Survival of patients with chronic myeloproliferative neoplasms and new primary cancers: a population-based cohort study

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Summary
Background Patients with chronic myeloproliferative neoplasms are at increased risk of new solid or haematological cancers, but how prognosis is affected in patients with preceding myeloproliferative neoplasms is unclear.

Methods We used data from population-based medical databases in Denmark from 1980 to 2011 to compare survival between cancer patients with and without a preceding diagnosis of myeloproliferative neoplasm, matched for age, sex, year of diagnosis, and type of cancer. We assessed outcomes by cancer stage and comorbidities.

Findings Data were available for 1246 patients with a history of myeloproliferative neoplasms and we matched 5155 patients without a history of myeloproliferative neoplasm for comparison. Among patients with new localised solid cancers, 5-year survival was 49·8% (95% CI 39·1–59·6) for patients with preceding essential thrombocythaemia, 47·9% (42·1–53·4) for those with preceding polycythaemia vera, and 48·0% (34·1–60·7) for those with preceding chronic myeloid leukaemia. The values were 72·4% (68·4–76·0), 63·9% (61·5–66·2), and 74·3% (68·2–79·4), respectively, in matched patients without preceding myeloproliferative neoplasms. The risk of death among patients with a solid tumour and preceding myeloproliferative neoplasm was 1·21–2·28 times higher than in patients without myeloproliferative neoplasms. Excess mortality risk was observed irrespective of whether new cancers were diagnosed within 5 years or 5 years or more after myeloproliferative neoplasm.

Interpretation Preceding myeloproliferative neoplasm is a predictor for poor outlook in patients who develop new primary cancers.

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Introduction Classic chronic myeloproliferative neoplasms encompass essential thrombocythaemia, polycythaemia vera, myelofibrosis, and chronic myeloid leukaemia.1 These neoplasms have an inherent tendency to evolve into myeloid cancers, such as acute myeloid leukaemia, and the risk of lymphoid haematological neoplasms is higher than that in the general population.2–4 Although adequate management can result in a long life expectancy,3–4 the prognosis for patients in whom myeloproliferative neoplasms transform into acute leukaemia is poor, with median survival being 2–5 months.3–11

We found that among 7229 patients with myeloproliferative neoplasms, risk of new solid cancers was 40% higher than that in the general population.7 The new cancers developed within a median of 4 years of follow-up. The reasons for this increased risk remain unknown, although underlying vulnerability to cancer, the myeloproliferative neoplasm itself, and treatment have been suggested.10–12 The latter hypothesis was supported in a study of 1445 patients with chronic myeloid leukaemia or other myeloproliferative neoplasms treated with tyrosine-kinase inhibitors (TKIs), where there were 40% fewer second cancers when compared with the number expected from the Surveillance, Epidemiology, and End Results database during the 8–9 years of follow-up.10

We did a population-based registry study to investigate how the outlook of patients who develop new primary solid or haematological cancers is affected by a preceding diagnosis of myeloproliferative neoplasm.

Methods
Registries We identified all patients in three Danish national databases, the Danish National Patient Registry (DNPR), Danish Cancer Registry (DCR), and Danish Civil Registration System (CRS),18–21 who had received a diagnosis of myeloproliferative neoplasm from 1980 to 2011. Since 1968, all residents of Denmark have received a unique civil registration number from the CRS, which allows unambiguous individual-level linkage across all Danish registries.18 The CRS records the date of birth, sex, date of emigration, and vital status of all Danish residents and is continuously updated.21

The DNPR contains information on all discharges from Danish public hospitals since 1977 and on outpatient specialist clinic visits since 1995.21 Denmark has very few private hospitals, and none is engaged in
cancer management. Data recorded in the DNPR include civil registration number, dates of outpatient clinic visits, dates of hospital admission and discharge, and up to 20 diagnoses coded by physicians according to the International Classification of Diseases, eighth revision (ICD-8) in 1977–93 and tenth revision (ICD-10) thereafter. Diagnostic coding of haematological malignancies in the DNPR has been validated. We selected all cases of myeloproliferative neoplasms according to the ICD-8 and ICD-10 codes (appendix). Because there is no specific diagnosis code for primary myelofibrosis in ICD-10, we separated patients into three groups based on the available diagnosis codes for essential thrombocythaemia, polycythaemia vera, and chronic myeloid leukaemia.

