Received: 13 December 2021 | Revised: 10 February 2022 | Accepted: 14 February 2022

DOI: 10.1111/ejh.13757

ORIGINAL ARTICLE

European Journal of Haematology WILEY

Risk of multiple myeloma and other malignancies among first- and second-degree relatives of patients with multiple myeloma: A population-based study

Øystein O. Langseth[1,2] | Tor Å. Myklebust[3,4] | Tom B. Johannesen[4] | Øyvind Hjertner[1,2] | Anders Waage[1,2]

[1]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway

[2]Department of Hematology, St. Olav's University Hospital, Trondheim, Norway

[3]Department of Registration, Cancer Registry of Norway, Oslo, Norway

[4]Department of Research and Innovation, Møre and Romsdal Hospital Trust, Ålesund, Norway

Correspondence
Øystein O. Langseth, Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway.
Email: oystein.olstad.langseth@ntnu.no

Funding information
This work was funded by a grant (id: 46079300) from the Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU), and St. Olavs University Hospital, Trondheim, Norway

Abstract

Objectives: We conducted a population-based study to assess the risk for multiple myeloma (MM) and other cancers in first- and second-degree relatives of MM patients, and to investigate whether evidence of anticipation is present in familial MM.

Methods: We retrieved 24 845 first-degree relatives and 41 008 second-degree relatives of 7847 MM patients, and 86 984 first-degree relatives, and 138 660 second-degree relatives of 26 511 matched controls. A Cox model was used to assess the risk for MM and other cancers in relatives of MM patients. Anticipation was assessed by a Cox model, where all parents and offspring of MM patients were included in the risk set.

Results: In second-degree relatives of MM patients, no overall significant association with an MM diagnosis was observed (HR 1.99; 95%CI:0.86–4.57). In parents and offspring of MM patients, we found no significant difference in the ages at onset of MM (HR 1.28;95% CI:0.50–3.28). In affected parent-offspring pairs, we observed no statistically significant difference in overall survival between the generations (HR 0.74; 95%CI:0.20–2.69).

Conclusions: Overall, second-degree relatives of MM patients were not associated with an increased risk for MM. Our study supports that genetic anticipation is not present in familial MM.

KEYWORDS
hematologic neoplasms, multiple myeloma, population-based study, relatives. anticipation

1 | INTRODUCTION

The occurrence of two or more cases of multiple myeloma (MM) in the same family has been described since the early 1900s. Since the first report of plausible familial myeloma by Meyerding in 1920, briefly mentioning a MM patient with an aunt with a bone disease and fractures,[1] numerous case reports followed. To date, well over 100 families with multiple cases of MM have been reported.[2-9] In studies of myeloma families, the phenomenon of anticipation has

Novelty statements
1. What is the new aspect of your work? Herein, we assess the risk for myeloma and other malignancies in first- and second-degree relatives of myeloma patients.
2. What is the central finding of your work? We did not find evidence that the known increased risk for myeloma in first-degree relatives extends to second-degree relatives.
3. What is (or could be) the specific clinical relevance of your work? Our findings are of interest for patients with myeloma and their relatives.

been proposed, denoting decreasing age at onset and/or increased severity of a disease in successive generations,[2,10] whereas others found no evidence for this.[11] Extensive efforts have been made to establish a genetic foundation for inheritable susceptibility to MM, and genome-wide association studies have identified variants at 24 loci associated with MM.[12] Epidemiologic studies show that first-degree relatives of MM patients have an approximately two- to four-fold increased risk for MM compared to reference populations.[13-19] The risk for other malignancies in first-degree relatives of MM patients vary between studies. To our knowledge, population-based studies assessing risk for MM and other malignancies beyond first-degree relatives are limited to one brief report, describing an excess of MM, prostate cancer, and melanoma in first-, second-, and third-degree relatives of MM patients.[20]

In this population-based study, we aimed to assess familial aggregation and anticipation of MM, and to investigate the risk for MM and other malignancies in first- and second-degree relatives of MM patients.

