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Trends in myeloma incidence, mortality and survival in New Zealand (1985–2016)

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ABSTRACT

Background: Myeloma, one of the most common haematological malignancies worldwide arises in the bone marrow. Incidence rates vary by age and ethnicity but reasons behind these trends are unknown. Treatment of myeloma has changed significantly over recent decades, resulting in longer survival and decreased mortality.

Methods: From data supplied by the Ministry of Health, all new registrations of and deaths from myeloma between 1985 and 2016 were extracted. Trends in age-specific rates were assessed using the method of Armitage. Age-standardised rates were calculated, and trends in age-adjusted rates analysed using the Mantel-Haenszel extension chi-square test. Age-adjusted incidence and mortality rate ratios were calculated. Myeloma-specific survival was visualised using Kaplan-Meier curves and multivariable hazard ratios calculated using Cox regression.

Results: Between 1985 and 2016, 7826 New Zealanders were registered with myeloma. Over this time the age-specific incidence of myeloma increased significantly for men, who had higher rates than women. Myeloma mortality was highest in Maori men. Men had higher mortality rates than women in all time periods. Since 1995–1999, mortality has decreased in women whereas in men it has declined since about 2000–2004. Survival has increased significantly since 1990 but Maori still have a higher risk of death than non-Maori.

Conclusion: The patterns of variation in myeloma incidence, mortality and survival, as well as their trends over time may be used to assist research into the causes and management of myeloma in New Zealand.

1. Introduction

Myeloma is a malignancy characterised by clonal expansion of plasma cells in the bone marrow causing anaemia, hypercalcaemia, lytic bone lesions, renal failure, recurrent infection, and other end-organ damage with significant patient morbidity [1,2]. Although prognosis has improved, myeloma remains incurable and prognosis, particularly in the elderly, is still poor.

Although myeloma is one of the most common haematological malignancies worldwide, it is still a rare form of cancer, contributing about 1.5% of new cancer diagnoses [3–5]. It has been shown that almost all cases of myeloma arise from the precursor monoclonal gammopathy of unknown significance (MGUS) [6,7] but only a minority of MGUS progress to myeloma, with a risk of progression to myeloma (or related disorder) of about 1% per annum [8].

Incidence rates increase with age and are also known to vary by ethnicity, with blacks having higher rates and Asians lower rates [3] than people of European descent; however, recently myeloma incidence has increased in some Asian countries [9].

The aetiology of myeloma remains unknown. Many risk factors playing an important role in other cancers have not been clearly associated with myeloma [10], and most of the strongest myeloma risk factors still show inconsistent results. Some evidence points to obesity as an important risk factor for myeloma [11,12] whereas other studies have shown non-significant increases in risk [13,14]. Exposure to ionizing radiation, organic solvents and employment in agriculture have also shown conflicting results, and an inherited component has been suggested [15]. How much of the incidence trends are attributable to improving case ascertainment in an ageing population rather than increasing obesity, and occupational and environmental exposures is uncertain.

We have used the New Zealand Cancer Registry and mortality databases of the Ministry of Health to investigate and report trends in myeloma incidence since 1985 and trends in mortality since 1988.

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Table 1
Characteristics of patients with a first diagnosis of myeloma reported to the NZCR, and deaths from myeloma.