We took the first hospital admission or visit to an outpatient clinic associated with a diagnosis of myeloproliferative neoplasm to be the date of diagnosis. We identified diagnoses of new primary cancers through linkage to the DCR, which has recorded all cancer diagnoses since 1943 and uses the ICD-10 classification system. Clinical stage at time of diagnosis is classified in the DCR as localised, regional spread, distant metastatic spread, or unknown. The DCR has been found to be 95–98% complete and valid.

**Patients**

The inclusion criteria have been described previously. Eligible patients were aged 20 years or older at the time of diagnosis of myeloproliferative neoplasm and developed a new primary cancer afterwards. We excluded patients with myeloproliferative neoplasms that were preceded by a diagnosis of another cancer, except for non-melanoma skin cancer or carcinoma in situ of the cervix uteri. Patients with a diagnosis of a new primary solid or haematological cancer within 1 year after diagnosis of myeloproliferative neoplasm were deemed to have concurrent cancers and were also excluded.

For each patient with a history of myeloproliferative neoplasm and a second cancer, we identified five patients in the databases matched for new primary cancer type but with no preceding myeloproliferative neoplasm. The patients in the comparison cohort were also matched for sex, age (in 1-year age groups), and time of cancer diagnosis, within the following time periods: 1980–84, 1985–89, 2000–04, 2005–09, and 2010–11. For 90 patients with myeloproliferative neoplasms (24 with essential thrombocythaemia, 57 with polycythaemia vera, and nine with chronic myeloid leukaemia) fewer than five matching patients could be identified.

Ethics approval for this study was provided by the Danish Data Protection Agency.

**Comorbidity**

We used the Charlson Comorbidity Index (CCI) to assess effects of comorbidities on survival. The CCI is a weighted index that summarises the number and seriousness of 19 chronic disorders. Four of these are cancers, which we excluded. Information on the remaining CCI disorders was obtained through retrieval of diagnoses from the DNPR recorded within the 5 years before the diagnosis of the new primary cancer. CCI scores were grouped into three categories: low comorbidity (score of 0); moderate comorbidity (1–2); and severe comorbidity (a score of 3 or higher).

**Statistical analysis**

For all patients, follow-up began on the date of the first hospital admission or first visit to an outpatient specialist clinic associated with the diagnosis of the new primary solid or haematological cancer. Follow-up continued until death, emigration, or Jan 1, 2013, whichever occurred first. Analyses were done separately for solid and haematological cancers. Patients with myeloproliferative neoplasms who received another diagnosis of myeloproliferative neoplasm or chronic myeloid leukaemia during follow-up were not deemed to have a new cancer.

We used the prevalence proportion ratio (PPR) to compare extent of cancer spread and CCI scores of the new primary cancer at diagnosis among patients with and without preceding myeloproliferative neoplasms. PPRs and 95% CIs were calculated by dividing the proportion of cancer patients with the greatest spread or highest CCI score and preceding myeloproliferative neoplasms by the proportion of cancer patients with the greatest spread or highest CCI score but no preceding myeloproliferative neoplasms. We also used PPR calculations to compare differences between subgroups of cancer spread (localised, regional, or unknown) and severity of comorbidity.

The cumulative incidence of cancer during the first 5 years after the diagnosis of myeloproliferative neoplasm was computed with 95% CIs, with death taken to be a competing risk. The values were compared with those in the similar age group of the general population in Denmark. We used the Kaplan-Meier method to construct survival curves after the diagnosis of a new primary cancer and to compare mortality across categories of cancer spread and comorbidity. We used Cox’s proportional hazards regression analysis to compare death rates between cancer patients with and without preceding myeloproliferative neoplasms. We calculated hazard ratios (HRs) and 95% CIs for myeloproliferative neoplasm exposure (essential thrombocythaemia, polycythaemia vera, or chronic myeloid leukaemia), adjusted for age, CCI score, and cancer stage (solid cancers only). HRs were computed separately for cancers that occurred within 5 years or 5 years or more after the diagnosis of myeloproliferative neoplasm. Since patients diagnosed as having myeloproliferative neoplasms in outpatient clinics could be included only from 1995, we stratified analyses by the time periods 1980–94 and 1995–2011. In 2000, TKIs began to be used to treat chronic myeloid leukaemia in...
Denmark. To assess the possible effect of this new treatment on the outlook of patients with chronic myeloid leukaemia and a subsequent cancer, we stratified analyses by the time periods 1980–99 and 2000–11.

