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Familial risks and temporal incidence trends of multiple myeloma

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ABSTRACT

In several cancer registration areas, the trends in the incidence and mortality of multiple myeloma (MM) have been rising over the last few decades. Pedigrees studies on families with multiple affected members have supported the hypothesis of a contributing hereditary etiology of MM due to shared genetic factors. The aim of our study was twofold: 1) to assess incidence trends of MM over the period 1961–2003 using national cancer registry data and; 2) to quantify the familial risk of MM using the 2004 update of the Swedish Family-Cancer Database. For men, the age-standardized rates were 4.33 per 100 000 in 1961–65 and 4.79 in 2001–03. The corresponding rates for women were 2.76 and 3.43. In the elderly, MM rates have risen from 28.7 per 100 000 to 36.2 in men, and from 20.2 to 24.5 in women. MM clustered in families with MM (standardized incidence ratio, SIR = 2.45), non-Hodgkin lymphoma (SIR = 1.34) and chronic lymphocytic leukaemia (SIR = 2.45). No association was found for Hodgkin lymphoma and other leukaemias. Significant associations were found for rectal, stomach, cervical, prostate, bladder, endocrine glands and connective tissue malignancies. Our study adds further evidence that the incidence of MM in Sweden has been constant for several decades. The apparent increase observed in the elderly is, at least in part, attributable to improved diagnostics and certification. MM aggregates in families with MM, chronic lymphocytic leukaemia and, to a lesser extent, with non-Hodgkin lymphoma. If environmental factors can be excluded, the pattern of familial risk of MM is consistent with an autosomal dominant mode of inheritance.

1. Introduction

Multiple myeloma (MM) is a malignancy arising from mature plasma B-cells in the bone marrow producing a serum monoclonal immunoprotein.[1] Common clinical features include progressive skeletal destruction, anaemia, recurrent bacterial infections and renal failure.[1] Among haematopoietic malignancies MM is the one with the poorest prognosis and lowest survival rates (i.e. 5-years 15–30%).[1–3] The etiology of MM remains obscure, but a number of environmental exposures such as radiation and pesticides exposure, chronic antigenic stimulation and virus infections, and specific dietary patterns have been found to be implicated as possible predisposing factors.[1,4,5]

In several cancer registration areas the trends in the incidence and mortality rates of MM have been rising over the last few decades, but the extent to which differences are attributable to definitions and diagnosis practices or to a real increase is unclear.[6–9] Time trend variations of MM may give clues on its carcinogenic pathway, as a change in incidence

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should point to the possible role of a new environmental etiologic factor. Most migrant studies have shown that the incidence of cancer moves to the level of the new host population in one or two generations,[10] but only limited information is available for MM.[11,12] Thus, the assessment of the risk of MM in immigrants and their offspring in Sweden could make a substantial contribution to the understanding of the environmental component.

Although there is some evidence of a familial clustering within families, the roles of genetic background and environment are poorly understood.[13–27] Chance alone, familial common environmental exposures, or shared inherited genes, may be responsible for the observed familial aggregation. Thus, using data from the national cancer registry and from the 2004 updated version of the Swedish Family-Cancer Database, we have assessed here the incidence trends of MM over the period 1961–2003 and we have quantified the familial risk of MM and other related malignancies, with a particular focus on the role of sex, age and mode of inheritance.

1.1. *Incidence rates*

MM constitutes less than 1% of all cancers worldwide and approximately 10% of all lymphoproliferative (LP) malignancies, with about 16 000 new cases each year in Europe, and 500 in Sweden.[1,3,28] Worldwide, incidence rates vary from 0.4 to 5 per 100 000 with higher rates in the Western compared to Asian Countries.[3] The incidence is 2-fold higher in Afro-Americans than in the Caucasian population, with a consistent higher incidence in males in any population.[2] Mortality from MM has risen steadily over the last few decades in the US and across Europe.[3,8] The increase in mortality was larger in the elderly and was less marked in the Nordic countries, including Sweden, which had originally high mortality rates.[8] According to several reports the incidence rates of MM have been increasing with a similar pattern in men and women,[29,30] with the exception of a report from Malmö (Sweden) in which the increase in incidence was restricted to males.[31] However, to which extent this increase is real or artifactual, due to advancements in the diagnosis and certification of the disease is not completely understood.[6,8,9,31] Sweden, where MM rates are among the highest worldwide, is a population of interest for addressing the issue of trends of MM because it is has long been covered with comprehensive and uniform medical surveillance of LP malignancies.[31]

1.2. *Familial aggregation and genetics*

The evidence of a familial aggregation of MM is based on several case reports,[21,25,32,33] three studies on identical twins,[23,34,35] a few case-control[15,16,20] and cohort studies.[14,36–38] The risk of MM in first-degree relatives of cases of MM has been generally reported to vary between 2.0 and 4.0.[20,23,34,39] A common etiologic pattern of MM with other LP has been suggested. An excess risk of MM of about 2-fold was consistently reported among those who had a family history of any LP malignancy,[15,20,21,38] but few studies had the power to investigate the role of specific types of LP malignancies.[40]

