Myeloproliferative Neoplasms

*Trends in incidence, prevalence and survival*

Christina Roaldsnes

Master thesis
Institute of Health and Society
Faculty of Medicine

UNIVERSITY OF OSLO

June 2016
Myeloproliferative Neoplasms – trends in incidence, prevalence and survival
© Christina Roaldsnes

2016

Myeloproliferative neoplasms, trends in incidence, prevalence and survival

Christina Roaldsnes

http://www.duo.uio.no/

Trykk: Reprosentralen, Universitetet i Oslo
Foreword

When I first started working as a research nurse in 2006, my daily activity consisted of carrying out clinical trials in accordance with good clinical practice. With time, the wish to gain a better understanding of study-design, methods, analysis and results presented, has led me to the Master study of Health Sciences at the University of Oslo.

I presently work as a project coordinator for the section of Research Haematology, Sykehuset Østfold, where I coordinate various research projects and partake in a registry study on ITP. Myeloproliferative neoplasm is a rare disease. It is associated with lower survival and little is published on this disease in Norway. In 2014 we received data on MPN from the Cancer Registry of Norway and the result is presented in this paper and thesis.

This thesis is written in two parts where the first part consists of introduction, theoretical framework and study design. The second part is written as a paper following the European Journal of Haematology’s guidelines for manuscript.

The knowledge gained at this course and the writing of the paper and thesis, has given me a better understanding of professional medical research and it inspires me to do further research.

I am grateful for the opportunity to work with research on a daily basis. I would also like to express my gratitude to co-authors Henrik Frederiksen and René Holst for helpful contributions and guidance with the paper. I would like to thank Waleed Ghanima for guidance and giving me this opportunity, and my colleagues and family for their patience.
# Table of contents

Myeloproliferative Neoplasms – trends in incidence, prevalence and survival ...................... III
Foreword ........................................................................................................................................ VII
Table of contents .................................................................................................................. IX
1 Introduction ......................................................................................................................... 5
   Research question ............................................................................................................... 6
2 Theoretical background ....................................................................................................... 7
   2.1 Myeloproliferative neoplasms ..................................................................................... 7
      2.1.1 Polycythemia vera ............................................................................................... 8
      2.1.2 Essential thrombocythemia .................................................................................. 9
      2.1.3 Myelofibrosis ...................................................................................................... 10
      2.1.4 Unclassified MPN .............................................................................................. 11
3 Definitions .................................................................................................................................. 12
   3.1 Epidemiology .................................................................................................................. 12
   3.2 Incidence rate .................................................................................................................. 12
      1.2.1 Age adjusted incidence rates .............................................................................. 12
   3.3 Prevalence ....................................................................................................................... 13
   3.4 Survival ............................................................................................................................ 13
      3.4.1 Standardized mortality rate .................................................................................. 13
4 Material and methods ............................................................................................................ 14
   4.1 Design ............................................................................................................................... 14
   4.2 Study population ............................................................................................................. 14
      4.1.1 Sample size ............................................................................................................ 15
   4.3 Statistics ............................................................................................................................ 15
5 Discussion .................................................................................................................................. 17
   5.1 Results ............................................................................................................................... 17
   5.2 Methods ............................................................................................................................. 17
6 Conclusion and further studies .............................................................................................. 18
7 Ethical consideration .............................................................................................................. 19
References ..................................................................................................................................... 20
Paper ........................................................................................................................................... 41

IX
Appendix A Approval from Regional Ethics Committee

Appendix B Author's guidelines for European Journal of Haematology
Abstract

Purpose: We aimed to study trends in incidence, prevalence and survival of myeloproliferative neoplasm in Norway.

Background: Polycythemia vera (PV), essential thrombocytthemia (ET) and myelofibrosis (MF) are clonal disorders collectively named myeloproliferative neoplasms (MPN). Published data on epidemiology of MPN after the discovery of JAK2 mutation and the introduction of 2008 WHO classifications are scarce.

Method: We identified 2453 persons diagnosed with MPN from the Cancer Registry of Norway between 1993 and 2012. We report age-adjusted incidence rates, prevalence, relative survival and standardized mortality rates.

Results: The overall age-adjusted yearly incidence rate of PV increased from 0.4/10^5 to 0.7/10^5, ET increased from 0.3/10^5 to 0.9/10^5 and MF from 0.2/10^5 to 0.5/10^5. Prevalence of PV, ET and MF was 9.2, 8.6 and 3.0 per 10^5 inhabitants, respectively. The 5-year relative survival (RS) of ET and PV was slightly reduced with no improvement. The 5-year RS of MF 58.1% (2008-2012). Standardized mortality rate (SMR), defined as the ratio of the mortality rate of the MPN population to that of the general population, was 1.9 (95% CI 1.2 - 2.7).

Conclusions: The incidences of ET, PV, and MF almost doubled during the years 2007-2012 as compared to 1995-2006. This increment in incidence may be related to identification of the JAK2 mutation and the derived 2008 WHO-guidelines for MPN. The RS was only slightly reduced for PV and ET and did not improve with time. RS was substantially reduced for MF but improved over time.

Keywords: myeloproliferative neoplasm, polycythemia vera, essential thrombocytthemia, myelofibrosis, unclassified MPN, epidemiology, incidence, prevalence, survival
Sammendrag

Formål: Vårt formål er å undersøke trenden for insidens, prevalens og overlevelse av myeloproliferativ neoplasi i Norge.

Bakgrunn: Polycytemia vera (PV), essensiell trombocytemi (ET) og myelofibrose (MF) er klonale lidelser kollektivt navngitt myeloproliferative neoplasmer (MPN). Publiserte data på epidemiologi av MPN etter oppdagelsen av JAK2 mutasjon og innføring av 2008 WHO’s klassifikasjoner, er få.


Resultater: Den generelle aldersjusterte årlige insidens av PV økte fra 0.4 / 10^5 til 0.7 / 10^5, ET 0.3 / 10^5 til 0.9 / 10^5 og MF 0.2 / 10^5 til 0.5 / 10^5. Prevalens av PV, ET og MF var henholdsvis 9.2, 8.6 og 3.0 per 10^5 innbyggere. 5-års relativ overlevelse av ET og PV var bare litt redusert. 5-års relativ overlevelse av MF var 58,1% (2008-2012). Standardisert mortalitet (SMR), definert som forholdet mellom mortalitets rater av MPN populasjonen og den av bakgrunnspopulasjonen, var 1,9 (95% CI 1.2 til 2.7).

# ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM</td>
<td>Bone Marrow</td>
</tr>
<tr>
<td>CALR</td>
<td>Calreticulin</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CML</td>
<td>Chronic Myeloid Leukemia</td>
</tr>
<tr>
<td>CRN</td>
<td>Cancer Registry Norway</td>
</tr>
<tr>
<td>ET</td>
<td>Essential Thrombocythemia</td>
</tr>
<tr>
<td>JAK</td>
<td>Janus Kinase</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate Dehydrogenase</td>
</tr>
<tr>
<td>MF</td>
<td>Myelofibrosis</td>
</tr>
<tr>
<td>MPN</td>
<td>Myeloproliferative Neoplasms</td>
</tr>
<tr>
<td>MPL</td>
<td>Myeloproliferative Leukemia Protein</td>
</tr>
<tr>
<td>PV</td>
<td>Polycythemia Vera</td>
</tr>
<tr>
<td>RS</td>
<td>Relative Survival</td>
</tr>
<tr>
<td>SMR</td>
<td>Standardized Mortality Rate</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
1 Introduction

Myeloproliferative neoplasms (MPN) are relatively rare hematological disorders. MPN are clonal diseases of the bone-marrow and include polycythemia vera (PV), essential thrombocythemia (ET), myelofibrosis (MF) and unclassified MPN. Although rare diseases, they are associated with lower patient survival with variations compared to the general population [1, 2].