As we had no information on smoking status, we used diagnosis of chronic obstructive pulmonary disease (COPD) as a proxy measure (appendix). Because blood test results for heavy smokers might resemble those of myeloproliferative neoplasms, diagnostic misclassification could occur. To assess the potential effect of diagnostic misclassification of myeloproliferative neoplasm on survival, we stratified analyses according to whether a diagnosis of COPD had been made before or at the time of the diagnosis of myeloproliferative neoplasm. The assumption of proportional hazards was assessed graphically in all models and found to be appropriate.

Information on causes of death was retrieved from the Danish Register of Causes of Death. The immediate causes of death, which were derived from death certificates, were separated into six categories, according to ICD-8 codes from 1970–94 and ICD-10 codes thereafter: cardiovascular disease and thrombotic events, haematological cancers, all other cancers, infection, haemorrhagic episodes, and others. The analyses were done with SAS version 9.2.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results
From 1980 to 2011, we identified 2141 patients with essential thrombocythaemia, 4561 with polycythaemia vera, and 1164 with chronic myeloid leukaemia who had no previous or current cancer diagnosed other than myeloproliferative neoplasm, and who were alive 1 year after diagnosis. Of these, 302 patients with essential thrombocythaemia, 834 patients with polycythaemia vera, and 110 patients with chronic myeloid leukaemia subsequently developed a new primary cancer and were included in this study (table 1). Median follow-up for those who developed new solid cancers was 2.0 years (IQR 0.8–4.0) for patients with essential thrombocythaemia, 1.9 years (0.4–4.3) for patients with polycythaemia vera, and 2.2 years (0.7–5.4) for patients with chronic myeloid leukaemia, and for those who developed new haematological cancers, was 0.7 years (IQR 0.2–1.8), 0.6 years (0.1–1.5), and 0.1 years (0.0–0.3), respectively.

The distribution of solid tumours was largely as expected except for non-melanoma skin cancer, which was more frequent in patients with previous myeloproliferative neoplasms. Distribution of specific cancer types was similar in patients with essential thrombocythaemia and polycythaemia vera, although breast cancer was more frequent in patients with essential thrombocythaemia and lung cancer was more frequent in those with polycythaemia vera (table 1). The small number of chronic myeloid leukaemia cases precluded comparison of these patients with those who had other subtypes of myeloproliferative neoplasms. After the diagnosis of a new primary cancer, 6–14% of the patients were later diagnosed as having a second and up to 1% a third cancer, with no clear differences in frequency between patients with preceding myeloproliferative neoplasms and those without.

At the time of diagnosis of new solid cancers in patients with preceding myeloproliferative neoplasms, the median age was 73.6 years (IQR 66.2–81.0) for those with essential thrombocythaemia, 72.1 years (65.3–78.6) with polycythaemia vera, and 70.3 years (63.6–77.0) for patients with chronic myeloid leukaemia and a subsequent cancer.

<table>
<thead>
<tr>
<th>Solid cancers</th>
<th>Essential thrombocythaemia (n=302)</th>
<th>Polycythaemia vera (n=834)</th>
<th>Chronic myeloid leukaemia (n=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All non-haematological cancers</strong></td>
<td>250 (100%)</td>
<td>708 (100%)</td>
<td>95 (100%)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>6 (12%)</td>
<td>20 (16%)</td>
<td>4 (27%)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>4 (8%)</td>
<td>10 (8%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td>8 (15%)</td>
<td>11 (9%)</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Myeloid leukaemia</td>
<td>25 (48%)</td>
<td>59 (47%)</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Other leukaemia</td>
<td>8 (15%)</td>
<td>22 (18%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Haematological cancer unspecified*</td>
<td>1 (2%)</td>
<td>4 (3%)</td>
<td>2 (12%)</td>
</tr>
<tr>
<td>All haematological cancers</td>
<td>52 (100%)</td>
<td>126 (100%)</td>
<td>15 (100%)</td>
</tr>
</tbody>
</table>

Data are number (%). *Cancer types with fewer than five cases reported per site in all three chronic myeloproliferative neoplasm groups.