The large majority of cases of MM occur over age 60 years and less than 5% of cases occur under age 40.[41,42] The mean age at diagnosis of familial cases was usually reported to be not materially different from sporadic cases.[15,21] Genetic anticipation (i.e. the tendency in multigenerational families of earlier disease onset or greater disease severity in later generations for cases occurring in successive generations) has been suggested for MM by several family reports.[21,27,32,43] However, population-based data have not confirmed this hypothesis.[44]

MM affects men more than women, but the effect of sex on the familial risk at a population level has been rarely quantified. Three studies reported no material difference in the familial risk of MM between sexes,[15,16,32] whereas one family study reported a higher incidence for women.[27] Most family studies suggested an autosomal dominant mode of inheritance with low penetrance of MM, but little information is available from population-based studies.[24,27]

Compared to other racial groups, Afro-Americans, especially males, have a 2-fold higher frequency of MM,[45,46] likely to be due to cultural and/or inherited susceptibility. However, in a large case-control study from the US the familial risk was not substantially different between Blacks and Whites.[16]

MM, unlike most LP malignancies, appears to have a complex and heterogeneous karyotype profile. Multiple chromosomal gains and losses, and chromosome translocations that deregulate a variety of oncogenes, are the most frequent changes reported.[1,47,48] A pre-malignant lesion called monoclonal gammopathy of undetermined significance, presenting genetic changes similar to MM, has long been reported to cluster in members of families with cases of MM, but its prognostic significance is poorly understood.[21,24,25,32,47–49]

Observations from multiple case families identified in a clinical setting can be useful for clarifying the molecular genetic basis of the disease, but they provide little information on the individual risk at a population level. Moreover, hospital-based studies that rely on a relatively small number of cases, with non-systematic ascertainment of cases and self-reported family history of cancer with no medical verification may have yielded inflated risk estimates.

2. Patients and methods

Age-incidence data by calendar periods from 1961 to 2003 of MM were derived from the Cancer Registry of Sweden and from the EUCAN database.[28,50] Incidence rates were standardized according to the European standard population.

The Swedish Family-Cancer Database was created in the mid-1990s by linking census information, death notifications, and the administrative family register at Statistics Sweden to the Swedish Cancer Registry.[51] For each child there are data on both parents at the time of birth. Each person has been assigned a unique technical identification number, allowing construction of families. The Database was updated at the end of 2004 to include persons born in Sweden after 1931 with their biological parents, totalling 10.5 million individuals. The Database is organized in more than 3.6 million nuclear families, with parents and offspring. Neoplasms were retrieved from the Swedish Cancer Registry from 1958 to 2002. The Swedish Cancer Registry is based on compulsory reports of individual cases provided by clinicians and pathologist/cytologists and

is considered to be now almost 100% complete.[28] Pathologists or cytologists reported every cancer diagnosis on surgically removed tissues, biopsies, cytological specimens, bone marrow aspirates and autopsies. The incidence of tumours according to the Database has been validated previously.[51] Data on parity were complete, and data on socioeconomic index and area of residence were based on population censuses from the years 1960, 1970, 1980 and 1990.

Four-digit diagnostic codes from the seventh revision of the International Statistical Classification of Diseases (ICD-7) and subsequent ICD classifications are available. In the current study, MM was indicated by ICD-7 code 203. In the present analysis, we assessed the risks of MM and other LP malignancies, including non-Hodgkin lymphoma, Hodgkin lymphoma and leukaemias. Thus, the analyses considered diagnoses made between 1958 and 2002 and included 11 752 patients diagnosed with MM. A total of 25 526 offspring had a parental history of MM and 2 348 had a history of MM in siblings. The age of parents was not limited, but the maximum age of offspring was 70 years.

Follow-up was started on the date of birth, the date of immigration, or 1st of January 1958, whichever occurred last. Follow-up ended on the date of diagnosis of the first primary neoplasm, date of death, date of emigration, or the closing date of the study, 31st December 2002, whichever occurred first. Standardized incidence ratios (SIRs) were used to estimate familial relative risks. SIRs were calculated in individuals for whom only parents were affected and offspring for whom only siblings were affected. SIRs were computed as the ratio of the number of observed cases to the number of expected cases. The expected numbers of each cancer were based on incidence rates standardized for sex, age (5-year bands), socioeconomic status (6 groups), residential area (4 groups), and parity (6 groups, ranging from no births to more than 5 births). Confidence intervals (95% CIs) were calculated under the assumption of a Poisson distribution.[52]

