Increasing Trends of Multiple Myeloma Mortality in England and Wales; 1950–79: Are the Changes Real?[1,2,3]

Ramon Velez, *M.D.*, *M.Sc.*,[4,5,6] Valerie Beral, *M.R.C.P.*,[7] *and* Jack Cuzick, *Ph.D.*[8,9]

ABSTRACT—National statistics for England and Wales for the period of 1950–79 were examined to study the secular trends in multiple myeloma mortality and to evaluate the extent to which these changes may be due to biases associated with improvements in medical care. Age-adjusted mortality has increased more than fivefold during this 30-year period. Contrary to the impression obtained from clinical series, a slightly greater increase in age-adjusted mortality has occurred in males. Examination of age- and sex-specific mortality trends showed that the greatest apparent increase in myeloma mortality occurred in individuals over 70 years of age. The data are consistent with either a cohort effect, indicating a true increase in mortality. or an age-dependent diagnostic effect in which a greater percentage of deaths among the elderly are now being certified as myeloma. Analyses of mortality data by social class and region point toward improved case ascertainment being responsible for at least part of the apparent increase in reported mortality. The increase in reported mortality in the younger age groups may reflect a true increase in the incidence of this disease. This increase, however, would account for only a proportion of the total Increase. even when extrapolated to the older age groups.—JNCI 1982; 69:387–392.

The apparent increase in incidence and mortality from multiple myeloma has become the subject of increasing interest. In the United States the reported increase in incidence of myeloma has been proportionally greater than that for any other site of cancer (*1–3*). However, a recent study of the population of Olmsted County, Minnesota, which has been under careful medical surveillance by the Mayo Clinic for several decades, has failed to show any increase in the iricidence of the disease ***(4)***. The purpose of this study was to determine whether a similar trend in myeloma mortality has occurred in England and Wales and to assess the extent to which these changes may be due to change in diagnostic factors. Our analyses are based largely on routinely collected, published, and unpublished vital statistics for England and Wales. Comparisons have also been made with data from a cancer registry in Texas, where secular trends are tabulated for 3 ethnic groups ***(5)***.

MATERIALS AND METHODS

Mortality data were obtained from the Registrar General's Statistical Review for England and Wales (6) for the period of 1950–73 and from the OPCS Mortality Statistics (7) for the period of 1974–79. Unpublished mortality data by region for England and Wales were also obtained from OPCS.

Multiple myeloma has been separately classified under the ICD rubric 203 since the sixth revision of the ICD in 1948. There have been no changes in this classification in subsequent revisions.

The denominators for rate calculations for England and Wales are based on census year populations and intercensal estimates published by the Registrar General and OPCS. Age- and sex-adjusted myeloma mortality rates for England and Wales were calculated by the direct method with the use of the World Health Organization's European population standard. The data on standardized mortality ratios by social class were obtained from the Registrar General's decennial supplements (*8–10*). The regression lines of logarithm of incidence versus calendar year fitted to the Texas Cancer Registry data have been determined by the least-squares method. The analyses of age, cohort, and calendar year effects by a log-linear model was done by the same method as that used by Holman et al. (*11*).

RESULTS

Review of vital statistics.—In 1979 there were 1,602 deaths attributed to multiple myeloma (ICD 203) in England and Wales (7). This statistic represents approximately 1% of all cancer deaths and 18% of deaths from cancers of the lymphatic and hematopoietic system. Although these numbers by themselves are not particularly striking, the proportional increase in mortality from myeloma since 1950 is noteworthy. Since the case fatality rate for multiple myeloma is high, changes in mortality should reflect changes in incidence rates over time.

ABBREVIATIONS USED: df=degree(s) of freedom; ICD=International Classification of Diseases; OPCS=Office of Population Censuses and Surveys (England); SMR=standardized mortality ratios(s).

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[3] This work was initiated by Dr. Velez while in the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine, and in the Department of Community Medicine, St. Thomas' Hospital Medical School, London, England.

[4] Department of Medicine, Duke University Medical Center, Durham, N.C. 27710.

[5] *Address reprint requests to* Dr. Velez, HSR & D and Clinical Epidemiology Unit, Durham Veterans Administration Medical Center, 508 Fulton St., Durham, N.C. 27705.

[6] Recipient of a Milbank Memorial Fund fellowship in clinical epidemiology.

[7] Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine, Keppel St., London WC1E 7HT.

[8] Cancer Epidemiology and Clinical Trials Unit, University of Oxford, 9 Keble Rd., Oxford, OX1 3QG, England.

