

COMPARISON OF TRENDS IN THE INCIDENCE OF MULTIPLE MYELOMA IN MALMÖ, SWEDEN, AND OTHER COUNTRIES, 1950-1979

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Abstract Dramatic increases in mortality from multiple myeloma have been reported in the United States and the United Kingdom over the past three decades. To assess what fraction of this increase, if any, might be attributable to a change in the incidence of this disease, we examined the incidence of multiple myeloma during 1950 to 1979 in Malmö, Sweden, a city chosen because of its medical community's longstanding interest in this disease. The average annual incidence rates per 100,000 population were 4.9 for males and 3.7 for females (adjusted to the European age-standardized population).

These rates are among the highest in the world. Unlike secular trends for myeloma in the United States and the United Kingdom, where large increases in mortality rates have been reported, the rates in Malmö have increased only slightly, and the increase was restricted to males, suggesting the possibility of environmental causes. We suggest that the rates in Malmö may represent the asymptote of myeloma's incidence that will be approached in other white populations as case ascertainment among them becomes complete. (*N Engl J Med* 1984; 310:421-4.)

MULTIPLE myeloma, like other fatal diseases, is characterized by incidence and mortality rates that are similar. A dramatic rise in multiple myeloma's incidence and mortality over the past three decades has been reported in studies from the United States,^{1,2} England and Wales,³ and most other countries.⁴ Fraumeni compared data from the United States Second and Third Cancer Surveys (1947 to 1948 and 1969 to 1971) and found the percentage increase in the age-adjusted incidence of multiple myeloma to be greater than that of any other cancer, including lung cancer.⁵ This apparent change in the incidence of multiple myeloma has led some investigators to hypothesize a relation between this disease and increased exposures to environmental or occupational carcinogens.^{6,7}

A recent study conducted in Olmsted County, Minnesota, identified incidence rates for multiple myeloma in that community that were higher than those expected from national mortality rates. However, under further analysis, no increase in incidence was detected during the period 1945 through 1977.⁸ This higher but stable incidence was attributed to more complete case ascertainment.

The obvious etiologic importance of an increase in multiple myeloma prompted us to undertake an investigation of its incidence in Malmö, Sweden, where the medical community has had a longstanding interest in this disease. Our objectives were to describe time trends for multiple myeloma's incidence in Malmö from 1950 to 1979, to compare these findings with the data reported for Olmsted County, and to compare age-specific incidence rates over time in Malmö with national mortality rates in the United States and in England and Wales. The results of the study indicate

that national mortality rates for multiple myeloma are not an accurate index of trends in true incidence rates. Although mortality rates have increased dramatically, much of the increase can be attributed to improved case ascertainment. However, in a stable study population under comprehensive medical surveillance, an increase in the incidence of multiple myeloma in males suggests increased or newly introduced environmental hazards as an etiologic factor.

This study illustrates the difficulty of interpreting changes in the incidence and mortality of cancer over time.^{9,10} Changing rates may be real — e.g., cases are due to environmental exposures that affect underlying incidence of the disease — or they may be artifacts — cases are due to improved diagnostic techniques or case-ascertainment methods or both. Medical surveillance in Malmö provides nearly ideal conditions for accurately determining the rate of multiple myeloma.

METHODS

Population and Initial Case Identification

Malmö is the third largest city in Sweden. The population increased from 192,668 in 1950 to 236,716 in 1979. The community's medical needs are served by three hospitals: Malmö General Hospital (the main hospital and the only one with an emergency service), Vaernhems Hospital for chronic diseases, and the Malmö Eastern Hospital for mental disorders. Records were obtained for all patients with a clinical diagnosis of multiple myeloma, plasmacytoma, or extramedullary plasmacytoma from medical-records discharge files, pathology files, and plasma protein-electrophoresis reports at these three hospitals from 1950 through 1979. For the period 1969 through 1979, a computerized diagnostic-registration system provided another data source. Autopsy records were checked for additional cases. The frequency of autopsies was over 95 per cent for hospitalized patients and 60 per cent for all persons dying in Malmö since 1960, ensuring accurate estimates of cases not diagnosed during life.