3. Results

3.1. Incidence and time trends

The age-adjusted incidence rates for MM in Sweden from 1961–65 to 2001–03 are plotted in Fig. 1. For men, the overall age-adjusted incidence rates were 4.33 per 100 000 in 1961–1965 and 4.79 per 100 000 in 2001–03 (+10.6%). The highest incidence rate (5.10) was registered for the 1991–1995 *quinquennia*. In the subsequent calendar periods, the rates seemed to decrease steadily. The corresponding rates for women were 2.76 per 100 000 and 3.43 per 100 000 (+24.3%). A slight, but monotonic increase in incidence was registered for women from the *quinquennia* 1981–85 onwards. The age specific incidence of MM in the calendar periods 1961–75, 1976–90 and 1991–2003 are shown in Fig. 2. The rates for men below age 70–74 were similar in the different calendar periods across

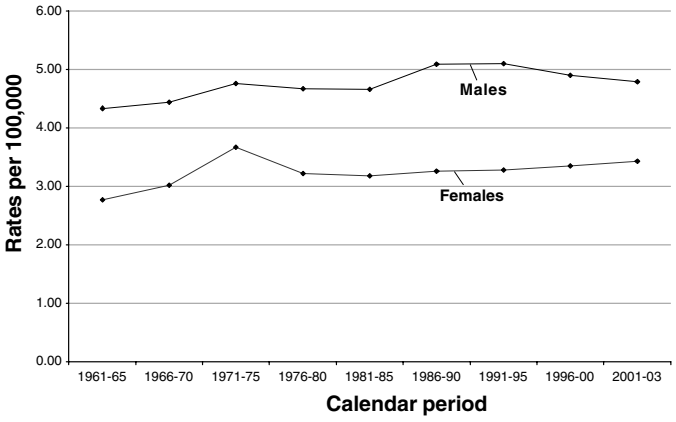

Fig. 1 – Incidence trends in age-adjusted incidence rates of MM in Sweden by sex.

Fig. 2 – Age specific incidence trends of MM in Sweden for different calendar periods by sex.

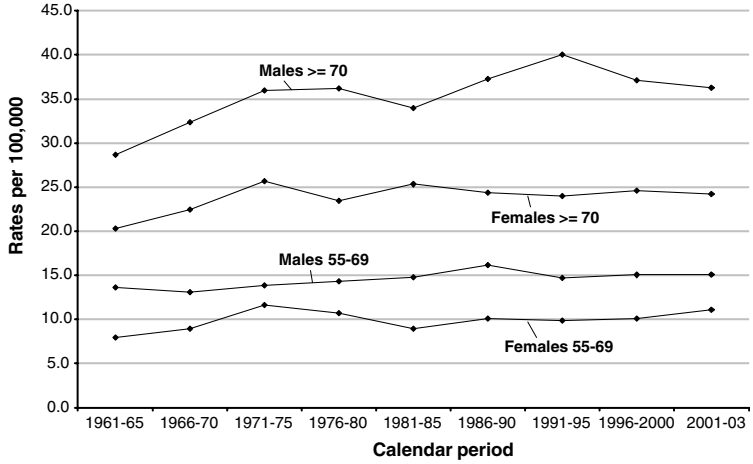

Fig. 3 – Incidence trends of MM in Sweden in adults and elderly according to sex.

different age groups. For men older than 70–74 the incidence rates increased with calendar periods. Sex-specific incidence rates for adults (i.e. 55–69 years of age) and older individuals (i.e. ⩾70 years of age), truncated at 84 years of age, are shown in Fig. 3. For men aged 70 years or older, the incidence of MM increased from 28.7 in 1961–65 to 40.0 in 1991–95 (+28.25%). In the two following *quinquennia* the incidence decreased to 37.1 in 1996–00 and 36.2 in 2001–03. The rise in incidence for women of corresponding age was less marked compared to men, the corresponding rates being 20.3 and 24.5. The incidence in adults remained constant or slightly increased across different calendar periods.

In an exploratory analysis, we investigated the risk of MM in the first and second generation of immigrants. In the first generation of immigrants the SIR appeared to be higher for immigrants from Denmark (SIR = 1.24, 95% CI, 0.95–1.59), Italy (SIR = 1.23, 95% CI, 0.53–2.44), Poland (SIR = 1.29, 95% CI, 0.79–2.00), Holland (SIR = 1.33, 95% CI, 0.42–3.14), Czech (SIR = 1.42, 95% CI,0.68–2.63), and Spain (SIR = 1.85, 95% CI,0.58–4.35), and lower for Estonia (SIR = 0.95, 95% CI, 0.63–1.38), Germany (SIR = 0.79, 95% CI, 0.57–1.08) and the US (SIR = 0.75, 95% CI, 0.43–1.22). Due to the rarity of the disease and to the low number of immigrants the estimates on the second generation born in Sweden were based on a fewer number of cases and were available only for selected countries. Overall, the risk in the second generation appeared to level off towards the risk of the general Swedish population. The SIRs were 0.71 for Finland (95% CI, 0.34–1.31), 1.03 for Denmark (95% CI, 0.37–2.25), 1.36 for Norway (95% CI, 0.79–2.18), 1.35 for Estonia (95% CI, 0.25–4.00), 1.43 for Germany (95% CI, 0.61–2.83) and 1.61 for the US (95% CI, 0.73–3.07).

