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Patterns of previous and secondary malignancies in patients with multiple myeloma

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Abstract

Objectives: In contrast to secondary primary malignancies (SPM) following multiple myeloma (MM), less is known about previous malignancies. We therefore conducted a population-based study to assess the patterns of previous malignancies in MM patients as well as the risk for SPM.

Methods: Using data from the Cancer Registry of Norway, we included 9574 MM patients and 37 810 matched control subjects. The association between previous malignancies and a subsequent diagnosis of MM was analysed by a logistic regression model and the risk for SPM by a Cox model.

Results: A previous diagnosis of myeloproliferative neoplasia (MPN) (OR 3.57; 95% CI:1.45-8.80) and Hodgkin lymphoma (HL) (OR 3.66; 95% CI: 1.40-9.55) was associated with the subsequent development of MM. For MPN, the association with MM was explained by an excess of primary myelofibrosis (PMF) in the MM group. The overall incidence of a previous malignancy was not different between MM patients and the control subjects (OR 0.93; 95% CI: 0.87-1.00). MM patients had an increased risk for secondary acute myelogenous leukaemia/myelodysplastic syndromes (HR 6.1, 95% CI: 3.9-9.5).

Conclusions: A previous diagnosis of HL and PMF was associated with a subsequent diagnosis of MM, whereas the overall incidence of previous cancers was not increased for MM patients.

KEYWORDS

haematologic neoplasms, multiple myeloma, neoplasms, second primary

1 | INTRODUCTION

Population-based studies show that relative survival in MM patients has improved substantially since the 1990s.[1,2] As patients are living longer with their disease, the awareness concerning secondary primary malignancies (SPM) has been raised. The overall incidence of SPM is not increased compared to the general population in most studies.[3-6] A common finding is an increased risk for acute myelogenous leukaemia and/or myelodysplastic syndromes (AML/MDS), whereas the results for other cancer diagnoses are less consistent. Different mechanisms of SPM development have been discussed, including host-, myeloma- and treatment-related factors.[7]

In contrast to SPM, less is known about pre-existing malignancies in MM patients. Studies have shown that solid malignancies are

more common prior to MM, and that prostate, breast, gynaecological and gastrointestinal cancer are the most common pre-existing entities.[8-10] Both previous cancers and SPM have been shown to have a negative impact on survival in MM patients and a previous cancer diagnosis may increase the risk for SPM.[11-13] However, these studies did not compare the incidence of previous cancers to a reference population. It therefore remains unclear whether the incidence of previous cancer differs between MM patients and a reference population. Using a population-based cohort of MM patients and a matched control cohort, we have assessed the patterns in previous cancer diagnoses in MM patients. We also assess the risk for SPM in the same cohort of MM patients.

Novelty Statements

1. What is the new aspect of your work?
Herein, we explore the patterns of previous cancers in patients with multiple myeloma.
2. What is the central finding of your work?
Compared to a reference population, patients with multiple myeloma do not have an overall excess of cancers earlier in life, but some haematologic malignancies (Hodgkin lymphoma and myeloproliferative neoplasia) seem to be more frequent in patients who eventually develop multiple myeloma.
3. What is (or could be) the specific clinical relevance of your work?
This article addresses questions that are of interest for patients with two or more cancer diagnoses.

2 | METHODS

2.1 | Data sources

Information on all MM cases was provided by the Cancer Registry of Norway (CRN). The CRN was established in 1951 and contains near complete nationwide cancer statistics from 1 January 1953. All physicians, hospitals and laboratories are obliged by law to report all cases of cancer to the registry. The coding system used is described elsewhere.[14] Briefly, each cancer case is among other variables reported with a code from the International Classification of Diseases of Oncology, third edition (IDC-O-3) and a code from the International Classification of Diseases, revision 7 (ICD-7). Monoclonal gammopathy of undetermined significance (MGUS) is not reported to the CRN. The completeness of case ascertainment is approximately 98%-99% for solid cancers and above 94% for haematological cancers including MM.[14,15] Matched controls were provided by the National Population Registry. The registry was established in 1964 based on the census from 1960 containing demographic information of every resident.[16] Vital status for all patients in the CRN is updated by monthly reports from the National Population Registry as well as consecutive information of cause of death and death certificates from the Cause of Death Registry, National Institute of Public Health.[14]

