*[, et al](#_ENREF_63" \o "Wolanskyj, 2006 #233)* [2006](#_ENREF_63" \o "Wolanskyj, 2006 #233)).

Our study is among the first to demonstrate the absence of gender disparity in RS among patients <60 years with PV. We confirm findings from a SEER-Medicare study (2000-2005) that older males with PV have more favorable survival than older women, and that the converse association is noted for ET ([Price](#_ENREF_48" \o "Price, 2014 #114)*[, et al](#_ENREF_48" \o "Price, 2014 #114)* [2014](#_ENREF_48" \o "Price, 2014 #114)). We extend these results by demonstrating that the survival advantage for older males with PV and older (as well as younger) females with ET persists for more than a decade. Older age is an established risk factor for thrombosis in PV and ET and a negative prognostic indicator in PMF ([Tefferi and Pardanani 2015](#_ENREF_59" \o "Tefferi, 2015 #268)). Older age remains a significant risk factor for thrombosis in ET, after adjusting for risk factors included in the International Prognostic Score for thrombosis in the World Health Organization - Essential Thrombocythemia (IPSET-thrombosis) ([Barbui](#_ENREF_4" \o "Barbui, 2012 #273)*[, et al](#_ENREF_4" \o "Barbui, 2012 #273)* [2012](#_ENREF_4" \o "Barbui, 2012 #273)). In PMF, age is an independent risk factor for survival, after adjusting for risk factors included in the Dynamic International Prognostic Scoring System (anemia, leukocytosis, peripheral blood blasts, and constitutional symptoms) ([Passamonti](#_ENREF_42" \o "Passamonti, 2010 #270)*[, et al](#_ENREF_42" \o "Passamonti, 2010 #270)* [2010](#_ENREF_42" \o "Passamonti, 2010 #270)). In addition, older age is a poor prognostic feature in the Sokal and Hasford scoring systems used in *BCR-ABL1*-positive CML ([Hasford](#_ENREF_22" \o "Hasford, 1998 #269)*[, et al](#_ENREF_22" \o "Hasford, 1998 #269)* [1998](#_ENREF_22" \o "Hasford, 1998 #269), [Sokal](#_ENREF_57" \o "Sokal, 1984 #272)*[, et al](#_ENREF_57" \o "Sokal, 1984 #272)* [1984](#_ENREF_57" \o "Sokal, 1984 #272)). Consistent with these prognostic scoring systems, we describe consistently worse survival among older individuals (>60 years) for all evaluable MPNs and MDS/MPNs compared to younger individuals. Limited to a pediatric population, survival of juvenile myelomonocytic leukaemia is dependent on prognostic features ([Emanuel 2008](#_ENREF_18" \o "Emanuel, 2008 #260)), and a 45% 5-year overall survival was reported in a population-based study (1990-1999) in the United Kingdom ([Passmore](#_ENREF_45" \o "Passmore, 2003 #261)*[, et al](#_ENREF_45" \o "Passmore, 2003 #261)* [2003](#_ENREF_45" \o "Passmore, 2003 #261)). We report slightly more favorable 55.7% 5-year RS in our study, notably similar to that reported in the SEER Program for acute myelomonocytic leukaemia among the youngest age groups ([Dores](#_ENREF_17" \o "Dores, 2012 #125)*[, et al](#_ENREF_17" \o "Dores, 2012 #125)* [2012](#_ENREF_17" \o "Dores, 2012 #125)).