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 January 1, 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.[21] Briefly, each cancer case is reported according to the International Classification of Diseases of Oncology, third edition (IDC-O-3), and the completeness of case ascertainment is approximately 98–99% for solid cancers and above 94% for hematological cancers including MM.[21,22] Matched controls and relatives were provided by the National Population Registry (NPR). The registry was established in 1964 based on the census from 1960 containing demographic information of every resident.[23] Vital status for all patients in the CRN is updated by monthly reports from the NPR as well as consecutive information of cause of death and death certificates from the Cause of Death Registry, National Institute of Public Health.[21]

2.2 | Study population

All cases of MM (ICD-O-3 code 9732/3X) diagnosed between January 1, 1982, and December 31, 2013, were retrieved from the CRN. Patients with a MM diagnosis based on incidental finding at autopsy or death certificate only or no identifiable relatives were excluded. Population-based controls (control probands) were retrieved in a 4:1 ratio from the NPR, matched by year of birth, sex, and county of residence. Each control proband had to be alive at the time of MM diagnosis for the corresponding case proband. Relatives of case and control probands were selected from the NPR. First-degree relatives for a given proband consisted of parents, siblings, and children. Second-degree relatives consisted of grandparents, uncles and aunts, nephews and nieces, and grandchildren. Information on half-siblings was not obtainable. The relatives of case and control probands constitute the study population. Relatives with missing information on vital status or a cancer diagnosis based on autopsy or death certificate only were excluded.

2.3 | Statistical methods

We used a Cox proportional hazards model to estimate the risk, denoted by the hazard ratio (HR), for MM and other malignancies in relatives of MM patients versus relatives of controls. An individual became at risk for a given cancer diagnosis after the date of birth or at the start of cancer registration (January 1, 1953), whichever occurred last. Follow-up ended at the date of diagnosis of the cancer of interest, date of emigration, date of death, or end of study December 31, 2015, whichever occurred first. The interaction between the exposure (relative of MM patient or relative of control) and type of kinship was assessed in the model,[24] and we adjusted for sex of the relatives, sex of the proband, and 15-year birth cohort in all analyses. The association between exposure and a diagnosis of MM was evaluated in all relatives, first-, and second-degree relatives. For MM, associations in subtypes of first- and second-degree were assessed. In families with more than one case of MM, each MM patient will generate his or her own controls and both sets of relatives are included in the data set. As a result, a dependency may be introduced in the data and some individuals will be duplicated in the data set.[24,25] To accommodate for this dependency, a matching cluster was defined, including the combined set of all relatives of MM-cases and controls in families with at least one case of MM. We used a clustered sandwich estimator of variance, relaxing the assumption of independent observations within the matching clusters.[25] HRs with 95% confidence intervals not including one were considered statistically significant.

To assess anticipation in parent–child pairs we first compared the age at diagnosis by a paired t-test, next based on survival methods as proposed by Daugherty et al.[11] Here, all parents and offspring of MM patients are studied, and the age at MM diagnosis for parents and offspring is assessed by an unadjusted Kaplan-Meier method as well as by a Cox proportional hazards model adjusted for sex and 15-year calendar period of birth. To assess increased disease severity in the offspring generation, we also compared the overall survival after MM diagnosis in the parent-offspring pairs by a Cox model adjusted for sex, 10-year calendar periods of year of birth, and 10-year calendar periods of MM diagnosis with the parent generation as the reference category.

The proportional hazards assumption in all Cox models was checked using Schoenfeld residuals, and for the majority of the analyses the assumption was met. For analyses where the proportional hazards assumption was questionable, we estimated models

stratified on different follow-up intervals. No relevant interaction effects across follow-up time were observed.

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

3 | RESULTS

We retrieved 10 035 case probands diagnosed with MM between January 1, 1982, and December 31, 2013, from the CRN. We excluded 421 patients with a MM diagnosis based on accidental finding at autopsy or death certificate only. Furthermore, 1767 patients had no identifiable relatives. All first- and second-degree relatives for these 7847 MM patients and their 26 511 matched controls were selected from the Norwegian Population Registry. From a total of 289 666 relatives, 694 were excluded due to missing information on vital status, and 161 were excluded due to a cancer diagnosis based on incidental findings at autopsy or death certificate only. The study population thus consisted of 288 811 individuals (65 168 relatives of MM patients and 223 643 relatives of matched controls) (Table 1).