2.2 | Study population

All cases of MM (ICD-O-3 code 9732/3x) aged 18 years or older diagnosed between 1 January 1982 and 31 December 2013 were retrieved from the CRN along with information on all additional cancer diagnoses before and after the date of MM diagnosis. Control subjects were selected from the National Population Registry in a 4:1 ratio matched on sex, year of birth and county of residence. Each control subject had to be alive at the time of diagnosis for the corresponding MM patient, hereafter referred to as the matching date. We excluded patients with a MM diagnosis, or any other cancer diagnosis based on accidental fining at autopsy or death certificate only. If a MM patient was excluded for any cause, the corresponding matched controls were also excluded. Follow-up ended on 31 December 2015.

2.3 | Statistical methods

In the data from the CRN, the date of diagnosis of any cancer is provided as the 15th of every month. A previous cancer was defined as any cancer diagnosis registered prior to the matching date (the previous calendar month or before), and an SPM was defined as any cancer diagnosis registered after the matching date (the following calendar month or later).

The association between previous cancers and a subsequent diagnosis of MM was analysed in a case-control setting. We used an unconditional logistic regression model with a MM diagnosis at the matching date as the dichotomous dependent variable adjusted for the matching factors.[17,18] This association is represented by the odds ratio (OR), and 95% confidence intervals not including one were considered statistically significant. As this is a pure exploratory study of associations, no formal adjustment of the significance level due to multiple testing was performed. Acknowledging the possibility that two cancer diagnoses within a short timeframe may be subject to surveillance bias,[19] a sensitivity analysis was performed. Here, all individuals with a cancer diagnosis other than MM within three months from the matching date were excluded.

The risk for SPM was analysed using a Cox proportional hazards regression model adjusting for sex, calendar period of matching (1982-1994,1995-2004,2005-2013), age-category at the matching date (<65 years, 65-79 years, ≥80 years) and a dichotomous variable indicating the presence of a previous and/or synchronous cancer. A synchronous cancer was defined as any cancer diagnosed in the same calendar month as the matching date. As a sensitivity analysis, we repeated the analyses after excluding all MM patients and controls with any cancer diagnosis before or up to three months after the matching date. Any individual was at risk from the matching date to the date of diagnosis of the cancer