*Strengths and limitations*

Among the strengths of this descriptive epidemiologic population-based study is the large number of cases that allowed us to calculate IRs and RS for individual MPNs and MDS/MPNs during 2001-2012. We had sufficient cases to assess gender differences by age and to provide a detailed assessment of IRs by racial/ethnic groups not previously reported. We cannot exclude the possibility of underascertainment or underreporting of cases, which has been documented to occur in myeloid neoplasms ([Craig](#_ENREF_14" \o "Craig, 2012 #121)*[, et al](#_ENREF_14" \o "Craig, 2012 #121)* [2012](#_ENREF_14" \o "Craig, 2012 #121)), particularly among the elderly where diagnostic evaluation might not be as aggressively sought as in younger individuals. In addition, the overlap in clinical, laboratory, morphologic, and molecular features of MPNs and MDS/MPNs may present diagnostic challenges, despite the availability of clonal markers in the 21st century ([Jaffe](#_ENREF_25" \o "Jaffe, 2001 #51)*[, et al](#_ENREF_25" \o "Jaffe, 2001 #51)* [2001](#_ENREF_25" \o "Jaffe, 2001 #51), [Swerdlow](#_ENREF_58" \o "Swerdlow, 2008 #13)*[, et al](#_ENREF_58" \o "Swerdlow, 2008 #13)* [2008](#_ENREF_58" \o "Swerdlow, 2008 #13)). MPNs and MDS/MPNs also have a potential to transform to myelofibrosis ([Kreft](#_ENREF_27" \o "Kreft, 2005 #168)*[, et al](#_ENREF_27" \o "Kreft, 2005 #168)* [2005](#_ENREF_27" \o "Kreft, 2005 #168)), MDS, or acute leukaemia, with clinical, morphologic, and molecular features that can evolve over time. Not surprisingly, there is known inter-observer variability in establishing MPN diagnoses ([Alvarez-Larran](#_ENREF_2" \o "Alvarez-Larran, 2014 #119)*[, et al](#_ENREF_2" \o "Alvarez-Larran, 2014 #119)* [2014](#_ENREF_2" \o "Alvarez-Larran, 2014 #119)), and a potential for disease misclassification in our study and those by other investigators ([Mehta](#_ENREF_34" \o "Mehta, 2014 #114)*[, et al](#_ENREF_34" \o "Mehta, 2014 #114)* [2014](#_ENREF_34" \o "Mehta, 2014 #114), [Moulard](#_ENREF_37" \o "Moulard, 2014 #37)*[, et al](#_ENREF_37" \o "Moulard, 2014 #37)* [2014](#_ENREF_37" \o "Moulard, 2014 #37), [Sant](#_ENREF_53" \o "Sant, 2010 #96)*[, et al](#_ENREF_53" \o "Sant, 2010 #96)* [2010](#_ENREF_53" \o "Sant, 2010 #96), [Titmarsh](#_ENREF_62" \o "Titmarsh, 2014 #218)*[, et al](#_ENREF_62" \o "Titmarsh, 2014 #218)* [2014](#_ENREF_62" \o "Titmarsh, 2014 #218)) lacking a centralized pathology and clinical review. Our assessment of delayed reporting was an effort to address potential misclassification through correction and updating of diagnoses. We used calendar year as a surrogate for *JAK2 V617F* mutation status because information on this clonal marker was not available in the SEER database prior to 2011. However, by including cases from the most recent decade, we were able to maximize the number of cases diagnosed during an era when molecular testing was available. Lastly, because information on chemotherapy and other medical therapies is not publicly available in the SEER database, our survival analyses did not include treatment information.

*Summary*

In summary, diverse MPNs and MDS/MPNs incidence patterns support variable etiologies and/or susceptibility by age, sex, and race/ethnicity. While changes in classification schemes and misclassification across entities may have influenced our results, these high quality data from the SEER Program reflect diagnoses established in the general US population. We found that microscopic confirmation of PV and ET decreased over the study period, and note that the forthcoming WHO classification describes an increased role for histologic confirmation in new diagnostic algorithms, including PV ([Tefferi and Pardanani 2015](#_ENREF_59" \o "Tefferi, 2015 #268)). As MPN diagnoses are facilitated by genetic testing, improved classification schemes ([Tefferi](#_ENREF_60" \o "Tefferi, 2014 #214)*[, et al](#_ENREF_60" \o "Tefferi, 2014 #214)* [2014](#_ENREF_60" \o "Tefferi, 2014 #214)), and increased awareness of reporting requirements to cancer registries ([Selinger and Ma 2009](#_ENREF_55" \o "Selinger, 2009 #210)), more timely reporting and a decrease in disease misclassification (based on adherence to diagnostic criteria) is expected. Given the major role of molecular diagnostics in the MPNs and MDS/MPNs, strong consideration should be given to expanded collection of data on molecular markers by cancer registries ([Polednek 2011](#_ENREF_47" \o "Polednek, 2011 #199)). Information on molecular markers would further enrich population-based analyses and potentially unveil additional etiologic and susceptibility clues. Lastly, differences in patient survival by age suggest that those >60 years may benefit most from inclusion in clinical trials.

