

科技资料

Epidemiology & Biology of Multiple Myeloma

G.I. Orams M. Potter (Eds.)

Epidemiology and Biology of Multiple Myeloma

With 30 Figures

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Dedication

The participants and contributors to this workshop dedicate this book to the memory of Elliott F. Osserman (1925–1989). His enthusiasm for the pursuit of clinical and scientific understanding of multiple myeloma was and still is an inspiration to many of us.

Elliott became one of the foremost clinical authorities on myeloma in the United States and his work in this field was recognized internationally. He took great pride in getting his patients through this difficult disease and extending their lives with comfort; he treated many well-known people in the New York area and beyond. But in addition to this commitment to outstanding clinical medicine, Elliott continued to study in depth each of his cases of multiple myeloma looking for new clues about its origin and nature. It was during such an inquiry that he found an unusual protein in the urine of one of his patients that he identified as lysozyme. Actually this patient had developed a myelomonocytic leukemia that was secreting lysozyme. Elliott became fascinated with the relationship of the leukemia to the plasma cell and speculated the two processes might be associated with a common lineage. He devoted many of his later studies to its structure and biosynthesis of human lysozyme.

The picture of Elliott (right) and Jan Waldenstrom was taken when they both attended a myeloma workshop given in honor of Jan Waldenstrom at the NIH in 1980. I am sure Elliott would be pleased to be remembered beside of his great friend and colleague.



Preface

On March 27, 1990, the National Cancer Institute sponsored a workshop on the epidemiology of multiple myeloma, held at the National Institutes of Health. This book comprises articles prepared by participants in this workshop. Discussed in these papers are: the descriptive and analytic epidemiology, differences in risk factors between blacks and whites, monoclonal gammopathies and their progression, and hypotheses regarding the etiology and pathogenesis of multiple myeloma.

Several epidemiologic research areas received particular attention during this workshop, and are reviewed in detail in this volume. There have been striking increases in the incidence of multiple myeloma over the past thirty years, especially among older individuals and blacks, which may not be entirely explained by changes in diagnostic capabilities. Occupational and environmental exposures have been associated with an increased risk of multiple myeloma, including farming exposures, occupational exposure to petroleum and rubber processing, exposure to ionizing radiation, and associations with persistent virus infections. The most striking epidemiological finding is reflected in the differences in incidence rates of multiple myeloma which are twice as high in blacks as compared with whites. Further, since 1950 the mortality rates for multiple myeloma have quadrupled in blacks while doubling for whites. Among hematopoietic malignancies, multiple myeloma is the only one with increased incidence and mortality rates among blacks.

Two major possibilities for explaining ethnic/racial differences in susceptibility to multiple myeloma are genetic and environmental factors. The present studies have not implicated specific determinants for either of these two factors as yet. Limited studies available from African populations suggest that plasma cell dyscrasias may be as prevalent among African blacks as among American blacks, suggesting the importance of racial factors, but these peoples are also exposed to different sets of environmental factors. The relative importance of genetic and environmental factors will require careful attention in projected studies.

A major question concerns the relationship of monoclonal gammopathy of undetermined significance (MGUS) to multiple myeloma. MGUS can convert to myeloma rapidly or over an extended period after the initial detection of the abnormal monoclonal component. Is MGUS the primary disease? Evidence from the progression of other forms of tumors indicates neoplasms can progress to a malignant state without presenting a benign precursor lesion, and this may occur in myeloma. MGUS nonetheless can represent a

step in the plasma cell tumor development. Is MGUS a lesion that should be studied coincidentally with myeloma, rather than focusing on just myeloma alone? This raises the larger question: are there genetic and environmental factors that increase the incidence of MGUS?

The biology of myeloma was discussed in two parts: the clinical disease and the experimental models. There are a number of questions which have not been resolved in the field of clinical myeloma. There has been considerable discussion of whether the entire neoplastic development takes place at the level of the plasma cell or whether antecedent genetic changes begin in the B-cell lineage as far back as the hematopoietic stem cell. It is possible that mutations affecting growth accumulate in a B-cell lineage but only become manifest when the cells begin secreting immunoglobulin. In this context, evidence for expression of inappropriate genes in myeloma was discussed. A second issue concerns the role of IL-6 in myeloma development. IL-6 has been shown to be an important requirement for in vitro growth of myelomas and plasmacytomas; also a few myelomas have been shown to produce IL-6 in an autocrine way. Many, but not all, workers currently consider that IL-6 is generated exogenously by stromal cells, and this raises the question of whether changes in the stromal microenvironment play an important role in plasma cell tumor development. The availability of IL-6 now makes it possible to establish more myeloma lines in culture when appropriate stromal elements are added. Third, myeloma has not thus far been associated with a consistent oncogenic mutation. Interestingly, the c-myc gene has not been activated by chromosomal translocations in clinical myeloma as it is in some of the experimental forms. The general picture that seems to emerge in many of the myeloma cases that have been studied cytogenetically is that there are multiple karyotypic abnormalities, suggesting some genetic instability in these cells. Fourth, the mode of spread of myeloma is not yet clearly established. Bone marrow plasma cells in normal individuals are thought to arise in extramedullary sites as B-lymphocytes that migrate to bone marrow sites. Circulating cells apparently lacking plasma cell morphology have been cultured from the blood with IL-6 and IL-3, and these suggestively could be responsible for sending myeloma cells to different sites.