		Incidence				Mortality		
		Maori (1991–2016); N = 635 n (%)	non-Maori (1991–2016); N = 6304 n (%)	Total (1985–2016); N = 7826 n (%)		Maori (1996–2015); N = 254 n (%)	non-Maori (1996–2015); N = 2865 n (%)	Total (1988–2015); N = 4000 n (%)
Sex	Male	335 (52.8)	3617 (57.4)	4443 (56.8)		139 (54.7)	1593 (55.6)	2200 (55.0)
	Female	300 (47.2)	2687 (42.6)	3383 (43.2)		115 (45.3)	1272 (44.4)	1800 (45.0)
Age	< 50 yrs	91 (14.3)	405 (6.4)	557 (7.1)		22 (8.7)	62 (2.2)	130 (3.3)
	50–59 yrs	158 (24.9)	831 (13.2)	1103 (14.1)		49 (19.3)	253 (8.8)	388 (9.7)
	60–69 yrs	193 (30.4)	1555 (24.7)	2001 (25.6)		76 (29.9)	568 (19.8)	874 (21.9)
	70–79 yrs	141 (22.2)	1945 (30.9)	2388 (30.5)		78 (30.7)	962 (33.6)	1364 (34.1)
	80+ yrs	52 (8.2)	1568 (24.9)	1777 (22.7)		29 (11.4)	1020 (35.6)	1244 (31.1)
Median age in years		64	72	71		67	75	74
Year of diagnosis	1991–1994	51 (7.1)	664 (92.9)	715	Year of death			
	1995–1999	95 (8.4)	1032 (91.6)	1127	1996–2000	56 (8.0)	645 (92.0)	701
	2000–2004	96 (7.8)	1129 (92.2)	1225	2001–2005	45 (6.0)	703 (94.0)	748
	2005–2009	120 (9.0)	1213 (91.0)	1333	2006–2010	59 (7.6)	719 (92.4)	778
	2010–2014	184 (10.6)	1554 (89.4)	1738	2011–2015	94 (10.5)	798 (89.5)	892
	2015–2016	89 (11.1)	712 (88.9)	801				

2. Methods

The New Zealand Cancer Registry (NZCR) was established in 1948 and since July 1994, all cancer diagnoses, except non-melanoma skin cancer, have required notification to the NZCR under the Cancer Registry Act 1993. From data supplied by the Statistical Services of the Ministry of Health, all new diagnoses of multiple myeloma or plasmacytoma (ICD-10 code C90 includes myeloma and plasmacytoma) registered with the NZCR between 1985 and 2016 were extracted. As new cancer diagnoses can only be counted after routine notification to the Cancer Registry, the date of diagnosis recorded at registration and the number of registrations made enables the annual national incidence rate to be calculated. ICD-10 code C90 is hereafter referred to as myeloma for simplicity. Over the time period covered by this study, the NZCR changed from ICD-9 to ICD-10 cancer codes. We found that some retrospective conversions from ICD-9 to ICD-10 for myeloma and plasmacytoma were inaccurate so codes prior to 2000, when ICD-10 was introduced, were checked and corrected as necessary. Diagnoses listed as 'suspicious for' or 'probable' myeloma or plasmacytoma were not included.

Mortality data were obtained from a data download of the mortality collection of the Ministry of Health [16]. This information was available for 1988 to 2015 and included both ICD-9 and ICD-10 codes so no retrospective conversions were required.

For myeloma-specific survival analyses, mortality data were matched to the Cancer Registry data to obtain information about deaths in people with a previous myeloma diagnosis. The main cause of death was categorised as myeloma or other. Survival time was measured in months from the date of diagnosis (after 1 January 1990) to the date of death: patients still alive were censored on 1 December 2015.

Population data by relevant ethnic group, sex, age and year were the mean annual population estimates from Statistics New Zealand [17].

Ethnic classifications used prioritised ethnicity groups as defined by the Ministry of Health whereby each individual is allocated to a single ethnicity on the basis of the following priority: Maori, Pacific peoples, Asian, other groups except New Zealand European, New Zealand European. Information using this categorisation of ethnic group was only available for registrations made since 1991 so the time period in the earliest years (1991 to 1994) was truncated to four years for analyses of incidence by ethnic group. In the mortality collection, reliable coding of ethnicity was only available from 1996 to 2015. Ethnicity was dichotomised into Maori and non-Maori: there were insufficient myeloma diagnoses or deaths in Pacific peoples and other subgroups for formal trend analyses.

Age-specific incidence and mortality rates were calculated for each sex, from age 25 years for incidence and from age 40 years for mortality. Statistical tests for trends in age-specific rates were assessed using the method of Armitage [18]. Age-standardised rates were calculated using the WHO standard population (WHO 2000–2025) and trends in age-adjusted rates, and heterogeneity of the trends, analysed using the Mantel-Haenszel extension chi-square test [19]. To avoid any undue influence of the first time period, changes in age-standardised rates were expressed as an annual percentage change compared to the average rate over each relevant time period. Age-adjusted incidence and mortality rate ratios, and ratios of age-adjusted rates were calculated where appropriate.