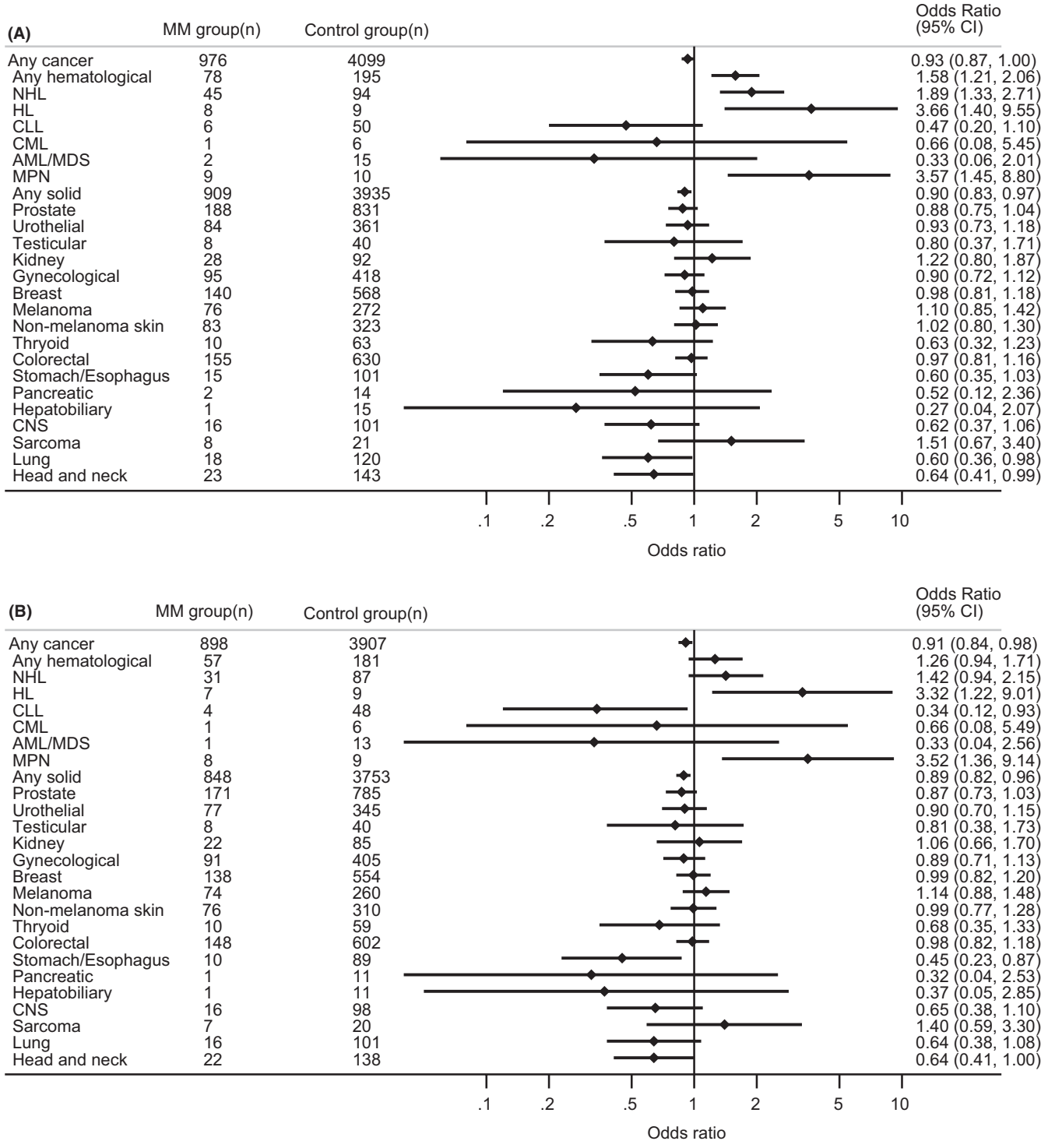

FIGURE 1 Association between different cancers and subsequent multiple myeloma. A: All cancers diagnosed prior to the matching date. B: Excluding all cancers diagnosed ≤ 3 months prior to the matching date. Abbreviations: 95% CI, 95% confidence interval; n, number of cases; MM, multiple myeloma; NHL, Non-Hodgkin lymphoma; HL, Hodgkin lymphoma; CLL, Chronic lymphocytic leukaemia; CML, Chronic myeloid leukaemia; AML, Acute myelogenous leukaemia; MDS, Myelodysplastic syndromes; MPN, Myeloproliferative neoplasia; CNS, Central nervous system. Acute lymphoblastic leukaemia was omitted due to 1 case in the MM group and 0 cases in the control group

of interest, emigration, death or end of study 31 December 2015, whichever occurred first.

We performed all statistical analyses in STATA-MP version 15.1 (Statacorp, College Station, TX, USA).

This study was approved by the Regional Ethics Committee of Central Norway (reference number 2014/1453). As we only had access to non-identifiable data and no contact with the study subjects, written consent was by law deemed unnecessary.