Three experimental systems were discussed. Most plasmacytomas in mice are induced by the intraperitoneal implantation of plastics or injection of paraffin oils. These agents initiate a complex inflammatory process which appears to be essential for plasmacytoma development as the tumors arise histologically in this abnormal tissue. Plasmacytomagenesis can be inhibited in the BALB/c mouse, a genetically susceptible strain, by treatment with indomethacin; further, plasmacytomas cannot be induced in high incidence in pathogen-free BALB/c mice. These papers emphasize the review of available data, or provide descriptions of ongoing projects and preliminary results. The possibilities for further analyses of collected data are described, and directions for new research on multiple myeloma and related malignancies are suggested. Benign monoclonal gammopathies do arise in mice, particularly the C57BL/KaLwRij mice. In these mice, plasma cell neoplasms resembling multiple myeloma arise spontaneously. The evidence currently

suggests that the plasma cell tumors in C57BL/KaLwRij mice do not arise from benign monoclonal gammopathies. Spontaneous plasma cell neoplasms, called immunocytomas, occur in the LOU/C inbred strain of rats. Many of these tumors secrete IgE myeloma proteins. Recently there has been a dramatic and unexplained reduction in the incidence of these tumors in the Louvain colony. Possible factors involved are discussed.

G. IRIS OBRAMS
MICHAEL POTTER

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We appreciate the key role of the Organ Systems Coordinating Branch, National Cancer Institute, especially Dr. William Straile, in the support and organization of this workshop.

Special recognition is due to Mrs. Edythe Cohen, whose efforts were critical to the editing of the epidemiology manuscripts.

We are especially indebted to Ms. Victoria Rogers, who edited the clinical and experimental manuscripts and compiled this book.

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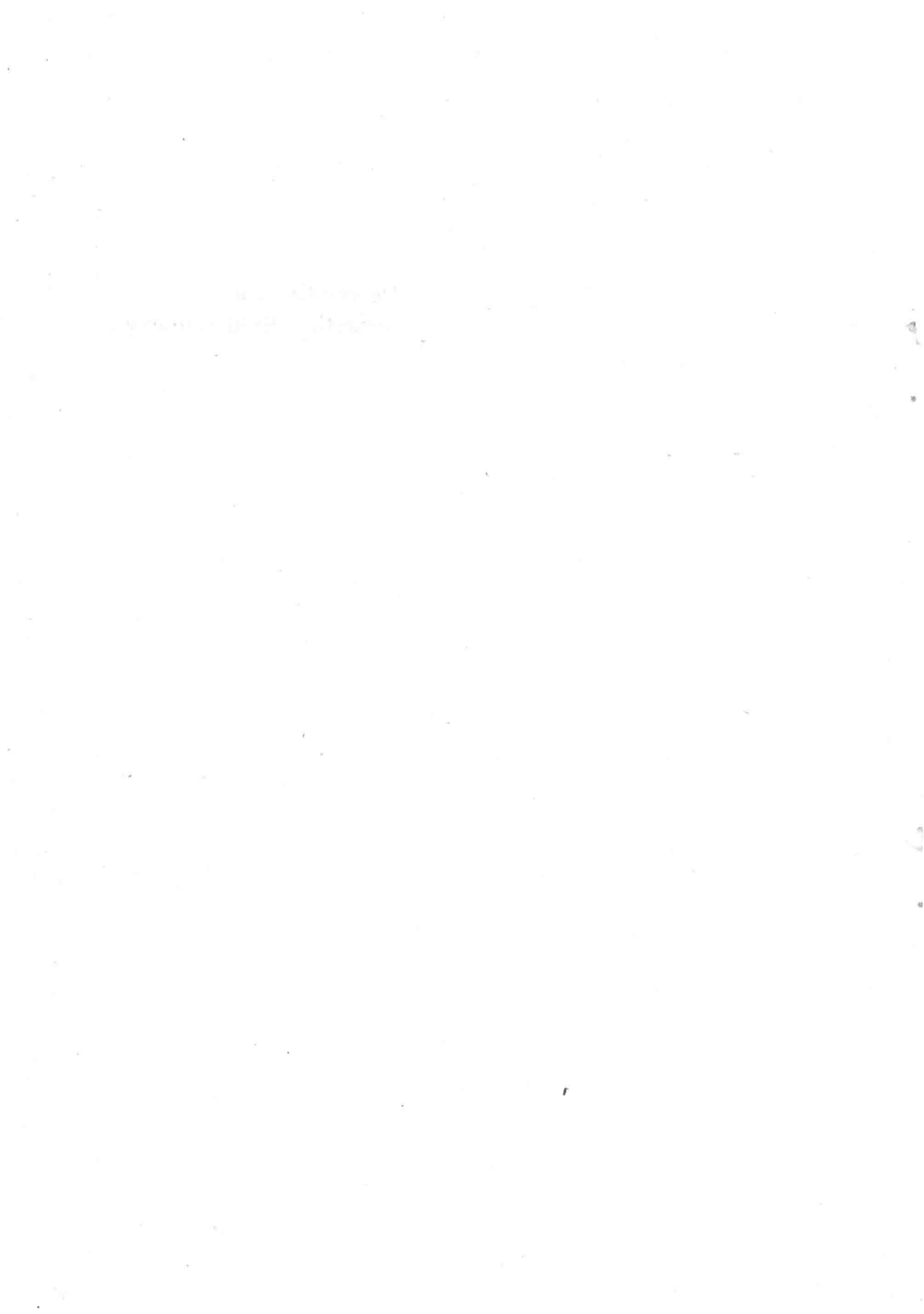
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Descriptive and Analytical Epidemiology