Inclusion and Exclusion Criteria

Minimal criteria for a diagnosis of myeloma were a monoclonal immunoglobulin in serum or monoclonal light chains in urine (or both) plus at least one of the following: 10 per cent or more plasma cells and atypical plasma-cell morphology in the bone marrow; osteolytic lesions found on x-ray examination that could be explained only by increased plasma cells; or macroscopic osteolytic lesions found at an autopsy in which microscopy revealed plasma-cell pro-

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liferation. A diagnosis was further confirmed by a clinical course compatible with myeloma. Cases without an observed M component in serum or urine were accepted if there was histologic evidence of a solitary plasmacytoma or if the diagnosis was made first at autopsy and no serum or urinary protein electrophoresis was performed.

Patients with an M component whose conditions did not fulfill previously stated criteria were excluded, as were patients not living in Malmö at the time of diagnosis.

Statistical Procedures

Sex, year, and age at diagnosis were recorded for each case. Census data for Malmö's population were used to calculate age-specific and sex-specific incidence rates in 10-year age groups. For comparison of rates over time and with other sources, the direct method of age standardization by five-year age groups was used.¹¹ The total U.S. population for 1950¹² and, alternatively, the European standard population were the standard populations.¹³ Analyses for trends were performed by means of the Mantel-Haenszel extension chi-square test.¹⁴

RESULTS

In Malmö, multiple myeloma was diagnosed in 329 residents from January 1, 1950, to December 31, 1979. Of these, 163 were male and 166 were female. More than 90 per cent of the patients were seen by one of us (I.T., O.Z., or J.G.W.) at the Department of Internal Medicine, Malmö General Hospital.

The average, age-adjusted incidence rates for multiple myeloma in Malmö during three decades are shown in Table 1. There is a small and statistically significant trend toward increasing rates among males. No increase in the age-adjusted rates is evident among females. Figure 1 indicates that the increases in the incidence rates of myeloma among males were not confined to older age groups. These data may reflect a small but genuine increase in the incidence of the disease.

The average, age-specific incidence rates per 100,000 population in Malmö for 1970 through 1979 are shown in Table 2. These rates are comparable to rates reported from Olmsted County.⁸

Sex-specific and age-specific incidence rates for the periods 1950 through 1959, 1960 through 1969, and 1970 through 1979 are plotted on a log-log scale in Figure 1. It is noteworthy that the incidence rates continue to increase with age, even in the older age

Table 1. Average Annual Age-Adjusted Incidence Rates of Multiple Myeloma per 100,000 Population (Malmö, Sweden, 1950 to 1979). According to Sex

PERIOD	MALES		FEMALES		TOTAL	
	CASES	RATE	CASES	RATE	CASES	RATE
1950-59	32	2.9 (3.9)	38	2.6 (3.5)	70	1.7 (3.7)
1960-69	50	3.5 (4.6)	69	3.5 (4.5)	119	3.4 (4.6)
1970-79	81	4.6 (6.2)	59	2.2 (3.0)	140	3.2 (4.3)
Significance of trend	5.52, *P = 0.02 ‡		1.10, †NS ‡		0.81, †NS ‡	

*Census data for the 1955, 1965, and 1975 populations were used for calculation.

†Age-adjusted to 1950 U.S. (total) population and European standard population (values in parentheses).

‡Mantel-Haenszel extension chi-square (one degree of freedom). NS denotes not significant.

Table 2. Average Annual Age-Specific Incidence Rates of Multiple Myeloma per 100,000 Population (Malmö, Sweden, 1970 to 1979). According to Sex.