3.1 | Familial aggregation of MM

Overall, being a first-degree relative of MM patients was associated with an approximately two-fold increased risk for acquiring an MM diagnosis compared to relatives of controls (Table 2) Significant positive associations were observed for all types of first-degree relatives with comparable HRs, and the strongest association was found in siblings of MM patients. In second-degree relatives of MM patients, no overall significant association with an MM diagnosis was observed. Based on very few observed cases, a significant association was observed for nieces and nephews (Table 2).

We found 62 families with more than one case of MM. First-degree kinships were found in 56 families, and second-degree kinships were found in nine. There were 48 parent-offspring pairs and 10 sibling pairs. Some families had more than two cases of MM. Among the parent-offspring pairs, father-son was the most common relationship ($n = 18$), followed by mother-daughter ($n = 13$), mother-son ($n = 10$) and father-daughter ($n = 7$). Opposite sexes were present in 6 out of 10 sibling pairs. Considering second-degree kinships we found 2 grandparent-grandchildren pairs and 5 pairs of uncles/aunts - nieces/nephews.

In the parent-offspring pairs, the parent generation was born between 1869 and 1962, and the offspring generation between 1913 and 2015.

3.2 | Evidence for anticipation in familial MM?

The parent generation was diagnosed with MM between 1967 and 2015 and the offspring generation between 1989 and 2015. The median age at MM diagnosis in the offspring generation was 60 years (mean 60 years) compared to 77 years (mean 75.6 years) in the parent generation. In the paired *t*-test the difference in means was statistically significant ($p < 0.001$). The analysis was repeated with a non-parametric test due to some violation of the normality assumption in the parent's ages at diagnosis, and the difference in medians was also statistically significant in a paired Wilcoxon Signed-Ranks test ($p < 0.001$). However, when we applied survival methods as proposed by Daugherty et al.,[11] no evidence of anticipation was found. Here, all parents and offspring of the MM patients are under study (3485 parents and 18 017 offspring). Applying the Kaplan-Meier method, there was no statistically significant difference in age of MM diagnosis ($p = 0.097$ Log-Rank). In the Cox proportional hazards model adjusted for sex and 15-year birth cohort, no statistically significant difference in the age at MM diagnosis was detected (HR 1.28; 95% CI: 0.50–3.28) In 48 affected parent-offspring pairs, there was no clear sign

TABLE 1 Distribution of relatives of MM patients and controls

	Relatives of MM patients	Relatives of controls	Born between	Median age (years) at end of follow-up, relatives of MM patients	Median age (years) at end of follow-up, relatives of controls
First-degree relatives	24 845	86 984	1869–2015	58	57
Siblings	3343	12 394	1900–2003	63	63
Parents	3485	13 075	1869–1962	82	82
Offspring	18 017	61 515	1913–2015	54	53
Second-degree relatives	41 008	138 660	1866–2015	28	27
Grandparents	294	983	1866–1942	83	84
Grandchildren	32 614	109 951	1936–2015	26	25
Uncle/aunt	302	916	1900–1977	75	74
Nephew/niece	7113	24 809	1920–2015	37	36
All relatives	65 168	223 643	1866–2015	37	36

TABLE 2 Hazard ratios for MM in relatives of MM patients vs. relatives of controls

	Cases[b]	HR[a] (95% CI)
All relatives	101/182	1.89 (1.40–2.57)[c]
All first-degree relatives	91/167	1.89 (1.37–2.61)[c]
Offspring	31/49	1.90 (1.20–2.98)[c]
Siblings	17/27	2.29 (1.09–4.84)[c]
Parents	43/91	1.77 (1.23–2.55)[c]
All second-degree relatives	10/15	1.99 (0.86–4.57)
Grandchildren	¼	0.68 (0.07–6.20)
Grandparents	¼	0.81 (0.09–7.31)
Uncles/aunts	¾	2.25 (0.53–9.63)
Nieces/nephews	5/3	4.76 (1.19–18.9)[c]

Note: Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Cases in relatives of MM patients/cases in relatives of controls.

[b]Adjusted for sex of the relatives, sex of the proband, and 15-year birth cohort.

