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Incidence and survival of multiple myeloma: a population-based study of 10 524 patients diagnosed 1982–2017

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Summary

Population-based studies from high-quality nationwide cancer registries provide an important alternative to clinical trials in the assessment of the impact of modern myeloma treatment. Based on data from the Cancer Registry of Norway, we investigated trends in incidence and relative survival (RS) for 10 524 patients in three age groups diagnosed between 1982 and 2017. Nationwide myeloma drug consumption statistics were obtained from the Norwegian Institute of Public Health. Patients aged <65 years had a steady increase in both 5- and 10-year RS across all calendar periods from 1982. For patients aged 65–79 years, RS was stable until the calendar period 1998–2002, followed by an improvement in both 5- and 10-year RS. The 5-year RS for patients aged ≥80 years also increased significantly between the first and the last calendar period. In conclusion, we demonstrate a significant improvement in 5-year RS in all age groups. Improved RS in patients aged ≥80 years at the time of diagnosis is only rarely described in other population-based studies. For patients aged ≥65 years, the improvement in RS coincides with the introduction of modern drugs, whereas patients aged <65 years had an ongoing improvement before the introduction of autologous stem-cell transplant.

Keywords: epidemiology, haematological malignancies, multiple myeloma, cancer, myeloma therapy.

Multiple myeloma (MM) is a malignant B-cell disorder characterised by the clonal proliferation of plasma cells and the presence of monoclonal protein in the serum and/or urine, and is the second most common haematological malignancy following Non-Hodgkin lymphoma.[1–3] The median age at diagnosis is ~70 years and reported incidence rates vary world-wide. The highest incidence rates are found in Australasia, North America and Western Europe, with age-standardised incidence rates at approximately five per 100 000 persons in 2016.[4] During the second half of the 20th century, melphalan and prednisone remained the mainstay of myeloma treatment, but since the 1990s the treatment landscape has evolved remarkably.[5] High-dose melphalan followed by autologous stem-cell transplant (HDM-ASCT) became the standard of care for patients aged <65 years in the mid-1990s.[6,7] Since the year 2000, numerous drugs have been added to the treatment armamentarium.[8]

Despite a rapidly growing number of available treatment options, MM is still considered an incurable disease.[9] However, several population-based studies have described an increase in long-term relative survival (RS) during recent decades. This improved survival is most evident for younger patients, and the introduction of HDM-ASCT is suggested as the most likely explanation.[10–12] For patients aged >75 years at diagnosis, the improvement in RS is less pronounced and absent in most studies.[13] In randomised controlled trials (RCTs), the inclusion and exclusion criteria are typically strict and older and co-morbid patients are often under-represented. Population-based studies from high-quality cancer registries thus provide an important source for the assessment of changes in survival in a patient population.[11,14,15]

In the present study, we provide up-to-date real-world observations on changes in incidence and RS in patients with MM diagnosed between 1982 and 2017, based on data from the Cancer Registry of Norway (CRN) along with nationwide drug consumption statistics.

Patients and methods

Cancer registration and study population

The CRN contains nationwide cancer statistics from 1953 based on compulsory reporting of cancer cases by all

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hospitals, laboratories and general practitioners.[16,17] All cases of MM (International Classification of Diseases for Oncology [ICD-O]-3 code 9732/xx) in patients aged ≥18 years, between 1 January 1982 and 31 December 2017, were retrieved from the registry. Follow-up ended at death by any cause, emigration or the end of study at 31 December 2017, whichever occurred first. Age at diagnosis was divided into three categories: <65 years (transplant eligible), 65–79 years (youngest transplant ineligible) and ≥80 years (oldest transplant ineligible). We split the calendar periods of MM diagnosis into seven categories with respect to historical treatment standards, 1982–1987 and 1988–1992 (melphalan-prednisone), 1993–1997 (early HDM-ASCT), 1998–2002 (introduction of thalidomide), 2003–2007 (early thalidomide upfront, introduction of bortezomib), 2008–2012 (thalidomide and bortezomib upfront, introduction of lenalidomide), and 2013–2017 (lenalidomide upfront, early pomalidomide, daratumumab, panobinostat and carfilzomib). We present crude and age-standardised incidence rates during the study period.