Descriptive Epidemiology of Multiple Myeloma

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According to estimates by the American Cancer Society, almost 12,000 new cases of multiple myeloma are diagnosed and about 9,000 deaths occur in the United States each year (Silverberg et al, 1990). These account for more than one percent of all cancer cases and almost two percent of deaths due to cancer. Although multiple myeloma may arise at any adult age, it tends to occur in older individuals; the median age at diagnosis was 69.1 years, based on 1973-77 Surveillance, Epidemiology, and End Results (SEER) program data, compared to 65.4 years for all forms of cancer combined (Young et al, 1981).

The impact of this malignancy varies by race and sex (Table 1). Based on data from areas with substantial black populations in the SEER program, incidence rates are more than twice as high among blacks than whites, with the standardized incidence ratio (SIR) being 229 and 239 among men and women, respectively. Whereas rates for many other cancers also are higher among blacks than whites, within the hematopoietic system, multiple myeloma is the only one with a clear excess among blacks. Compared to whites, SIRs range from 88 and 103 for myelocytic leukemia to 67 and 70 for non-Hodgkin's lymphoma, and 66 and 50 for Hodgkin's disease among men and women, respectively. Similar to many other malignancies, a male excess is apparent for multiple myeloma, with rates 39% and 45% higher among men than women among blacks and whites, respectively.

Since the early 1950s, national multiple myeloma mortality rates have more than doubled among whites and about quadrupled among nonwhites (Fig. 1), based on data from the National Center for Health Statistics. Data specific for blacks are available since the early 1970s; their rates are the highest and show the greatest proportional increases. Rates among white men during the early 1980s do not appear to be continuing the prior rate of increase.

The rise in mortality rates occurred predominantly among older age groups (Fig. 2). Among both whites and nonwhites, little change occurred among those under age 50. In the early years, rates increased among most groups over age 50 years, whereas in more recent years the changes have been greatest among those age 70 years and older.

Although multiple myeloma was quite rare in the past, the proportional increase has been one of the largest of any site (Devesa et al 1987), most likely affected by the introduction of improved diagnostic tools over the past several decades (Blattner 1982). Substantial increases in both incidence and mortality have been observed for multiple myeloma in many countries, whereas relatively stable rates have been reported in others (Linoss et al 1981, Velez et al 1982, Cuzick et al 1983, Turesson et al 1984, Nandakumar et al 1988, Hansen et al 1989, Cuzick 1990). The variations are believed to be largely the result of differences in diagnostic capability. Striking increases in the older age groups are consistent with improved medical technology and its expanded use in the high-risk older population.

Table 1. Comparison of incidence* of various hematopoietic cancers among blacks and whites in Atlanta, Connecticut, Detroit, and San Francisco-Oakland during 1977-83.