**Acknowledgements:**

This work was supported by the Oklahoma City Veterans Affairs Health Care System in Oklahoma City; and the Intramural Research Program, National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

The content of this publication does not necessarily reflect the views or polices of the Department of Veterans Affairs or the Department of Health and Human Services.

**Authorship:**

*Contributions:*S.A.S., S.S.D., L.M.M., R.E.C., M.S.L., and G.M.D. conceived and designed research; G.M.D. performed statistical analysis; S.A.S., L.M.M., S.S.D., D.P.C., R.E.C., M.S.L., and G.M.D analyzed and interpreted data; S.A.S. and G.M.D. wrote the manuscript; and S.A.S., S.S.D., L.M.M., D.P.C., R.E.C., M.S.L., and G.M.D. critically reviewed and edited the manuscript for important intellectual content.

*Conflict of interest disclosure:* The authors declare no competing financial interests.

**Figure legends**

**Figure 1. Age-specific incidence rates of myeloproliferative neoplasms and myelodysplastic/myeloproliferative neoplasms according to sex, SEER-18, 2001-2012.** Per SEER Program convention, IRs based on fewer than 16 cases were omitted from the figure ([Howlader](#_ENREF_23" \o "Howlader, 2015 #237)*[, et al](#_ENREF_23" \o "Howlader, 2015 #237)* [2015](#_ENREF_23" \o "Howlader, 2015 #237)).

**Figure 2. Age-adjusted incidence rates of myeloproliferative neoplasms and myelodysplastic/myeloproliferative neoplasms, according to year of SEER submission file, SEER-17, 2001-2012.** The six 2-year calendar periods reflecting year of diagnosis include 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, and 2011–2012.

**Figure 3. Relative survival of patients with myeloproliferative neoplasms and myelodysplastic/myeloproliferative neoplasms according to sex and age at diagnosis, SEER-18, 2001-2012.** Individuals were diagnosed 2001-2011 and followed through 2012. Survival is presented by sex and age (<60 years vs. ≥60 years) at diagnosis. Survival rates based on fewer than 25 cases (total) were omitted from the figure. The total number of cases among each sex/age group is indicated within the legend.

**Supplementary information legends**

**Supplementary figure. Frequency of method of diagnosis of myeloproliferative neoplasms and myelodysplastic/myeloproliferative neoplasms diagnosed in SEER-18 according to calendar period, 2001-2012.** Categories include: [Microscopic] microscopically confirmed (positive histology, positive cytology, positive histology and positive immunophenotyping and/or positive genetic studies, positive microscopic confirmation with method unspecified); [Lab test] laboratory test/marker study; [Clinical] clinical diagnosis only (direct visualization without microscopic confirmation, radiography without microscopic confirmation, clinical diagnosis only); and [Not specified] other method of diagnosis/unknown.

**Supplementary table 1.** Incidence rates and incidence rate ratios of myeloproliferative neoplasms and myelodysplastic/myeloproliferative neoplasms diagnosed in SEER-17 according to calendar year of diagnosis and data submission file.

**Supplementary table 2.** Number of cases of myeloproliferative neoplasms and myelodysplastic/myeloproliferative neoplasms diagnosed in SEER-18 according to method of diagnosis and calendar period, 2001-2012.

**Supplementary table 3.** Five-year relative survival of patients with myeloproliferative neoplasms and myelodysplastic/myeloproliferative neoplasms diagnosed in SEER-18 according to age, 2001-2011.

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