Trends in myeloma-specific survival were estimated and displayed using the Kaplan-Meier method, with year of diagnosis categorised into 5-year groups from 1990 to 2009 and 6 years for 2010–2015. Cox proportional hazards were used for the univariable and multivariable calculation of hazard ratios, with year of diagnosis entered as a continuous variable. No data were imputed. Survival analyses were conducted in Stata 13.

As this study used anonymised, routinely collected data, no ethical committee approval was required.

3. Results

Between 1985 and 2016 there were 7826 people registered by the NZCR as having a first diagnosis of multiple myeloma or plasmacytoma. Just over half were male and diagnoses were most commonly made between the ages of 70 and 79 years. Over 90% of diagnoses were in non-Maori: there were 635 diagnoses in Maori over the 32 years. The median age at diagnosis was 64 years for Maori and 72 years for non-Maori (Table 1). The incidence rate of myeloma increased with age: the incidence in 65–99 year olds was about 4-fold greater than in 45–64 year olds and about 30-fold greater than in 35–44 year olds. From 1988–2015, 4000 people died of myeloma, with a slightly higher proportion in men than women (Table 1). The median age at death was 67 years for Maori and 75 years for non-Maori.

The overall age-standardised incidence rate (ASIR) for myeloma in 2015–2016 was 5.29 per 100,000 person-years (Table 2). In 2015–2016, Maori men had the highest ASIR of 8.81 followed by Maori women at 6.81 per 100,000 person-years. Over the same years, non-Maori men and women had ASIRs of 6.57 and 3.64, respectively, giving age-standardised incidence rate ratios for Maori to non-Maori of 1.37

Table 2
Crude and age-standardised (WHO 2000–2025) incidence and mortality rates per 100,000 person-years.

		Crude IR 2015/2016	ASIR 2015/2016	Crude MR 2014/2015	ASMR 2014/2015
Total population		7.47	5.29	4.06	2.31
Maori	Male	8.16	8.81	3.63	5.52
	Female	6.55	6.81	2.07	2.58
non-Maori	Male	9.47	6.57	5.16	2.83
	Female	5.64	3.64	3.45	1.63

IR = incidence rate; ASIR = age-standardised incidence rate; MR = mortality rate; ASMR = age-standardised mortality rate.

(95% CI 1.00–1.85) for men and 1.94 (95% CI 1.40–2.68) for women.

Although fluctuating from year to year because of low numbers of deaths from myeloma, particularly in Maori, age-standardised mortality rates (ASMR) for 2014–2015 were also highest in Maori men and lowest in non-Maori women, 5.52 and 1.63 per 100,000 person-years, respectively.

The incidence trends from 1985 showed significant heterogeneity across age groups so cannot meaningfully be combined. Between 1985 and 2016 the age-specific incidence rates of myeloma in the total population increased significantly for men in several age groups (Fig. 1 and Table 3). In women there was a suggestion of small increases but these did not reach significance. There was statistically significant departure from linearity in the oldest age groups so a linear trend could not be determined.

The age-standardised incidence rates in non-Maori have increased significantly since 1991 in men (31% increase; $p < 0.001$) but not women (6.1% increase; $p = 0.422$) (Fig. 2). In all periods men have had significantly greater incidence rates compared to women, with male to female rate ratios ranging from 1.49 to 1.80, all statistically significantly greater than 1.0. In Maori the age-standardised incidence rates fluctuated more from year to year because of few diagnoses of myeloma (Fig. 2). Maori men had a non-significant linear increase in incidence of 21% and Maori women a non-significant linear increase of 17% over this time. The period-specific adjusted Maori male to female rate ratios also fluctuated widely.