[c]95% confidence interval not including one.

of impaired survival in the offspring generation (HR 0.74; 95%Ci: 0.20–2.60).

3.3 | Risk for other malignancies in relatives of MM patients

The risks for other malignancies in all relatives are displayed in Table 3. Relatives of MM patients were not associated with increased risk for any non-MM hematological malignancy. For solid tumors, second-degree relatives of MM patients were associated with an increased risk for melanoma. In all relatives, an increased risk for sarcoma was observed, and for first- and second-degree relatives the HRs were of similar magnitude, but statistical significance was not reached.

4 | DISCUSSION

In this population-based study, we have investigated the risk for MM and other malignancies in first- and second-degree relatives of MM patients. In line with previous studies,[15,17,18] we confirm the increased risk for MM in first-degree relatives of MM patients. In second-degree relatives, nieces and nephews of MM patients were associated with a near five-fold increased risk for MM, an association not previously reported in relatives of MM patients. This finding was based on a low number of cases, and confirmation from other studies is necessary. To our knowledge, only one other population-based study has addressed the occurrence of cancer beyond first-degree relatives of MM patients. In 2008, Camp et al. reported briefly from a study of 13 288 first-degree relatives, 45 575 second-degree relatives, and 118 363 third-degree relatives of 1354 MM patients.[20] A significant excess of cases of MM, prostate cancer, and melanoma was found in all types of relatives. Seventy-two pedigrees with a significant increase in cases of MM and prostate cancer were also observed.[20] In second-degree relatives we found a borderline significantly increased risk for melanoma, possibly corresponding to findings by Camp et al. However, other large-scale studies on first-degree relatives described no association between MM and melanoma. Whether a true association exists thus remains an open question. Studies from the Swedish Family Cancer Database have shown an increased risk for urinary bladder cancer in first-degree relatives of MM patients.[15,17] We observed no signs of increased risk for urothelial cancer in first-degree relatives, whereas a possible but non-significant positive association was observed in second-degree relatives. No increased risk for urothelial cancer in first-degree relatives in our data may be due to a smaller sample size than the Swedish studies, but the number of observed cases was comparable to the study by Kristinsson et al.[17] It, therefore, remains unclear whether first-degree relatives of MM patients have an increased risk for urothelial cancer. In two studies from the Swedish Family Cancer Database, associations between MM and bone- and connective tissue tumors in first-degree relatives were observed.[15,18] Our data provide further support for this association.

Of note, grandchildren of probands accounted for approximately 80% of all second-degree relatives in our data. At the end of follow-up, the median age of this generation was 25 years, and only 1.7% had reached the age of 50 years. Taking into account a median age of MM diagnosis of around 70 years, a possible increased risk for MM in grandchildren of MM patients cannot be excluded based on our data, as additional decades of follow-up would be necessary. Furthermore, grandparents of MM patients and controls were underrepresented in our data (about 0.7% of the total number of second-degree relatives). This generation was born before 1942, possibly precluding their appearance in the population registry.

In the 62 families with more than one case of MM, all types of kinship were represented. In the study of 25 MM families by Lynch et al, parent-offspring pairs were the most common, and there were signs of sex linkage. Affected mothers were more likely to have affected daughters and affected fathers were more likely to have affected sons.[5] In the study by Altieri et al., male patients more often had an affected son, and females more often had an affected daughter, suggesting a pattern consistent with an autosomal dominant mode of inheritance.[15] Sex-linked and recessive traits have been hypothesized to be of less importance.[5] A similar tendency of inheritance patterns was observed in our population-based data.