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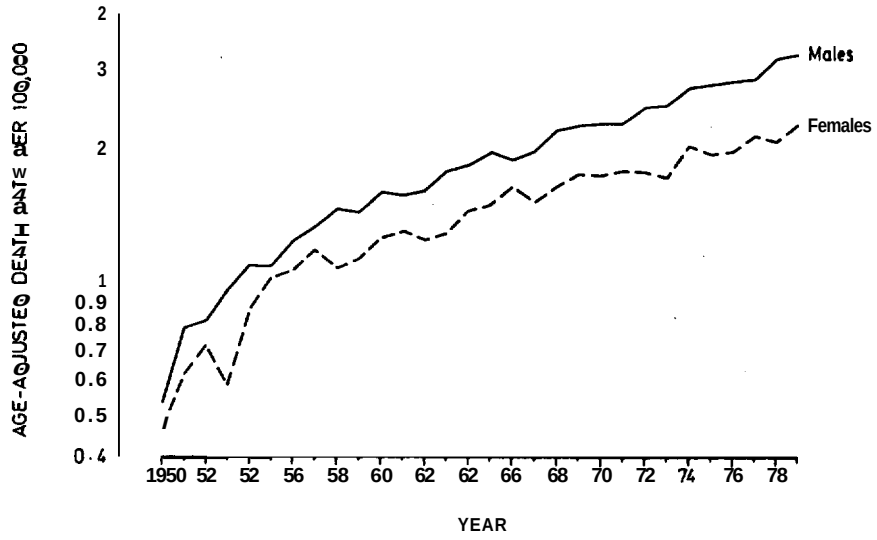
TEXT-FIGURE I.—Death rates for multiple myeloma in England and Wales, 1950–79. Age-adjusted to the European standard population.



The age-adjusted mortality trends for both sexes from 1950 to 1979 are shown in text-figure 1. The proportionate increase during this 30-year period was 515% for males and 398% for females.

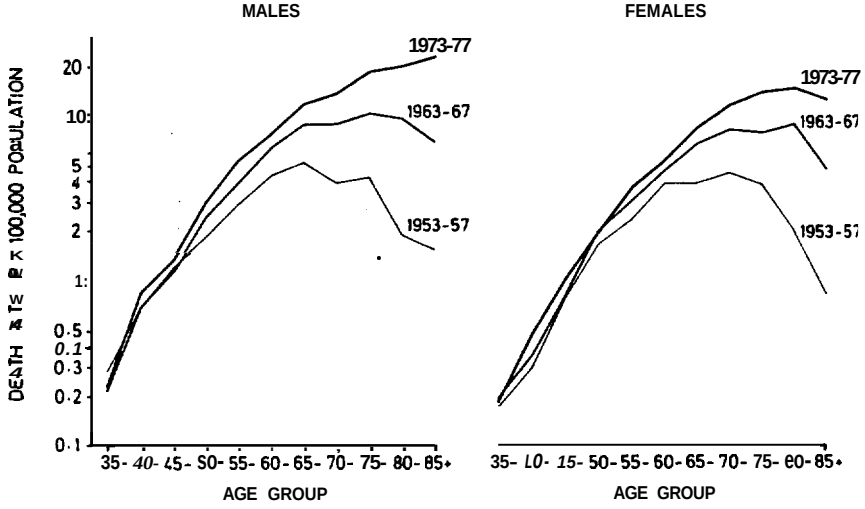
The sex ratio of age-adjusted mortality rates shows an excess of males which, remarkably, has increased in recent times. In 1950 the male:female ratio was 1.15, whereas it was 1.26 in 1960, 1.31 in 1970, and 1.42 in 1979.