Table 1: Types of new primary cancers, by type of preceding myeloproliferative neoplasm
for those with polycythaemia vera, and 63·7 years (55·5–72·9) for those with chronic myeloid leukaemia. For patients with new haematological cancers, the median ages at the time of diagnosis were 70–4 years (64·1–75·9), 72·1 years (65·0–78·1), and 75·4 years (65·2–81·7), respectively. The cumulative incidence of solid cancer in the first 5 years after diagnosis for essential thrombocythaemia, polycythaemia vera, and chronic myeloid leukaemia was, respectively, 7·8% (95% CI 6·6–9·1), 6·8% (6·1–7·6), and 4·7% (3·5–6·1). The cumulative incidence of new haematological cancer was, respectively, 1·6% (1·1–2·3%), 1·2% (0·9–1·5), and 1·0% (0·5–1·8).

From our database, we were able to match 5155 patients with solid tumours or haematological malignancies without previous myeloproliferative neoplasm. Data on the extent of spread of solid cancers were available for 82–92% of patients and were similar in patients with and without preceding myeloproliferative neoplasms (table 2). Patients with preceding myeloproliferative neoplastic neoplasms had more comorbidities than those without preceding myeloproliferative neoplasms (table 2). Patients who developed new haematological cancers, the prevalence of comorbidities was generally similar in patients with and without preceding myeloproliferative neoplastic neoplasms (table 2). Owing to the small numbers of patients in the different categories, however, the estimated prevalence ratios were imprecise.

5-year survival after diagnosis of a new solid cancer, stratified by myeloproliferative neoplasm subtype, was consistently reduced over time in patients who had localised cancers or low comorbidity scores and preceding myeloproliferative neoplasms (figures 1, 2). Among patients with preceding myeloproliferative neoplasms and with new localised cancers, 5-year survival was 49·8% (95% CI 39·1–59·6) for patients with essential thrombocythaemia, 47·9% (42·1–53·4) for those with polycythaemia vera, and 48·0% (42·3–52·6) for those with chronic myeloid leukaemia. In patients with localised cancers but no preceding myeloproliferative neoplasms, 5-year survival was 72·4% (68·4–76·0), 63·9% (61·5–66·2), and 74·3% (68·2–79·4), respectively. Similarly, among patients with myeloproliferative neoplasms but no comorbidities, 5-year survival was 50·7% (95% CI 40·1–60·4) for those with essential thrombocythaemia, 38·8% (33·4–44·2) for those with polycythaemia vera, and 48·3% (35·6–59·9) for those with chronic myeloid leukaemia. In comparison, among patients without preceding myeloproliferative neoplasms and with new localised cancers, 5-year survival was 60·3% (56·6–63·8), 48·2% (46·1–50·1), and 61·0% (55·5–66·0), respectively. The combined effect of comorbidity and extent of cancer spread on survival is shown in the appendix. Among patients with metastasis or high comorbidity scores at the time of diagnosis of new cancers, survival was similar in those with and without myeloproliferative neoplasms (figures 1 and 2).