3.2. *Familial aggregation*

In our Database we found 11 752 (6694 males, 5058 females) cases of MM diagnosed between 1958 and 2002. We found 28 parent-child and 4 sibling pairs, where both family members were diagnosed with MM. The age at diagnosis of familial cases (mean, 54 years, range 36–65) was lower compared to non-familial cases (mean, 67, range 15–95) ($P = 0.03$). The SIRs were calculated for offspring whose parent only or sibling only was affected, i.e. using parent only or sibling only as probands, in order to discriminate between dominant and recessive effects.

Table 1 shows the sex-specific risks of MM for offspring with a parent or a sibling affected with MM in strata of sex. Overall, the SIR for individuals with a parental history of MM was 2.45 (95% CI, 1.63–3.55). The risk was higher in daughters of affected cases compared to sons (SIR = 3.01 and 2.07, respectively), in sons where only the father was affected (SIR = 2.44, 95% CI, 0.64–6.3) and in daughters where only the mother was affected (SIR = 4.58, 95% CI, 2.18–8.45). We found a similar, although not statistically significant, excess risk for familial history of MM in siblings.

Table 2 gives the risks of MM and other LP malignancies for an early age at diagnosis (i.e. <50 years). The risk appeared to be higher in offspring with an affected mother and in siblings. In particular, a notable high risk was found for daughters with an affected mother (SIR = 5.49, 95% CI, 1.03–16.24).

Table 1 – SIRs[a] of MM in offspring by family history of MM

Offspring	Parent only												Sibling only											
	Father and/or Mother				Father only				Mother only				Brother and/or Sister				Brother only				Sister only			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Males	14	**2.07**	1.13	3.48	9	**2.44**	1.11	4.65	5	1.62	0.51	3.81	3	3.10	0.58	9.17	2	3.36	0.32	12.36	1	2.68	0	15.34
Females	14	**3.01**	1.64	5.07	4	1.62	0.42	4.20	10	**4.58**	2.18	8.45	1	1.50	0	8.59	0	–	–	–	0	–	–	–
All	28	**2.45**	1.63	3.55	13	**2.11**	1.12	3.62	15	**2.84**	1.59	4.70	4	2.44	0.64	6.32	3	3.01	0.57	8.90	1	1.57	0	8.97

a Adjusted for age, sex, residential area, socioeconomic index and birth cohort.

Table 2 – SIRs[a] of MM in offspring with family history of MM, for age at diagnosis <50 years of age

Offspring	Parent only												Sibling only											
	Father and/or Mother				Father only				Mother only				Brother and/or Sister				Brother only				Sister only			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Males	3	1.59	0.30	4.69	1	0.94	0.00	5.41	2	2.40	0.23	8.83	2	9.09	0.86	33.42	1	7.72	0	44.23	1	11.05	0	63.34
Females	3	2.44	0.46	7.23	0	–	–	–	3	**5.49**	1.03	16.24	0	–	–	–	0	–	–	–	0	–	–	–
All	6	1.92	0.69	4.21	1	0.57	0.00	3.29	5	**3.62**	1.14	8.52	2	5.51	0.52	20.25	1	4.69	0	26.91	1	6.66	0	38.18

a Adjusted for age, sex, residential area, socioeconomic index and birth cohort.

Table 3 shows the familial risk of MM in offspring with a first-degree relative affected with any of the most common LP malignancies. We found a non-significant excess risk for a familial history of chronic lymphocytic leukaemia in individuals with an affected father (SIR = 1.99). When we reversed the comparison by calculating the risk of LP neoplasms in offspring with a first-degree relative affected with MM, we found a significant increased risk of non-Hodgkin lymphoma (SIR = 1.34, 95% CI, 1.03–1.72) and of chronic lymphocytic leukaemia (SIR = 2.45, 95% CI, 1.59–3.63) (Table 4).

The SIRs of MM in offspring with a familial history of 26 different common malignancies are presented in Table 5. We found a significant increased risk for a paternal history of prostate (SIR = 1.23, 95% CI, 1.02–1.47) and bladder (SIR = 1.49, 95% CI, 1.05–2.05) cancer. The highest statistically significant risk was found for a history of connective tissue neoplasms in mothers (SIR = 4.03, 95% CI, 1.72–7.98). The risk of MM was increased in subjects with a history of cancer of the rectum in mothers (SIR = 1.65, 95% CI, 1.03–2.50) or brothers (SIR = 2.58, 95% CI 1.02–5.34). Sisters of women with cervical cancer had an increased risk of MM (SIR = 2.14, 95% CI, 1.02–3.95).