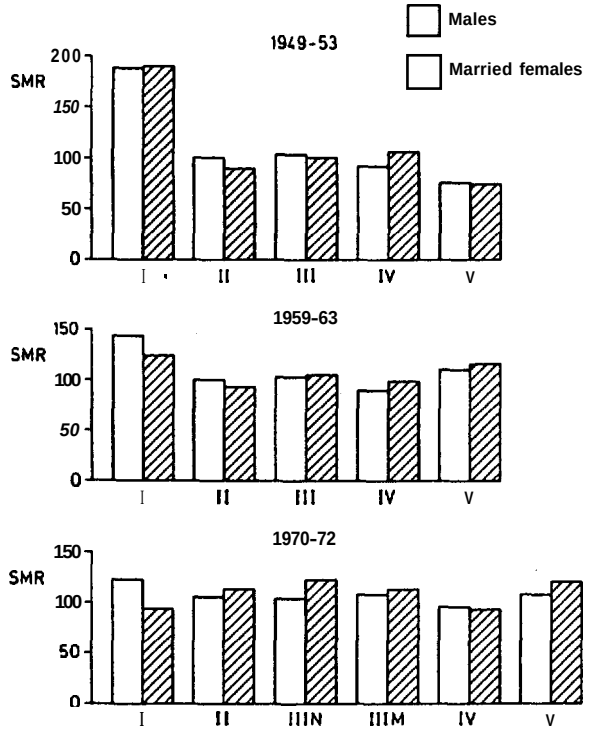
Text-figure 2 illustrates the changes in age- and sex-specific multiple myeloma mortality rates for the 5-year periods 1953–57, 1963–67, and 1973–77. Although some increase has occurred in all age groups, most of the increase in myeloma mortality has been concentrated in the older age groups. Consequently, the shape of the age–mortality curve has changed over time: In 1953–57 peak mortality was at ages 65–69 in males and 70–74 in females, but in 1973–77 the mortality rates continued to increase with advancing age for both sexes.

Social class.—Text-figure 3 summarizes SMR by social class for occupied males and females for the periods of 1949–53, 1959–63, and 1970–72. During 1949–53 a high SMR was found among social class I males and females, while other groups were similar and no clear trend was seen across social classes II through V. The same pattern was apparent during 1959–63, but the excess SMR was smaller in social class I. By the last 5-year period excess SMR had almost disappeared, and the rates among different social classes became similar.

It is useful to compare these observations with the change for leukemia which occurred at an earlier time. Table 1 compares mortalities for all types of leukemias and for all cancers for occupied males by social class for the periods of 1930–32, 1949–53, 1959–63, and 1970–72. The general pattern for leukemias is similar to that for myeloma, although a clear trend is not seen for high SMR among the higher social classes (I and II) and low SMR in the lower social classes (IV and V). These differences were most marked for the period 1930–32 and again have diminished over time. In contrast, the pattern for mortality from all cancer by social class shows a gradient in the opposite direction, with excess mortality among classes IV and V and lesser mortality among the other social classes. For all cancers, the trend with social class has become more marked in recent times—a reflection, for the most part, of the greater reduction in

3 decades in England and Wales.





TEXT-FIGURE 3.—Standardized mortality ratios for multiple myeloma by social class in England and Wales.

smoking which has led to less lung cancer among social classes I and 11.

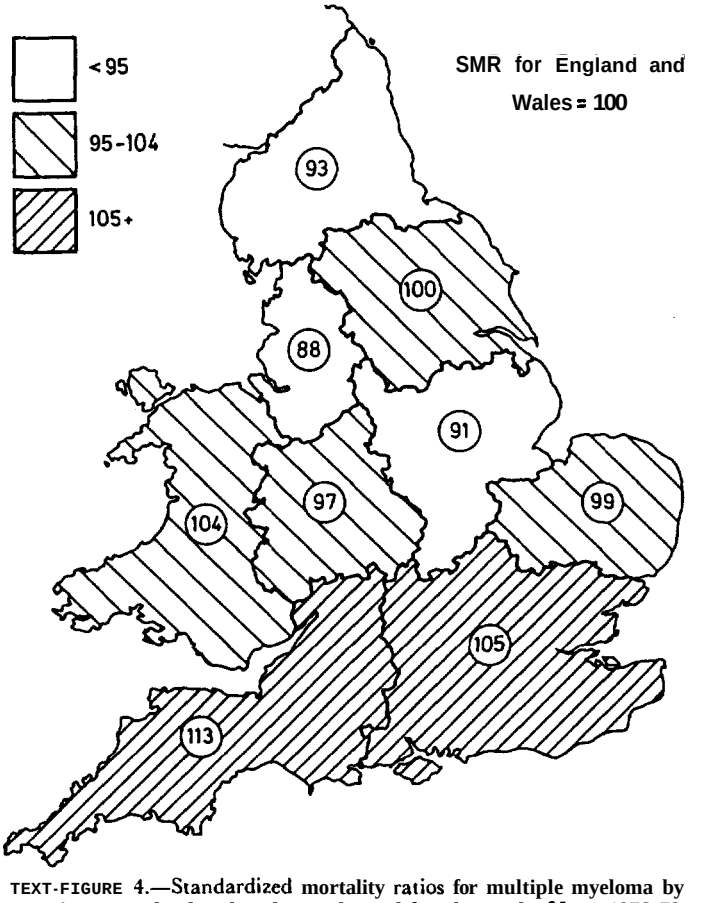
Geographic variations.—Text-figure **4** shows the SMR for multiple myeloma for the standard regions of England and **Wales** (1976–78). There was some variation in SMR by region with the highest mortality in the Southwest (SMR=113) and Southeast (SMR—105) and the lowest mortality in the Northwest (SMR=88) and East Midlands (SMR=91).