Patients with essential thrombocythemia develop a proliferation of blood platelets, whereas patients with polycythemia vera develop a proliferation of red blood cells. These patients are at risk of thrombosis, bleeding and transformation to myelofibrosis and leukemia. Early myelofibrosis is characterized by increased granulocyte, megakaryocyte and often increased level of blood platelets and these patients are also at risk of thrombosis. MF later progresses to fibrosis in the bone-marrow and may lead to anemia, enlarged spleen, bone-marrow failure, fatigue and shorter survival [3].

Patients with MPN has a risk of vascular events (thrombosis and bleeding) and transformation to hematological malignancies and studies in Europe has shown lower relative survival of MPN patients than controls [4].

Most patients are 60 years or older at the time of diagnosis and they may have reduced quality of life due to fatigue, pruritus, night sweats and bone-pain. Some patients with ET and PV may live for many years with the disease whereas others with more advanced disease and in particular MF, have their life expectancy significantly reduced (median survival of MF is 2-5 years) [3, 5].

Treatment of ET and PV is directed to prevent thrombosis and transformation to secondary myelofibrosis and leukemia [6]. The only curative treatment of myelofibrosis is allogeneic stem cell transplantation which in itself is associated with procedural mortality. Although new treatment of JAK2 inhibitors are available, stem cell transplantation remains the only potential curative treatment [7]. Other treatments give relief of symptoms [6].

The discovery of mutations of the gene Janus Kinase 2 (JAK2 V617F) in 90 % of patients with PV and 50-60 % of patients with ET and MF, has made diagnosis and treatment of these
disorders more accurate. The WHO classifications of MPN were adjusted in 2008 after these findings [8].

Since the discovery of JAK2 mutation, familial predisposition for MPN has been described [1]. There has also been described a higher age-specific incidence of ET in females [3, 9].

Studies of incidence and prevalence of MPN are few and have mainly been performed in Sweden and USA. In a Swedish study in 2004, they found annual incidence of PV was 1.97 per 100,000 inhabitants. Annual incidence of ET was 1.55 per 100,000 and MF was 0.38 per 100,000 [10]. A recent literature review of epidemiology of MPN in the European Union revealed that estimated incidence rate of myelofibrosis ranged from 0.1 per 100,000 per year to 1 per 100,000 per year. Incidences of PV ranged from 0.4 per 100,000 per year to 2.8 per 100,000 per year [5].

The discovery of mutation of JAK2 gene in patients diagnosed with MPN may have an impact on incidence and prevalence rates. The introduction of WHO’s new criteria for diagnosis and classification which require bone-marrow histology and molecular and cytogenetic tests are factors that may also have an impact on epidemiology of MPN.

On the basis of this we aim to study national incidence, prevalence and survival of MPN.

**Research question**

In an observational study we aimed to answer the following questions:

1. What is the national incidence and prevalence of myeloproliferative neoplasms during 1993-2012?

2. Is relative survival and mortality rate in MPN patients affected by the disease?
2 Theoretical background

The theoretical basis for this study and thesis is written and seen from a biologic or biomedical perspective. Disease in a biological perspective is seen as biological responses that affects the individual and the society in various ways. Epidemiology is a biological research method where we find descriptive studies, case-control studies and cohort studies. A common feature of epidemiological studies is that they are observational studies [11]. In cohort studies a defined population is followed for a set period of time to identify for instance incidence rates and survival.

2.1 Myeloproliferative neoplasms

The word myeloproliferative neoplasms (MPN) stems from “myelo”- which means bone marrow, “proliferative”-meaning quick growth or reproduction and “neoplasms” meaning new growth. It is a generic term for diseases characterized by overproduction of mature and functional blood cells of the bone-marrow. The most common of these diseases are polycythemia vera, essential thrombocythemia, myelofibrosis and unclassified MPN (disorders with similar pathogenesis but not enough to fall into the category of the first 3 disorders). The WHO classification of MPN has been altered in line with discoveries of molecular pathogenesis [8].

Nowell and Hungerford from Philadelphia described for the first time in 1960 a typical chromosomal deviation in patients with cancer, appropriately named the Philadelphia chromosome [6].

In 1982 the ABL- BCR gene was identified to be a cancer-gene that was activated when connected to another gene, a so called fusion gene, and was found to be present in patients with Chronic Myeloid Leukemia (CML). This discovery led to the search for other cytogenetic changes in myeloproliferative diseases other than the Philadelphia chromosome positive disease. In 2005 it was discovered that a mutation of the Janus Kinase 2 gene (JAK2 V617F) was present in 50% of patients with essential thrombocythemia (ET) and myelofibrosis (MF) and in 95 % of patients with polycythemia vera (PV) [6]. This discovery has led to new international criteria for diagnosis.
The World Health Organization (WHO) has this year updated the classification of myeloid neoplasms and acute leukemia [12].

2.1.1 Polycythemia vera

Polycythemia vera is characterized by increased production of erythrocytes (red blood cells) and consequently increase in erythrocyte volume fraction, resulting in increased risk of vascular thrombosis/thromboembolism [6] The revised WHO 2016 criterion for polycythemia vera:

Major criteria:

1. Hemoglobin level of >16.5 g/dl males and >16.0 g/dl females, or haematocrit >0.49 % in men and > 48 % in females

2. 2. BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)

3. Presence of JAK2 exon 12 mutation

Minor criterion:

Subnormal serum erythropoietin level

Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion.
2.1.2 Essential thrombocythemia

Essential thrombocythemia is characterized by increased production and number of blood platelets (thrombocytosis) [6].

The revised WHO 2016 criteria for essential thrombocythemia (ET):

Major criteria

1. Platelet count >450 x 10^9/L

2. BM biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers

3. Not meeting WHO criteria for BCR-ABL1 CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms

4. Presence of JAK2, CALR, or MPL mutation

Minor criterion

Presence of a clonal marker or absence of evidence for reactive thrombocytosis

Diagnosis of ET requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion.
2.1.3 Myelofibrosis

Myelofibrosis is characterized by progressive accumulation of connective tissue and endothelial proliferation in the bone marrow accompanied by extramedullary hematopoiesis with enlargement of the spleen and liver [13]

The revised WHO 2016 diagnostic criteria for myelofibrosis is:

Major criteria:

1. Megakaryocytic proliferation and atypia, without reticulin fibrosis >grade 1, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis

2. Not meeting the WHO criteria for BCR-ABL1 CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms

3. Presence of JAK2, CALR, or MPL mutation or in the absence of these mutations, presence of another clonal marker, or absence of minor reactive BM reticulin fibrosis

Minor criteria:

Presence of at least 1 of the following, confirmed in 2 consecutive determinations:

a. Anemia not attributed to a comorbid condition

b. Leukocytosis ≥11 x 10^9/L

c. Palpable splenomegaly

d. LDH increased to above upper normal limit of institutional reference range

Diagnosis of prePMF requires meeting all 3 major criteria, and at least 1 minor criterion
2.1.4 Unclassified MPN

Some patients with myeloproliferative disease may not meet all the 2008 WHO criteria for polycythemia vera, essential thrombocytemia or myelofibrosis, and these patients fall under the category “Unclassified MPN” [8]. Their incidence and progression may also be followed as these are also registered in the Cancer Registry of Norway.
3 Definitions

3.1 Epidemiology

Epidemiology originates from Greek and literally meaning “the study of what is upon the people” epi- “upon, among”, demos –“people”, logo –“study, word” [14]. Epidemiology is the study of the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems. Various methods can be used to carry out epidemiological investigations: surveillance and descriptive studies can be used to study distribution; analytical studies are used to study determinants [15]. It is the study of how often diseases occur in different groups of people and why. Epidemiological information is used to plan and evaluate strategies to prevent illness and as a guide to the management of patients in whom disease has already developed. All findings are related to a defined population [16].

3.2 Incidence rate

Incidence rate measures the occurrence of new cases of individuals with a certain disease in a defined population over a limited period of time [17]. Incidence rate is measured by dividing the number of new cases of a disease in a given period by the total number of person-years in the same given period.