Nationwide consumption of myeloma drugs

To obtain information on the time of the actual introduction for the different drugs used in myeloma treatment, drug consumption data were retrieved from the Norwegian Prescription Database and The Norwegian Drug Wholesales Statistics, Norwegian Institute of Public Health. We present the amount in grammes of active ingredient per year in order to illustrate trends in the consumption of nine different drugs used in myeloma treatment. We chose to use grammes as the common unit of measurement because the number of prescriptions or the number of 'defined daily doses' were not available for all drugs. The Norwegian Prescription Database contains data on prescription drugs dispensed through pharmacies since 2004. We retrieved the number of users (patients with at least one prescription dispensed) for the immunomodulatory agents (IMIDs) thalidomide, lenalidomide and pomalidomide from the online database (http://norpd.no). When the number of users is less than five, the database returns '<5' as the number of users. In these cases, we set the number of users to one to achieve uniformity. We identified the number of patients in three age groups; <65, 65–79 and ≥80 years, being alive at the beginning of each calendar year, and compared the fractions of myeloma drug users in each age group with respect to the development in consumption of thalidomide, lenalidomide and pomalidomide.

Statistical analyses

We present RS ratios (RSRs) with 95% confidence intervals (CIs) estimating the ratio between the observed and expected survival. Expected survival was estimated from a national population table stratified by year, sex and age by the Ederer-II method.[18] RS is the preferred approach to address trends in cancer survival to account for competing causes of death.[19] For the calendar periods up to 2007, we applied the cohort method, as every patient will have 10 years of follow-up. For the period 2008–2012, the RSR up to 5 years was estimated by the cohort method, and the 10-year RSR was predicted by the period approach.[20] In the most recent calendar period 2013–2017, no patients had 5 or 10 years of follow-up. To provide up-to-date estimates on long-term survival, 5- and 10-year RSRs were predicted by the period approach for this calendar period. Additionally, excess mortality during the first 5 years after diagnosis was modelled using a generalised linear model, assuming a Poisson distribution for the number of deaths with the log of the person time at risk as offset.[19,20] 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 unidentifiable data and no contact with the study subjects, written consent was by law deemed unnecessary.

RESULTS

Patients and incidence of multiple myeloma 1982–2017

Between 1 January 1982 and 31 December 2017, 11 764 cases of MM were reported to the CRN. We excluded patients with a MM diagnosis based on incidental finding at autopsy or death certificate only (15 and 422 patients, respectively). Patients with 0 days of follow-up were also excluded (799 patients), as well as four patients listed as emigrated before the date of MM diagnosis, leaving 10 524 patients available for analysis. During the study period, 8458 deaths occurred, and the median (interquartile range) follow-up was 2·4 (0·8–4·9) years. In all, 10 patients emigrated and were censored at the date of emigration. The median age at diagnosis was 71 years and 53·7% were males. The distribution of patients within calendar period of diagnosis and age group is presented in Table S1. Between 1982 and 2017, the age-standardised incidence rate was stable until approximately the year 2000, whereupon an increase was observed. The incidence rate standardised to the Norwegian population in 2014 rose from 7·3 in 1999 to 8·4 in 2017, and the incidence rate standardised to the world population[21] increased from 3·6 to 4·2 (Fig 1). As MM is mainly a disease of the elderly, the difference between these two rates is explained by a larger proportion of older people in the Norwegian 2014 population than in the world standard population.

Myeloma drug consumption

There was an increasing use of thalidomide from the introduction in 2001 until 2008, whereupon there was a steady

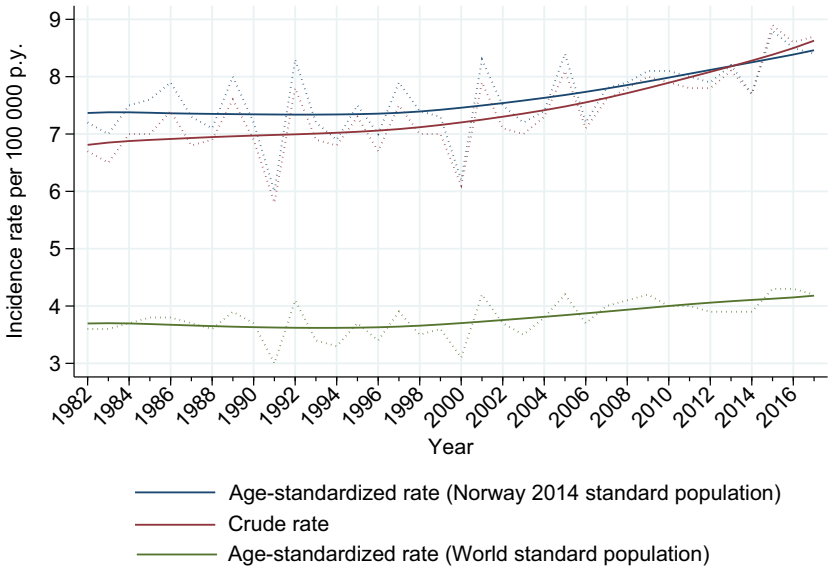

Fig 1. Crude and age-standardised incidence rates in Norway 1982–2017. Standardised to the population in Norway in 2014 and to the world population. Actual values in dots. Locally weighted scatterplot smoothed (LOWESS) curves in solid. Data collected from the Cancer Registry of Norway, the Statistics Bank. Abbreviations: p.y, person years.