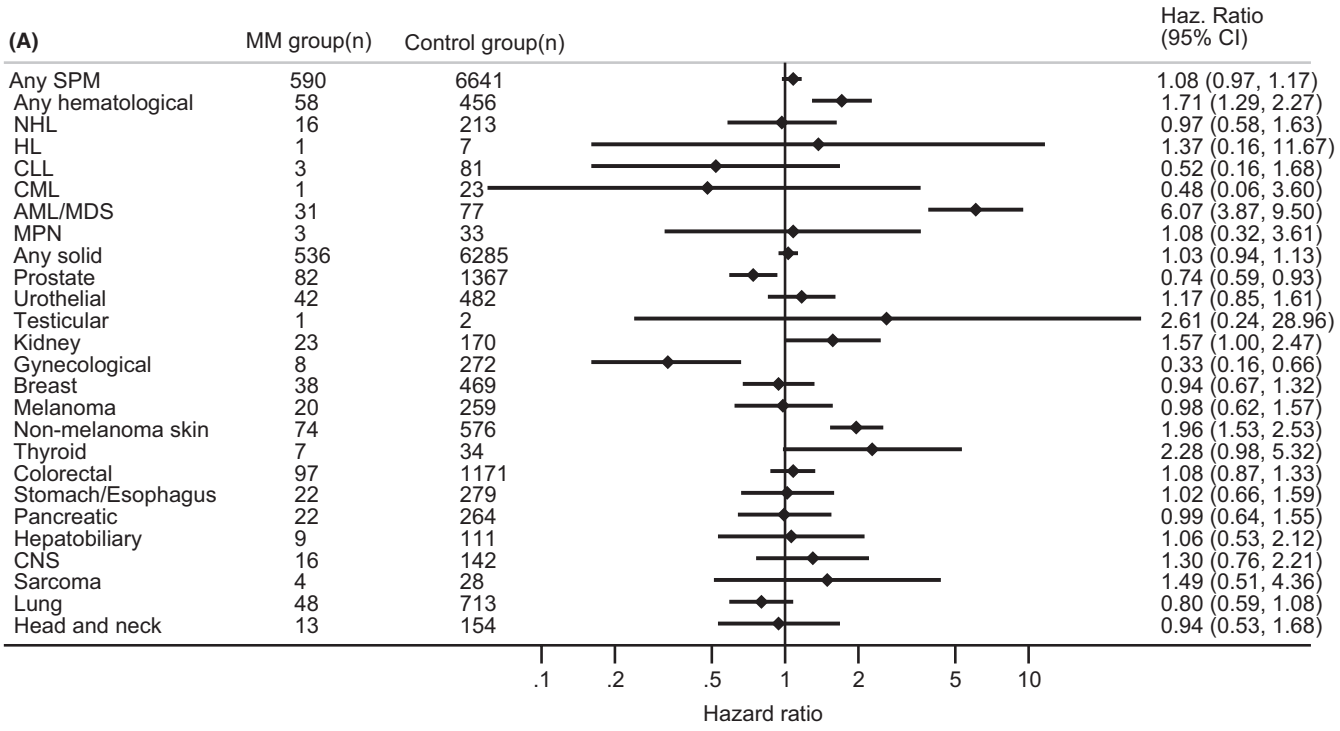

FIGURE 2 Risk for secondary primary malignancies following multiple myeloma. A: All cancers diagnosed after the matching date. B: Excluding all cancers diagnosed ≤ 3 months after the matching date. Abbreviations: SPM, Secondary primary malignancy; MM, multiple myeloma; n, number of cases; 95% CI, 95% confidence interval; NHL, Non-Hodgkin lymphoma; HL, Hodgkin lymphoma; CLL, Chronic lymphocytic leukaemia; CML, Chronic myeloid leukaemia; AML, Acute myelogenous leukaemia; MDS, Myelodysplastic syndromes; MPN, Myeloproliferative neoplasia; CNS, Central nervous system. Acute lymphoblastic leukaemia was omitted due to 0 cases in the MM group and 7 cases in the control group

3 | RESULTS

Initially, 10 029 MM patients and 39 846 matched controls were retrieved from the registries. We excluded 419 MM patients and the corresponding 1665 controls due to an MM-diagnosis based on autopsy or death certificate only. Thirty-six MM patients and 371 controls were excluded due to any other cancer diagnosis based on autopsy and death certificate only, leaving 9574 MM patients and

37 810 controls available for analysis. Among the MM patients, 976 (10.2%) had at least one previous malignancy and the most common previous cancer types in MM patients were prostate, colorectal, breast and gynaecological cancer (Figure 1).