AGE GROUP	MALES		FEMALES		TOTAL	
	CASES	RATE	CASES	RATE	CASES	RATE
≤39	0	0	0	0	0	0
40-49	4	2.7	2	1.3	6	2.0
50-59	14	8.4	6	3.3	20	3.1
60-69	25	18.1	16	9.5	41	13.4
70-79	24	35.4	18	16.9	42	24.0
≥80	14	64.5	17	36.6	31	45.5
Totals	81		59		140	
Adjusted rates *		4.6 (6.2)		2.2 (3.0)		3.2 (4.3)

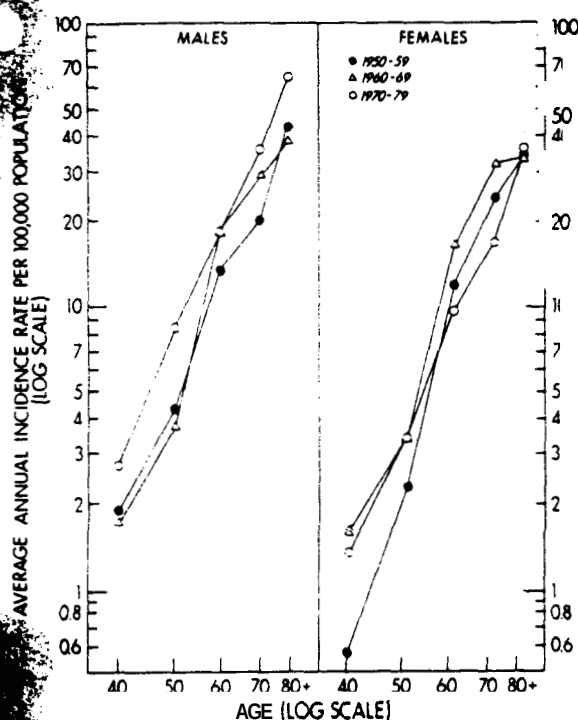
*Age-adjusted to 1950 U.S. (total) population and European standard population (values in parentheses).

groups, and that the data are well fitted by a straight line on a log-log plot.^{15,16}

DISCUSSION

Changes in the incidence of multiple myeloma over time may provide clues to its cause.¹⁷ Since most myelomas are thought to be associated with environmental exposures, a change in the incidence of a particular cancer should alert investigators to the possible role of environmental carcinogens.¹⁸ A classic example of such a time trend is the steep increase in lung cancer that first occurred among men earlier in this century. The major etiologic factor implicated in the increase in lung cancer was cigarette smoking.¹⁹ Retrospective reasoning related this increase to differential exposure to the major etiologic agent — cigarette smoking. When investigating or interpreting an increase in any disease, however, it is necessary to ascertain first whether the increase is real or is a reflection of improvements in recognition and clinical diagnosis.²⁰ This first step is particularly important in the case of multiple myeloma, a disease in which diagnosis is highly dependent on the use of medical-care facilities and laboratory investigation.³ In addition, since myeloma is a disease of old age, factors that increase the use of medical services by the elderly are likely to produce concomitant increases in the frequency of diagnosis and reporting of myeloma.

The general structure of Swedish medical care²¹ and the particular organization of medical services in Malmö make this city especially suitable for population-based studies.^{22,23} Improved medical care for the elderly has been a national priority in Sweden since 1950. In addition, Malmö's population has remained relatively stable since 1950 and has had unrestricted access to the city's medical center, which is staffed by diagnosticians especially interested in multiple myeloma. Since there are few private doctors in Malmö, a majority of outpatient visits (60 per cent) are made within the medical-center clinics. Thus, Malmö provides a stable study population for whom diagnosis



1. Annual Incidence Rates of Multiple Myeloma per 100,000 Population (Malmö, Sweden, 1950 to 1979), According to Age and Sex

treatment are concentrated at one site — the Department of Medicine of Malmö General Hospital.

Our study of trends in the incidence of multiple myeloma in Malmö has yielded two important findings: rates in males have increased, but the magnitude of this increase is small, occurring over the same period in which a very large increase in mortality rates for both sexes was reported in the United States and Great Britain. The average annual age-adjusted incidence of multiple myeloma for males in Malmö has increased progressively ($P = 0.02$, Mantel-Haenszel extension chi-square test) over the three decades between 1950 and 1979. There has been no such trend in the incidence rates among females. Increases in the age-specific incidence rates of myeloma among males in the period 1970 through 1979 are not restricted to the oldest age group (Fig. 1). The Olmsted Study identified a stable male-to-female ratio of 1.6 for 1955 through 1977.⁸ This ratio differs from that in Malmö, where the male-to-female ratio increased. The increasing incidence rates among males may provide a clue to some etiologic factor or factors that have been introduced into Malmö. One can infer that such a factor is more likely to have been introduced in the work environment and to have affected males preferentially.