decline, coinciding with the introduction of lenalidomide (Fig 2). Bortezomib was introduced in 2005 and lenalidomide in 2008, both drugs with a steady increase in consumption in the following years. Lenalidomide was until 2015 only approved for second-line treatment or later. For melphalan, there was a slight decrease from 1987 to the mid-1990s followed by a moderate increase. The latter is probably due to the introduction of HDM-ASCT. The second-generation proteasome inhibitors, carfilzomib and ixazomib, were introduced in 2016 and 2017, respectively. Pomalidomide came into use in 2014, daratumumab and panobinostat in 2016.

Figure 3 shows the development of the estimated fraction of patients in the three age groups that were treated with thalidomide, lenalidomide and pomalidomide. In patients aged >65 years, thalidomide was the most frequently used IMID until 2014, followed by a decline in the use of thalidomide and a rapid increase in the use of lenalidomide. There was also a steady increase in the use of pomalidomide since 2014, exceeding the use of thalidomide in 2017. The pattern of IMID use was similar for the age groups 65–79 and ≥80 years, but lenalidomide was taken into use in the ≥80 years group 2 years later than the 65–79 years group (2010 vs. 2008). A similar delay was seen for pomalidomide. In 2017, 40% of patients aged 65–79 years had at least one prescription dispensed for lenalidomide (468 users), 4% (42 users) had at least one prescription for thalidomide and 9% (106 users) had at least one prescription for pomalidomide. The corresponding numbers for patients aged ≥80 years were 27% (138 users), 3% (16 users) and 5% (25 users), respectively.

Relative survival (RS)

Patients diagnosed aged <65 years had a steady and near linear increase in both 5- and 10-year RSR across all calendar periods under study. Between 1982–1987 and 2013–2017, the 5-year RSR improved from 0·36 (95% CI 0·31–0·41) to 0·67 (95% CI 0·63–0·71). The 10-year RSR improved from 0·18 (95% CI 0·15–0·22) to 0·44 (95% CI 0·40–0·49) (Fig 4, Table 1).

For patients aged 65–79 years, the 5- and 10-year RSRs were stable at approximately 0·3 and 0·1, respectively, until the calendar period 1998–2002. In the following calendar periods, an improvement in both 5- and 10-year RSR was observed. The 5-year RSR improved significantly from 0·31 (95% CI 0·27–0·35) in the first calendar period of diagnosis to 0·42 (95% CI 0·38–0·46) during 2008–2012, which is the last calendar period with complete 5-year follow-up. The predicted 5-year RSR for the last calendar period was 0·46 (95% CI 0·42–0·50). There were also signs of improved 10-year RSR, at 0·20 (95% CI 0·16–0·24) during 2013–2017 compared to 0·11 (95% CI 0·08–0·14) during 1982–1987.

The 5-year RSR for patients aged ≥80 years was 0·11 (95% CI 0·07–0·17) during 1982–1987 and the 10-year RSR was 0·03 (95% CI 0·01–0·11). In the following four calendar periods the RSR estimates fluctuated before a rising tendency during the last two periods. The 5-year RSR improved significantly to 0·24 (95% CI 0·19–0·30) during 2008–2012 and further rose to a predicted value of 0·28 (95% CI 0·22–0·34) during 2013–2017. There were also signs of improvement in 10-year RSR for this age group, but no significant change was observed.