When we calculated the familial risk for any cancer in offspring whose parents or sibling were diagnosed with MM we confirmed the aggregation of MM with cervical cancer (SIR = 2.11, 95% CI, 1.00–3.89), and we found significant increased risk for stomach cancer (SIR = 1.98, 95% CI, 1.15–3.18) and endocrine glands (SIR = 1.54, 95% CI, 1.16–2.00) in subjects with a mother affected with MM (Table 6).

4. Discussion

Our study confirms and further quantifies the available evidence that the incidence of MM in Sweden has not substantially changed in the last 4 decades,[31] reflecting the pattern of mortality rates.[6,8] The current data together with updated reports from the United States[6] and the European Union[9] confirm the systematic tendency of communities under careful medical surveillance toward levelling of rates at around 4 per 100 000. Thus, the upward trend observed in the older

Table 3 – SIRs[a] of MM by family history of other lymphoproliferative malignancies

Familial site	Parent only												Sibling only											
	Father and/or Mother				Father only				Mother only				Brother and/or Sister				Brother only				Sister only			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
NHL	10	0.54	0.26	1.00	4	0.42	0.11	1.08	6	0.68	0.24	1.48	5	0.83	0.26	1.96	1	0.27	0	1.57	4	1.69	0.44	4.37
HL	1	0.32	0.00	1.81	1	0.55	0.00	3.15	0	–	–	–	0	–	–	–	0	–	–	–	0	–	–	–
CLL	9	1.37	0.62	2.61	8	1.99	0.85	3.95	1	0.38	0	2.22	0	–	–	–	0	–	–	–	0	–	–	–
Leukaemia	16	0.80	0.46	1.30	13	1.17	0.62	2.00	3	0.34	0.06	0.99	1	0.25	0	1.43	1	0.42	0	2.40	0	–	–	–

MM = plasma cell (multiple) myeloma; NHL = non-Hodgkin lymphoma; HL = Hodgkin lymphoma; CLL = Chronic lymphocytic leukaemia.
a Adjusted for age, sex, residential area, socioeconomic index and birth cohort.

Table 4 – SIRs[a] of other lymphoproliferative malignancies by family history of MM

Offspring Site	Parent only												Sibling only											
	Father and/or Mother				Father only				Mother only				Brother and/or Sister				Brother only				Sister only			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
NHL	61	**1.34**	1.03	1.72	33	1.32	0.91	1.86	28	1.36	0.90	1.97	6	0.99	0.36	2.17	4	1.09	0.28	2.82	2	0.84	0.08	3.08
Hodgkin lymphoma	16	1.06	0.61	1.73	9	1.03	0.47	1.97	7	1.10	0.44	2.27	0	–	–	–	0	–	–	–	0	–	–	–
CLL	25	**2.45**	1.59	3.63	12	**2.68**	1.42	4.59	13	**2.24**	1.15	3.92	2	1.50	0.14	5.51	2	2.46	0.23	9.04	0	–	–	–
Leukaemia	40	1.17	0.83	1.59	24	1.25	0.80	1.86	16	1.06	0.60	1.72	1	0.24	0.00	1.35	0	–	–	–	1	0.60	0.00	3.44

MM = plasma cell (multiple) myeloma; NHL = non-Hodgkin lymphoma; CLL = Chronic lymphocytic leukaemia.
a Adjusted for age, sex, residential area, socioeconomic index and birth cohort.

Table 5 – SIRs[a] for MM in offspring with first-degree family members affected with non-lymphoproliferative malignancies

