

# Associated cancers in parents and offspring of polycythaemia vera and myelofibrosis patients

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## Summary

Polycythaemia vera (PV) and primary myelofibrosis (MF) show concordant familial clustering but limited population level data are available on the aggregation of other discordant neoplasms in these families. We used the Swedish Family-Cancer Database to assess risks for VP and MF in families of cancer patients. A total of 3530 first PV and 1606 MF patients were identified, with high concordant familial risks. Several discordant familial associations were found for PV (acute myeloid leukaemia, Hodgkin disease, prostate and bladder cancers) or for MF (chronic lymphatic leukaemia, colorectal, kidney and cervical cancers) or for both (nervous system, eye and endocrine tumours).

**Keywords:** polycythaemia vera, myelofibrosis, leukaemia, family history, discordant cancers.

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Chronic myeloproliferative neoplasms (MPNs) include, according to the 2008 World Health Organization (WHO) classification of tumours, polycythaemia vera (PV) and primary myelofibrosis (MF) (Tefferi & Vardiman, 2008). Together these account for 15–20% of all leukaemias in the Swedish Cancer Registry (Centre for Epidemiology 2007; Hemminki *et al*, 2008b). MPNs are characterized by a clonal stem cell expansion of one or more of the myeloid lineages in the bone marrow (Jaffe *et al*, 2001). They have also a tendency to transform from one phenotype to another. After an insidious onset these diseases may progress stepwise into a terminal bone marrow failure. According to WHO, the incidence for PV was given as 8–10 per million per year, compared 5–15 for MF, the latter with a statement that the actual incidence of MF is not known (Jaffe *et al*, 2001). These rates are in the lower range of the current Swedish rates (Centre for Epidemiology 2007; Hemminki *et al*, 2008b). The aetiology of MPN is largely unknown, except that radiation and toxic chemicals, such as benzene are known risk factors (Jaffe *et al*, 2001). In PV, cytogenetic abnormalities are rare

and non-specific but they increase in the course of disease progression, which may eventually lead to myelodysplastic syndrome or acute leukaemia. In MF, some 60% of the patients have non-specific chromosomal abnormalities (Jaffe *et al*, 2001). A specific mutation in the JAK2 gene, V617F, or some rarer mutations have been described in practically all patients with PV and in some 50% of patients with MF (Skoda & Prchal, 2005; Bellanne-Chantelot *et al*, 2006; Tefferi & Vardiman, 2008). However, these are considered somatic events which do not explain familial aggregation of the disease (Bellanne-Chantelot *et al*, 2006; Rumi, 2008).

We have studied familial associations in PV from years 1958–1998 based on the Swedish Family-Cancer Database and found a familial relative risk of 11 (Hemminki & Jiang, 2001). Familial cluster of MPN has also been described in an Italian study where 7.6% of the cases reported an affected family member (Rumi *et al*, 2007). A recent case-control study described familial risks in MPNs from Sweden where some 1.7% of the cases were familial (Landgren *et al*, 2008). Having access to an updated Family-Cancer Database covering years

1958–2006 from the Cancer Registry, we wanted to examine familial risk for PV and MF for concordant disease or for any discordant neoplasm. Essential thrombocythaemia was not included because its coding system has frequently changed.

## Methods

The Swedish Family-Cancer Database was created in the 1990s by linking information from the Multigeneration Register, national censuses, Swedish Cancer Registry and death notifications (Hemminki *et al*, 2001a). Data on family relationships were obtained from the Multigeneration Register, where children born in Sweden in 1932 and later are registered with their biological parents as families. The Swedish Cancer Registry is based on compulsory reports of diagnosed cases, with coverage of the cancer registration close to 100% (Centre for Epidemiology 2007). The current 2008 update of the Database includes 12 million individuals and their cancers from years 1958 to 2006. Individuals without identified parents were excluded from the study. The age structure of the Database (children born after 1932) implicates that the maximum age of diagnosis in the second generation is 74 years. The age of individuals in the first generation is not limited.