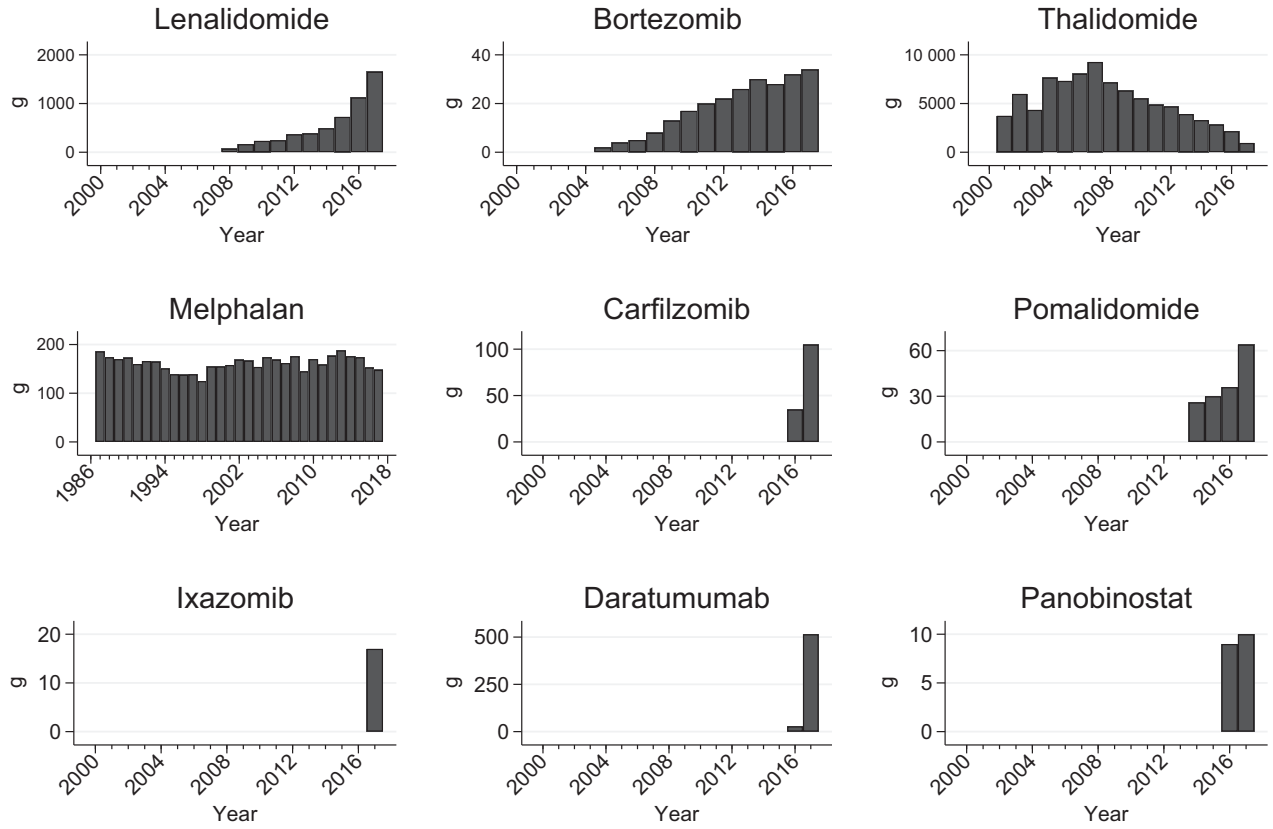

Fig 2. Annual drug consumption in Norway 2000–2017. The amount of active ingredient in grammes consumed per year is presented for nine myeloma drugs. Data collected from the Norwegian Drug Wholesales Statistics and the Norwegian Prescription Database. Abbreviations: g, grammes.

