# Neoplastic Diseases of the Blood

## Second Edition

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# 23

# *EPIDEMIOLOGY OF MULTIPLE MYELOMA*

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Multiple myeloma is the prototype of a group of conditions known as monoclonal gammopathies. A common presenting complaint is bone pain or pathologic fracture associated with radiographic evidence of punched-out bony destruction. As a result of this clinical characteristic, myeloma has traditionally been considered a bone tumor, for purposes of disease classification. It was not until 1950 that multiple myeloma was assigned its own code number, 203, under the category of "neoplasms of lymphatic and hemopoietic tissues" in the *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death*.[1]

## DEMOGRAPHIC FEATURES AND GEOGRAPHIC VARIATION

### U.S. Incidence

According to the most recent U.S. incidence data, 1982 to 1986, from the Surveillance, Epidemiology, and End Results (SEER) Program, multiple myeloma accounts for 1.0 percent of all malignancies in whites and 2.2 percent in blacks.[2] The average annual age-adjusted (1970 U.S. standard) incidence rates per 100,000 for whites are 4.6 in males and 3.1 in females, while for blacks, the rates are nearly double, at 10.8 in males and 7.2 in females.[2] Figure 23-1 presents the distribution of the histologic subtypes of lymphoreticular neoplasms. Among blacks, multiple myeloma accounts for 33 percent of lymphoreticular neoplasms, compared with 13 percent among whites, while all leukemia occurs equally in blacks and whites (30 percent and 32 percent, respectively).

A distinctive feature of myeloma is its late age of onset. In the United States from 1982 to 1986, the median age at diagnosis was 68.0 for males and 71.0 for females.[2] The average annual age-specific incidence curves for the United States increase sharply with age, regardless of race or gender, and blacks have higher rates than whites at virtually all ages[2] (Fig. 23-2). A male predominance is seen in both races, although black females have higher rates than do white males.

### U.S. Incidence Trends

The incidence of multiple myeloma in the United States appears to be increasing. However, it is not clear whether this increase is real or attributable to improved diagnostic practices. The percentage increase in myeloma incidence rates from the Second National Cancer Survey (1947 to 1948) and the Third National Cancer Survey (TNCS) (1969 to 1971) was greater than for any other form of cancer for both whites and nonwhites.[3] The upward trend was greater among nonwhites than whites, especially at older ages. Comparison of the TNCS age-adjusted incidence rates[4] with more recent 1982 to 1986 calculations from the SEER program[2] reveals a 33.3 percent increase in the rates of myeloma in black males and appreciably smaller percentage increases in black females, white males, and white females (10.8 percent, 15.0 percent, and 14.8 percent, respectively). Some evidence suggests that the increase may be partly due to improvement in diagnosis. Linos and colleagues[5] reviewed the time trends in incidence of myeloma in Olmsted County, Minnesota, over 1945 to 1977. Case ascertainment was based on a thorough search of laboratory and medical records and death certificates. Average annual incidence rates of multiple myeloma did not increase during the three decades (rates of 2.9, 3.0, and 2.7 per 100,000 respectively). In an in-depth evaluation of cancer trends among whites, using U.S. data from 1947 to 1984, Devesa

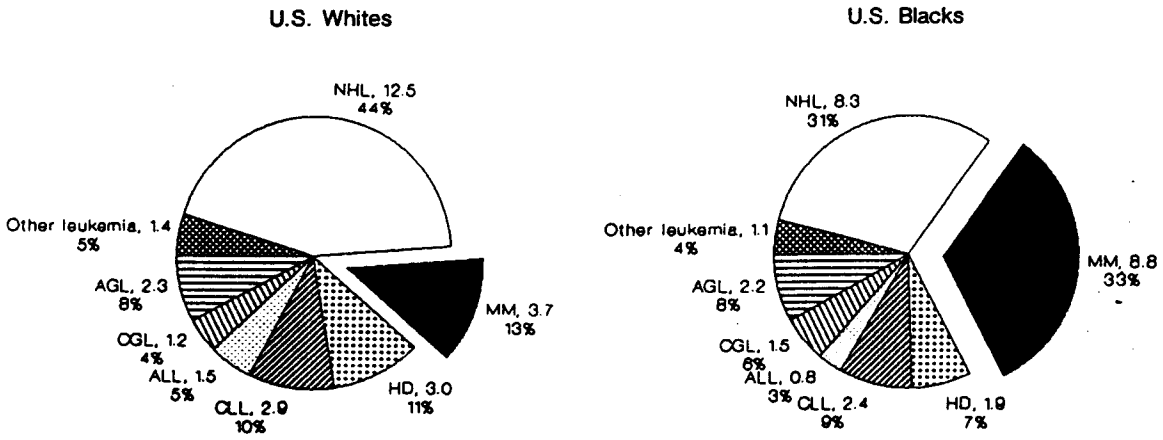


**Fig. 23-1.** Incidence rate per 100,000 person-years (age-adjusted, U.S. 1970 standard) and relative proportion (%) of lymphoreticular malignancies in U.S. whites and blacks, 1982 to 1986.[2] AGL, acute granulocytic leukemia; ALL, acute lymphocytic leukemia; CGL, chronic granulocytic leukemia; CLL, chronic lymphocytic leukemia; HD, Hodgkin's disease; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma.