Comparing mean and median age at MM diagnosis in parent-offspring pairs, anticipation could seemingly be observed. However, these methods are prone to bias, mainly due to the shorter follow-up of later-born generations, which cause the right truncation of the data.[10,11] When applying survival methods on all parents and offspring of MM patients, no evidence for younger age at diagnosis in the offspring generation was observed. Due to the advances in myeloma treatment, one could expect superior survival in the offspring generation in parent-offspring pairs given that no anticipation/

TABLE 3 Hazard ratios for hematological and solid cancers in relatives of MM patients vs. relatives of controls

	All relatives		First-degree relatives		Second-degree relatives	
	Cases[b]	HR[a] (95% CI)	Cases[b]	HR[a] (95% CI)	Cases[b]	HR[a] (95% CI)
Any cancer	3798/12 330	1.04 (1.00–1.08)	3088/10 253	1.03 (0.99–1.07)	710/2077	1.07 (0.98–1.17)
Any hematological cancer (non-myeloma)	333/1026	1.09 (0.95–1.24)	251/734	1.17 (1.00–1.35)	82/292	0.91 (0.71–1.16)
Non-Hodgkin lymphoma	133/411	1.07 (0.87–1.33)	119/336	1.19 (0.95–1.49)	14/75	0.58 (0.31–1.09)
Hodgkin lymphoma	48/163	0.99 (0.72–1.37)	28/89	1.09 (0.71–1.67)	20/74	0.89 (0.54–1.45)
AML/MDS	47/140	1.13 (0.82–1.57)	39/102	1.32 (0.91–1.91)	<10/38	0.68 (0.31–1.45)
Acute lymphoblastic leukemia	37/113	1.11 (0.76–1.62)	10/34	1.03 (0.51–2.08)	27/79	1.15 (0.73–1.80)
Chronic lymphocytic leukemia	40/99	1.35 (0.93–1.96)	37/87	1.44 (0.98–2.12)	<10/12	0.73 (0.15–3.59)
Chronic myelogenous leukemia	19/56	1.16 (0.69–1.95)	12/47	0.89 (0.47–1.68)	<10/<10	2.45 (0.91–6.59)
Myeloproliferative neoplasia	14/56	0.82 (0.46–1.48)	11/49	0.75 (0.39–1.44)	<10/<10	1.32 (0.34–5.05)
Any solid tumor	3434/11 285	1.02 (0.98–1.07)	2809/9489	1.01 (0.97–1.06)	625/1796	1.08 (0.98–1.19)
Central nervous system	312/969	1.08 (0.94–1.23)	208/639	1.11 (0.94–1.30)	104/330	1.02 (0.82–1.27)
Head and neck	95/335	0.95 (0.76–1.20)	88/291	1.03 (0.81–1.31)	<10/44	0.49 (0.22–1.08)
Gynecological	296/1909	0.99 (0.87–1.13)	237/842	0.97 (0.84–1.13)	59/167	1.09 (0.80–1.48)
Hepatobiliary	43/124	1.17 (0.82–1.66)	37/112	1.13 (0.77–1.66)	<10/12	1.47 (0.55–3.93)
Lung	275/945	0.96 (0.84–1.11)	255/865	0.99 (0.86–1.15)	20/80	0.72 (0.43–1.19)
Melanoma	276/850	1.08 (0.94–1.24)	206/691	1.01 (0.86–1.18)	70/159	1.37 (1.02–1.85)[c]
Non-melanoma skin cancer	136/452	1.02 (0.84–1.24)	121/401	1.04 (0.85–1.28)	16/51	0.88 (0.50–1.55)
Kidney	110/336	1.10 (0.88–1.37)	89/272	1.12 (0.88–1.42)	21/64	1.01 (0.61–1.69)
Pancreatic	73/284	0.88 (0.68–1.14)	72/257	0.97 (0.75–1.27)	<10/27	0.11 (0.01–0.81)[c]
Sarcoma	49/109	1.52 (1.09–2.14)[c]	28/64	1.52 (0.97–2.37)	21/45	1.55 (0.91–2.56)
Testicular	132/422	1.05 (0.86–1.28)	66/226	1.02 (0.77–1.34)	66/296	1.09 (0.82–1.45)
Colorectal	461/1554	1.02 (0.92–1.14)	404/1401	0.99 (0.88–1.11)	58/153	1.20 (0.88–1.65)
Thyroid	65/203	1.07 (0.81–1.42)	47/142	1.13 (0.81–1.57)	18/66	0.96 (0.54–1.62)
Unknown primary	58/192	1.04 (0.77–1.40)	51/169	1.06 (0.77–1.45)	<10/19	0.93 (0.42–2.07)
Urothelial	181/588	1.04 (0.89–1.23)	154/536	0.98 (0.82–1.18)	29/54	1.56 (0.98–2.49)
Stomach	108/405	0.93 (0.75–1.16)	98/366	0.95 (0.76–1.19)	10/38	0.79 (0.38–1.64)
Esophagus	29/93	1.04 (0.69–1.58)	27/84	1.09 (0.71–1.67)	<10/<10	0.65 (0.14–3.04)
Breast	479/1580	1.02 (0.91–1.14)	402/1373	1.00 (0.89–1.13)	77/207	1.13 (0.85–1.51)
Prostate	540/1647	1.09 (0.98–1.22)	482/1509	1.07 (0.96–1.20)	58/138	1.25 (0.88–1.79)