1.2.1 Age adjusted incidence rates

In epidemiology and demography there will be age-dependent incidence, prevalence and mortality rates [18]. In Nordic and West-European countries the elderly population is increasing in proportion to longer lifespan with the availability of increased welfare and medical advances. Comparisons of a disease and mortality rate between populations may be misleading if the underlying age composition differs in population of different countries/continents. This can be compensated by age standardization or age-adjustment. The most commonly used method is direct age standardization using weighted average of age-specific rates using an arbitrary standard population [18].
3.3 Prevalence

Prevalence, in a medical perspective, represents the burden of a disease at a particular time. It is the total number of existing cases with a specific disease among the whole population [17].

3.4 Survival

Survival studies are studies in which individuals are followed from the time they experience a particular event such as the diagnosis of a disease, and the time until another event such as death or the end of the study-period [17]

3.4.1 Standardized mortality rate

Death rates and disease incidence rates are usually strongly related to age, and often differ for males and females. Direct or indirect standardization are two methods to produce comparable measures between populations adjusting for age and sex differences.

In direct standardization, the age-sex specific rates from each of the populations under study are applied to rates in a standard population. The result is a set of standardized rates.

In indirect standardization, the age-sex specific rates from a standard population are applied to each of the study populations. The result is a set of standardized ratios [18].
4 Material and methods

4.1 Design

This is an observational cohort study on all persons newly registered with MPN during the period 1993 – 2012, identified through the Cancer Registry of Norway (CRN).

4.2 Study population

Norway has per April 1st 2016 a population of 5 223,300 [19] and universal medical care is provided for the entire population. Every citizen of Norway is given their unique and personal 11-digit identification number. Our aim was to identify all persons ≥18 years of age with MPN from the CRN based on the version of International Classification of Diseases (ICD 10 and ICDO3):

<table>
<thead>
<tr>
<th>Myeloproliferative neoplasms (MPN)</th>
<th>ICD 10</th>
<th>ICDO3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polycythemia vera</td>
<td>D45</td>
<td>995039</td>
</tr>
<tr>
<td>Essential Trombocythemia</td>
<td>D47.3</td>
<td>996239</td>
</tr>
<tr>
<td>Myelofibrosis</td>
<td>D47.4</td>
<td>996139</td>
</tr>
<tr>
<td>Unclassified MPN</td>
<td>D47.1</td>
<td>996039</td>
</tr>
</tbody>
</table>

The CRN provided the patients a unique ID-number (PID) specific for this project in order to de-identify the data and to be able to cross the data with other registries such as Norwegian Patient Registry if needed. The Statistics of Norway provided data on population counts for a defined time-span. This is needed in order to calculate incidence and prevalence.
Since the reporting of neoplasms to the CRN has been compulsory following a directive from the Ministry of Health and Social Affairs in 1951, the data can be considered reasonably accurate and close to complete [20].

An application to the CRN was submitted December 2013 on behalf of Sykehuset Ostfold HF. The data was delivered in excel files and SPSS format. The data is saved as a file that only designated study-personnel is given access to, in the hospital’s internal server.

Data on the Norwegian population rate is used in calculating incidence and prevalence, and is available at Statistics Norway[19].

4.1.1 Sample size

It was a total of 2459 persons in this cohort. Six cases were excluded due to the date of diagnosis was after the date of emigration. These cases would not generate any follow-up time or person years. A sample size as large as this may strengthen the validity of data and analysis.

4.3 Statistics

The Cancer Registry of Norway provides data on incidence, prevalence and relative survival of MPN. Descriptive analysis by frequency, means and median, inter-quartile range, were used on demographic variables. Survival analysis were calculated using IBM SPSS for estimating person-years by gender and subgroups, cross-tabulation for identifying the relationship between gender/age group and MPN subgroups. Kaplan Meier and calculations for standardizing mortality rates were used for survival and mortality.

Analysis of standardized mortality rates were calculated in excel by dividing number of deaths per 100,000 in the MPN population/gender/age group by deaths per 100,000 in the general population/gender/age group in the same time-span 1993-2012. Both populations were divided into age groups 18-49, 50-59, 60-69, 70-79 and 80 and above. These age groups were chosen to enable us to compare with similar studies in other countries such as Sweden.
[1]. I refer to the paper for a further description of analysis. Statistics Norway provided us with data on number of deaths in the general population divided in gender and age-group in the period 1993-2012.
5 Discussion

5.1 Results

The results are presented and discussed in the paper in this thesis. Main findings were that incidence rates of the three subgroups of MPN - PV, ET and MF doubled from 1993 to 2012. Relative survival (RS) was only slightly reduced for PV and ET and did not improve with time whereas RS was reduced to 50% in MF but improved with time. Standardized mortality rate was 1.9 in age group 60-69 in the MPN population. The calculations of SMR were done in excel format and to the best of our knowledge, but should be interpreted with some caution. We cannot rule out the possibility of human error.

5.2 Methods

The strength of a registry study such as this, is that reporting of neoplasms is compulsory by law. The assumption then is that all parties do their utmost to ensure correct reporting of the disease, and the data received from CRN is estimated to be 97.8% complete [20]. However, the limitations of this study is that CRN is our only source of data and the quality of this is dependent on correct registration. There will always be an uncertainty of the amount of incorrect and missing registration of MPN. We have no information on what the 2,2% of under reporting to the CRN consists of. This may be an information bias in our study. Furthermore, the controls in the general population is matching for gender and age group but not for the year of birth. This may affect the validity of data, but the size of the cohort may compensate for this. We have used the general population as control group but in those numbers there will also be included persons with MPN diagnosis. MPN is on the other hand a rare disorder and this may not have such a large effect on the cohort results.

We consider the standardized mortality analysis to be reproducible, as the data on deaths in the general population (1993-2012) from Statistics Norway are easily accessible and the data from CRN are stored as a file at the hospital’s server.
6 Conclusion and further studies

The results of this study is presented and further discussed in the paper.

The incidence rates of PV, ET an MF doubled from 1993 to 2012, but unclassified MPN remained stable throughout the study. The WHO’s new criteria for diagnosis in 2008 may have had an effect on the trend in incidence rates in our study.

The relative survival was only slightly reduced for PV and ET with little change with time, whereas relative survival in MF was reduced to 50% but improved to 58% with time. As standardized mortality rates were higher than the general population and SMR in females were higher than males in three subgroups, it would be of interest to study the effects of treatment and the incidence of secondary haematological and solid cancer in the MPN population on survival.
7 Ethical consideration

This project does not involve any direct patient intervention and data is de-identified. It is thereby not considered to be of any disadvantage for the individual. It should be in the interest of the individual, patient group and the society to obtain up to date knowledge about epidemiology of MPN in Norway.

This project (ref.: 2013/1258) has been approved by Regional Ethics Committee 18.09.2013.

All data from Cancer Registry is given a personal identification number specific for this project and therefore all data is de-identified to protect the integrity of all persons included in the study. The results of this study will, if permitted and accepted, be published in national and international Journals related to hematology/oncology.
References

Myeloproliferative neoplasms: Trends in incidence, prevalence, and survival.

Christina Roaldsnes¹, René Holst², Henrik Frederiksen³, Waleed Ghanima⁴

Ostfold Hospital, Norway¹, Institute of Regional Health Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark², Odense University Hospital, Denmark³, Institute of Clinical Medicine, University of Oslo, Norway⁴

Corresponding author:

Christina Roaldsnes
Research Haematology
Ostfold Hospital, Kalnes
Kalnesveien 300
PB 300, 1714 Graalum
E-mail: christina.roaldsnes@so-hf.no
Mobile phone: +47 41267921

Abstract: 241 words
Manuscript: 2365 words
References: 35
Tables: 5
Figures: 3
Abstract

Background: Polycythemia vera (PV), essential thrombocythemia (ET) and myelofibrosis (MF) are clonal disorders collectively named myeloproliferative neoplasms (MPN). Published data on epidemiology of MPN after the discovery of the JAK2 mutation and the introduction of the 2008 WHO classifications are scarce. We aimed to study the incidence, prevalence and survival of MPN in Norway.