The codes used for PV were ICD-7 208 with WHO/HS/CANC/24.1 histology code 276; for MF the ICD code was 209 and histology code 216 (Centre for Epidemiology 2007). Family history was defined using affected parents or siblings as probands (Hemminki *et al*, 2001b). For the cohort design, standardized incidence ratios (SIRs) with confidence intervals (95%CI or 99%CI; the latter to account for multiple testing) were the outcome measure (Hemminki *et al*, 2001b). The reference rates were calculated from 5-year-age, region, period- and socio-economic status-specific incidence rates for MPN in the whole population. Two independent analyses were carried out: risk of MPN in offspring of parents with cancers, or, in a reverse order, risk of cancer in offspring of parents with MPN.

## Results

A total of 3530 first PV and 1606 MF patients were identified. Table I shows familial association for PV, listing cancer sites with at least five familial cases or significant results in any of the four comparisons. Significant risk increases at the 5% level are shown in bold type and those with at least 1% significance are additionally underlined. The SIR for PV in offspring was 12.6 when a parent was diagnosed with PV. Another leukaemia association for PV was with AML, SIR 3.75. The risk for PV in offspring was increased when a parent was diagnosed with pituitary tumours (SIR 4.87) or thyroid cancers (2.43). In a reversed analysis, the risks for urinary bladder cancer (1.55), Hodgkin disease (2.00) and non-thyroid endocrine gland tumours (2.56) were increased in offspring when parents were diagnosed with PV; among endocrine tumours, the highest SIR of 5.20 was observed for adrenal tumours. Many of the

associations with endocrine gland tumours were significant at the 1% level.

Among siblings, one pair presented with PV and MF, SIR 26.7. Risks for siblings of PV patients were also increased for prostate, eye and nervous system cancers; among the eye cancers, one was melanoma and the other glioma. The large difference in sibling pairs affected by PV and prostate cancer (i.e., 16 and 20) was due to one family of many affected brothers with prostate cancer.

For MF, sibling risk was 27.3 (Table II). MF risk in offspring was increased to 2.77 when a parent was diagnosed with CLL. For other discordant associations, MF was increased in offspring when a parent was diagnosed with kidney (1.93) and eye cancers (9.28); in the parents with eye cancer, melanoma was diagnosed in three parents and retinoblastoma in the fourth parent. For reversed associations, offspring nervous system (1.76) and non-thyroid endocrine gland tumours (2.70) were in excess when parents were diagnosed with MF. Among siblings, increased associations were found between MF and colorectal cancer (2.78/1.97), MF and cervical cancer (3.22) and MF and myeloma (5.12).

## Discussion

Our results on MPNs differ from those of Landgren *et al* (2008) in some respects even though the majority of data for both studies originated from the Swedish Cancer Registry. Their PV patient numbers were higher than ours, but our familial risk was twice theirs (12.6 compared to 6.6, parental proband) and only we found the association of PV with AML. Somewhat more MF cases were recorded by us and only we found the very high sibling risk for MF and its high risk with CLL. The explanation to the differences may be diagnostic classification, for which we used both ICD and histology; a higher diagnostic accuracy would be expected to convey higher familial risks. Although the overall diagnostic accuracy of lymphoproliferative disease has been shown to be good in the Swedish Cancer Registry, MPNs have not been covered (Turesson *et al*, 2007). The Cancer Registry started to use SNOMED (Jaffe *et al*, 2001) as an additional histology classification since 1993, with 99.7% and 100% agreement with the present PV and MF cases, respectively. We thus believe that the diagnostic accuracy of the present PV and MF cases is high. The results point to the very high familial risk of MPN compared to cancers in general for which the familial risk are around 2.0 (Hemminki *et al*, 2008a).

There are little previous data on discordant familial associations of MPNs and cancer. In the analysis of discordant familial associations a large number of comparisons are done and some of the positive associations may be due to chance; for this reason even 99%CIs were shown. In the present study essentially three independent analyses were carried out (risk of MPN in offspring of parents with cancers, risk of cancer in offspring of parents with MPN and risk in siblings) but the results gave limited support to each other because of small case

**Table I.** Number of cases (*N*) and standardized incidence ratio (SIR) of polycythemia vera for individuals with relatives affected by cancer (left); number of cases and standardized incidence ratio of cancer for individuals with relatives affected by polycythemia vera (right).