### Table 2: Prevalence of comorbidity and extent of cancer spread among patients with a solid cancer

<table>
<thead>
<tr>
<th>Extent of spread</th>
<th>Preceding ET (n=250)</th>
<th>No preceding ET (n=1234)</th>
<th>Prevalence ratio* (95% CI)</th>
<th>Preceding PV (n=708)</th>
<th>No preceding PV (n=3464)</th>
<th>Prevalence ratio* (95% CI)</th>
<th>Preceding CML (n=95)</th>
<th>No preceding CML (n=457)</th>
<th>Prevalence ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>210 (84%)</td>
<td>1006 (82%)</td>
<td>...</td>
<td>592 (84%)</td>
<td>2918 (84%)</td>
<td>...</td>
<td>87 (92%)</td>
<td>393 (86%)</td>
<td>...</td>
</tr>
<tr>
<td>Localised</td>
<td>147 (70%)</td>
<td>698 (69%)</td>
<td>1·00 (0·92–1·11)</td>
<td>366 (62%)</td>
<td>1805 (62%)</td>
<td>1·00 (0·93–1·07)</td>
<td>61 (70%)</td>
<td>271 (69%)</td>
<td>1·01 (0·87–1·18)</td>
</tr>
<tr>
<td>Regional spread</td>
<td>34 (16%)</td>
<td>155 (15%)</td>
<td>1·05 (0·75–1·48)</td>
<td>101 (17%)</td>
<td>498 (17%)</td>
<td>1·00 (0·82–1·21)</td>
<td>11 (13%)</td>
<td>63 (16%)</td>
<td>0·79 (0·43–1·43)</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>29 (14%)</td>
<td>153 (15%)</td>
<td>0·91 (0·63–1·31)</td>
<td>125 (21%)</td>
<td>615 (21%)</td>
<td>1·00 (0·84–1·19)</td>
<td>15 (17%)</td>
<td>59 (15%)</td>
<td>1·14 (0·68–1·93)</td>
</tr>
</tbody>
</table>

Patients with and without preceding myeloproliferative neoplasms were matched for age, sex, year of cancer diagnosis, and cancer site. ET=essential thrombocythaemia. PV=polyctyaemia vera. CML=chronic myeloid leukaemia. CCI=Charlson Comorbidity Index score. *Calculated as the ratio of the proportions of patients in the two groups with respect to the denoted category. †Excludes cancers. Percentages restricted to patients with available data.

### Table 3: Prevalence of comorbidity among patients with new haematological cancers

<table>
<thead>
<tr>
<th>CCI</th>
<th>Preceding ET (n=52)</th>
<th>No preceding ET (n=205)</th>
<th>Prevalence ratio† (95% CI)</th>
<th>Preceding PV (n=126)</th>
<th>No preceding PV (n=529)</th>
<th>Prevalence ratio† (95% CI)</th>
<th>Preceding CML (n=15)</th>
<th>No preceding CML (n=71)</th>
<th>Prevalence ratio† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>36 (69%)</td>
<td>153 (75%)</td>
<td>0·93 (0·76–1·11)</td>
<td>79 (63%)</td>
<td>396 (75%)</td>
<td>0·84 (0·73–0·97)</td>
<td>8 (53%)</td>
<td>46 (65%)</td>
<td>0·82 (0·50–1·36)</td>
</tr>
<tr>
<td>1-2</td>
<td>12 (23%)</td>
<td>44 (22%)</td>
<td>1·08 (0·61–1·88)</td>
<td>41 (22%)</td>
<td>107 (70%)</td>
<td>1·61 (1·19–2·18)</td>
<td>6 (40%)</td>
<td>21 (20%)</td>
<td>1·35 (0·66–2·77)</td>
</tr>
<tr>
<td>≥3</td>
<td>4 (8%)</td>
<td>8 (4%)</td>
<td>1·92 (0·62–6·29)</td>
<td>6 (5%)</td>
<td>26 (5%)</td>
<td>0·97 (0·41–2·30)</td>
<td>1 (7%)</td>
<td>4 (6%)</td>
<td>1·18 (0·14–9·85)</td>
</tr>
</tbody>
</table>

Patients with and without preceding myeloproliferative neoplasms were matched for age, sex, year of cancer diagnosis, and cancer type. ET=essential thrombocythaemia. PV=polyctyaemia vera. CML=chronic myeloid leukaemia. CCI=Charlson Comorbidity Index score. *Excludes cancers. †Calculated as the ratio of the proportions of patients in the two groups with respect to the denoted category.
The risk of death was increased in patients with and without myeloproliferative neoplasms who developed new solid cancers (table 4). Increased risk remained irrespective of whether the new cancer was diagnosed within 5 years or 5 years or more after the diagnosis of myeloproliferative neoplasm. The mortality risk was substantially increased in patients with preceding myeloproliferative neoplasms and distant metastases or high comorbidity scores at the time of diagnosis of a new solid cancer (table 4). For patients with a haematological cancer, preceding myeloproliferative neoplasms were associated with a poorer outlook than no preceding neoplasm, but the HRs were imprecise (table 4).