3.1 | Association between previous cancers and a subsequent MM-diagnosis

Figure 1A displays the results from the logistic regression model assessing the association between different cancers and a subsequent MM diagnosis. A previous haematological malignancy was associated with MM (OR 1.58; 95% CI:1.21-2.06). Among these, non-Hodgkin lymphoma (NHL) (OR 1.89; 95% CI:1.33-2.71), Hodgkin lymphoma (HL) (OR 3.66; 95% CI:1.40-9.55) and myeloproliferative neoplasms (MPN) (OR 3.57; 95% CI:1.45-8.80) showed statistically significant positive associations with MM. In the MM group, 6/9 MPN cases were primary myelofibrosis (PMF) compared to 1/10 in the control group (according to the ICD-O-3 code). A previous PMF diagnosis showed a strong association with MM in the logistic regression model (OR 24.3; 95% CI:2.91-201.5).

There was no overall difference in the presence of previous cancers between the two groups (OR 0.93; 95% CI:0.87-1.00), and a previous solid cancer had a negative association with MM (OR 0.90; 95% CI:0.83-0.97). No single tumour-group showed positive associations, and we observed statistically significant negative associations for lung cancer (OR 0.60; 95% CI: 0.36-0.98) and head and neck cancers (OR 0.64; 95% CI 0.41-0.99).

Results from the sensitivity analysis restricted to previous malignancies diagnosed more than three months prior to the matching date are presented in Figure 1B. HL and MPN maintained a positive association with MM (OR 3.33; 95% CI:1.23-9.05 and OR 3.52; 95% CI: 1.36-9.15, respectively.) For NHL, the association with MM was now weaker with no statistical significance (OR 1.43; 95% CI: 0.95-2.15). The negative associations for lung and head and neck cancers were non-significant in the sensitivity analysis (OR 0.64; 95%CI:0.38-1.08 and OR 0.64, 95% CI: 0.41-1.00, respectively).

Results from the SPM-analysis are displayed in Figure 2A. Myeloma patients had no overall increased SPM-risk (HR 1.08; 95% CI: 0.97-1.17) nor an increased risk for any solid SPM (HR 1.03; 95% CI: 0.94-1.13). We found a statistically significant increased risk for any haematological SPM (HR 1.71; 95% CI: 1.29-2.27) explained by a sixfold increased risk for AML/MDS (HR 6.07; 95% CI: 3.87-9.50), and no increased risk for any other haematological SPM. Among the solid cancers, MM patients had an increased risk for non-melanoma skin cancer (HR 1.96; 95% CI: 1.53-2.53), a borderline significant increased risk for kidney cancer (HR 1.57; 95% CI: 1.00-2.47) and a decreased risk for prostate cancer (HR 0.74; 95% CI: 0.59-0.93) and gynaecological cancers (HR 0.33; 95% CI: 0.16-0.66). In the sensitivity analysis, the hazard ratio for kidney cancer was non-significant (HR 1.57; 95% CI: 0.98-2.51); otherwise, the results were near identical (Figure 2B).