Familial site	Parent only												Sibling only											
	Father and/or Mother				Father only				Mother only				Brother and/or Sister				Brother only				Sister only			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Upper aerodigestive tract	19	1.17	0.70	1.83	14	1.15	0.63	1.93	5	1.21	0.38	2.85	4	1.10	0.29	2.86	3	1.15	0.22	3.40	1	0.99	0.00	5.66
Oesophagus	5	0.85	0.27	2.00	4	0.95	0.25	2.44	1	0.60	0.00	3.46	2	2.04	0.19	7.50	1	1.29	0.00	7.41	1	4.84	0.00	27.73
Stomach	37	0.91	0.64	1.25	24	0.89	0.57	1.32	15	1.08	0.60	1.78	2	0.72	0.07	2.64	2	1.13	0.11	4.14	0	–	–	–
Small intestine	6	1.98	0.71	4.35	4	2.52	0.66	6.52	2	1.39	0.13	5.11	0	–	–	–	0	–	–	–	0	–	–	–
Colon	55	1.01	0.76	1.31	29	1.10	0.74	1.58	26	0.90	0.59	1.32	8	1.14	0.49	2.25	2	0.56	0.05	2.05	6	1.73	0.62	3.78
Rectum	42	1.34	0.97	1.82	21	1.16	0.72	1.78	22	**1.65**	1.03	2.50	10	**2.14**	1.02	3.94	7	**2.58**	1.02	5.34	3	1.51	0.29	4.48
Colorectum	95	1.12	0.91	1.37	50	1.13	0.84	1.49	47	1.12	0.82	1.49	17	1.53	0.89	2.46	8	1.34	0.57	2.66	9	1.73	0.78	3.30
Liver	27	1.12	0.74	1.63	12	1.17	0.60	2.05	15	1.08	0.60	1.78	4	1.73	0.45	4.46	1	0.89	0.00	5.09	3	2.52	0.47	7.46
Pancreas	18	0.76	0.45	1.21	10	0.82	0.39	1.51	8	0.70	0.30	1.39	5	2.04	0.64	4.80	2	1.56	0.15	5.75	3	2.55	0.48	7.54
Lung	47	0.98	0.72	1.31	38	1.06	0.75	1.46	9	0.72	0.33	1.37	8	0.86	0.37	1.70	4	0.80	0.21	2.06	4	0.91	0.24	2.36
Breast	59	0.86	0.65	1.11	0	–	–	–	59	0.87	0.66	1.12	36	1.09	0.77	1.52	0	–	–	–	36	1.10	0.77	1.52
Cervix	19	1.39	0.83	2.17	0	–	–	–	19	1.39	0.83	2.17	10	**2.14**	1.02	3.95	0	–	–	–	10	**2.14**	1.02	3.95
Endometrium	15	0.84	0.47	1.40	0	–	–	–	15	0.84	0.47	1.40	6	1.11	0.40	2.44	0	–	–	–	6	1.11	0.40	2.44
Ovary	18	1.12	0.66	1.77	0	–	–	–	18	1.12	0.66	1.77	8	1.44	0.62	2.86	0	–	–	–	8	1.44	0.62	2.86
Prostate	123	**1.23**	1.02	1.47	123	**1.23**	1.02	1.47	0	–	–	–	11	0.96	0.48	1.72	11	0.96	0.48	1.72	0	–	–	–
Testis	2	2.83	0.27	10.40	2	2.83	0.27	10.40	0	–	–	–	0	–	–	–	0	–	–	–	0	–	–	–
Kidney	25	1.07	0.69	1.58	18	1.41	0.83	2.23	8	0.75	0.32	1.49	3	0.71	0.13	2.10	3	1.12	0.21	3.32	0	–	–	–
Urinary bladder	47	**1.42**	1.04	1.89	38	**1.49**	1.05	2.05	9	1.15	0.52	2.20	6	1.02	0.37	2.24	5	1.14	0.36	2.68	1	0.67	0.00	3.86
Melanoma	12	0.94	0.48	1.65	6	0.98	0.35	2.14	6	0.90	0.32	1.97	13	1.35	0.71	2.31	7	1.56	0.62	3.22	6	1.16	0.42	2.53
Skin	26	0.97	0.63	1.42	13	0.81	0.43	1.39	13	1.19	0.63	2.03	2	0.63	0.06	2.31	1	0.51	0.00	2.94	1	0.80	0.00	4.59
Eye	2	1.03	0.10	3.78	2	1.96	0.18	7.21	0	–	–	–	1	1.50	0.00	8.59	0	–	–	–	1	3.02	0.00	17.29
Nervous system	15	0.88	0.49	1.45	5	0.66	0.21	1.56	10	1.05	0.50	1.93	7	0.85	0.34	1.76	3	0.76	0.14	2.24	4	0.93	0.24	2.41
Thyroid gland	8	1.64	0.70	3.26	2	1.48	0.14	5.43	6	1.71	0.62	3.74	2	0.77	0.07	2.84	1	1.48	0.00	8.51	1	0.52	0.00	2.99
Endocrine glands	14	1.39	0.76	2.34	6	2.35	0.84	5.14	8	1.06	0.45	2.10	5	1.09	0.35	2.57	1	0.58	0.00	3.34	4	1.39	0.36	3.60
Bone	3	3.21	0.60	9.49	1	2.12	0.00	12.16	2	4.30	0.41	15.83	1	1.93	0.00	11.05	1	3.22	0.00	18.48	0	–	–	–
Connective tissue	10	**2.33**	1.11	4.30	2	0.87	0.08	3.18	8	**4.03**	1.72	7.98	1	0.74	0.00	4.23	1	1.46	0.00	8.39	0	–	–	–
Any	537	1.03	0.95	1.12	350	1.10	0.98	1.22	283	1.03	0.91	1.15	85	1.05	0.84	1.29	33	0.94	0.65	1.33	53	1.07	0.80	1.40

a Adjusted for age, sex, residential area, socioeconomic index and birth cohort.