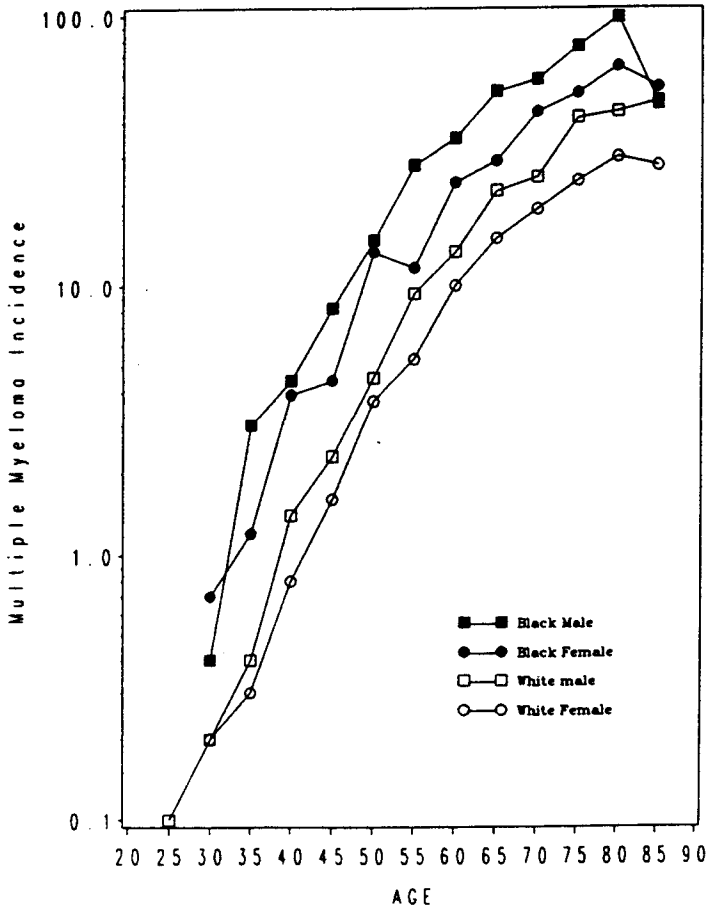


**Fig. 23-2.** Multiple myeloma average annual age-specific incidence for United States, 1982 to 1986.[2] Age plotted at beginning of 5-year age interval. Rates per 100,000 person-years.

et al.[6] found that age-specific mortality has steadily increased, but disproportionately in older age groups. This finding suggests that the dramatic increase in incidence and mortality rates for multiple myeloma may be due in part to improved medical technology and its use in older, high-risk populations.

## U.S. Mortality

The age patterns of mortality for multiple myeloma closely parallel the incidence curves. Shown in Figure 23-3 are the age-specific mortality rates for multiple myeloma in the United States from 1950 to 1984 (Devesa SS, personal communication). With few exceptions, nonwhite rates exceed white rates in all age groups, increases occurred primarily among those over 60 years of age, and the peak mortality shifted over time from age 60 to age 80. Nonwhite females experienced the highest increase over the 35-year period, 330 percent compared with 304 percent for males. Increases were one-half as great among white males and females, 154 percent and 146 percent, respectively (Devesa SS, unpublished data).

Since the 1950s, multiple myeloma mortality increased approximately 15.0 percent per 5-year interval among whites, ranking third behind lung cancer and melanoma among males and second behind lung cancer among females.[7] Among nonwhites, mortality rates increased 21.6 percent among males, and 23.3 percent among females per 5-year interval, ranking second only to lung cancer.[8] During the 1970s, mortality rates increased 50 percent more rapidly among nonwhites than among whites and by 1980 in some areas had risen to more than twice those for whites, particularly in the South (Pickle LW, personal communication). In an attempt to investigate the role of changes in diagnostic and coding practices, Davis et al.[9] suggested that the increases were the result of an artifact of disease misclassification. Improved identification of disease among older persons cannot be ruled out, however.