4 | DISCUSSION

To our knowledge, this is the first study assessing the previous cancer history in MM patients compared to a reference population. Patients with MM had a previous cancer history with significantly increased incidence of NHL, HL and MPN. For NHL, 13/43 cases of previous NHL in MM patients were diagnosed within the last three months before the MM diagnosis and the significant association with MM disappeared in the sensitivity analysis. Several previous studies have addressed secondary malignancies NHL with conflicting results regarding the risk for MM as a second malignancy. Increased risk[20] decreased risk [21,22] and neither increased nor decreased risk[3,23-25] have been reported. A meta-analysis published in 2011 based on six studies found a significantly increased pooled relative risk of 1.77 for MM in NHL survivors.[26] In a 2017 analysis of German registry data on 110 164 NHL patients, Baras et al found an overall approximately twofold increased standardised incidence ratio (SIR) for MM. However, the increased risk for secondary multiple myeloma was confined to the first two months after the lymphoma diagnosis, and as noted by the authors, the increased SIR for MM could in part be due to misclassifications and/or surveillance effects.[27] These results line up with ours and suggest that an NHL diagnosis does not increase the risk for subsequent MM, but rather that a diagnosis of MM or NHL is associated with a synchronous diagnosis of the other. A possible explanation may be that a bone marrow biopsy is frequently performed during the work-up for both MM and NHL, and this may lead to an incidental diagnosis of asymptomatic MM or NHL.

In contrast to NHL, all eight cases of HL in the MM group were diagnosed more than 3.5 years prior to the myeloma, and HL maintained a significant association to MM in both analyses. In two large studies on approximately 32 500 and 18 000 HL patients, respectively, no overall increased risk for secondary MM was found.[27,28] In the latter study by Baras et al, a statistically significant increased SIR for MM was observed during the first two months after HL diagnosis, with no increased risk beyond this time frame. In a smaller study on approximately 1300 HL patients, an increased relative risk was noted (RR 9.4; 95% CI: 1.9-27.4), but only three MM cases were observed.[29] Thus, we cannot find convincing evidence from the existing literature to support our findings for a possible association between HL and secondary MM.

The association between a previous MPN-diagnosis and MM was also consistent in both the main and sensitivity analyses. Apart from one, all cases of MPN in the MM-group were diagnosed more than one year prior to the myeloma. The risk of second malignancies in patients with MPN was recently assessed in a large Swedish population-based study by Landtblom et al[30] The MPN-patients had a borderline significant increased risk for MM (HR 1.7; 95%CI:1.0-3.0), whereas the subgroup with PMF had a ninefold increased risk (HR 9.0; 95% CI:1.8-44.0). These results concur with our findings as the association in our data between a previous MPN diagnosis and subsequent MM was explained by an excess of PMF cases in the MM group. Combined with Landtblom's study, our results support a possible

TABLE 1 Overview of population-based studies addressing secondary primary malignancies with standardised incidence ratios and 95% confidence intervals for cancer diagnoses with statistically significant increased risk

	Author, year, country, period of MM diagnosis, number of patients							
	Chen,[31] 2016 Germany 1997-2010 N = 18 735	Chen,[31] 2016, Sweden, 1997-2010, N = 7560	Razavi,[6] 2013, USA (SEER 9) 1973-2008 N = 36 491	Tzeng,[32] 2013 Taiwan 1997-2009 N = 3970	Chakraborty,[33] 2012 USA (SEER 17) 1973-2008 N = 3245	Mailankody,[4] 2011 Sweden 1986-2005 N = 8740	Dong & Hemminki,[3] 2001 Sweden 1958-1996 N = 8656	Present study[a], 2020 Norway 1982-2013 N = 9574
AML/MDS	4.9 (3.2-7.3)	2.3 (1.3-3.7)	6.5 (5.4-7.8)	16.3 (14.7-18.0)		11.5 (8.2-15.7)	8.19 (5.7-11.4)	6.07 (3.9-9.5)
NHL			1.3 (1.1-1.6)	7.6 (6.8-8.4)			1.74 (1.1-2.6)	
ALL			5.1 (2.4-10.7)	10.5 (9.3-11.8)				
CML			2.4 (1.5-3.8)					
Leukaemia					3.07 (2.57-3.64)			
Kidney		2.3 (1.2-4.0)	1.3 (1.1-1.7)		1.51 (1.13-1.98)			
Nervous system		1.9 (1.1-3.1)						
Melanoma			1.4 (1.1-1.77)					
Non-melanoma skin			2.0 (1.2-3.6)		1.43 (1.09-1.85)	2.2 (1.7-2.8)		1.96 (1.5-2.5)
Small intestine			2.0 (1.2-3.3)					
Urinary bladder			1.2 (1.1-1.4)					
Thyroid			1.6 (1.1-2.5)					
Naso-pharyngeal				1.3 (1.1-1.6)				
Kaposi sarcoma					3.30 (1.06-7.69)			
Gastro-intestinal						1.3 (1.1-1.53)		
Overall	0.9 (0.8-0.9)	1.3 (1.2-1.4)	1.0 (0.9-1.1)	0.9 (0.8-1.1)	1.0 (1.0-1.1)	1.3 (1.2—1.4)	1.0 (0.9-1.7)	1.1 (1.0-1.2)