We found no difference in survival between 1980–94 and 1995–2011 by preceding diagnosis of myeloproliferative neoplasm, cancer stage, or comorbidity in the analysis of change in myeloproliferative neoplasm case ascertainment strategy (data not shown). In the assessment of effect of use of TKIs, 62 and 33 patients with preceding chronic myeloid leukaemia were diagnosed in 1980–99 and 2000–11, respectively, as having new solid cancers (adjusted HRs 2.97, 95% CI 1.91–4.62 and 0.77, 0.36–1.62). The number of patients with preceding chronic myeloid leukaemia and new haematological cancers (n=15) was too small to allow this stratification. In the analysis of effect of diagnostic misclassification on survival, the risk of death remained raised in patients with preceding myeloproliferative neoplasms: essential thrombocythaemia, HR 1.61 (95% CI 1.29–2.02) without COPD and 1.31 (1.17–1.48) without COPD and 1.49 (0.66–3.35) with COPD; polycythaemia vera, 1.26 (1.01–1.59) without COPD and 1.18 (0.30–4.74) with COPD; and chronic myeloid leukaemia, 1.83 (1.31–2.66) without COPD and 2.51 (1.52–4.16) with COPD; and chronic myeloid leukaemia, 1.83 (1.31–2.66) without COPD and 2.51 (1.52–4.16) with COPD; and chronic myeloid leukaemia, 1.83 (1.31–2.66) without COPD and 2.51 (1.52–4.16) with COPD.

Information on the immediate cause of death was retrieved from 889 patients with cancer and preceding essential thrombocythaemia or polycythaemia vera (appendix). For patients with preceding essential thrombocythaemia and a new solid cancer, increased 5-year mortality and HRs for death were also associated with infection or bleeding (appendix).

Figure 1: Survival in patients with and without preceding myeloproliferative neoplasms and with new solid cancers, stratified by extent of spread (A) Patients with and without preceding ET. (B) Patients with and without preceding PV. (C) Patients with and without preceding CML. ET=essential thrombocythaemia. PV=polythychaemia vera. CML=chronic myeloid leukaemia.
Previous CML and CCI ≥3
Previous CML and CCI 1–2
Previous CML and CCI 0
No previous CML and CCI 1–2
No previous CML and CCI 0

Previous PV and CCI ≥3
Previous PV and CCI 1–2
Previous PV and CCI 0
No previous PV and CCI ≥3
No previous PV and CCI 1–2
No previous PV and CCI 0

Previous ET and CCI ≥3
Previous ET and CCI 1–2
Previous ET and CCI 0
No previous ET and CCI ≥3
No previous ET and CCI 1–2
No previous ET and CCI 0

Discussion
In patients with preceding myeloproliferative neoplasms and localised solid cancer, 5-year survival was significantly lower than that in matched cancer patients without preceding myeloproliferative neoplasms. When adjusted for cancer stage and comorbidity score, preceding myeloproliferative neoplasms were associated with higher risk of mortality than in patients with new primary solid and haematological cancers and no history of myeloproliferative neoplasms. The effect of previous chronic myeloid leukaemia on the prognosis of new cancers, however, was only evident for cancers diagnosed from 1980 to 1999, before this cancer was treated with TKIs.

The mechanism by which preceding myeloproliferative neoplasms affect the prognosis of new primary cancers is unknown. Thrombocytosis is an almost universal finding in untreated patients with myeloproliferative neoplasms, and platelets have been suggested to interact with tumour cells in solid cancers and promote growth, progression, and invasion. High platelet counts also have been suggested as a risk factor for cancer-associated venous thromboembolism, which in itself is associated with worsened prognosis. In our study, mortality due to cardiovascular or thrombotic disease was more frequent in patients with preceding myeloproliferative neoplasms than in those without and, therefore, these comorbidities might have contributed to worsened prognosis.