Method: We identified 2453 persons diagnosed with MPN from the Cancer Registry of Norway between 1993 and 2012. We report age-adjusted incidence rates, prevalence, relative survival and standardized mortality rates.

Results: The overall age-adjusted yearly incidence rate of PV increased from 0.4/10^5 to 0.7/10^5, ET increased from 0.3/10^5 to 0.9/10^5 and MF from 0.2/10^5 to 0.5/10^5. Prevalence of PV, ET and MF was 9.2, 8.6 and 3.0 per 10^5 inhabitants, respectively. The 5-year relative survival (RS) of ET and PV was slightly reduced with no improvement. The 5-year RS of MF was 58.1% (2008-2012). Standardized mortality rate (SMR), defined as the ratio of the mortality rate of the MPN population to that of the general population, was 1.9 (95% CI 1.2 - 2.7).

Conclusions: The incidences of ET, PV, and MF almost doubled during the years 2007-2012 as compared to 1995-2006. This increment in incidence may be related to identification of the JAK2 mutation and the derived 2008 WHO-guidelines for MPN. The RS was only slightly reduced for PV and ET and did not improve with time. RS was substantially reduced for MF but improved over time.

Keywords: Myeloproliferative neoplasms, polycythemia vera, essential thrombocythemia, myelofibrosis, unclassified MPN
Introduction

Polycythemia vera (PV), Essential thrombocythemia (ET), and Myelofibrosis (MF) are clonal hematological disorders collectively named as Myeloproliferative Neoplasms (MPN). Discovery of the JAK2 mutation in 2005 [1-3], altered the WHO classification for the MPN diagnosis in 2008 [4], and this as well as the availability of new treatments [5, 6] for MPN may have had an impact on the incidence, prevalence and survival of MPN. Published data on the epidemiology of MPN after the discovery of JAK2 mutation and the introduction of the 2008 WHO classifications for MPN, in particular the prevalence of MPN, are scarce [7].

A literature review of the incidence of MPN in Europe included studies published between 2000 and 2012 and showed a wide variation of incidence rates of PV (0.7-2.6 per 10⁵ person-years), ET (0.34-1.7 per 10⁵ person-years) and MF (0.1 – 1.0 per 10⁵ person-years) [7]. Myeloproliferative neoplasms have an increased mortality due to leukemic transformation, progression to other malignancies or complications of the disease such as thromboembolic events [8-10]. This study aimed to determine trends in incidence, prevalence and survival of patients with MPN diagnosis in Norway 1993-2012.
Method

Study population

Persons with MPN were identified through the Cancer Registry of Norway (CRN) using ICD 10 and ICDO3 codes: PV-ICD10- D45 and ICDO3 - 995039, ET-ICD10 - D47.3 and ICDO3 - 996239, MF-ICD10 - D47.4 and ICDO3 - 996139 and unclassified MPN - ICD10 - D47.1 and ICDO3 - 996039.

The Cancer Registry of Norway (CRN), Institute of Population-based Cancer Research, was established in 1951 [11]. CRN is an independent institution, part of South Eastern Norway Regional Health Authority but covering the entire country. Patients are identified through a unique and permanent 11-digit personal identification number which is assigned to all newborns and people living in Norway.

The reporting of neoplasms has been mandatory since the implementation of a directive from the Ministry of Health and Social Affairs in January 1952 [11]. The data items that must be reported to the CRN are: All malignant neoplasms and precancerous disorders and all benign tumors of the central nervous system and meninges [11]. MPN is classified as malignant hematological disease and registration of MPN patients to the CRN has been included since 1953. By use of the unique personal identification number, the CRN receives cancer diagnosis from various sources such as hospitals, pathology departments, general practitioners and the National Statistics Office (Statistics Norway).

The data in the CRN are considered accurate and close to complete after CRN conducted a comprehensive evaluation of the quality of data collected on both solid and non-solid tumours on material for the period 1953-2006. [11, 12]. The evaluation focused on comparability, completeness, accuracy and timeliness of data. The overall completeness was estimated at 98.8% for registration period 2001-2005 and 93.8% of the cases were morphologically verified [11].

We identified 2459 patients registered in the Cancer Registry of Norway during the period 1993-2012. We excluded 6 persons as they received their diagnosis after they had emigrated from Norway, leaving 2453
MPN patients during this period. Median age of total population was 69 years (IQR:57-78), median age in PV, ET, MF and unclassified MPN was 73 years (IQR:59-79), 65 years (IQR:52-75), 72 years (IQR:62-80), and 71 years (IQR: 61-81), respectively (table 1).

**Statistics**
The incidence rate of PV, ET, MF and unclassified MPN was calculated by dividing the number of new cases of MPN during 1993-2012 by the total person years at risk x 100,000 to express the rate per 100,000 person-years [13]. The incidence rates of the four diagnoses were calculated for each gender, in 20- year age intervals (0-19, 20-39, 40-59, 60+), and in calendar year spanning 1995-97, 1998-2000, 2001-2003, 2004-2006, 2007-2009 and 2010-2012. The observed Norwegian MPN incidence rates was adjusted using the World Standard Population [14] yielding age-adjusted incidence rates where the age composition of our population is estimated to be the same as the World standard population.

We estimated the prevalence by dividing the number of persons alive with PV, ET and MF by the population of Norway per 31 December 2011. We calculated relative survival of the MPN population by dividing the observed survival of the MPN population by the expected survival of a group from the general Norwegian population with the same age and sex composition [15].

To estimate the distribution of age, gender and mortality among others in the MPN population, we received a data extraction of all persons ≥18 years in Norway diagnosed with MPN during the period 1993-2012, (mortality included year 2013). We chose to divide the MPN population into age groups of 18-49, 50-59, 60-69, 70-79, and >80 years.

In order to standardize the mortality rates in the MPN population, we used mortality rates from the general population obtained from Statistics Norway presented as number of deaths per 100,000 per year, per general population, gender-wise and in 5-year age-groups [13].
The calculations of mortality rates were made by dividing number of deaths in the age-sex group for the whole period by the number of person-years in the same age-sex-group. Mortality rate in the MPN population was standardized by dividing total mortality rate per age-group with the total mortality rate, per age-group in the general population for the same period resulting in a standardized mortality rate (SMR).

If the given mortality rate of a given age-group in MPN population = \( p \), and total persons in that age-group = \( n \), then standard error (SE) was calculated as follows:

\[
SE = \sqrt{\frac{p(1-p)}{n}}
\]

95% confidence interval of mortality rate MPN was calculated: \( p \pm 1.96 \times SE \). Lower and upper confidence interval of mortality rate in MPN population divided by total mortality rate in middle-population gives us 95% confidence interval of standardized mortality rate (SMR).

The study was approved by the Norwegian Regional Ethics Committee (2013/1258 REK Sør-Øst B)
Results

In total 2453 persons ≥18 years were registered with myeloproliferative neoplasms (MPN) during 1993-2012; 1184 males (48 %) and 1269 females (52 %). The MPN patients contributed with 12266 person years of follow-up from diagnosis to death, study end, or immigration whichever came first.

We identified 1015 persons with PV, 791 with ET, 427 with MF, and 220 with unclassified MPN. Median ages were 70, 65, 72, and 71 years for PV, ET, MF, and unclassified MPN, respectively (Table 1). The incidence rates of all subgroups apart from unclassified MPN almost doubled in the study period as shown in Table 2.

The national prevalence of PV, ET, and MF per 31.12.2011 was 9.2/100,000, 8.6/100,000 and 3.0/100,000 respectively. The 5-year survival improved for the total MPN group with time, but among the specific MPN diagnoses only 5-year survival in myelofibrosis improved with time (Table 3).