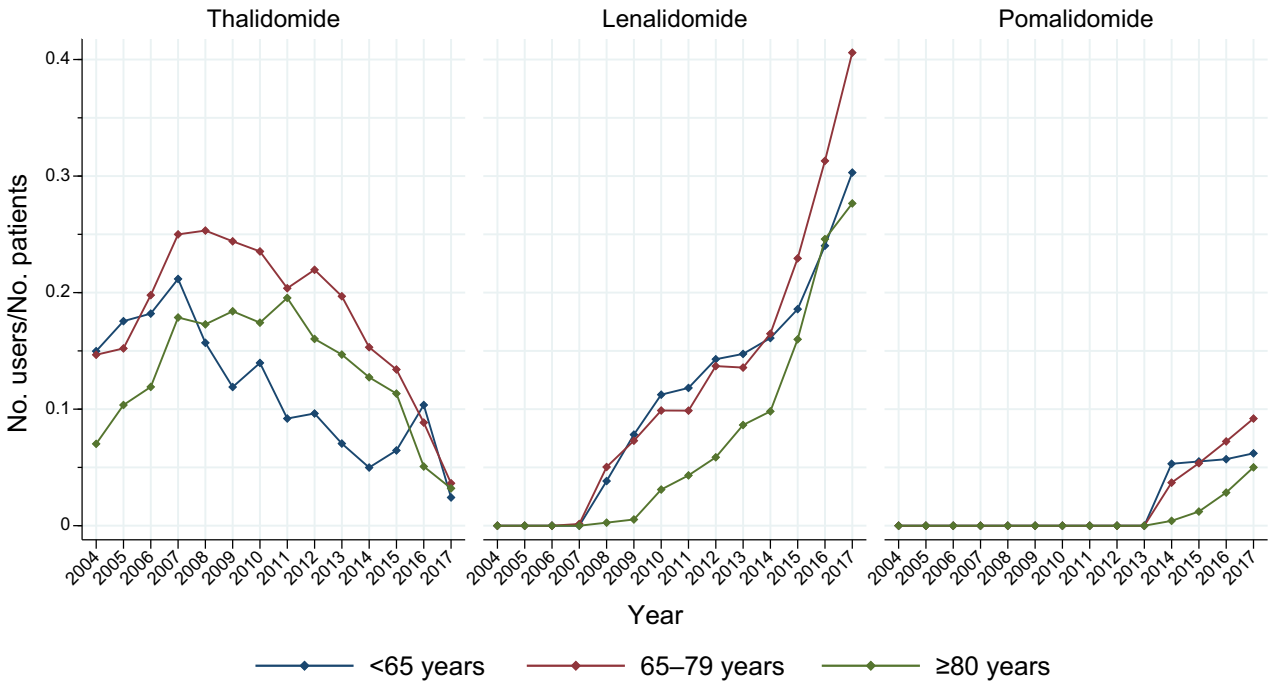

Fig 3. Development of treatment with thalidomide, lenalidomide and pomalidomide between 2004 and 2017 in three age groups. The ratio between the number of users of a drug and the number of patients at the actual time points is presented. Based on data from the Norwegian Prescription Database. Abbreviations: No. users, number of users; No. patients, number of patients.

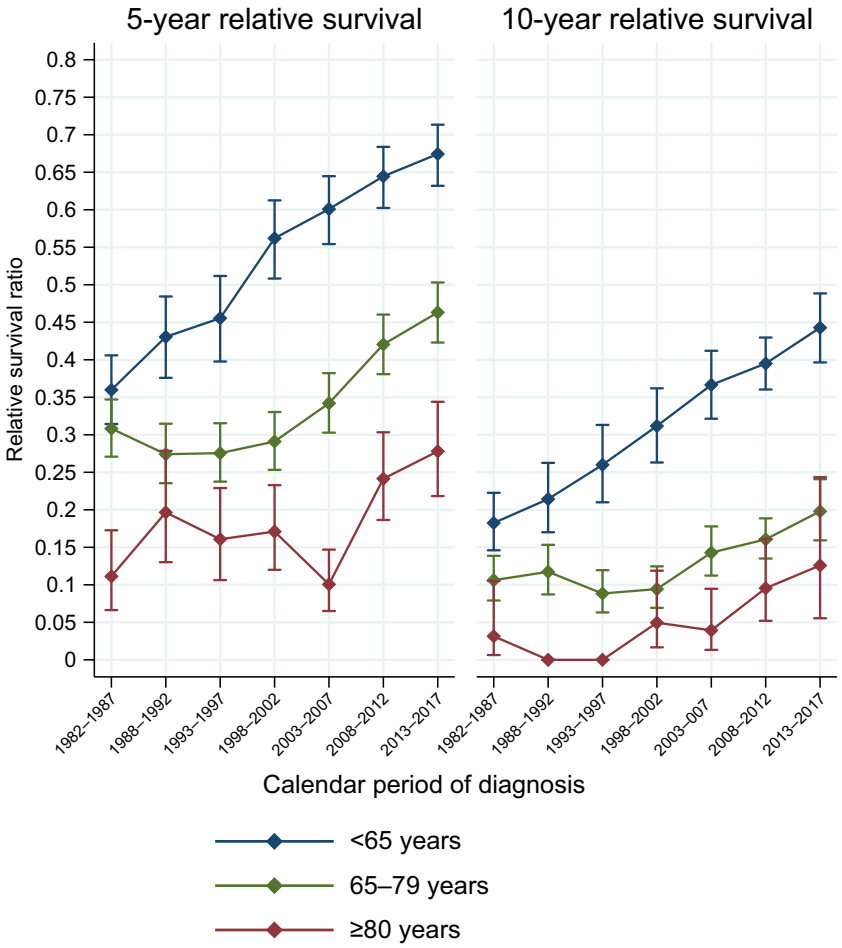

Fig 4. Five- and 10-year relative survival ratios with 95% confidence intervals by age group and calendar period of diagnosis.