Geographic variations in multiple myeloma mortality have been noted over time. Between 1950 and 1980, U.S. whites experienced particularly high mortality rates in the North Central region.[7] Rates among white males increased with significantly greater rapidity in the Ohio Valley region, upper Michigan, central plains, southern Florida, southwestern Colorado, and southern Nevada, whereas those among white females were most striking in the mid-Atlantic coast states, eastern Kentucky, southern Indiana, southern Iowa, Missouri, southern Louisiana, eastern Texas, and northeastern New Mexico. The reasons for such geographic variations could include agricultural exposure and pesticide use.

## International Incidence

A number of international studies of multiple myeloma incidence are available.[10–26] Time trends in incidence from selected population-based registries from around the world are shown in Figure 23-4.[27–29] Comparisons between international incidence rates of myeloma based on cancer registry data must be made cautiously, since the populations served may vary with regard to age-adjusted rates, in the accuracy of case ascertainment (e.g., pathology versus death certificate only), and in the level of

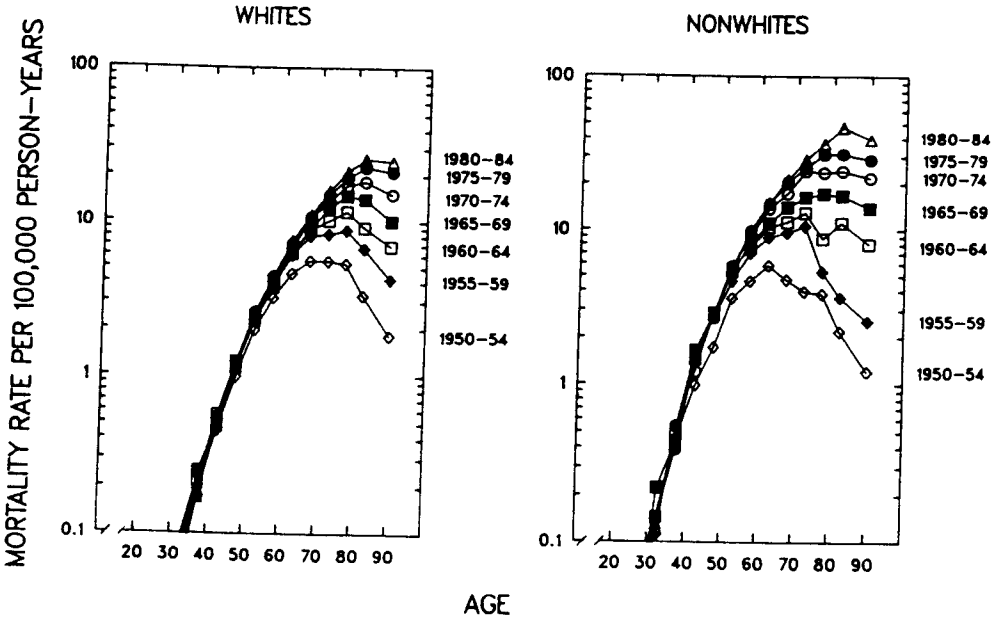


**Fig. 23-3.** Multiple myeloma, age-specific mortality for U.S. white and nonwhite males and females, 1950 to 1984. Age plotted at midpoint of 5-year age interval, with the exception of the 85+ interval which is plotted at age 90. (Devesa SS: personal communication.)