Abbreviations: AML, Acute myelogenous leukaemia; CLL, Chronic lymphocytic leukaemia; CML, Chronic myeloid leukaemia; HL, Hodgkin lymphoma; MDS, Myelodysplastic syndromes; NHL, Non-Hodgkin lymphoma; SEER: Surveillance, Epidemiology, and End Results.

[a]Hazard ratios are presented.

association between PMF and the subsequent development of MM. In another study from Sweden, patients with MGUS had an approximately fivefold increased risk for MPN, whereas the risk was not increased for patients with MM.[4] In our data, it is unknown whether the MPN/PMF cases in the MM group were preceded by MGUS.

Solid cancers were more common than haematological prior to the myeloma, and prostate cancer, breast cancer and colorectal cancer were among the most frequent. This is in line with findings from other studies[9,10] and not surprising as these are known common cancers. However, a previous solid cancer was negatively associated with MM, and no single diagnosis showed a significant positive association. Lung and head and neck cancers were negatively associated with MM in the main analysis, but not in the sensitivity analysis. We cannot point to any factors which may explain a potential protective role of a previous lung or head and neck cancer for the development of subsequent MM, and this may indeed be random findings due to a large number of tests.

We found MM patients to have a sixfold increased risk for secondary AML/MDS, a twofold increased risk for non-melanoma skin cancer and no overall increased risk for SPM. Key findings from population-based studies addressing SPM are summarised in Table 1. The overall risk for SPM was not increased in reports from the United States, Germany, Taiwan and Denmark, whereas two out of three studies from the Swedish Cancer Registry reported an approximately 30% increased risk.[4,31] Increased risk for secondary NHL was found in three studies,[3,6,32] and increased risk for kidney cancer was found in two.[6,31] The increased risk for AML/MDS is consistent in all studies. Increased risk for non-melanoma skin cancer was found in one study from the Swedish Cancer Registry by Mailankody et al, who also reported an increased risk for patients with monoclonal gammopathy of undetermined significance.[4] Our results further underline the well-known increased risk for secondary AML/MDS in MM patients and support a possible association with secondary non-melanoma skin cancer.

Strengths of our study include a population-based design using data from a high-quality cancer registry with nationwide coverage. A limitation to our study is the lack of individual information regarding treatment, disease characteristics and comorbidity. Furthermore, our data do not contain information on MGUS as this condition is not reported to the CRN. Although this study was carried out on close to 10 000 MM patients, the observed number of cases for some previous cancers was low, which warrants cautious interpretation. Previous cancers diagnosed before 1953 were not included, but we allowed for a 30-year lead-time window by including MM patients from 1982.

In conclusion, we demonstrate that the overall incidence of previous cancers in MM patients is not greater than in an age-matched control cohort. We found significant associations between Hodgkin lymphoma and primary myelofibrosis and the subsequent development of MM. With regard to SPM, the well-known increased risk for AML/MDS is further underlined by our study.

CONFLICT OF INTEREST

The authors have no competing interests.

AUTHOR CONTRIBUTIONS

ØOL and AW designed the study and wrote the manuscript. ØOL and TÅM performed the statistical analysis. All authors interpreted the data and critically revised, discussed and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data sets analysed during the current study are available from the corresponding author upon reasonable request.

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