Of the total MPN population, 1012 (41.2%) died during the study-period 1993-2012. Among 179 persons, the date of the MPN diagnosis was concurrent with the date of death. The mean time from diagnosis to death was 45.7 months (range 0-227 and SD 48.52), and standardized mortality rate was generally higher in the combined group of MPN patients than in the general population (Table 4). In table 5 the SMRs for the specific MPN diagnoses PV, ET, MF, and unclassified MPN was elevated only in persons with myelofibrosis; SMR 2.6 (95% CI 2.1-3.2) and in patients with unclassified MPN; SMR 1.8 (95% CI 1.2-2.4). The SMR in MPN did not differ much between the genders, but SMR seem to be generally higher in females when looking at PV, MF, unclassified MPN and genders.
Discussion

Myeloproliferative neoplasms are relatively uncommon haematological cancer diseases, and published data on epidemiology are scarce and most previous reports are from before 2005, and with short follow-up time [16-19]. These studies show a wide variation in methods of recruitment of MPN patients including registries of haematological malignancies [20], medical records from outpatient clinics or pathology departments [21, 22], and national cancer registries [23], and with wide variations in incidences [7]. The incidence rates of PV, ET (females especially) and MF doubled in our study-period in Norway. Increased incidence of PV/ET is in line with other studies [20, 21, 24-27] In Sweden (1999) the main increment of ET was seen among males and no increments in PV or MF was observed [25]. These studies suggest that the wider use of automated platelet counts in routine examination as one possible explanation for the increasing incidence [23].

The discovery of the JAK2 mutation in 2005 and the subsequent alteration of the WHO classification of MPN diagnoses is another possible explanation for the increased incidence rates found in our study. But in contrast to Deadmond et al [26], we see a similar increment of incidences of both PV and ET. This may suggest that it is the altered WHO’s diagnostic criteria that ensures a more accurate diagnosis through the bone-marrow investigations – and thereby decreases the fraction with non-diagnostic bone-marrow biopsy. Another possibility for the increasing MPN incidences may also be improved reporting practice from both clinicians and pathologists as well as a real increase in the incidence of MPNs in the population in Norway.

Comparing the Norwegian to the Swedish data it seems that the incidence rates of MPN is lower in Norway, although the Swedish incidence data dates back to 1999 and is confined to the city of Gothenburg. The CRN has rigorous methods to ensure registration of all patients diagnosed with cancer including MPN. The Norwegian Patient Registry (NPR) and the Cancer Registry of Norway (CRN) are inter-linked since 2010, the CRN receives data from Norwegian patient registry on all hospitals jointly as well as CRN acquires and registers information from pathology
laboratories all over the country. CRN reviews individual patients by an expert panel to ensure correct classification whenever there is conflict in the reported diagnosis [12].

On the other hand, CRN recognizes that “there remains a variable degree of under-reporting particularly for hematological malignancies” which is estimated to be 2.2% [11]. Different methods of reporting are likely to have influenced the observed incidence rates, and the effect of this on our results is unknown. Furthermore, data from CRN also includes the subgroup “unclassified MPN”. This subgroup may contain patients with PV, ET, or myelofibrosis who do not fulfill all of the WHO criteria for PV, ET or MF diagnosis, however, this subgroup remains stable in numbers of cases throughout the study-period.

The Swedish Cancer Registry was established in 1958 and seems to have similar methods of reporting. The percentage of cases with incomplete registration is reported be less than two percent in the Swedish Cancer registry [28].

In line with several previous studies we found that the MPN population have a reduced life expectancy compared to the general population [29-32]; this was particularly evident in myelofibrosis. The 5- year relative survival was only slightly reduced for both ET and PV, but did not improve from 2003 -2008. Some previous studies have reported on life expectancy of ET patients comparable to the general population [10, 23]. Other studies have found lower survival in ET and PV patients than in the general population [29-31], but noticed an improvement in survival over time [29].

Although we do not have the result of survival among females with MF diagnosed 2003-2008 due to small number of patients, it seems that the 5-year relative survival has improved for patients with MF during this period. This may account for the overall slight improvement in relative survival for the total MPN population related to improved diagnostics and therapies. Myelofibrosis remains however the MPN subtype with the poorest 5-year survival of 56.7% in females and 59.5% in males.
Survival may be reduced in MPN for several reasons. In a recent study Hultcrantz et al found that patients with MPN have a higher mortality rate than controls mainly due to transformation into more aggressive haematological malignancies such as acute myeloid leukemia (AML) [8]. The MPN treatments Busulfan, Pipobroman, and P32 have all been shown to increase the rate of AML [33-35], and therefore these drugs have not been widely used in MPN for a long period. It is unlikely that this explains the improved survival in our study, which may however, still be an effect of MPN directed as well as supportive therapy. Survival of PV and ET showed on the other hand no improvement in time. This is in contrast with Swedish data, where an improvement in RSR in ET and PV, has been reported [29]. The reason for these discrepancies is unknown.

When looking at SMR for the MPN population one should take into consideration that there were 179 persons who had the MPN diagnosis on the same date as their date of death. We found that SMR were lower among MPN patients in age group 80+ than in the general population. The reason for this finding is unknown. However, it may suggest that cancer diagnostic tests are not performed to the same extent among frail elderly, and therefore there may be a selection towards more elderly with less comorbidity than in the general population in the CRN. SMR in genders differed only when dividing the population into subgroups, and it is not clear why females seem to have a higher SMR in PV, MF and unclassified MPN than males in our study.

One of the limitations of this study is that CRN is our only source of data and the quality of this is dependent on correct registration. There will always be an uncertainty of amount of incorrect and missing registration of MPN. We have no information on what the 2,2% of under reporting to the CRN consists of.
In conclusion we found that incidence rates of PV, ET, and MF has increased from 1993 to 2012 and that the MPN population has a higher mortality rate compared to the general population in age-group 60-79 years. Relative survival in PV and ET, although only slightly reduced compared to general population, did not improve during our study-period. On the other hand, RS was markedly lower in persons with myelofibrosis but improved during study period. As the MPN population has a higher mortality rate than the general population, it would be of interest to study in more detail the effects of treatment and incidence of secondary haematological and solid cancer in the MPN population on survival.
Aknowledgments

I would like to thank Waleed Ghanima PhD for giving me the opportunity and guidance to write this manuscript in collaboration with my co-authors. I am also grateful for helpful instruction and guidance that I received from René Holst in statistics. Henrik Frederiksen PhD has given me helpful corrections in writing this manuscript.

Disclosure of interest

W.Ghanima, Research funding, lecture honoraria and participated in advisory group meetings for Novartis. C.Roaldsnes, H.Frederiksen, R. Holst: There are no relevant conflicts of interest to disclose
References


Table 1 Description of population

<table>
<thead>
<tr>
<th></th>
<th>PV</th>
<th>ET</th>
<th>MF</th>
<th>Unclass MPN</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No (%) of patients 1993-2012</strong></td>
<td>1015 (100)</td>
<td>791 (100)</td>
<td>427 (100)</td>
<td>220 (100)</td>
<td>2453 (100)</td>
</tr>
<tr>
<td><strong>Follow-up person years (12266) median (25-75% percentiles)</strong></td>
<td>4.3 (1.3-8.1)</td>
<td>4.5 (2.1-8.3)</td>
<td>2.0 (0.6-4.1)</td>
<td>3.0 (0.7-7.8)</td>
<td>3.8 (1.3-7.6)</td>
</tr>
<tr>
<td><strong>Age at Diagnosis median (25-75% percentiles)</strong></td>
<td>70 (59-79)</td>
<td>65 (52-75)</td>
<td>72 (62-80)</td>
<td>71 (61-81)</td>
<td>69 (57-78)</td>
</tr>
<tr>
<td><strong>Males n (%)</strong></td>
<td>506 (49.9)</td>
<td>313 (39.6)</td>
<td>249 (58.3)</td>
<td>116 (52.7)</td>
<td>1184 (48)</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td>509 (50.1)</td>
<td>478 (60.4)</td>
<td>178 (41.7)</td>
<td>104 (47.3)</td>
<td>1269 (52)</td>
</tr>
</tbody>
</table>

*PV=polycythemia vera, ET=essential thrombocythemia, MF= myelofibrosis, Unclassified MPN*
Table 2 Incidence rate per 10^5 person-years during 1995-2012 in MPN subgroups incidence given as average per year for 3-year period