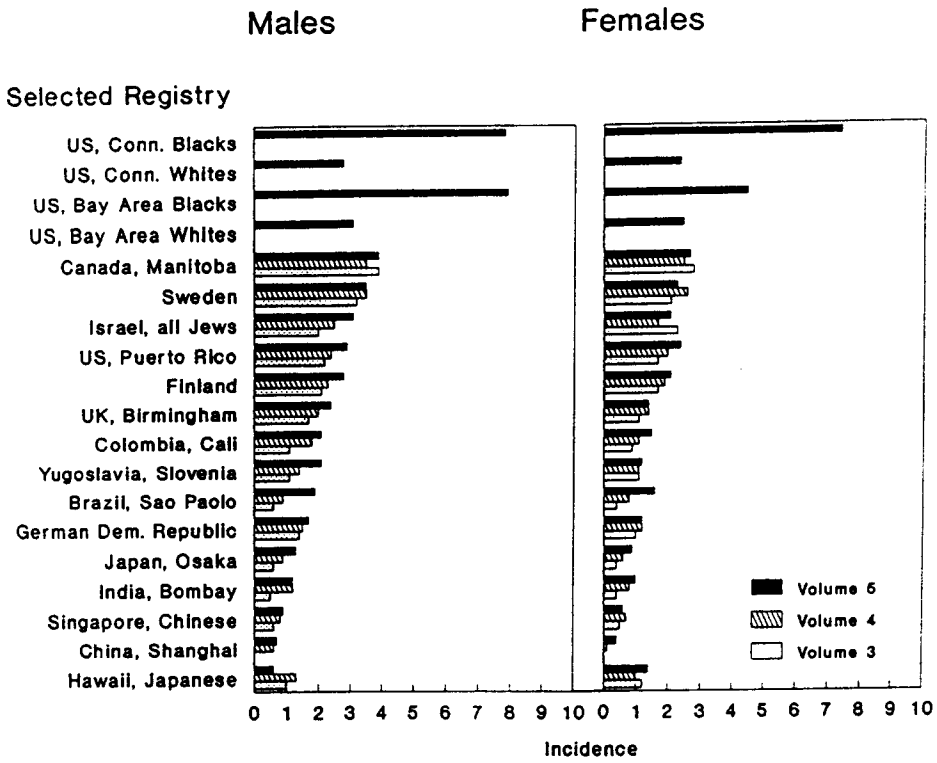


**Fig. 23-4.** Multiple myeloma, age-adjusted incidence (world standard population) from selected registries. Rates per 100,000 person-years. (From *Cancer Incidence in Five Continents*, Vol. 3, 1966 to 1973; Vol. 4, 1971 to 1977; Vol. 5, 1977 to 1982.[27-29])

medical care and diagnostic precision.[27-30] The striking feature of these data is that rates of multiple myeloma have risen consistently over time for these selected registries. Male rates continue to be higher than female rates, with the highest rates occurring among the U.S. black population and the lowest rates occurring in several Asian populations.

The incidence rates in Scandinavia are similar to those in the North American white population, while the rates are slightly lower in England and Eastern Europe and substantially lower in Asian countries (Fig. 23-4). The incidence data for multiple myeloma in South America are generally unavailable. In Norway,[24] multiple myeloma is the most frequent form of lymphoreticular malignancy (32 percent), with higher incidence rates in the rural population over 60 years of age, a finding that parallels that of Kyle et al.[31] in the United States. High rates were also suggested for Ireland[15,16] and Scotland,[13,22] although on the basis of small numbers of cases. In a study of hematopoietic malignancies in southern France,[12] multiple myeloma was the fourth most common of these diseases. A cancer incidence study from Czechoslovakia reported an increase in incidence of multiple myeloma between 1968 and 1985.[14]

Ludwig et al.[19] reported a relatively low incidence of multiple myeloma in Austria between 1969 and 1979 and commented that the apparent north-south gradient in Europe could result from diversity in quality of diagnosis and registration, although ethnic differences could not be ruled out. This conclusion was supported by an analysis of U.S. mortality data, which also showed a north-south gradient and a statistically significant ethnic association with persons of Scandinavian ancestry.[32]

Unfortunately, comprehensive incidence data for African populations are largely unavailable, but such data are necessary to provide valuable insights into variations within the black population around the world. Excess incidence of multiple myeloma among blacks has been noted previously.[2,33,34] High incidence rates occur in American black populations (Fig. 23-4) on both the East and West Coasts.[2] Low rates occur among African blacks, perhaps because of the small percentage of older blacks, limited diagnostic facilities, and incomplete ascertainment of African cases. A previous report of myeloma in South African blacks[35] suggested that rates may actually be higher, since some persons might not seek conventional medical care. Case series from French West Africa,[36] Rhodesia,[37] Zambia,[38] Nigeria,[39-41] Kenya,[42,43] and South Africa[44] suggest a younger median age at diagnosis and a sizeable male excess of multiple myeloma. In a case survey of all black Zimbabwean patients presenting at two central hospitals in Harare from 1982 to 1984,[45] multiple myeloma accounted for 21.3 percent of lymphoreticular malignancies (including leukemia, non-

Hodgkin's lymphoma, Hodgkin's disease, and multiple myeloma), and 25.7 percent from 1979 to 1981. These percentages of multiple myeloma are dramatically lower than those from the latest SEER incidence data[2] (see Fig. 23-1). However, a recent survey of cancer in developing nations[30] revealed that African cancer registries generally reported myeloma incidence rates that did not exceed 0.8 per 100,000 population, in sharp contrast to Western nations. The dramatic differences in rates may reflect differences in recognition of disease in limited sectors of the total population. National cancer registries for African nations reported the age-adjusted proportion of myeloma out of all cancers to be less than 1 percent. Rates appear to be high among Jamaicans, in whom the median age at diagnosis is 50 to 55 years, and survival time is short.[46]

Multiple myeloma incidence rates for Maori people of New Zealand approximated those of U.S. whites.[26] Incident myeloma cases from Tasmania[18] were more likely to have a rural residence than control subjects early in life, which may indicate the role of a prenatal or childhood exposure.