Men had higher mortality rates than women in all time periods with male to female rate ratios for each period ranging from 1.38 to 1.98 and all statistically significantly above 1.0. There was no significant heterogeneity in the age-specific trends of myeloma mortality in the population overall so age-standardised mortality rates could be used as a summary measure of mortality trends. Men showed a non-significant linear decrease in mortality of 11% and women a significant

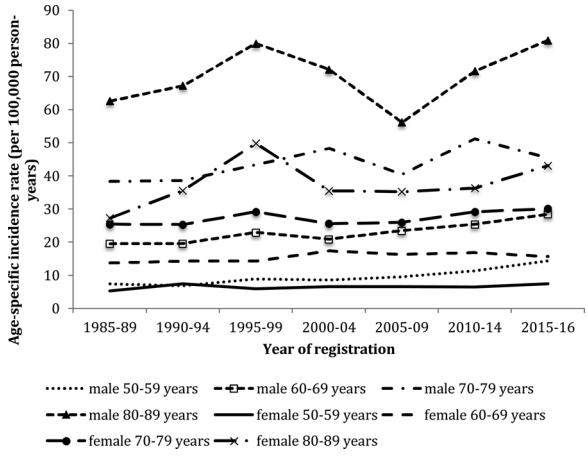

Fig. 1. Trends in age-specific incidence of myeloma for the total population by age group and sex over 5-year periods from 1985 to 2016.

($p = 0.029$) linear decrease of 23% (Fig. 3). However, a linear trend did not fit the data for either men or women very well. Men appeared to have a decrease in mortality rate from about 2000–2004, and women showed the highest mortality in 1995–1999 and decreased thereafter.

When the trends in mortality rates were examined by ethnic group (Fig. 4), there was only a statistically significant linear decrease, of 31%, in non-Maori women. The point estimates of mortality rates in Maori women and non-Maori men also decreased slightly from 1996 to 2000 to 2011–2015 but the decreases were not statistically significant ($p = 0.847$ for Maori women; $p = 0.067$ for non-Maori men).

Myeloma-specific survival probability curves by year of diagnosis are shown in Fig. 5. From 1990–1994 to 2010–2015 survival from myeloma significantly increased ($p < 0.001$). Over this time, the median survival time increased from 23.7 months in 1990–1994, to 56.4 months in 2005–2009. The median survival time has not yet been reached for patients diagnosed in 2010–2015.

In univariable Cox regression (Table 4), only age at diagnosis and year of diagnosis were significant predictors of risk of myeloma death, with the risk increasing with age but decreasing with more recent diagnosis. However, after adjustment for age at diagnosis, sex and year of diagnosis, ethnicity was also a significant predictor of myeloma death: Maori had a 36% higher risk of death from myeloma compared to non-Maori.

4. Discussion

Age-standardised incidence rates of myeloma were higher in men than women, and higher in Maori compared to non-Maori. We found that the incidence rate of myeloma overall has significantly increased in New Zealand since 1985 and this increase was greatest in men. When separated by ethnic group, the significant increase in incidence was restricted to non-Maori men. In contrast, mortality rates in the total population have decreased since about 2000–2004 in men and 1995–1999 in women. This decrease was statistically significant only in non-Maori women. Since 1990, survival from myeloma has increased significantly but, after adjustment for confounders, risk of death was still significantly higher in Maori than non-Maori.

Although myeloma is a rare disease, New Zealand was one of the 20 countries with the highest myeloma incidence and mortality in the world in 2012 [20], and the higher incidence and mortality in men, compared to women, is similar in many other countries [21]. Similar to what has occurred in Great Britain [22], but unlike some other countries [22–24], New Zealand's incidence rates have significantly increased since 1985.

Treatment of myeloma has changed markedly over the time covered in this study. In the late 1990s some new therapies were introduced for myeloma: autologous stem cell transplantation was the first major breakthrough followed more recently by immunomodulatory drugs and proteasome inhibitors. These have resulted in better prognosis and improved survival, particularly in younger patients [2,24]. We have also shown improving survival since 1990, and some decrease in mortality since about 2000–2004. Mortality rates have also decreased in the USA [2,15] and some other countries [24] over a similar timeframe.

The aetiology of myeloma is poorly understood and the risk factors for myeloma remain elusive so the reasons for these trends are yet to be explained. Increasing myeloma incidence may be due to changing histological criteria, an increase in population disease prevalence due to increasing exposure to risk factors, an improvement in case ascertainment and diagnosis, an enhancement in cancer registration practice (see below), or any combination of these factors. In New Zealand there is no screening programme for myeloma. Myeloma is mainly diagnosed because of symptoms but it can also be detected incidentally. So although better case ascertainment may have contributed to the incidence trend, the proportional contributions of all factors are unknown.