Results from the model-based approach for the first 5 years after diagnosis is shown in Table S2. The model fit was assessed by the ratio of deviance to residual degrees of freedom, equal to 0·95, 0·93 and 1·27, respectively. Using the calendar period 1982–1987 as reference, we found a statistically significant reduction in excess mortality during 1993–1997 for the age group <65 years (excess mortality rate [EMR] 0·79, 95% CI 0·65–0·96). In the age groups 65–79 and ≥80 years, a statistically significant reduction in excess mortality was observed during 2008–2012 (EMR 0·71 95% CI 0·62–0·82) and 0·66 (95% CI 0·54–0·81), respectively. In the age group 65–79 years, female sex was associated with reduced excess mortality (EMR 0·90, 95% CI 0·83–0·97). We found very low estimates for the 5-year RSR during 1982–1987 and 2003–2007 in the group of patients aged ≥80 years at diagnosis. To confirm our results for this group, we repeated the regression model using the calendar period 1993–1997 as reference and found a statistically significant reduced EMR during 2008–2012 (EMR 0·74, 95% CI 0·60–0·91) and 2013–2017 (EMR 0·67, 95% CI 0·54–0·83), data not shown.

Discussion

In this population-based study on 10 524 patients with MM, we have provided real-world and up-to-date observations of incidence and changes in RS during the past three decades.

We found an increasing long-term RS in patients aged <65 years across all calendar periods. In Norway, HDM-ASCT became the standard treatment for this age group in 1994.[22] Our present data show that the improvement in both the 5- and 10-year RSR had already began approximately 10 years before the introduction of HDM-ASCT. In a study from the Swedish Cancer Registry, a similar pattern for patients aged 51–60 years at the time of diagnosis can be observed. Across four 10-year calendar periods between 1973 and 2013, the improvement in the 5-year RSR was near linear from the first calendar period.[23] These observations from two independent cancer registries in comparable countries suggest that factors other than HDM-ASCT have contributed to the improved outcome for the youngest patients with MM up to the mid-1990s.

Table 1. The 5- and 10-year relative survival ratios (RSRs) across all calendar periods and age groups

		Calendar period of diagnosis						
	Age at diagnosis, years	1982–1987	1988–1992	1993–1997	1998–2002	2003–2007	2008–2012	2013–2017
5-year RSR (95% CI)	<65	0·36 (0·31–0·41)	0·43 (0·38–0·48)	0·46 (0·40–0·51)	0·56 (0·51–0·61)	0·60 (0·55–0·65)	0·65 (0·60–0·68)	0·67 (0·63–0·71)
	65–79	0·31 (0·27–0·35)	0·27 (0·24–0·32)	0·28 (0·24–0·32)	0·29 (0·25–0·33)	0·34 (0·30–0·38)	0·42 (0·38–0·46)	0·46 (0·42–0·50)
	≥80	0·11 (0·07–0·17)	0·20 (0·13–0·28)	0·16 (0·11–0·23)	0·17 (0·12–0·23)	0·10 (0·07–0·15)	0·24 (0·19–0·30)	0·28 (0·22–0·34)
10-year RSR (95% CI)	<65	0·18 (0·15–0·22)	0·21 (0·17–0·26)	0·26 (0·21–0·31)	0·31 (0·26–0·36)	0·37 (0·32–0·41)	0·40 (0·36–0·43)	0·44 (0·40–0·49)
	65–79	0·11 (0·08–0·14)	0·12 (0·09–1·15)	0·09 (0·06–0·12)	0·09 (0·07–0·13)	0·14 (0·11–0·18)	0·16 (0·14–0·19)	0·20 (0·16–0·24)
	≥80	0·03 (0·01–0·11)	0·00 (0·00–0·00)	0·00 (0·00–0·00)	0·05 (0·02–0·12)	0·04 (0·01–1·00)	0·10 (0·05–0·16)	0·13 (0·06–0·24)

RSR, relative survival ratio; CI, confidence interval.

The attained 5-year RSR during the last two calendar periods (2008–2012 and 2013–2017) in our present study was 0·64 and 0·68, respectively. In a report from the Surveillance, Epidemiology and End Results (SEER) database, the 5-year RSR was 0·62 in this age group for the calendar period 2008–2012.[24] A population-based study from the Netherlands reported a 5-year RSR of 0·56 for the period 2001–2005,[12] and a study from the Swedish Myeloma Registry reported a 5-year RSR of approximately 0·7 for the period 2011–2015.[25] Our present results for this age group are thus in accordance with those reported by others.

Interestingly, we also observed a significant improvement in the 5-year RSR among patients aged ≥80 years at diagnosis. In 2018, Turesson et al.[13] published a review of population-based studies addressing trends in RS in patients with myeloma. A common finding in many reports is the lack of improved survival for older patients, and patients aged >75–80 years were also not represented in some studies.[10–12,23,26–29] However, three studies from the SEER database reported an improvement in RS for the oldest patients.[24,30,31] In 2011, Pulte et al.[30] reported a modest but significant improvement in 10-year RSR from 0·064 to 0·084 between 1998 and 2007 in patients aged ≥75 years. The most recent study from the SEER database included patients diagnosed from 1993 to 2012 and reported an improved 5-year RSR of 0·21 to 0·34 for patients aged ≥75 years.[24] In our present data, there was a decline in the 5-year RSR for the group of patients aged >80 years in the period 2003–2007. This contrasted with the upward trend in the periods 1988–1997, as well as with the 10-year RSR. We cannot really explain this finding except that it may represent random variation, which occasionally may occur.