A study of the incidence of multiple myeloma in northern Israel from 1970 to 1979[23] found the overall incidence of multiple myeloma to be similar to that of Central European countries.[19] Incidence was significantly higher among males compared with females, Jews compared with Arabs, urban areas compared with rural areas, and among persons over age 65.[23] Incidence for all these groups rose significantly over time. Among the Jewish population, annual incidence of multiple myeloma was significantly higher for European Jews versus Afro-Asians or native Israelis; this variance may be attributable to differences in cultural factors, including nutrition, and to living in an urban environment, which may increase the chances of exposure to industry and pollutants, rather than to genetic differences.

The incidence of myeloma is low in several Asian countries, including the People's Republic of China,[20] South Korea,[17] and Japan.[10,26,47] Rates in U.S. Oriental populations closely resemble those of their native countries.[26] A low rate of differentiated B-cell malignancies (including non-Hodgkin's lymphoma, multiple myeloma, and chronic lymphocytic leukemia) in Japan was reported previously.[47] The low rates of these malignancies probably reflect genetic factors[26] as well as the excess of T-cell malignancies. T-cell malignancies occur because regions of Japan that are endemic for adult T-cell leukemia (ATL) coincide with areas endemic for the viral etiologic agent, human T-cell leukemia/lymphoma virus type I (HTLV-I).[48,49] A role for genetic factors is also suggested by the higher percentage of immunoglobulin D (IgD) myeloma in Orientals.[50,51] Since IgD involves a less-differentiated plasma cell, this increase may be consistent with the tendency of Orientals to develop undifferentiated, as opposed to differentiated, forms of B-cell neoplasms.[52]

Several investigators from various countries have monitored incidence trends of multiple myeloma.[53–55] Comparisons of these studies are difficult, as trend variation may occur because of differences in the quality and reporting of data. Data from Western Australia[54] revealed that multiple myeloma incidence increased 26.7 percent among males and 17.7 percent among females between the decade 1960 to 1969 and the 5-year period 1980 to 1984. Over each period, the male rates rose for all age groups except for the 80+ age group.

A similar trend pattern was seen in a study of multiple myeloma incidence in Malmo, Sweden, from 1950 to 1979.[55] There was a small and statistically significant trend of increasing incidence among males, but not among females. Turesson et al. suggested that the relatively small increase in incidence may be attributable to the stability of the population and to the comprehensive health care system available in Sweden. In a Danish study of multiple myeloma incidence trends,[53] rates increased from 1943 to 1962, but not after 1962. The more precise diagnostic criteria employed after 1962 may have contributed to the leveling off of incidence rates during the period 1963 to 1982.

## International Mortality

Shifts in the age distribution of a population and improved survivorship (as a result of better therapy) can influence mortality trends. Changes in incidence rates may result from increases in exposure to an environmental agent, which may cause similar increases in mortality from multiple myeloma. When specimens are not reviewed by trained pathologists using standard criteria, misdiagnosis or misclassification of the disease may result. Changes in the coding for death certification, increased awareness of the clinical manifestations of multiple myeloma by physicians, greater access to medical care, and errors in population enumeration may result in artificial changes in mortality rates. Referral bias may spuriously increase mortality rates in areas with medical institutions that serve patients from outlying areas. Incorrect inferences concerning mortality trends may also occur when an investigation is conducted that is not representative of the population at risk of the development of multiple myeloma.

Multiple myeloma mortality is increasing in a number of countries.[56,57] For 1960 to 1975, rates were high in Northern Europe, North America, Australia, and New Zealand; however, mortality in Great Britain was not as high as in the Scandinavian countries, the United States, and Canada.[56] The lowest rates were reported in eastern Europe, southern Europe, and Japan.[56] Countries with lower multiple myeloma mortality rates, such as Japan, had experienced the largest increases in mortality over time. Cuzick et al.[56] suggest that since high-quality medical care has been available in Japan for a number of years, the increase in multiple myeloma mortality is not related to underdiagnosis. Factors related to increased affluence, such as greater availability and utilization of health care, may be related to the increased incidence of multiple myeloma. In countries with high mortality, such as Sweden, increased rates occurred only among

those over age 64. France has myeloma mortality rates that are among the lowest in Europe.[56] Mortality rates for myeloma in New Zealand were reported to be slightly higher than for the United States, while Australian mortality rates were generally lower.[56] Cuzick et al.[56] found that male-to-female ratios for myeloma exceeded 1.0 for most countries, with few exceptions. This finding supports the hypothesis that men may experience important environmental exposures more often than women, leading to an earlier onset of disease.