Cohort analysis.—Text-figure 5 portrays mortality by birth cohort. This is plotted on **a** log–log scale ***so*** that a power law age–incidence curve appears as a straight line. This simple type of age–incidence curve is suggested by general principles *(12)* and provides **a** good fit for cancer at a number of sites *(13).* The fit to the present data is also quite good. The shifting of the curves to the left with more recent cohorts is what one would expect if successive cohorts were experiencing a greater mortality from this disease. The increases are largest between the earlier cohorts but continue until the 1905 birth cohort when the curves appear to have almost stabilized. **A** more mathematical analysis *(If)* can be based on a model that includes terms to account for both cohort effects and calendar year effects (that could arise from an age-independent change in diagnostic or certification practices). Such a model attributes the bulk of the increase to a cohort effect. **A** model that corrects for age and birth cohort fits the data extremely well (χ^2 for error —42.07 on 30 df), and no further improvement is obtained if calender year terms are included (χ^2 for error —38.65 on 27 df). **A** model that includes only age and calendar year terms does not fit so well (χ^2 for error =561.8 on 40 df), and a much better fit is obtained when the cohort terms are included (χ^2 for error =38.65 on 27 df). However, the calendar year variables do not accommodate an age-dependent improvement in diagnosis and certification (which could masquerade **as** a cohort effect), and this likely possibility must be considered in the assessment of the validity of this model. This model assumes that the logarithm of the expected mortality rates in each 5-year calendar period and 5-year age group is a linear combination of indicator func-

TABLE *I.—Standardized mortality ratios by social class: occupied males in England and Wales during four 5-year periods*[a]

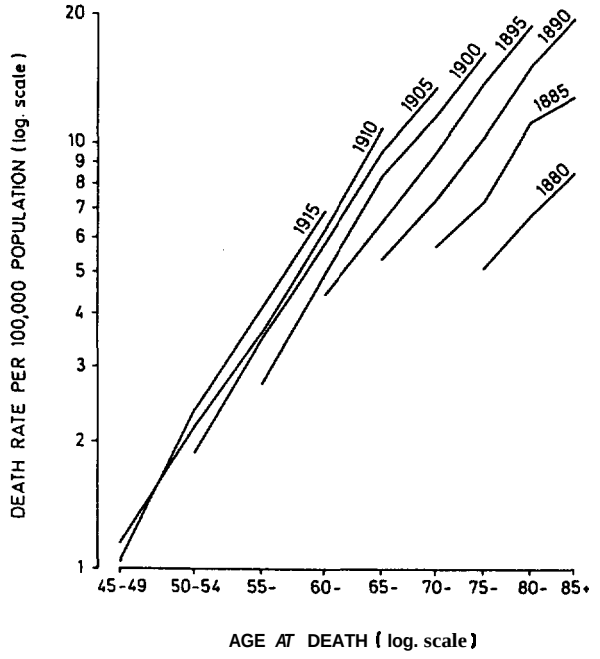
Period, yr	Social class[b]					
	I	II	IIIN	IIIM	IV	V
Leukemias						
1930-32	153	125	96		94	85
1949-53	107	98	104		93	89
1959-63	106	100	103		97	108
1970-72	113	100	107	101	104	95
All cancers						
1930-32	83	92	99		102	115
1949-53	94	86	104		95	113
1959-63	73	80	104		102	139
1970-72	75	80	92	113	116	131

[a] Source: Occupational Mortality Tables (*8, 9*).
[b] N = nonmanual occupations; M = manual occupations.