The improvement in long-term survival in the 65–79 and ≥80 years age groups became evident after approximately 2003 and coincides with the introduction of newer drugs such as thalidomide, lenalidomide and bortezomib. We found that the introduction of lenalidomide and pomalidomide was delayed by ~2 years in the ≥80 years age group compared to the younger age groups, which may explain why the improvement in 5-year RSR began later for this age group. Based on our present results, the oldest patients also seem to benefit from the introduction of new myeloma drugs. After approximately 20 years with no improvement in RS, patients aged ≥80 years have finally started to close in on the younger age groups, and the following years will show if this encouraging trend continues.

Strengths of our present study include a population-based design and a national cancer registry with excellent follow-up and a completeness of case ascertainment >94%.[17] Additionally, once approved, a drug will be available for the entire study population. This provides a unique opportunity to evaluate the effects of drug treatment at a population level, which is an important alternative to survival data extracted from RCTs on selected patients.

In addition to the development in myeloma-specific treatment, alternative explanations to the improved survival may exist. The data in the CRN do not differentiate between smouldering and active MM. An improvement in survival over time may also be attributable to a growing proportion of patients with smouldering MM. For example, the number of serum electrophoreses carried out at our centre, a university clinic with a population base of approximately 600 000, has had a steady incline from 1997 analyses in 2000 to 3853 in 2017. A more liberal use of this analysis will lead to an increasing number of incidentally diagnosed smouldering MM cases introducing a lead-time bias. The measurement of serum free light chains has been used in Norway since 2004.[32] The ready availability of this analysis, as compared to 24-h urine collection, may also have contributed to more incidental diagnoses of smouldering MM. Similar to most large studies from cancer registries, the lack of individual information regarding treatment, clinical features and biomarkers is also a limitation to our present study.

In conclusion, we demonstrate an improvement in the 5-year RS across all age groups in patients with MM diagnosed between 1982 and 2017, including patients aged ≥80 years. This improvement can be explained by the introduction of new treatment, although additional aspects may have contributed, especially for patients aged <65 years for who the improvement started a decade prior to the introduction of HDM-ASCT.

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Author contributions

Øystein O. Langseth and Anders Waage designed the study and wrote the manuscript. Øystein O. Langseth and Tor Å. Myklebust performed the statistical analysis. All authors interpreted the data and critically revised, discussed and approved the final version of the manuscript.

Conflict of interest

The authors have no competing interests.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Patient distribution within calendar period of diagnosis and age group.

Table S2. Excess mortality ratios during the first 5 years of follow-up.

References

1. Kazandjian D. Multiple myeloma epidemiology and survival: a unique malignancy. *Semin Oncol*. 2016;**43**:676–81.
2. Palumbo A, Anderson K. Multiple myeloma. *N Engl J Med*. 2011;**364**:1046–60.
3. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;**15**:e538–48.
4. Cowan AJ, Allen C, Barac A, Basaleem H, Bensenor I, Curado MP, et al. Global burden of multiple myeloma: a systematic analysis for the Global Burden of Disease Study 2016. *JAMA Oncology*. 2018;**4**:1221–7.
5. Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood*. 2008;**111**:2516–20.
6. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N Engl J Med*. 1996;**335**:91–7.
7. Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med*. 2003;**348**:1875–83.
8. Landgren O, Iskander K. Modern multiple myeloma therapy: deep, sustained treatment response and good clinical outcomes. *J Intern Med*. 2017;**281**:365–82.
9. Ravi P, Kumar SK, Cerhan JR, Maurer MJ, Dingli D, Ansell SM, et al. Defining cure in multiple myeloma: a comparative study of outcomes of young individuals with myeloma and curable hematologic malignancies. *Blood Cancer J*. 2018;**8**:26.
10. Brenner H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. *Blood*. 2008;**111**:2521–6.
11. Kristinsson SY, Landgren O, Dickman PW, Derolf AR, Bjorkholm M. Patterns of survival in multiple myeloma: a population-based study of patients diagnosed in Sweden from 1973 to 2003. *J Clin Oncol*. 2007;**25**:1993–9.
12. Schaapveld M, Visser O, Siesling S, Schaar CG, Zweegman S, Vellenga E. Improved survival among younger but not among older patients with Multiple Myeloma in the Netherlands, a population-based study since 1989. *Eur J Cancer*. 2010;**46**:160–9.
13. Turesson I, Bjorkholm M, Blimark CH, Kristinsson S, Velez R, Landgren O. Rapidly changing myeloma epidemiology in the general population: increased incidence, older patients, and longer survival. *Eur J Haematol*. 2018;**101**:237–44.
14. Booth CM, Tannock IF. Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence. *Br J Cancer*. 2014;**110**:551–5.
15. Costa LJ, Hari PN, Kumar SK. Differences between unselected patients and participants in multiple myeloma clinical trials in US: a threat to external validity. *Leuk Lymphoma*. 2016;**57**:2827–32.
16. Cancer Registry of Norway (CRN). Cancer in Norway 2018 - cancer incidence, mortality, survival and prevalence in Norway. Oslo: Cancer Registry of Norway; 2019.