Type of cancer	Type of relative affected by cancer				Type of relative affected by polycythemia vera			
	Parent		Sibling		Parent		Sibling	
	<i>N</i>	SIR (95% CI)	<i>N</i>	SIR (95% CI)	<i>N</i>	SIR (95% CI)	<i>N</i>	SIR (95% CI)
Any type	267	1.09 (0.95–1.26)	41	0.85 (0.62–1.16)	548	<b>1.14</b> (1.05–1.24)	102	<b>1.22</b> (1.00–1.48)
Upper aerodigestive tract	6	1.04 (0.47–2.33)	1	0.92 (0.13–6.54)	7	0.77 (0.37–1.61)	1	1.16 (0.16–8.26)
Oesophagus	2	0.59 (0.15–2.35)			5	1.48 (0.61–3.55)		
Stomach	15	0.82 (0.49–1.37)	1	1.04 (0.15–7.40)	8	1.38 (0.69–2.76)	1	0.67 (0.09–4.77)
Colorectum	45	1.08 (0.80–1.47)	7	0.76 (0.36–1.60)	42	1.17 (0.86–1.58)	6	0.64 (0.29–1.42)
Liver	7	0.68 (0.32–1.43)	2	0.78 (0.19–3.11)	8	1.26 (0.63–2.52)	2	1.85 (0.46–7.39)
Pancreas	14	1.39 (0.82–2.35)	2	1.16 (0.29–4.67)	2	0.27 (0.07–1.07)	2	0.95 (0.24–3.81)
Lung	23	1.03 (0.68–1.56)	6	1.25 (0.56–2.80)	26	0.94 (0.64–1.38)	7	1.23 (0.59–2.58)
Breast	37	1.10 (0.79–1.54)	19	1.07 (0.68–1.68)	93	0.96 (0.78–1.17)	19	1.29 (0.82–2.02)
Cervix	10	1.77 (0.95–3.31)	1	0.37 (0.05–2.60)	9	0.92 (0.48–1.76)	1	0.33 (0.05–2.36)
Endometrium	8	0.82 (0.41–1.64)	2	0.60 (0.15–2.39)	13	0.84 (0.49–1.46)	2	0.86 (0.21–3.44)
Ovary	5	0.70 (0.29–1.69)	1	0.42 (0.06–2.99)	11	0.76 (0.42–1.37)	2	0.91 (0.23–3.64)
Prostate	45	0.93 (0.69–1.26)	16	1.43 (0.87–2.36)	65	1.14 (0.90–1.46)	20	<b>2.43</b> (1.57–3.77)
Kidney	11	1.27 (0.70–2.30)	3	0.94 (0.30–2.93)	16	1.32 (0.81–2.16)	2	0.78 (0.19–3.10)
Urinary bladder	20	1.29 (0.82–2.01)	6	1.98 (0.89–4.43)	20	<b>1.55</b> (1.00–2.40)	6	1.89 (0.85–4.20)
Melanoma	7	0.90 (0.43–1.91)	5	0.77 (0.32–1.85)	37	1.02 (0.74–1.41)	5	0.93 (0.39–2.23)
Skin, squamous cell	14	0.96 (0.56–1.63)	1	0.38 (0.05–2.71)	13	1.18 (0.69–2.04)	1	0.39 (0.05–2.77)
Eye			2	3.76 (0.94–15.1)	1	0.44 (0.06–3.16)	2	<b>4.01</b> (1.00–16.1)
Nervous system	9	1.14 (0.59–2.21)	8	<b>2.01</b> (1.00–4.03)	34	1.11 (0.79–1.56)	8	1.67 (0.83–3.34)
Thyroid gland	5	2.20 (0.91–5.31)	1	0.75 (0.10–5.30)	9	1.39 (0.72–2.67)	2	1.04 (0.26–4.16)
Endocrine glands	6	1.17 (0.52–2.61)	2	0.89 (0.22–3.56)	26	<b>2.56</b> (1.74–3.77)	2	0.47 (0.12–1.89)
Adrenal					5	<b>5.20</b> (2.16–12.5)		
Parathyroid	3	0.71 (0.23–2.2)	1	0.50 (0.07–3.55)	15	<b>2.48</b> (1.49–4.12)	1	0.68 (0.10–4.81)
Pituitary	3	<b>4.87</b> (1.57–15.2)			6	<b>2.30</b> (1.03–5.13)		
Other			1	<b>7.16</b> (1.01–50.9)			1	1.25 (0.18–8.87)
Non-Hodgkin lymphoma	9	0.96 (0.50–1.86)	2	0.46 (0.12–1.85)	21	1.25 (0.81–1.92)	2	0.55 (0.14–2.19)
Hodgkin disease	3	2.05 (0.66–6.36)	1	1.75 (0.25–12.4)	9	<b>2.00</b> (1.04–3.84)	1	1.64 (0.23–11.6)
Myeloma	7	1.39 (0.66–2.92)	1	0.91 (0.13–6.50)	8	1.86 (0.93–3.72)	1	0.95 (0.13–6.76)
Leukaemia	28	<b>3.15</b> (2.15–4.59)	2	0.70 (0.18–2.82)	25	<b>1.76</b> (1.19–2.61)	2	1.84 (0.46–7.35)
Chronic lymphoid	5	1.49 (0.62–3.60)	1	1.04 (0.15–7.38)	4	1.12 (0.42–2.98)	1	1.10 (0.16–7.84)
Acute myeloid	8	<b>3.75</b> (1.87–7.53)			4	1.53 (0.57–4.08)		
Chronic myeloid	2	2.51 (0.63–10.1)			1	0.59 (0.08–4.17)		
Polycythemia vera	12	<b>12.6</b> (7.10–22.3)			12	<b>12.6</b> (7.10–22.3)		
Myelofibrosis	1	5.27 (0.74–37.5)	1	3.61 (0.51–25.7)	1	0.66 (0.09–4.72)	1	<b>26.7</b> (3.76–190)