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PV</td>
<td>Total</td>
<td>0.4</td>
<td>0.5</td>
<td>0.7</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.4</td>
<td>0.6</td>
<td>0.8</td>
<td>0.8</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.3</td>
<td>0.5</td>
<td>0.5</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>ET</td>
<td>Total</td>
<td>0.3</td>
<td>0.3</td>
<td>0.5</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.3</td>
<td>0.2</td>
<td>0.4</td>
<td>0.4</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.3</td>
<td>0.5</td>
<td>0.5</td>
<td>0.6</td>
<td>1.0</td>
</tr>
<tr>
<td>MF</td>
<td>Total</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.3</td>
<td>0.3</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Unclass</td>
<td>MPN</td>
<td>Total</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.3</td>
<td>0.1</td>
<td>0.2</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

PV = polycythemia vera, ET = essential thrombocythemia, MF = myelofibrosis, Unclassified MPN
### Table 3  5-year relative survival of MPN genders

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Gender</th>
<th>2003-2007</th>
<th>2008-2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloproliferative neoplasms %</td>
<td>F</td>
<td>82.3</td>
<td>88.3</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>77.1</td>
<td>83.9</td>
</tr>
<tr>
<td>Polycythemia vera %</td>
<td>F</td>
<td>93.3</td>
<td>91.1</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>94.7</td>
<td>90.1</td>
</tr>
<tr>
<td>Essential thrombocythemia %</td>
<td>F</td>
<td>98.9</td>
<td>97.2</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>93.3</td>
<td>94.0</td>
</tr>
<tr>
<td>Myelofibrosis %</td>
<td>F</td>
<td>*</td>
<td>56.7</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>50.0</td>
<td>59.5</td>
</tr>
</tbody>
</table>

*F= Female  M= Male  *

* = no estimate due to too few patients
Table 4: Standardized mortality rate in MPN population per 100,000 gender and agegroups (1993-2012)

<table>
<thead>
<tr>
<th>Age-group</th>
<th>Deaths n in MPN pop</th>
<th>Total n in MPN agegroups</th>
<th>Person years</th>
<th>Deaths per 10⁵ in MPN pop</th>
<th>Deaths per 10⁵ in general population</th>
<th>SMR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-49</td>
<td>Total</td>
<td>12</td>
<td>200</td>
<td>1067</td>
<td>1124</td>
<td>203</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>4</td>
<td>106</td>
<td>549</td>
<td>728</td>
<td>67</td>
<td>10.4</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>8</td>
<td>94</td>
<td>518</td>
<td>1544</td>
<td>133</td>
<td>11.5</td>
</tr>
<tr>
<td>50-59</td>
<td>Total</td>
<td>30</td>
<td>255</td>
<td>1478</td>
<td>2030</td>
<td>894</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>13</td>
<td>114</td>
<td>672</td>
<td>1934</td>
<td>346</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>17</td>
<td>141</td>
<td>805</td>
<td>2111</td>
<td>548</td>
<td>3.9</td>
</tr>
<tr>
<td>60-69</td>
<td>Total</td>
<td>125</td>
<td>517</td>
<td>2711</td>
<td>4611</td>
<td>2388</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>39</td>
<td>229</td>
<td>1240</td>
<td>3146</td>
<td>861</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>87</td>
<td>288</td>
<td>1471</td>
<td>5915</td>
<td>1533</td>
<td>3.9</td>
</tr>
<tr>
<td>70-79</td>
<td>Total</td>
<td>284</td>
<td>650</td>
<td>3145</td>
<td>9030</td>
<td>6824</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>122</td>
<td>335</td>
<td>1730</td>
<td>7051</td>
<td>2493</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>163</td>
<td>315</td>
<td>1415</td>
<td>11517</td>
<td>4352</td>
<td>2.6</td>
</tr>
<tr>
<td>80-</td>
<td>Total</td>
<td>559</td>
<td>831</td>
<td>3864</td>
<td>14464</td>
<td>31614</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>319</td>
<td>485</td>
<td>2299</td>
<td>13876</td>
<td>13693</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>240</td>
<td>346</td>
<td>1566</td>
<td>15329</td>
<td>17996</td>
<td>0.9</td>
</tr>
</tbody>
</table>

MPN=Myeloproliferative neoplasms, SMR=Standardized mortality rate, CI=Confidence Interval, n=number
<table>
<thead>
<tr>
<th>MPN subgroup</th>
<th>Deaths n in subgroup</th>
<th>Total n in MPN subgroup</th>
<th>Person years</th>
<th>Deaths per 10⁵ in MPN subgroup</th>
<th>Deaths per 10⁵ in general population</th>
<th>SMR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PV Total</td>
<td>428</td>
<td>1015</td>
<td>5240</td>
<td>8168</td>
<td>7325</td>
<td>1.1</td>
<td>0.9 - 1.4</td>
</tr>
<tr>
<td>Female</td>
<td>222</td>
<td>509</td>
<td>2556</td>
<td>8684</td>
<td>3059</td>
<td>2.8</td>
<td>2.0 - 3.6</td>
</tr>
<tr>
<td>Male</td>
<td>206</td>
<td>506</td>
<td>2683</td>
<td>7677</td>
<td>4267</td>
<td>1.8</td>
<td>1.3 - 2.3</td>
</tr>
<tr>
<td>ET Total</td>
<td>179</td>
<td>791</td>
<td>4599</td>
<td>3892</td>
<td>7325</td>
<td>0.5</td>
<td>0.4 - 0.7</td>
</tr>
<tr>
<td>Female</td>
<td>102</td>
<td>478</td>
<td>2822</td>
<td>3614</td>
<td>3059</td>
<td>1.2</td>
<td>0.6 - 1.7</td>
</tr>
<tr>
<td>Male</td>
<td>77</td>
<td>313</td>
<td>1776</td>
<td>4335</td>
<td>4267</td>
<td>1.0</td>
<td>0.5 - 1.5</td>
</tr>
<tr>
<td>MF Total</td>
<td>261</td>
<td>427</td>
<td>1340</td>
<td>19475</td>
<td>7325</td>
<td>2.7</td>
<td>2.2 - 3.2</td>
</tr>
<tr>
<td>Female</td>
<td>107</td>
<td>178</td>
<td>596</td>
<td>17950</td>
<td>3059</td>
<td>5.9</td>
<td>4.0 - 7.7</td>
</tr>
<tr>
<td>Male</td>
<td>154</td>
<td>249</td>
<td>744</td>
<td>20698</td>
<td>4267</td>
<td>4.9</td>
<td>3.7 - 6.0</td>
</tr>
<tr>
<td>Unclass MPN Total</td>
<td>144</td>
<td>220</td>
<td>1087</td>
<td>13242</td>
<td>7325</td>
<td>1.8</td>
<td>1.2 - 2.4</td>
</tr>
<tr>
<td>Female</td>
<td>66</td>
<td>104</td>
<td>515</td>
<td>12801</td>
<td>3059</td>
<td>4.2</td>
<td>2.1 - 6.3</td>
</tr>
<tr>
<td>Male</td>
<td>78</td>
<td>116</td>
<td>572</td>
<td>13641</td>
<td>4267</td>
<td>3.2</td>
<td>1.7 - 4.7</td>
</tr>
</tbody>
</table>

MPN=myeloproliferative neoplasms, SMR=standardized mortality rate, CI=confidence interval
PV=Polycythemia vera, ET=Essential thrombocythemia, MF=Myelofibrosis,

Unclass MPN=Unclassified myeloproliferative neoplasms

Figure 1 Trends in incidence of myeloproliferative neoplasms by sub groups and gender 1993-2012
Figure 2 Relative survival of 3 subgroups of MPN by gender 1993-2012
Diagnosis 1 = PV, diagnosis 2 = ET, diagnosis 3 = MF, diagnosis 4 = Unclassified MPN

Figure 3 Overall survival of MPN subgroups by gender 1993-2012
Acknowledgements

I would like to thank the co-authors Henrik Frederiksen PhD, René Holst PhD and Waleed Ghanima PhD for all the contributions to this article.