Because of the registry-based design of this study, we did not have access to detailed clinical data on severity of myeloproliferative neoplasms or treatment of these or new primary cancers. Since 2000, however, almost all patients with chronic myeloid leukaemia in Denmark have been treated with TKIs. After 2000, the outlook for patients with and without preceding chronic myeloid leukaemia who developed new solid cancers became similar. After 1 year of TKI therapy, most patients have minimum residual disease, whereas patients with other myeloproliferative neoplasms generally have persistent or progressive disease. With regard to the effect of treatment on cancer prognosis, our findings support the clinical evidence that TKIs do not promote development of new cancers. The distinction between the effect of other treatments for myeloproliferative neoplasms and the effect of persistent disease is difficult, but our findings underscore the need for effective management of myeloproliferative neoplasms other than chronic myeloid leukaemia. For patients with preceding essential thrombocythaemia and polycythaemia vera, survival after being diagnosed as having a new primary cancer was

Figure 2: Survival in patients with and without preceding myeloproliferative neoplasms and with new solid cancers, stratified by comorbidity score
(A) Patients with and without preceding ET. (B) Patients with and without preceding PV. (C) Patients with and without preceding CML ET-essential thrombocythaemia. PV-polycythaemia vera. CML-chronic myeloid leukaemia.
CCI-Charlson Comorbidity Index score.
cancer patients with two neoplastic diseases would have case reports. A limitation of our study, however, is low occurring because of hydroxyurea has been reported in early-stage cancers or no comorbidity. Generally, accuracy of coding diagnoses has been high in the DNPR. A possible study limitation of this study, however, is that diagnosis of myeloproliferative neoplasms was defined by ICD codes, which might not be entirely accurate. When we stratified analyses according to COPD diagnosis, however, survival remained poorer among cancer patients with preceding myeloproliferative neoplasms but without COPD than among cancer patients without myeloproliferative neoplasms and COPD. Additionally, the effect of myeloproliferative neoplasms on survival seemed to persist or even increase over time. Cancer-associated reactive thrombocytosis or polycythaemia or polycythaemia vera, and modern generally good in patients with essential thrombocythaemia or polycythaemia vera, or chronic myeloid leukaemia have a good outlook and, therefore, the prevalence of these cancer types is high. For clinicians caring for patients with multiple primary cancers, one of which is a myeloproliferative neoplasm, understanding of how prognosis might be affected by myeloproliferative neoplasms is of interest. We found reduced survival in patients with preceding myeloproliferative neoplasms compared with that in cancer patients without preceding cancers of this type. Survival was also adversely affected in patients with a preceding diagnosis of myeloproliferative neoplasm and a new cancer diagnosed at an early stage or without further comorbidity.

Panel: Research in context

Systematic review
We searched PubMed with the search term "myeloproliferative neoplasm AND secondary cancer". We identified 284 articles suitable for review but found no studies of the prognosis of secondary solid cancers in patients with myeloproliferative neoplasms.

Interpretation
Patients with essential thrombocythaemia, polycythaemia vera, or chronic myeloid leukaemia have a good outlook and, therefore, the prevalence of these cancer types is high. For clinicians caring for patients with multiple primary cancers, one of which is a myeloproliferative neoplasm, understanding of how prognosis might be affected by myeloproliferative neoplasms is of interest. We found reduced survival in patients with preceding myeloproliferative neoplasms compared with that in cancer patients without preceding cancers of this type. Survival was also adversely affected in patients with a preceding diagnosis of myeloproliferative neoplasm and a new cancer diagnosed at an early stage or without further comorbidity.
Contributors
HF, TSL, HCH, JS, and HTS conceived the idea for the study. All authors participated in designing the study. HF and TSI did the literature search. DFK did the data analyses and created the figures. All authors participated in the interpretation of the data. HF wrote the first draft of the paper, and all authors participated in writing subsequent drafts.

Declaration of interests
We declare no competing interests.

References