Bolding shows that the 95% CI does not overlap with 1.00; the underlined figure shows that the 95% CI does not overlap with 1.00.

numbers. However, for VP all SIRs with AML (if cases were found), bladder cancer and Hodgkin disease were above 1.00; similarly, for MF all associations with CLL and colorectal cancer were above 1.00. Considering two related diseases PV and MF together, joint associations with eye, nervous system and endocrine tumours were found, providing evidence for true links. Among patients with eye cancer, melanoma was the most common type; neither non-melanoma eye cancer nor cutaneous melanoma were increased. The association with endocrine tumours was contributed by many affected endocrine glands but particularly with pituitary tumours. The association of PV with AML is explained by relatedness of the conditions: MPNs may progress to AML and the two

phenotypes have partially overlapping natural histories (Jaffe *et al*, 2001). For most cancers, including breast and lung cancers, no increases were found.

The present data confirm the high familial risks of particularly PV, for which no susceptibility genes have yet been found (Rumi, 2008). Several discordant familial associations appeared to be supported by the present data, including some that were found for PV (acute myeloid leukaemia, Hodgkin disease, prostate and bladder cancers) or for MF (CLL, colorectal, kidney and cervical cancers) or for both (nervous system, eye and endocrine tumours). Many associations were based on small case numbers and they need to be confirmed in other setting. Nevertheless, these data suggest that there are

**Table II.** Number of cases (*N*) and standardized incidence ratio (SIR) of myelofibrosis for individuals with relatives affected by cancer (left); number of cases and standardized incidence ratio of cancer for individuals with relatives affected by myelofibrosis (right).