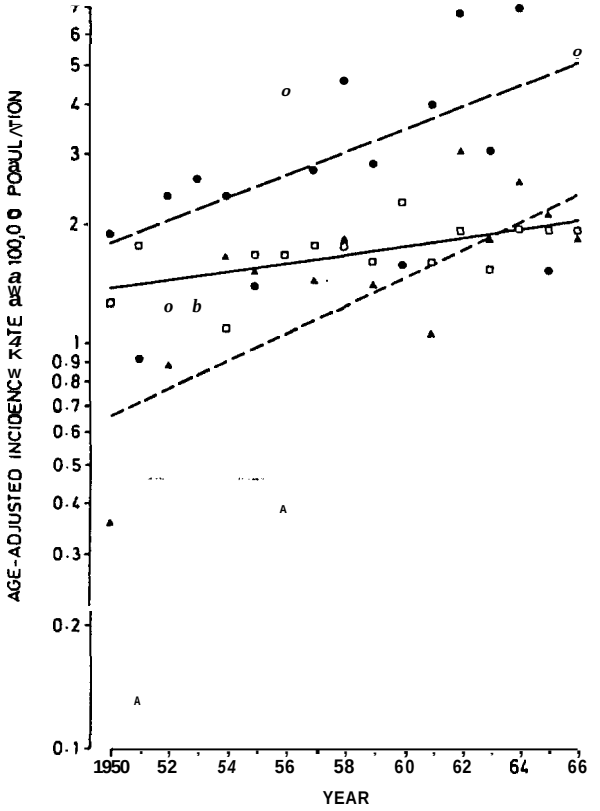


TEXT-FIGURE 4.—Standardized mortality ratios for multiple myeloma by region io England and Wales. Males and females aged ≥25 yr, 1976-78.

tions for 5-year age groups, 5-year birth cohorts, and 5-year calendar periods, and that the variations from the expected rates are independent Poisson random variables. A more detailed discussion of this model based on data from a number of countries will appear elsewhere.



TEXT-FIGURE 5.—Mortality from multiple myeloma in England and Wales in different cohorts born in 5-yr periods between 1880 and 1915.



TEXT-FIGURE 6.—Age-adjusted multiple myeloma incidence rates by ethnic group in Texas, 1950–1966. 1960 U.S. population used as standard. □——□, whites; ●---●, non-whites; ▲-----▲, Spanish surnamed.

Texas cancer *registry.*—Shown in text-figure 6 are the age-adjusted multiple myeloma incidence rates for white, Spanish, and nonwhite populations living in a defined geographic area in Texas. The slopes of the rise of the regression lines of logarithm of incidence versus calendar year are steeper for Spanish and nonwhite populations compared to the white population.

DISCUSSION

The clinical presentation of multiple myeloma varies widely, with initial symptoms ranging from vague migratory bone pain, back pain, pathologic fractures, pneumonia, neurologic symptoms, and/or anemia to acute renal failure *(14, 15).* Diagnosis requires the aid of various tests, which have changed in their type and availability in the last 50 years. The first diagnostic test was the examination of urine for Bence Jones protein *(16).* Unfortunately, this test is positive in less than 50% of proven cases of this disease *(17, 18).* Thus other ancillary tests, such as bone marrow examination, skeletal X-rays, serum, and urine electrophoresis must be employed when this diagnosis is suspected. Before these procedures became widely available, the diagnosis of myeloma was often confirmed only at autopsy *(19).*

The gradual introduction of these diagnostic tests has spanned nearly 4 decades. Although bone marrow examinations were first performed in 1929 *(20),* it was not until 1938 that the value of this procedure was recognized in the diagnosis of myeloma *(21).* It remained an infrequently used procedure, however, until the late 1940's, when a greater understanding of the cell types in normal marrow made the identification of abnormalities easier *(22).* Needle biopsies, that could be taken easily under local anesthetic, as opposed to the more diflicult and painful trephine cuts used previously, became available in the 1950's and early 1960's and also led to the wider use of bone marrow investigation *(23, 24).* Similarly, serum electrophoresis was first described as being of diagnostic value in myeloma in 1938 *(25).* However, the method was laborious and remained a research tool until the 1950's *(26–28),* when, with the development of paper and cellulose acetate electrophoresis, this procedure became more widely available. We inquired at 10 London teaching hospitals to establish the time when serum electrophoresis became available. The responses gave the average year when this occurred as 1956, with a range from 1950 to 1962.

A diagnosis of multiple myeloma is highly dependent an the use of medical facilities and laboratory tests. The effects of these factors must be taken into consideration when one interprets mortality statistics *(29).* The sharpest increase in reported mortality rates occurred between 1950 and 1960 (text-fig. 1). This increase coincides with the period of the most rapid advances in the laboratory diagnosis of this disease.