	-----Males-----			-----Females-----		
	No.	Rate	SIR#	No.	Rate	SIR#
Multiple myeloma:						
Black	440	10.3	229	424	7.4	239
White	1403	4.5		1411	3.1	
Hodgkin's disease:						
Black	155	2.5	66	95	1.3	50
White	1342	3.8		1027	2.6	
Non-Hodgkin's lymphoma:						
Black	419	8.7	67	363	6.0	70
White	4,202	13.0		4,105	8.6	
Leukemias						
Black	537	11.6	83	451	7.4	93
White	4,310	13.9		3,372	8.0	
Lymphocytic						
Black	229	5.1	88	157	2.6	76
White	1777	5.8		1349	3.4	
Myelocytic						
Black	242	4.9	88	229	3.6	103
White	1762	5.6		1514	3.5	

*Rates per 100,000 person-years, age-adjusted using the 1970 U.S. standard.

#Standardized incidence ratio, relative to the rate among whites in the same geographic areas.

Based on data from the SEER program.

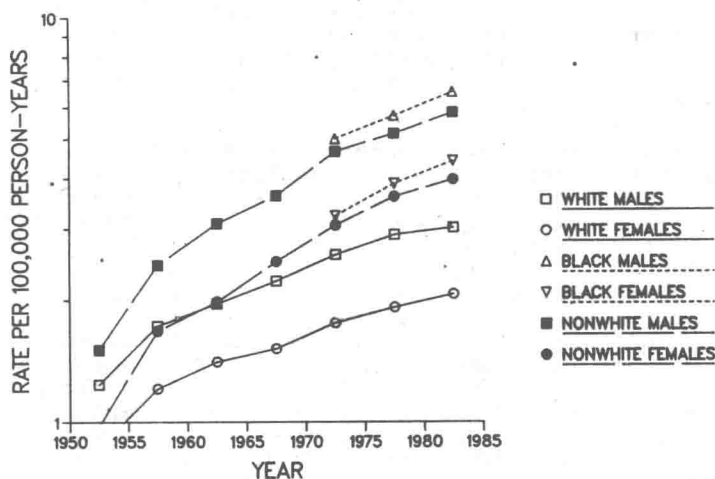


Fig. 1. Age-adjusted (1970) multiple myeloma mortality trends in the US by race and sex, 1950-54--1980-84.

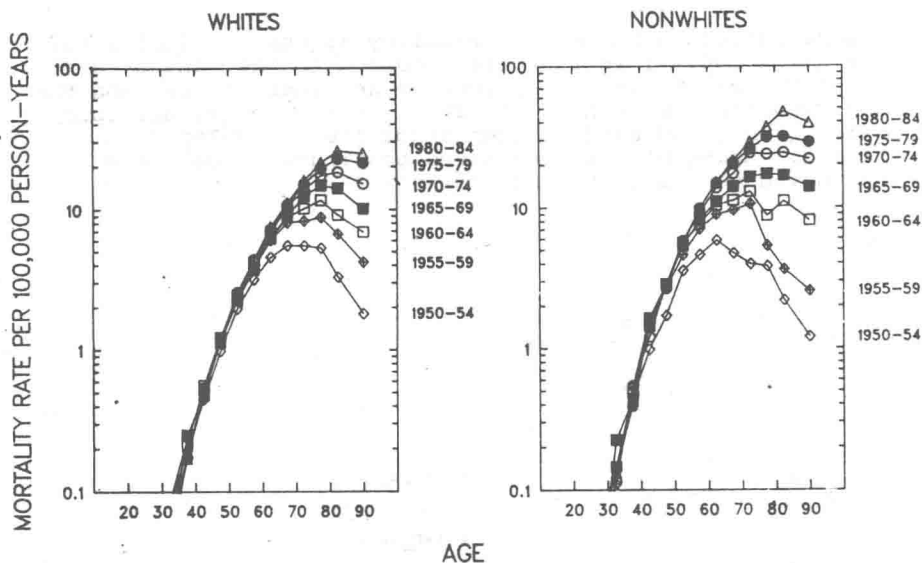


Fig. 2. Age-specific US multiple myeloma mortality curves among whites and nonwhites, 1950-54--1980-84.

During recent years, 1975-85, mortality rates rose consistently with age, except for a slight decline at the oldest ages among blacks (Fig. 3). Among both blacks and whites, the male:female ratio is somewhat smaller at younger than older ages, as indicated by the vertical distance between the curves. On the other hand, the black:white mortality ratio is larger at younger ages; compared to about a 50% excess among the oldest age groups, the ratio approaches three among those under age 50.