Note: Abbreviations: AML/MDS, acute myelogenous leukemia/myelodysplastic syndromes; CI, confidence interval; HR, hazard ratio.

[a]Cases in relatives of MM patients/cases in relatives of controls.

[b]Adjusted for sex of the relatives, sex of the proband, and 15-year birth cohort.

[c]95% confidence interval not including one.

increased severity of the disease was present. We observed no statistically significant difference in overall survival in parent-offspring pairs. Thus, our findings concur with those reported by Daugherty et al., supporting no evidence for anticipation in MM in terms of age of onset, whereas we cannot conclude whether the overall survival of MM, as a measure of disease severity, is altered in successive generations.

Strengths of our study include a population-based design based on high-quality data from a national cancer registry. The ascertainment of relatives through linkage of national registries overcomes potential recall bias associated with interview-based approaches. Our study also has its limitations. In this study, and in others of its kind, a large number of tests are carried out and the risk for chance findings warrants cautious interpretation of the results. The assessment of cancer risk in first-degree relatives should be considered confirmatory to other studies, and the assessment of second-degree relatives should be considered exploratory. As previously discussed, the registry-based ascertainment of relatives may have caused the group of second-degree relatives to be skewed toward later-born generations where only a small proportion had reached ages of risk for many cancers at the end of follow-up, MM included. The lack of individual data on patient characteristics and treatment is also a limitation to our study. Furthermore, information on MGUS is not available in the CRN, precluding the assessment of MGUS-risk in relatives of MM patients.

In conclusion, our data confirm the increased risk for MM in first-degree relatives as reported in several studies. Overall, second-degree relatives of MM patients were not associated with an increased risk for MM. Based on small numbers of observed cases, nephews and nieces of MM patients were associated with an increased risk for MM. This association is not previously described and is in need of confirmation by others. Our study does not support that genetic anticipation is present in familial MM.

ACKNOWLEDGEMENTS

This work was funded by a grant (id: 46079300) from the Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU), and St. Olavs University Hospital, Trondheim, Norway.

CONFLICT OF INTERESTS

The authors have no competing interests.

AUTHOR CONTRIBUTIONS

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

DATA AVAILABILITY STATEMENT

The datasets analyzed in the current study are available from the corresponding author upon reasonable request.