Table 6 – SIRs[a] for cancer in offspring by family history of MM

Offspring site	Parent only												Sibling only											
	Father and/or Mother				Father only				Mother only				Brother and/or Sister				Brother only				Sister only			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Upper aerodigestive tract	29	1.05	0.70	1.51	16	1.07	0.61	1.74	13	1.02	0.54	1.76	4	1.03	0.27	2.65	4	1.72	0.45	4.45	0	–	–	–
Oesophagus	5	0.70	0.22	1.66	4	1.05	0.27	2.73	1	0.30	0.00	1.73	2	1.80	0.17	6.63	2	2.99	0.28	11.01	0	–	–	–
Stomach	23	1.23	0.78	1.85	6	0.59	0.21	1.30	17	**1.98**	1.15	3.18	2	0.74	0.07	2.72	1	0.61	0.00	3.49	1	0.95	0.00	5.43
Small intestine	6	1.09	0.39	2.39	1	0.33	0.00	1.91	5	1.99	0.63	4.68	0	–	–	–	0	–	–	–	0	–	–	–
Colon	60	0.97	0.74	1.25	35	1.05	0.73	1.46	25	0.88	0.57	1.30	11	1.28	0.64	2.30	8	1.54	0.66	3.04	3	0.89	0.17	2.62
Rectum	33	0.90	0.62	1.26	21	1.06	0.66	1.62	12	0.70	0.36	1.23	10	1.87	0.89	3.45	5	1.53	0.48	3.61	5	2.39	0.75	5.62
Colorectum	93	0.94	0.76	1.16	56	1.05	0.80	1.37	37	0.81	0.57	1.12	21	1.51	0.93	2.31	13	1.54	0.81	2.63	8	1.46	0.62	2.89
Liver	20	1.23	0.75	1.91	10	1.15	0.55	2.12	10	1.33	0.63	2.46	3	1.27	0.24	3.76	2	1.41	0.13	5.19	1	1.06	0.00	6.05
Pancreas	19	1.05	0.63	1.65	13	1.35	0.71	2.31	6	0.72	0.26	1.57	5	1.87	0.59	4.41	3	1.84	0.35	5.46	2	1.92	0.18	7.05
Lung	61	0.93	0.71	1.19	31	0.88	0.60	1.25	30	0.98	0.66	1.40	8	0.81	0.35	1.61	4	0.67	0.17	1.74	4	1.03	0.27	2.66
Breast	303	1.04	0.92	1.16	163	1.04	0.88	1.21	140	1.04	0.87	1.22	41	1.08	0.77	1.46	22	0.97	0.61	1.47	19	1.23	0.74	1.93
Cervix	34	0.83	0.57	1.16	17	0.74	0.43	1.19	17	0.93	0.54	1.49	10	2.11	1.00	3.89	7	2.49	0.99	5.15	3	1.55	0.29	4.59
Endometrium	46	1.15	0.84	1.53	25	1.17	0.76	1.74	21	1.11	0.69	1.70	6	1.03	0.37	2.26	4	1.14	0.30	2.95	2	0.86	0.08	3.18
Ovary	56	1.28	0.97	1.67	27	1.14	0.75	1.66	29	1.44	0.97	2.08	8	1.40	0.60	2.76	2	0.58	0.06	2.15	6	2.60	0.94	5.70
Prostate	99	1.10	0.90	1.34	46	0.96	0.70	1.28	53	1.26	0.95	1.65	15	1.06	0.59	1.75	6	0.68	0.25	1.50	9	1.67	0.76	3.19
Testis	25	0.99	0.64	1.46	14	0.95	0.52	1.60	11	1.03	0.51	1.85	0	–	–	–	0	–	–	–	0	–	–	–
Kidney	34	1.14	0.79	1.60	16	0.99	0.56	1.61	18	1.32	0.78	2.10	3	0.72	0.14	2.12	0	–	–	–	3	1.82	0.34	5.38
Urinary bladder	42	0.99	0.71	1.34	23	1.00	0.63	1.50	19	0.97	0.58	1.52	6	0.98	0.35	2.15	5	1.34	0.42	3.16	1	0.42	0.00	2.39
Melanoma	99	1.04	0.84	1.26	46	0.87	0.64	1.16	53	1.24	0.93	1.62	13	1.15	0.61	1.97	7	1.04	0.41	2.15	6	1.31	0.47	2.88
Skin	18	0.69	0.41	1.10	6	0.43	0.15	0.94	12	1.00	0.52	1.76	2	0.57	0.05	2.09	1	0.48	0.00	2.73	1	0.71	0.00	4.07
Eye	7	1.29	0.51	2.66	7	2.29	0.91	4.75	0	–	–	–	0	–	–	–	0	–	–	–	0	–	–	–
Nervous system	72	0.98	0.77	1.24	38	0.93	0.66	1.27	35	1.08	0.76	1.51	7	0.81	0.32	1.68	5	0.97	0.31	2.28	2	0.58	0.05	2.13
Thyroid gland	27	1.19	0.79	1.74	12	0.95	0.49	1.67	15	1.49	0.83	2.47	2	0.75	0.07	2.75	1	0.62	0.00	3.58	1	0.93	0.00	5.33
Endocrine glands	56	**1.54**	1.16	2.00	29	1.45	0.97	2.08	27	**1.64**	1.08	2.39	4	0.86	0.22	2.24	2	0.72	0.07	2.66	2	1.08	0.10	3.96
Bone	4	0.69	0.18	1.78	1	0.30	0.00	1.70	3	1.23	0.23	3.65	1	1.72	0.00	9.84	1	2.85	0.00	16.32	0	–	–	–
Connective tissue	8	0.66	0.28	1.31	3	0.45	0.08	1.32	5	0.93	0.29	2.19	1	0.69	0.00	3.98	0	–	–	–	1	1.73	0.00	9.93
Any	1347	**1.07**	1.01	1.12	695	1.01	0.94	1.09	653	**1.13**	1.05	1.22	177	1.05	0.91	1.22	100	0.99	0.81	1.20	77	1.15	0.91	1.44

a Adjusted for age, sex, residential area, socioeconomic index and birth cohort.