Velez et al.[57] examined national death statistics from England and Wales for the period 1950 to 1979. Analysis of mortality by social class and region revealed increases in mortality for successive 5-year birth cohorts from 1880 to 1915. The apparent cohort effect could be an artifact of improved diagnosis and greater access to medical care; however, the increase in mortality may also be partly real.

A comparison of age-specific and age-adjusted mortality rates for Japan (1960 to 1975) to white and nonwhite rates in the United States for the same period confirms that multiple myeloma is less common in Japan, with the differences most marked in older age groups.[56] However, while mortality increases significantly across age groups 50 to 54, 60 to 64, and 70 to 74 for males in Japan, the trend is less significant for U.S. males.[56] The increasing trend with age is also stronger among Japanese females as compared with U.S. females.

In a nationwide mortality study by the Japanese Ministry of Health and Welfare,[58] from 1940 to 1982, multiple myeloma mortality increased steadily from 1969 to 1982 in males and females, with males consistently having higher rates. Rates for males and females increased 2.3- and 2.5-fold, respectively, but are low in comparison with populations from other nations.[56] Mortality was highest for persons over age 70.[58] An analysis of geographic variation indicated that age-adjusted death rates for multiple myeloma were highest in the Hokuriku district on the west coast of Japan, an area with a cold climate.[58] The lowest death rates were found in the Shikoku district in southern Japan.

## Socioeconomic Status

An association between higher socioeconomic status and multiple myeloma has been suggested from analysis of mortality data from several sources. In the United States, county mortality rates for multiple myeloma from 1950 to 1969 were positively associated with a higher median number of school years completed by the adult population among males and females.[59] Cuzick et al.,[56] in a study of international trends, correlated multiple myeloma mortality rates with three indices of socioeconomic status: number of doctors, number of hospital beds per 10,000 inhabitants, and gross national product (GNP). Number of doctors per 10,000 inhabitants was not associated with mortality, but a strong correlation with GNP after adjusting for number of hospital beds per 10,000 inhabitants was found. Cuzick et al. suggested that variations in mortality could be associated with differences in availability and usage of diagnostic procedures or medical care and with some correlate of affluence (e.g., GNP) or national wealth. However, in England and Wales,[57] the association of higher socioeconomic status with higher multiple myeloma mortality has diminished over time until the 1970s, when the association disappeared.

In contrast to mortality data, incidence data have not uncovered positive associations between multiple myeloma and socioeconomic status. Using incidence data from the TNCS, including census tract information on social class, Devesa[60] found a weak inverse association between income level and myeloma incidence. The rates among blacks remained higher than among whites after adjustments were made for differences in income. A study of socioeconomic status and black-white differences in cancer incidence on the basis of SEER data reported that poverty level (which considers household size and family income) did not explain much of the racial difference for myeloma incidence,[61] as blacks had a greater than twofold risk of myeloma than did whites, after adjustment.

Studies of multiple myeloma in Western Australia[54,62] did not find a striking association of socioeconomic class and risk of multiple myeloma. A marginal association with home ownership was noted in addition to a slight trend among occupational rank, indicating that professionals and managerial staff were at higher risk than were semiskilled workers and laborers. No trend from lowest to highest socioeconomic status was found in Western Australia,[62] in a study from Switzerland,[63] or among males for the period 1974 to 1978 in New Zealand.[64] Data from a hospital-based case control study of 153 multiple myeloma cases and 459 controls in Durham, North Carolina, found no association between several measures of socioeconomic status (e.g., highest annual family income, years of education, occupational history, and home ownership) and increased risk of multiple myeloma.[65]

## Survival

The prognosis for multiple myeloma is poor. U.S. blacks had a marginally higher 5-year relative survival rate for the 1980 to 1985 period than did whites. Black females had a noticeably higher rate than did white females. SEER data show that 5-year relative survival rates were 25.9 percent for black males and 32.0 percent for black females as compared with rates of 24.9 percent for white males and 26.6 percent for white females.[2] In a clinical study of multiple myeloma patients seen at 21 cancer treatment centers in the United States,[66] age, distance to treatment center, and type of therapy were statistically significant determinants of survival. Blacks had a more favorable survival than did whites, even after adjustment for potential confounding variables (age, sex, education, therapy, and treatment center). Differences in

survival may be the result of differences in severity of the disease.

In a comparative hospital-based record review conducted by Savage et al.,[67] clinical variables and poverty indicators were compared for 52 black patients with myeloma at Harlem Hospital Center (HHC) and for 46 black and 46 white patients with myeloma at Columbia Presbyterian Medical Center (CPMC). Blacks with myeloma at HHC had poorer survival rates than did the other two patient groups mainly because they presented with more advanced disease. Crowded living conditions and poverty level also influenced the poorer survival rates among HCC patients. Savage et al. suggested that the effect of low socioeconomic status (e.g., crowding, below-median family income, and a higher percentage of families living below the poverty level) was as important as, or more important than, the effects of either race or clinical features of the disease on survival.