17. Larsen IK, Smastuen M, Johannesen TB, Langmark F, Parkin DM, Bray F, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. *Eur J Cancer*. 2009;**45**:1218–31.
18. Ederer F, Heise H. Instructions to IBM 650 programmers in processing survival computations [methodological note No. 10]. Bethesda, MD: End Results Evaluation Section; 1959.
19. Dickman PW, Coviello E. Estimating and modeling relative survival. *Stata J*. 2015;**15**:186–215.
20. Brenner H, Gefeller O. An alternative approach to monitor cancer patients survival. *Cancer*. 1996;**78**:2004–10.
21. Doll R, Payne P, Waterhouse J. Table 38. In Cancer incidence in five continents: a technical report. International Union against Cancer. Berlin: Springer, 1966, p. 217–9.
22. Lenhoff S, Hjorth M, Holmberg E, Turesson I, Westin J, Nielsen JL, et al. Impact on survival of high-dose therapy with autologous stem cell support in patients younger than 60 years with newly diagnosed multiple myeloma: a population-based study. Nordic Myeloma Study Group. *Blood*. 2000;**95**:7–11.
23. Thorsteinsdottir S, Dickman PW, Landgren O, Blimark C, Hultcrantz M, Turesson I, et al. Dramatically improved survival in multiple myeloma patients in the recent decade: results from a Swedish population-based study. *Haematologica*. 2018;**103**:e412–5.
24. Costa LJ, Brill IK, Omel J, Godby K, Kumar SK, Brown EE. Recent trends in multiple myeloma incidence and survival by age, race, and ethnicity in the United States. *Blood Adv*. 2017;**1**:282–7.
25. Blimark CH, Turesson I, Genell A, Ahlberg L, Bjorkstrand B, Carlson K, et al. Outcome and survival of myeloma patients diagnosed 2008–2015. Real-world data on 4904 patients from the Swedish Myeloma Registry. *Haematologica*. 2018;**103**:506–13.
26. Andres M, Feller A, Arndt V; NICER Working Group. Trends of incidence, mortality, and survival of multiple myeloma in Switzerland between 1994 and 2013. *Cancer Epidemiol*. 2018;**53**:105–10.
27. Kristinsson SY, Anderson WF, Landgren O. Improved long-term survival in multiple myeloma up to the age of 80 years. *Leukemia*. 2014;**28**:1346–8.
28. Pozzi S, Marcheselli L, Bari A, Liardo EV, Marcheselli R, Luminari S, et al. Survival of multiple myeloma patients in the era of novel therapies confirms the improvement in patients younger than 75 years: a population-based analysis. *Br J Haematol*. 2013;**163**:40–6.
29. Pulte D, Jansen L, Castro FA, Emrich K, Katalinic A; GEKID Cancer Survival Working Group. Trends in survival of multiple myeloma patients in Germany and the United States in the first decade of the 21st century. *Br J Haematol*. 2015;**171**:189–96.
30. Pulte D, Gondos A, Brenner H. Improvement in survival of older adults with multiple myeloma: results of an updated period analysis of SEER data. *Oncologist*. 2011;**16**:1600–3.
31. Sun T, Wang S, Sun H, Wen J, An G, Li J. Improved survival in multiple myeloma, with a diminishing racial gap and a widening socioeconomic status gap over three decades. *Leuk Lymphoma*. 2018;**59**:49–58.
32. Piehler AP, Gulbrandsen N, Kierulf P, Urdal P. Quantitation of serum free light chains in combination with protein electrophoresis and clinical information for diagnosing multiple myeloma in a general hospital population. *Clin Chem*. 2008;**54**:1823–30.