Disclosure of interest

W.Ghanima, Research funding, lecture honoraria and participated in advisory group meetings for Novartis. C.Roaldsnes, H. Frederiksen, R. Holst: There are no relevant conflicts of interest to disclose
Appendix A   Approval from Regional Ethics Committee


Region: REK sør-øst B  Deres dato: 25.06.2013  Deres referanse:

Vår referanse må oppgis ved alle henvendelser

Til Waleed Ghanima

2013/1258 Insidens og overlevelse av myeloproliferative neoplasmer

Forskningsansvarlig: Sykehuset Østfold HF
Prosjektleder: Waleed Ghanima

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst) i møtet 23.08.2013. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikklovens § 4.

Prosjekтомtale

Komiteens vurdering


Prosjektleder skriver i søknaden at etter prosjektslutt, skal datamaterialet oppbevares aidentifisert i 10 år. Komiteen gjør oppmerksom på at i henhold til helseforskningsloven §38 skal ikke opplysninger lagres lenger enn det som er nødvendig for å gjennomføre prosjektet. Aidentifiserte opplysninger skal som hovedregel lagres i 5 år etter prosjektslutt av dokumentasjonshensyn, og skal deretter slettes eller anonymiseres. Hvis det er noen spesiell grunn som gjør det påkrevd å lagre data mer enn 5 år etter prosjektslutt, ber komiteen om en tilbakemelding om det.

Vedtak

Komiteen godkjenner prosjektet i henhold til helseforskningsloven § 9 og § 33.

Godkjenningen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden.

Komiteen gir tillatelse til at opplysninger som er innsamlet i helsetjenesten kan gis fra helsepersonell til bruk i forskning uten hinder av taushetsplikt, og til at disse opplysningene brukes i forskning uten pasientens samtykke, som beskrevet i søknaden, jf. helseforskningsloven §35.


Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder “Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren”

Klageadgang

Komiteens avgjørelse var enstemmig.

**Sluttmelding og søknad om prosjektendring**

Prosjektleder skal sende sluttmelding til REK sør-øst på eget skjema senest 30.06.2016, jf. hfl. §

12. Prosjektleder skal sende søknad om prosjektendring til REK sør-øst dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Med vennlig hilsen

Grete Dyb førsteamanuensis
dr. med. leder REK sør-øst B

Jakob Elster
Seniorrådgiver

**Kopi til: Sykehus i Østfold ved øverste administrative ledelse**
Appendix B  Author guidelines European Journal of Haematology

MANUSCRIPT TYPES
The EUROPEAN JOURNAL OF HAEMATOLOGY (EJH) accepts the following manuscript types:

Original Articles
Manuscripts containing original research from all fields in haematology are considered for publication. It is understood that neither the article nor any of its essential parts has been or will be published elsewhere, with the exemption of presentations at scientific meetings. For organization of the manuscript see below. Manuscripts must not exceed 4,000 words excluding abstract, references, tables, figures and legends. A maximum of 50 references is allowed. A maximum of six figures or tables is allowed. Additional figures/tables must be clearly marked as supplemental and will be published as such only electronically.

Review Articles
Review articles on recent developments or history of haematology may be solicited by the Editor-in-Chief. Suggestions are welcomed in the form of a one-page synopsis. Review articles must be exhaustive and should include appropriate reference to the literature. Review articles will go through the usual peer-review process before a final decision regarding publication is made. Manuscripts must not exceed 6,000 words excluding abstract, references, tables, figures and legends. A maximum of 80 references is allowed.

Letters to the Editor
EJH welcomes critical or ancillary comments to manuscripts published in the journal. These should be addressed to the Editor-in-Chief, indicating that they are regarded as a “letter to the editor” and not as an original article. They may contain one table or figure and should not be more than 500 words. The editor reserves the right to edit the letters for clarity. A title must accompany the letter.

Case Reports
EJH accepts a very limited number of case reports. These must provide fundamental new information on a relevant topic. Sole descriptions of unusual or rare clinical cases without a clear impact for future research are not sufficient to be published in this category. Reports
must be instructive and contain a critical review of the literature related to the presented case. Case reports must not exceed 1,000 words excluding abstract, references, tables, figures and legends. A maximum of 2 tables or figures and 5 references is allowed.

**Clinical Pictures**
As of 01.03.2015 this manuscript category will be closed and no submissions accepted.

**MANUSCRIPT SUBMISSION**
Manuscripts should be submitted online at: [https://mc.manuscriptcentral.com/ehj](https://mc.manuscriptcentral.com/ehj). For questions regarding submission, please contact the editorial office: [eurj-haematology@wiley.com](mailto:eurj-haematology@wiley.com). Resubmitted manuscripts should also be submitted in the above manner.

**ORGANIZATION OF MANUSCRIPTS**
Original manuscripts must be divided into the following consecutive sections, each beginning on a separate page:

- Title page
- Abstract & Key Words
- Introduction
- Patients and Methods/Materials and Methods
- Results
- Discussion
- Acknowledgements (optional)
- References
- Tables (if applicable)
- Illustrations (if applicable)
- Legends (if applicable)

Review articles, letters to the editor, and case reports do not require a specific structure. The pages of the manuscript, beginning with the title page, should be numbered consecutively. All sections of the manuscript must be double-spaced. Abbreviations, symbols and nomenclature should be standardized and in accordance with Baron DN (ed) Units, Symbols and Abbreviations. The Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE, 1994. Authors must make sure that their article is written in idiomatic English and that typing errors have been carefully eliminated.

For preparation of the manuscript sections please consider the following:
The title page should contain an informative title, author(s)'s names and their affiliations. Name, address, telephone and fax numbers and e-mail address of the corresponding author. If the title exceeds 40 characters (letters and spaces) a running title of no more than 40 characters must be supplied. The following information is also required on the title:

- Abstract word count
- Manuscript word count
- Number of references
- Number of figures and tables
- Number of supplemental illustrations/tables

Abstract and Key Words
The abstract must not exceed 200 words and should be arranged in a structured fashion (to include objectives, methods, results and conclusions.) It should state the purpose of the study, basic procedures (study subject /patients/animals and methods), main findings (specific data and statistical significance), and principal conclusions. Below the abstract, provide 3-10 key words that will assist indexers in cross-indexing the article. Use terms from the Medical Subject Headings list from Index Medicus whenever possible.

Introduction
Present the background briefly, but do not review the subject extensively. Give only pertinent references. State the specific questions you want to answer.

Patients and Methods / Materials and Methods
Describe selection of patients or experimental animals, including controls. Do not use patients' names or hospital numbers. Identify methods, apparatus (manufacturer's name and address), and procedures in sufficient detail to allow other workers to reproduce the results. Provide references and brief descriptions of methods that have been published. Identify drugs and chemicals, including generic name, dosage and route(s) of administration. Authors must indicate that the procedures were approved by the Ethical Committee of Human Experimentation in their country, and are in accordance with the current version of the Helsinki Declaration. All papers reporting experiments using animals must include a statement in the Material and methods section giving assurance that all animals received
humane care. The authors accept full responsibility for the accuracy of the whole content, including findings, citations, quotations and references contained in the manuscript.

Information regarding clinical trials
EUROPEAN JOURNAL OF HAEMATOLOGY will only consider publishing clinical trials that have been registered in a public trials registry. The name of the registry and the registration number should be stated at the end of the abstract of the manuscript. Trials must register at or before patients are enrolled. We define clinical trials according to ICMJE, as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause and effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as pharmacokinetics or major toxicity (e.g., phase I trials), would be exempt.

Registries that currently meet the EJH criteria include:


The Editor-in-Chief reserves the right to reject manuscripts that do not comply with the above mentioned requirements. The author will be held responsible for false statements or for failure to fulfill the above mentioned requirements.

Results
Present results in logical sequence in tables and illustrations. In the text, explain, emphasize or summarize the most important observations. Units of measurement should be expressed in accordance with Système International d'Unite (SI Units).

Discussion
Do not repeat in detail data given in the Results section. Emphasize the new and important aspects of the study. Relate the observations to other relevant studies. On the basis of your findings (and others’) discuss possible implications / conclusions.