Using clinical and socioeconomic status data from 153 multiple myeloma patients who participated in the North Carolina case control study,[65] Weston et al.[68] found that survival was not associated with current or highest income, education level, type of dwelling, or crowdedness of dwelling. By contrast, clinical factors such as hypercalcemia and renal insufficiency were closely correlated with survival. No differences in survival rates between blacks and whites were found.

Overall, the descriptive epidemiology of multiple myeloma has shown that it is a disease of older age. In the United States, myeloma rates for blacks are highest and continue to outpace myeloma rates among white populations. Improved diagnosis and better recognition of this cancer in older high-risk patients may be contributing to the increased incidence seen in this group. Internationally, incidence rates are highest in industrialized countries and are lowest in developing countries. The differences in rates reflect the presence of registries, usually in industrialized countries, that cover a larger proportion of the total population within a country and reflect greater access to medical care. Investigations of the role of socioeconomic status on myeloma risk have revealed a link with high socioeconomic status, GNP, and myeloma mortality. By contrast, no associations have been found for socioeconomic status and myeloma incidence. Studies of multiple myeloma survival point to an association between low socioeconomic status and poor survival; however, clinical factors are also important. It is possible that the measures of socioeconomic status available do not adequately describe myeloma risk and that differences in risk observed reflect the availability and level of medical care available.

## RADIATION EXPOSURES

Exposure to ionizing radiation is the best documented risk factor for multiple myeloma, but the mechanism by which the radiation induces the cancer has not yet been established.[10,69] There is evidence to suggest that multiple myeloma occurs after exposure to high doses of radiation after a long latent period, as in atom bomb survivors. By contrast, several other studies indicate a causal link with long-term, low dose exposure, as in radiologists and others exposed to diagnostic and therapeutic radiation.

### Atom Bomb Survivors

The strongest evidence linking radiation to myeloma has been provided by several studies on the mortality and incidence of cancer among atom bomb survivors.[70–72] All three studies reported an increased risk and incidence of multiple myeloma associated with radiation exposure for extended periods of follow-up, reflecting the long latency for emergence of multiple myeloma. Wakabayashi et al.[72] reported that survivors who received high doses of radiation, ≥100 cGy, had a significantly higher risk of multiple myeloma than did those who received lower doses of 0 to 9 cGy. Elevated serum Ig levels[73] and chromosomal aberrations in B lymphocytes[74] have also been reported, perhaps representing subclinical markers of multiple myeloma risk.

### Radiologists

Studies on the mortality experience of radiologists have provided information on the risk of multiple myeloma caused by occupational exposure to radiation. Lewis[75] observed five multiple myeloma deaths among 425 American radiologists who died between 1948 and 1961. Whether this significant excess was solely attributable to radiation exposure is uncertain, since actual radiation measurements were not available and possibly imprecise dose estimates were used.[76]

Matanoski et al.[77] also found excess deaths of myeloma among approximately 6,500 radiologists who were followed from 1920 to 1969 and hypothesized that long-term, low dose exposure may have had an etiologically related immunosuppressive effect. Leukemia risk was high for radiologists who entered practice in the earlier years, when radiation dose levels were higher. By contrast, there was a twofold excess of myeloma among those who entered practice more recently, suggesting that long-term exposure to low levels of external radiation is a risk factor for myeloma.[78]

### Diagnostic and Therapeutic x-Rays

Evidence that diagnostic x-rays contribute to the risk of multiple myeloma is weak. Two studies have indicated no difference in exposure to x-rays among multiple myeloma cases and controls,[79,80] while nonsignificant excess risks have been observed by others.[81–83] Blair and Hayes[84] discussed mortality patterns among U.S. veterinarians and noted that the proportionate mortality for multiple myeloma for practitioners who began their careers between 1908 and 1957 was elevated over proportionate mortality for practitioners who began their ca-

reers earlier. Risk of leukemia, like that of multiple myeloma, was higher among veterinarians who practiced during the 1950s and 1960s, when x-ray use was more widespread and safety precautions were not as stringent. By contrast, a cancer incidence study of 27,011 Chinese diagnostic x-ray workers over a 30-year period reported no excess multiple myeloma as compared with workers in other medical occupations in which x-ray exposure was not likely.[85]

## Nuclear Facilities

Some studies have indicated an increased risk of multiple myeloma mortality among workers in the nuclear industry. Four cases of myeloma occurred among workers at the Windscale Nuclear Processing Plant in Great Britain over 1950 to 1974, versus one expected case. Three of these workers were exposed to radiation, two of whom had accumulated doses of 4 and 3.3 rem, respectively, and one of whom had worked with plutonium. Retired and ex-workers were omitted, possibly producing an underestimate of the occurrence of myeloma in this population.[86]

Excess multiple myeloma mortality has been reported among male employees engaged in plutonium manufacturing at the Hanford Works in Washington state (11 observed myeloma deaths versus 7.6 expected).[87] However, only eight of these workers were exposed to radiation. Reanalysis of these data by Darby and Reissland[88] revealed that there was an excess of myeloma by two to three deaths for those workers whose total dose was $\geq 5$ rem 10 years previous to death.