Type of cancer	Type of relative affected by cancer				Type of relative affected by polycythemia vera			
	Parent		Sibling		Parent		Sibling	
	<i>N</i>	SIR (95% CI)	<i>N</i>	SIR (95% CI)	<i>N</i>	SIR (95% CI)	<i>N</i>	SIR (95% CI)
Any type	170	1.04 (0.87–1.24)	29	0.92 (0.63–1.34)	152	1.01 (0.87–1.19)	88	<b>1.35</b> (1.09–1.66)
Stomach	6	0.46 (0.21–1.04)			1	0.31 (0.04–2.22)		
Colorectum	36	1.29 (0.92–1.82)	12	<b>2.78</b> (1.57–4.93)	11	1.05 (0.58–1.89)	12	<b>1.97</b> (1.12–3.47)
Liver	9	1.19 (0.61–2.30)	1	1.61 (0.23–11.5)	1	0.62 (0.09–4.37)	1	0.65 (0.09–4.62)
Pancreas	9	1.22 (0.63–2.36)						
Lung	14	0.83 (0.49–1.41)	1	0.16 (0.02–1.13)	6	1.32 (0.59–2.94)	2	0.42 (0.11–1.69)
Breast	30	1.38 (0.95–1.99)	10	0.83 (0.45–1.56)	29	0.89 (0.62–1.28)	13	1.20 (0.70–2.07)
Cervix	2	0.39 (0.10–1.57)	3	1.94 (0.62–6.03)	2	0.37 (0.09–1.48)	3	<b>3.22</b> (1.04–9.98)
Endometrium	4	1.18 (0.44–3.15)	1	0.42 (0.06–2.96)	7	2.04 (0.97–4.28)	2	0.73 (0.18–2.94)
Prostate	30	1.02 (0.71–1.48)	7	1.26 (0.60–2.66)	12	0.83 (0.47–1.46)	11	1.28 (0.71–2.30)
Kidney	14	<b>1.93</b> (1.13–3.28)			2	0.55 (0.14–2.18)		
Urinary bladder	14	1.53 (0.90–2.61)	5	2.01 (0.83–4.85)	1	0.21 (0.03–1.52)	5	1.63 (0.68–3.92)
Melanoma	5	0.85 (0.35–2.06)	4	0.94 (0.35–2.53)	10	0.83 (0.45–1.54)	4	0.98 (0.37–2.62)
Skin, squamous cell	11	1.13 (0.62–2.05)	3	1.87 (0.60–5.81)	2	0.47 (0.12–1.86)	4	2.55 (0.96–6.79)
Eye	4	<b>9.28</b> (3.47–24.9)			1	1.94 (0.27–13.8)		
Nervous system	5	0.79 (0.33–1.91)	7	2.04 (0.97–4.31)	16	<b>1.76</b> (1.08–2.87)	7	1.57 (0.75–3.30)
Endocrine glands			2	1.08 (0.27–4.32)	12	<b>2.70</b> (1.53–4.75)	2	1.56 (0.39–6.23)
Adrenal					1	1.40 (0.20–9.96)		
Parathyroid			1	0.95 (0.13–6.78)	5	<b>2.53</b> (1.05–6.08)	1	1.18 (0.17–8.35)
Pituitary			1	2.29 (0.32–16.3)	4	<b>2.99</b> (1.12–7.99)	1	3.56 (0.50–25.3)
Other					2	<b>4.72</b> (1.18–18.9)		
Non-Hodgkin lymphoma	6	0.99 (0.44–2.22)			8	1.37 (0.68–2.73)		
Myeloma	3	0.67 (0.22–2.09)	2	2.36 (0.59–9.48)	1	0.46 (0.06–3.27)	2	<b>5.12</b> (1.28–20.5)
Leukaemia	12	<b>1.86</b> (1.05–3.30)	7	<b>4.31</b> (2.04–9.10)	5	0.94 (0.39–2.25)	7	<b>2.97</b> (1.42–6.24)
Chronic lymphoid	7	<b>2.77</b> (1.31–5.85)	1	2.20 (0.31–15.7)	1	1.14 (0.16–8.06)	1	2.05 (0.29–14.6)
Polycythemia vera	1	0.66 (0.09–4.72)	1	<b>26.7</b> (3.76–190)	1	5.27 (0.74–37.5)	1	3.61 (0.51–25.7)
Myelofibrosis			4	<b>27.3</b> (10.2–73.0)			4	<b>27.3</b> (10.2–73.0)

Bolding shows that the 95% CI does not overlap with 1.00; the underlined figure shows that the 95% CI does not overlap with 1.00.

probable common genetic risks factors MPN and cancer, some of which are shared for PV and MF.

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