Acknowledgements
Acknowledge only persons who have made substantive contributions to the study. Authors are responsible for obtaining permission from everyone acknowledged by name because readers may infer their endorsement of the data and conclusions. Authors are expected to
disclose any commercial or other relationships that could constitute a conflict of interest. Financial support should be acknowledged as a footnote on the title page. All contributors who do not qualify as authors should be mentioned under Acknowledgements. EUROPEAN JOURNAL OF HAEMATOLOGY adheres to the definition of authorship set up by The International Committee of Medical Journal Editors (ICMJE). According to the ICMJE authorship criteria should be based on 1) substantial contributions to conception and design of, or acquisition of data or analysis and interpretation of data, 2) drafting the article or revising it critically for important intellectual content and 3) final approval of the version to be published. Authors should meet conditions 1, 2 and 3.

Conflict of Interest and Sources of Funding
Authors are required to disclose all sources of institutional, private and corporate financial support for their study. Suppliers of materials (for free or at a discount from current rates) should be named in the source of funding and their location (town, state/county, country) included. Other suppliers will be identified in the text. If no funding has been available other than that of the author's institution, this should be specified upon submission. Authors are also required to disclose any potential conflict of interest. These include financial interests (for example patent, ownership, stock ownership, consultancies, speaker's fee,) or provision of study materials by their manufacturer for free or at a discount from current rates. Author’s conflict of interest (or information specifying the absence of conflicts of interest) and the sources of funding for the research will be published under a separate heading entitled "Conflict of Interest and Sources of Funding Statement". See ICMJE website for generally accepted definitions.

References
Number references consecutively in the order in which they are first mentioned in the text. Identify references in text, tables and legends by Arabic numerals (in parentheses). All references cited, and only these, must be listed at the end of the paper. References should be according to the style used in Index Medicus and the International List of Periodical Title Word Abbreviations (ISO 833). All authors must be listed.

Examples:

Standard journal articles
Chapter in a book

Proceedings

Tables
Tables should be numbered consecutively with Arabic numerals. Type each table on a separate page, and provide clear descriptive titles.

Illustrations
All figures should clarify the text and their numbers be kept to a minimum. Details must be large enough to retain their clarity after reduction in size. Illustrations should preferably fill a singlecolumn width (81 mm) after reduction, although 2/3-page width (112 mm) or full-page width (168 mm) will be accepted if necessary. Magnifications should be indicated in the legends rather than by inserting scales on figures. Halftones should exhibit high contrast.

We would like to receive your artwork in electronic form. Please save vector graphics (e.g. line artwork) in Encapsulated Postscript Format (EPS), and bitmap files (e.g. halftones) in Tagged Image File Format (TIFF) at a minimum resolution of 300 dpi. Detailed information on our digital illustration guidelines is available at the Author Services website. It is the policy of EJH for authors to pay the full cost for the reproduction of their colour artwork. Therefore, please note that if there is colour artwork in your manuscript when it is accepted for publication, WileyBlackwell requires you to complete and return a colour work agreement form before your paper can be published. However, you may have any colour figures published in colour on the journal web site free of charge.

Kindly return the completed form to the address stated in the form.

Please note that in cases where the Editor-in-Chief deems it necessary to publish one or more illustrations in colour, acceptance for publication will be conditional on the author opting for colour reproduction of those illustrations. Any article received by John Wiley & Sons A/S with colour figures will not be published until the form has been returned.
Legends
Legends should be typed double-spaced in consecutive order on a separate page. They should be brief and specific. If micrographs are used, information about staining methods and magnification should be given.

DECLARATIONS AND COPYRIGHT
The submission must be accompanied by a written statement, signed by the corresponding author on behalf of all authors stating that they agree to the submission, and that the material submitted is novel and not under editorial consideration in another journal. The submission of the manuscript by the authors means that they automatically agree to grant John Wiley & Sons A/S the exclusive licence to publish it if and when it is accepted for publication. The work shall not be published elsewhere in any language without the prior consent of the publisher. The articles published in this journal are protected by this licence, which covers translation rights and the exclusive right to reproduce and distribute all of the articles printed in the journal. No material published in the journal may be stored on microfilm or videocassettes or in electronic databases and the like or reproduced photographically without the prior written permission of the publisher.

If your paper is accepted, the author identified as the formal corresponding author for the paper will receive an email prompting them to login into Author Services; where via the Wiley Author Licensing Service (WALS) they will be able to complete the license agreement on behalf of all authors on the paper.

For authors signing the copyright transfer agreement
If the OnlineOpen option is not selected the corresponding author will be presented with the copyright transfer agreement (CTA) to sign. The terms and conditions of the CTA can be previewed in the samples associated with the Copyright FAQs below: CTA Terms and Conditions.

For authors choosing OnlineOpen
If the OnlineOpen option is selected the corresponding author will have a choice of the following Creative Commons License Open Access Agreements (OAA):

- Creative Commons Attribution Non-Commercial License OAA
- Creative Commons Attribution Non-Commercial-NoDerivs License OAA
To preview the terms and conditions of these open access agreements please visit the Copyright FAQs hosted on Wiley Author Services and visit the Wiley Open Access copyright & license web page.

If you select the OnlineOpen option and your research is funded by The Wellcome Trust and members of the Research Councils UK (RCUK) you will be given the opportunity to publish your article under a CC-BY license supporting you in complying with Wellcome Trust and Research Councils UK requirements. For more information on this policy and the Journal’s compliant selfarchiving policy please visit the Wiley Funder Policies website.

For RCUK and Wellcome Trust authors click on the link below to preview the terms and conditions of this license:

Creative Commons Attribution License OAA
To preview the terms and conditions of these open access agreements please visit the Copyright FAQs hosted on Wiley Author Services and visit the Wiley Open Access copyright & license web page.

MANUSCRIPT REVIEW
Upon receipt an associate editor sends the manuscript to two independent reviewers with particular expertise in the field. The reviewers’ reports are mailed to the associate editor who recommends on the fate of the manuscript to the Editor-in-Chief. The journal aims at having review of the manuscript completed within four weeks of receipt. The corresponding author will receive the reviewers’ comments and the editorial decision by e-mail.

EUROPEAN JOURNAL OF HAEMATOLOGY employs a plagiarism detection system. By submitting your manuscript to this journal you accept that your manuscript may be screened for plagiarism against previously published works.

MANUSCRIPT PRODUCTION

Online production tracking
Author Services enables authors to track their article - once it has been accepted- through the production process to publication online and in print. Authors can check the status of their articles online and choose to receive automated e-mails at key stages of production so they don’t need to contact the production editor to check on progress. The author will
receive an e-mail with a unique link that enables them to register and have their article automatically added to the system. Please ensure that a complete e-mail address is provided when submitting the manuscript. Visit Wiley Author Services for more details on online production tracking and a wealth of resources including FAQs and tips on article preparation, submission and more.

Proofs
Page proofs will be despatched via email notification of a link with a downloadable Acrobat PDF file to the corresponding author. Corrections should be returned within 3 days of receipt. Alterations to the text, other than corrections, may be charged to the author.

Offprints
A PDF offprint of the online published article will be provided free of charge to the corresponding author, and may be distributed subject to the Publisher’s terms and conditions. Paper offprints of the printed published article may be purchased if ordered via the method stipulated on the instructions that accompany the proofs. Printed offprints are posted to the correspondence address given for the paper unless a different address is specified when ordered. Note that it is not uncommon for printed offprints to take up to eight weeks to arrive after publication of the journal. Electronic offprints are sent to the corresponding author at his or her corresponding email address as given on the title page of the paper, unless advised otherwise.

CHECKLIST FOR AUTHORS
Complete this checklist before sending your final manuscript:

☐ Cover letter (optional)
☐ Five suggested reviewers (optional)
☐ Article properly formatted (double-spaced) and structured
☐ Sections in the right order
☐ Title page includes required information (see above)
☐ Abstract does not exceed 250 words

☐ Permission to reproduce any previously published material and patient permission to publish photographs