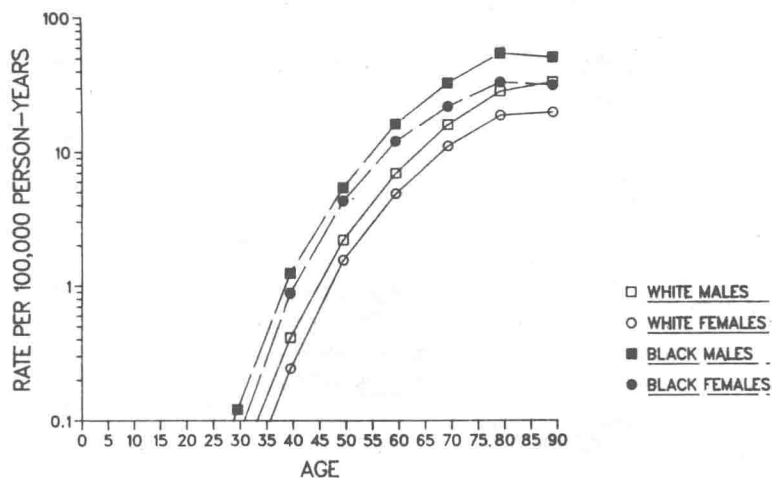


Fig. 3. Age-specific US multiple myeloma mortality rates by race and sex, 1975-85.

In contrast to substantial increases in mortality at the national level, incidence trends since 1969-71 in five areas common to the SEER program, the Third National Cancer Survey (TNCS) (Cutler and Young 1975), and the Connecticut Tumor Registry (Heston et al 1986), indicate that multiple myeloma rates have stabilized among whites since the mid-1970s (Fig. 4) (Devesa et al 1987). Among blacks, increases continued through the 1970s, but rates may have peaked in the early 1980s.

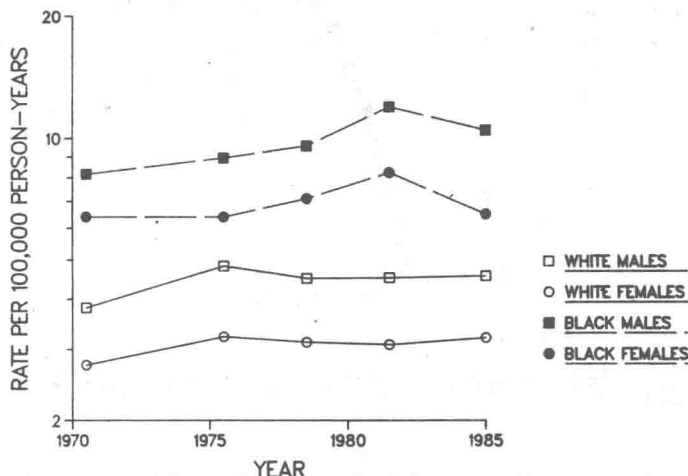


Fig. 4. Trends in age-adjusted (1970) incidence of multiple myeloma in the 5GA by race and sex, 1969-71 to 1984-86.

The age-specific incidence curves are higher than the mortality curves and generally similar in shape (Fig. 5). Although based on somewhat low numbers of cases (32, 37), rates are remarkably similar among black men and women under age 45, but not among whites.

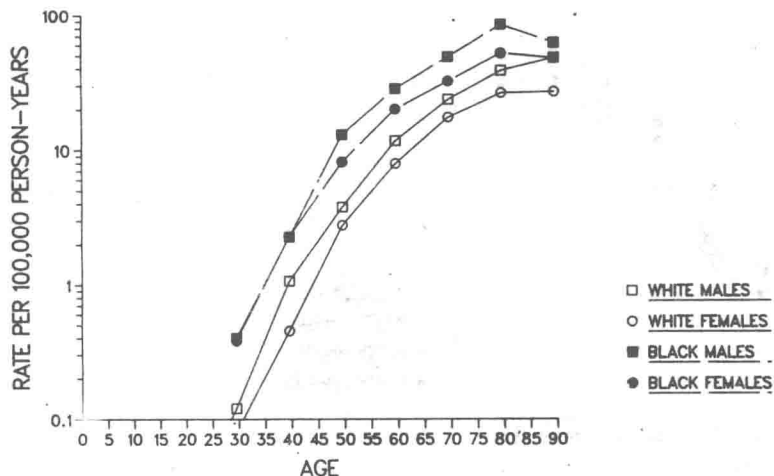


Fig. 5. Age-specific incidence of multiple myeloma in the 5GA by race and sex, 1975-85.