An increase in survival may predominantly be due to earlier

Table 3
Trends in age-specific incidence of myeloma in the total population from 1985 to 2016 by age group and sex.

Age group	50–59 years		60–69 years		70–79 years		80+ years	
Sex	male	female	male	female	male	female	male	female
Absolute increase in incidence per 100,000 person-years	0.202	0.032	0.266	0.102	0.348	0.122	0.178	0.138
p-value for linear trend[a]	p < 0.001	p = 0.345	p < 0.001	p = 0.075	p = 0.007	p = 0.182	p = 0.485	p = 0.330
p-value for departure from linearity[a]	p = 0.347	p = 0.673	p = 0.743	p = 0.770	p = 0.119	p = 0.681	p = 0.029	p < 0.001

[a] Mantel-Haenszel test with one degree of freedom.

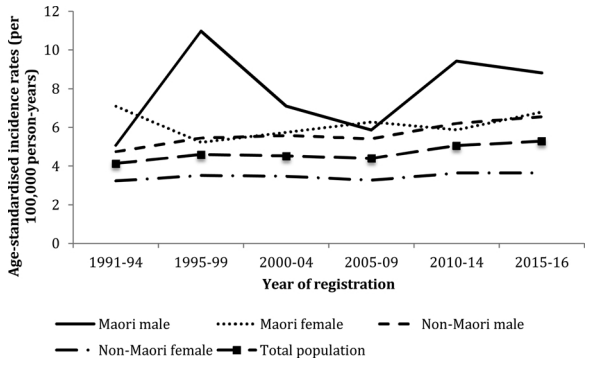

Fig. 2. Trends in age-standardised (WHO 2000–2025) incidence rates of myeloma by ethnic group and sex.1991–2016.

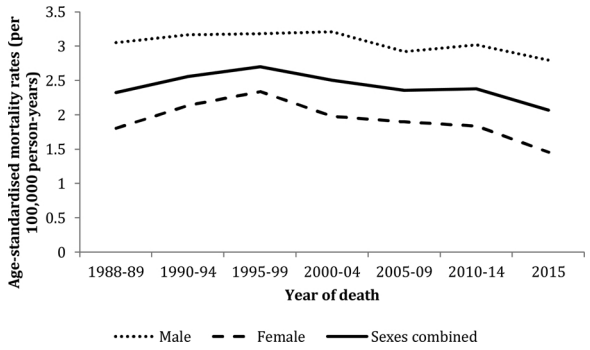

Fig. 3. Trends in age-standardised (WHO 2000–2025) mortality rates of myeloma for the total population overall and by sex, 1988–2015.

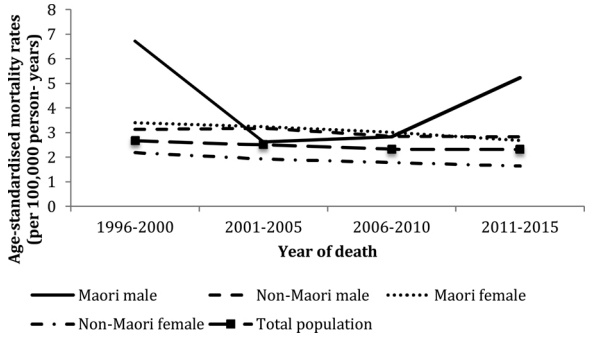

Fig. 4. Trends in age-standardised (WHO 2000–2025) mortality rates of myeloma for the total population, and by ethnic group and sex, 1996 to 2015.

diagnosis of disease, better treatment (which may prolong life without cure), more losses to follow-up, inaccurate recording of cause of death, improvement in comorbid conditions or any combination of these. Improving survival with little mortality benefit suggests that although patients may know they have the disease for longer, they are not cured.