The average annual, age-adjusted and sex-specific incidence rates for multiple myeloma in Olmsted County for the periods 1945 through 1954, 1955 through 1964, and 1965 through 1977 were 3.5, 4.5, and 2.9 per 100,000 males and 2.7, 1.7, and 2.3 per 100,000 females, respectively.⁸ There was no secular

trend in incidence rates for either males or females during this 33-year period.

It is instructive to compare age-incidence curves for cases occurring in three decades in Malmö with national mortality statistics for the United States²⁴ and England and Wales³ — countries that have had striking increases in reported mortality from myeloma. The age-specific incidence rates in Malmö increased progressively with age, continued to rise, and included the oldest age group (Fig. 1). This age-incidence pattern has been relatively unchanged during the past three decades, with the exception of age-specific rates for males. For both sexes combined, the age-specific rates for the group who were 80 years old or older increased from 37.9 per 100,000 for the decade 1950 through 1939 to 45.5 per 100,000 in the most recent decade, 1970 through 1979 — a 20 per cent increase (Fig. 1).

In contrast, for white Americans, the age-adjusted mortality rates per 100,000 (standardized to the European population) increased from 1.2 for males and 0.9 for females in 1950 to 3.4 for males and 2.4 for females in 1977 — increases of 188 per cent and 157 per cent for males and females, respectively.²⁴ In England and Wales, the age-adjusted rates per 100,000 increased from 0.5 for males and 0.4 for females in 1950 to 3.3 for males and 2.0 for females in 1979 — increases of 515 per cent and 398 per cent, respectively. These striking changes in the frequency of myeloma reported in national mortality statistics are most probably attributable to improvements in case ascertainment and diagnostic practices among the elderly. This is supported by the fact that most of the increase has occurred in the groups over 60 years old. Doll and Peto recommended that when national mortality statistics are used to assess time trends in cancer occurrence, the analysis should be limited to mortality rates among populations up to age 65.²⁵ The unreliability of recording cancer in the elderly makes it nearly impossible to distinguish true increases in incidence from increases attributable to improved case ascertainment.

Rates of other types of cancer that have shown striking changes in disease frequency over time illustrate these problems. The large proportionate increases in mortality from leukemia observed earlier in this century²⁶ were initially considered to support radiation exposure as a causative agent.²⁷ Only a small percentage of cases can now be attributed to radiation exposure. Most of the increased incidence of leukemia is attributed primarily to improvements in diagnosis²⁸ and access to medical care.²⁷ Deaths in the elderly may have been attributed to diseases of old age and infections, whereas the true cause may have been undiagnosed leukemia.²⁹ Population-based studies in communities under careful medical surveillance have shown no increase in the occurrence of leukemia among persons under 75 years old.^{30,31} These studies provide evidence that the increase in reported leukemia rates has largely been due to improvement in case ascertainment.

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In conclusion, we found the increase in the incidence of multiple myeloma in populations with comprehensive medical surveillance to be much smaller than the increase found when national mortality statistics were analyzed. This suggests that a large portion of the increase in mortality from multiple myeloma can be explained by improved case ascertainment, especially in the elderly. This conclusion is supported by previous studies of other types of cancer. We also found that incidence rates of multiple myeloma among males have increased in Malmö, Sweden. The Swedish study population was stable, had access to comprehensive medical care, was subject to uniform diagnostic criteria, and was part of a health-care-delivery system committed to excellent geriatric care. It is therefore unlikely that the increased incidence in males is an artifact due to improved case ascertainment. Rather, the data support the hypothesis that some occupationally related factor (or factors) that has increased or has been introduced into Malmö is a causative agent. Accumulating evidence, including a recent review article implicating radiation exposure as an environmental hazard of etiologic importance in some cases of myeloma,³² suggests that some cases of the disease may be preventable.

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