ORCID

Øystein O. Langseth https://orcid.org/0000-0003-0736-7086

REFERENCES

1. Meyerding HW. Multiple myeloma. *Radiology*. 1925;5(2):132-146.
2. Grosbois B, Gueguen M, Fauchet R, et al. Multiple myeloma in two brothers. An immunochemical and immunogenetic familial study. *Cancer*. 1986;58(11):2417-2421.
3. Deshpande HA, Hu X-P, Marino P, Jan NA, Wiernik PH. Anticipation in familial plasma cell dyscrasias. *Br J Haematol*. 1998;103(3):696-703.
4. Lynch HT, Sanger WG, Pirruccello S, Quinn-Laquer B, Weisenburger DD. Familial multiple myeloma: a family study and review of the literature. *JNCI*. 2001;93(19):1479-1483.
5. Lynch HT, Watson P, Tarantolo S, et al. Phenotypic heterogeneity in multiple myeloma families. *J Clin Oncol*. 2005;23(4):685-693.
6. Lynch HT, Ferrara K, Barlogie B, et al. Familial myeloma. *N Engl J Med*. 2008;359(2):152-157.
7. Jain M, Ascensao J, Schechter GP. Familial myeloma and monoclonal gammopathy: a report of eight African American families. *Am J Hematol*. 2009;84(1):34-38.
8. Gerkes EH, de Jong MM, Sijmons RH, Vellenga E. Familial multiple myeloma: report on two families and discussion of screening options. *Hered Cancer Clin Pract*. 2007;5(2):72.
9. Ogmundsdóttir HM, Haraldsdóttirm V, Jóhannesson GM, et al. Familiality of benign and malignant paraproteinemias. A population-based cancer-registry study of multiple myeloma families. *Haematologica*. 2005;90(1):66-71.
10. Boonstra PS, Gruber SB, Raymond VM, et al. A review of statistical methods for testing genetic anticipation: looking for an answer in Lynch syndrome. *Genet Epidemiol*. 2010;34(7):756-768.
11. Daugherty SE, Pfeiffer RM, Mellemkjaer L, Hemminki K, Goldin LR. No evidence for anticipation in lymphoproliferative tumors in population-based samples. *Cancer Epidemiol Biomark Prev*. 2005;14(5):1245.
12. Pertesi M, Went M, Hansson M, Hemminki K, Houlston RS, Nilsson B. Genetic predisposition for multiple myeloma. *Leukemia*. 2020;34(3):697-708.
13. Eriksson M, Hållberg B. Familial occurrence of hematologic malignancies and other diseases in multiple myeloma: a case-control study. *Cancer Causes Control*. 1992;3(1):63-67.
14. Brown LM, Linet MS, Greenberg RS, et al. Multiple myeloma and family history of cancer among blacks and whites in the U.S. *Cancer*. 1999;85(11):2385-2390.
15. Altieri A, Chen B, Bermejo JL, Castro F, Hemminki K. Familial risks and temporal incidence trends of multiple myeloma. *Eur J Cancer*. 2006;42(11):1661-1670.
16. Landgren O, Linet MS, McMaster ML, Gridley G, Hemminki K, Goldin LR. Familial characteristics of autoimmune and hematologic disorders in 8,406 multiple myeloma patients: a population-based case-control study. *Int J Cancer*. 2006;118(12):3095-3098.
17. Kristinsson SY, Björkholm M, Goldin LR, et al. Patterns of hematologic malignancies and solid tumors among 37,838 first-degree relatives of 13,896 patients with multiple myeloma in Sweden. *Int J Cancer*. 2009;125(9):2147-2150.
18. Frank C, Fallah M, Chen T, et al. Search for familial clustering of multiple myeloma with any cancer. *Leukemia*. 2016;30(3):627-632.
19. Schinasi LH, Brown EE, Camp NJ, et al. Multiple myeloma and family history of lymphohaematopoietic cancers: results from the International Multiple Myeloma Consortium. *Br J Haematol*. 2016;175(1):87-101.
20. Camp NJ, Werner TL, Cannon-Albright LA. Familial myeloma. *N Engl J Med*. 2008;359(16):1734-1735. author reply 5.

21. Larsen IK, Småstuen M, Johannesen TB, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. *Eur J Cancer*. 2009;45(7):1218-1231.
22. Aasbrenn M, Langmark F, Wisløff F. Er registreringen av myelomatose i Kreftregisteret god nok? 2712–4. 2008.
23. Hammer H. Det sentrale folkeregister i medisinsk forskning. *Tidsskrift-Norske Laegeforening*. 2002;122(26):2550.
24. Lee M, Rebora P, Valsecchi MG, Czene K, Reilly M. A unified model for estimating and testing familial aggregation. *Stat Med*. 2013;32(30):5353-5365.
25. Pfeiffer RM, Goldin LR, Chatterjee N, et al. Methods for testing familial aggregation of diseases in population-based samples: application to Hodgkin lymphoma in Swedish registry data. *Ann Hum Genet*. 2004;68(Pt 5):498-508.

How to cite this article: Langseth ØO, Myklebust TÅ, Johannesen TB, Hjertner Ø, Waage A. Risk of multiple myeloma and other malignancies among first- and second-degree relatives of patients with multiple myeloma: A population-based study. *Eur J Haematol*. 2022;108:486–492. https://doi.org/10.1111/ejh.13757