The age-adjusted male-to-female mortality ratio reveals a slight excess of males in the 1950's that has increased in the next 2 decades. This finding is in striking contrast to the impression gained from clinical series in which a larger male

preponderance was seen in the early part of this century (*19*) and is less apparent now. In 1961 Martin ***(30)*** reported the male-to-female ratio of cases of myeloma seen in London teaching hospitals as 3:2. More recently, Waldenstrom ***(31)*** has pointed out that in his recent experience the sex ratio has shifted toward a preponderance of females. The early large male excess is possibly partly an artifact due to a bias that used to exist (particularly before the introduction of the National Health Service) in favor of hospital referral of males rather than females for the investigation of obscure diseases (*32*), and its disappearance may be partly due to changes in referral patterns and in the sex distribution of the aged population. A greater percentage of females are now alive in the age groups in which myeloma incidence is highest, and the early case series were based on numbers and not rates. For example, in 1979 64% of the population of England and Wales above age 70 were female, whereas in 1950 only 59% were female. This bias can be removed by studying age-adjusted rates instead of cases for the two sexes (text-fig. 1), where the size of the normal population is accounted for.

Kyle et al. ***(33)*** examined the death certification of 31 patients in whom myeloma had been diagnosed at the Mayo Clinic in Olmsted County, Minnesota, during the period of 1945–64. He found that myeloma had been recorded as the underlying cause of death in 23 cases (74%). By contrast, in studying the recorded cause of deaths in a sample of incident cases from the Third National Cancer Survey, 1970–71, Percy et al. ***(34)*** found that 96% of the 699 incident cases of myeloma were certified as dying of this disease. This suggests that an increased awareness by clinicians of multiple myeloma, associated with changes in diagnostic habit and death certification, may contribute to the apparent increase in mortality trends.

MacMahon ***(35)*** has previously commented on the greater reported mortality from myeloma in social class I in the period 1949–53. A trend in the same direction has also been seen for the leukemias. The proportionate increase in mortality from leukemias earlier this century has been exceeded only by greater increases in lung cancer and coronary heart disease mortality ***(36)***. Although radiation exposure has been implicated as a causative factor in both leukemia (*37*) and myeloma (*38*), the increase in leukemia has been attributed primarily, although not exclusively (*37*), to improvements in diagnosis and better access to medical care (*36*), which may well be true also for myeloma.

Further support for the hypothesis that underascertainment is related to social class and access to medical care is provided by an examination of the data from a cancer registry in Texas (*5*), where cancer incidence in white, Spanish, and non-white populations has been analyzed. Both the Spanish and the non-white group represent socioeconomically disadvantaged populations. Over time both of these groups have benefited from greater access to medical care, and the increase in incidence of myeloma has been more pronounced in these 2 ethnic groups (text-fig. 6).

Studies of leukemia incidence have indicated that there is a consistent selective underascertainment among the elderly (*39–41*). Meadors ***(40)*** has suggested that this is the result of attributing leukemia deaths in the elderly to diseases of old age and infections. If correct diagnosis is a factor in myeloma mortality rates, as laboratory investigations increase, the greatest increases in registered mortality would be among the elderly where underdiagnosis is most prevalent. It is apparent from text-figure 2 that while myeloma mortality rates have increased in all age groups, the change is far greater in the older age groups.

Regional mortality data for England and Wales also support the view that access to medical care may be important in the diagnosis of myeloma. Mortality from all causes and all cancers is highest in regions in the North and lowest in the Southeast (*42*), but the reverse is true for myeloma (text-fig. 4). This observation is consonant with the disproportionately greater availability of medical facilities in the South ***(43)***.

In conclusion, it appears that technical improvements in the diagnosis of myeloma, as well as greater access to medical care especially among the elderly, have contributed to the increased recognition, and hence to the reported mortality, from this disease. Similar arguments were put forward to explain the reported increase in lung cancer earlier this century ***(44, 45)***, yet the increase in lung cancer was real. In the case of lung cancer, the increases were first noted in males, suggesting a specific etiologic agent much of which was later identified as cigarette smoking ***(46)***. For myeloma, the increase occurred in both sexes and has been only slightly greater in males, suggesting that any major new putative factor must have been introduced across broad sections of the population. The extremely good fit of the data to a model with only cohort effects also suggested that the increase may be at least partly real. Although much of the apparent increase in incidence of myeloma may be due to changes in diagnostic practice and referral, myeloma is certainly not as rare as it once was thought to be. Our knowledge of the etiology of this disease is meager and requires further investigation.

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