individuals is consistent with reports from other well surveyed areas of the world and is, at least in part, attributable to improvements in diagnostics techniques and in case ascertainment.[6,31] However, the diagnostic criteria for MM have not changed extensively in the past decades in Sweden, and the role of an environmental exposure responsible for the unfavourable upwards trend can not be completely ruled out.

We found a high familial aggregation of MM. The familial risk of MM appeared to be higher in sons with a father affected and in daughters with a mother affected. Although based on smaller numbers, an excess risk of similar magnitude was observed for a family history of MM in siblings. Daughters with a mother affected (SIR = 4.58) showed the highest familial risk, which is one of the highest found for any malignancy in this Database.[53]

Inherited malignancies tend to occur at an earlier age then sporadic ones at the same site. In our Database the age at diagnosis of familial cases was lower compared to non-familial cases. One could speculate that the younger age at diagnosis could be explained by the increased surveillance of family members of MM cases or by the relatively young age of the cohort.[31,44]

Our results are in broad agreement with previous studies of different design reporting an excess familial risk for MM of about 2- to 4-fold.[15,16,20,21,31,32,36,37] With reference to the spectrum of other LP malignancies that could share a common genetic or environmental risk factors with MM, only a few studies had the power to estimate the familial risk for familial concordant cancer, but generally reported little or no associations.[17,20,37,40] Our study provide consistent evidence of an association of MM with chronic lymphocytic leukaemia, a little evidence with non-Hodgkin lymphoma, and no evidence for Hodgkin lymphoma and other leukaemias.[38,40]

The observed pattern of the familial risk is consistent with an autosomal dominant mode of inheritance of MM, in agreement with previous reports.[27,32] In the parent-child sex pairs, we found a consistent sex correlation. Male patients more often had an affected son, whereas females more often had an affected daughter. This finding replicates results from a previous report, but gives little clarification for the mechanism, for which large studies are required.[32]

MM has been associated with many other different types of solid tumours. The cancer sites that were most commonly found to cluster in families with MM include colorectal,[54] breast,[15] melanoma,[24,55,55,56] lung,[15] ovarian[15,57] and prostate.[20,58] However, some of the associations reported come from hospital-based studies, where the risk of ascertainment bias can not be excluded. Thus, to which extend the reported associations are real or due to multiple comparisons is not clear.[55,56] We found significant associations for rectal, stomach, cervical, prostate, bladder, endocrine glands and connective tissue malignancies, a weak association with melanoma and ovarian malignancies, and no association with breast and lung cancer.

Familial aggregation of cancers can be due to chance alone, shared genetic background, or common environmental exposures within families, including exposure to high-dose radiations, pesticides, diesel exhaust and other occupational factors.[59–64] Consistently with the environmental hypothesis some early studies reported MM in married couples and community clusters.[65–69] We have assessed the effect of shared environment in adulthood from this Database by comparing cancer risks between spouses[70] and updated it using the new version of the database, and found no significant spouse concordance for MM (data not shown). Our results on immigrants are compatible with an environmental component of the disease, but of difficult interpretation because of the low number of cases.

Moreover, data from twin studies, reporting an increased risk for monozygotic compared to dizygotic twins with MM, suggest that environmental factors are unlikely to be the main determinants of familial risk for MM, although the numbers have been extremely small.[34,35]

In the present study, data on family history of MM and other malignancies were based on nationwide registered family structures and medical diagnoses with histopathologic confirmation, minimizing risks for recall biases and loss to follow-up. The ascertainment of relatives was complete, giving further reassurance. However, due to the rarity of LP malignancies, to the small proportion of familial cases and to the relatively young age of the cohort (i.e. maximum age of the offspring was 70 years of age), some of the subgroup analyses were based on a small number of cases.

In conclusion, the current investigation represents the largest population-based study on the familial risk of MM, and the only study assessing familial risk for concordant cancer in parents and offspring in a mutually exclusive way, and for different types of LP diseases. Our results provide evidence for a strong familial clustering for MM, chronic lymphocytic leukaemia and possibly of non-Hodgkin lymphoma. Family history is a well defined risk factor for cancer that can be measured with a reasonable accuracy, thus family histories of disease have an important role to play in targeting cancer screening procedures, if available, and clinical genetic counselling.[71]

Conflict of interest statement

None declared.

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