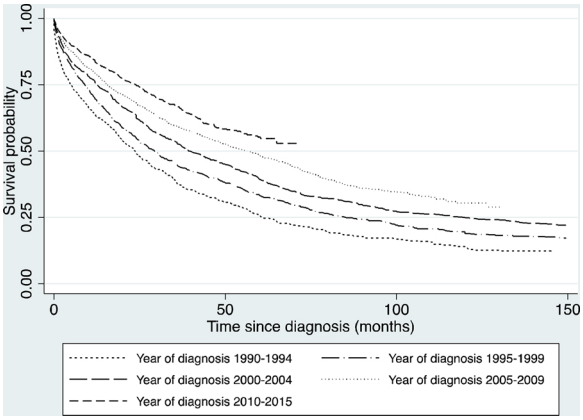

Fig. 5. Observed survival probabilities by time since diagnosis (in months) and year of diagnosis (1990–2015).

We found higher incidence rates in Maori compared to non-Maori (34% higher in men and 87% higher in women in 2015–2016). The incidence rates for Maori males and females (8.81 and 6.81 per 100,000 person-years, respectively) were comparable to but lower than those reported for African Americans (9.5 and 7.2 for men and women, respectively, in 2008–2012) [25]. Multiple myeloma has been shown to be more than twice as common in African Americans than European Americans [26], and in Blacks compared to Whites in England [1]. The reasons for these ethnic differences remain unclear but some work has suggested there are underlying biological differences between myeloma in African Americans and European Americans [27]. Whether these explain ethnic differences in New Zealand is unknown.

This study has several methodological strengths. New Zealand has a national population-based Cancer Registry and since the introduction of the Cancer Registry Act in July 1994, notification of cancer in New Zealand has been considered complete, particularly for cancers that require a specialist health service for diagnosis and management. Death-certificate-only and 'autopsy with histology reports' accounted for about 5.6% of myeloma registrations pre-1996 and about 3.5% for diagnoses made in 1996 or later, indicating that the vast majority of diagnoses are notified and that the improvement in cancer registration after 1994 is unlikely to explain the incidence trends. In addition, information about ethnic group is only missing for 2.5% of cancer notifications made since 1985. Although some errors in myeloma and plasmacytoma classification prior to 2000 were noted, all these diagnoses were checked and corrected where necessary. Any residual errors in classification are likely to be very small in number. There are some limitations in working with routinely collected data in that accuracy of data may be difficult to confirm. However, the authors have worked with these datasets over 30 years and have established routines for data checking.

There is no evidence of variation in treatment response between Blacks and Whites with myeloma in clinical trials [28,29] but there is evidence of differential access to effective treatment by ethnicity in the

Table 4
Crude and adjusted Cox regression model for observed myeloma survival.

Variables		Crude HR[a]	p-value	Adjusted[b] HR	p-value
Age at diagnosis	continuous	1.04	< 0.001	1.04	< 0.001
Sex	Male	1		1	
	Female	1.05	0.129	0.95	0.120
Ethnicity	non-Maori	1		1	
	Maori	0.97	0.866	1.36	< 0.001
Year of diagnosis	continuous	0.96	< 0.001	0.96	< 0.001

[a] HR = hazard ratio.
[b] Adjusted for all other factors in the table.

USA [30]. Future work is needed to examine detailed patterns of survival in New Zealand and identify any ethnic disparities in outcome, particularly in the light of changing treatment and management options. Further exploration of potential variation in the biology of myeloma among ethnic and other subgroups may also provide valuable information about the causes of this disease.

5. Conclusion

Myeloma remains an incurable disease and prognosis in some subgroups is still poor. In New Zealand, myeloma incidence is higher in men than women, and higher in Maori than non-Maori. Myeloma incidence has increased significantly since 1985 in men who have higher myeloma mortality than women. The highest mortality rate occurred in Maori men and the lowest in non-Maori women. Mortality rates appear to have been decreasing since the late 1990s and survival has improved significantly since 1990. Exploration of these differences and trends over time may provide further clues to the aetiology of myeloma and assist with improving myeloma management.

Declaration of interest

This project was funded by the Richdale Charitable Trust. The funder had no role in the design, analysis, interpretation, write-up or publication of this study.

Author statement

MJS designed the study, cleaned and checked the data, interpreted the results, drafted the article and approved the final version.

BC wrote the computer programmes and analysed the data, interpreted the results, revised the article and approved the final version.

IM conceived the study, helped with data interpretation, revised the article for intellectual content and approved the final version.

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