Most associations between multiple myeloma mortality and radiation have been observed when exposures 10 to 15 years before death are considered. In an updated analysis of mortality data from the Hanford site, Gilbert et al.[89] noted a statistically significant increase in myeloma mortality over a 30-year period. The strongest trend and significant dose-response relationship was noted when exposures occurring at least 10 years prior to death were considered. In a retrospective cohort study of workers at the Sellafield plant of British Nuclear Fuels,[90] a statistically significant dose-response relationship of radiation exposure with multiple myeloma mortality was seen for workers who incurred exposures at least 15 years before death. Beral et al.[91] analyzed a cohort of employees of the United Kingdom Atomic Energy Authority who were employed between 1946 and 1979. Approximately one-half of the employees had been monitored over 30 years for whole-body dose radiation that included contributions from x-rays, $\gamma$-rays, and neutrons. Worker deaths from multiple myeloma were well below that of the general population of England and Wales. No appreciable dose-response trend for cumulative radiation was evident; however, duration of exposure was not considered. These studies suggest that chronic exposure in the workplace to low levels of radiation may be an important causal link in the development of multiple myeloma.

Investigations have also been conducted to determine whether residential proximity to nuclear facilities increases the risk of multiple myeloma; however, a majority of the studies have failed to provide evidence of an elevated risk. Mortality studies by Forman et al.[92] and by Cook-Mozzafari et al.[93] attempted to explore this association but did not quantify radiation dose information and inferred exposure by considering distance from the nuclear facility. While Forman et al.[92] found a significant decrease in risk of multiple myeloma with increasing proximity to nuclear installations, Cook-Mozzafari et al.[93] were unable to find mortality from multiple myeloma that was significantly different from the rest of England and Wales. These findings are contradictory to the occupational studies by Smith and Douglas[90] and by Gilbert et al.,[89] who had access to radiation dosimeter measurements. Dousset[94] compared observed cancer mortality in the area of the Beaumont-Hague district of Normandy, France, which includes the La Hague nuclear facility, with the expected cancer mortality for the period 1975 to 1982. No significant excess of multiple myeloma mortality was found. However, a 7-year latent period may not have been long enough to observe an effect from radiation.

In a study of cancer incidence near Denver, Colorado, in areas surrounding the Rocky Flats nuclear weapons plant,[95] the number of lymphomas and myelomas combined exceeded the expected number for males. Increases in similar cancer types that were in excess among survivors of the atom bombings at Hiroshima and Nagasaki were noted in the Colorado population. As a consequence of the 1979 accident at the Three Mile Island (TMI) nuclear power plant near Harrisburg, Pennsylvania, cancer incidence in the region has been evaluated. A review of bone marrow examinations at a community hospital serving patients within a 10-mile radius of TMI revealed no increase in the number of myeloma cases seen for the 5-years since the accident.[96]

Jessop and Horsley[97] initiated a case control study to investigate an area of Britain in which a cluster of multiple myeloma was previously reported. A nuclear fuel reprocessing plant was thought to be responsible for the apparent excess of myeloma. Patients lived longer in coastal regions than did control patients and may therefore have had greater exposure to marine discharges of radioactive material. However, it was concluded that the radiation exposure was unlikely to be large enough to induce multiple myeloma.

Participants in atmospheric nuclear weapons tests have also been studied to determine whether such exposures cause an increased incidence and mortality of cancer including multiple myeloma. A British case control study of multiple myeloma among servicemen and male atomic weapons employees who were participants in atmospheric nuclear weapons tests in the Pacific Ocean[98] revealed significant differences for multiple myeloma mortality and incidence between test participants and unexposed controls. Investigation of excess multiple myeloma mortality among participants grouped by recorded doses of external radiation or type of test con-

ducted were inconclusive, owing to the small sample size. Because a large percentage of the participants are still alive, and because an adequate latent period must be considered to assess radiation exposure, further follow-up evaluation of this cohort is warranted.[99]

### Radium Dial Workers

Stebbings et al.[100] conducted a mortality study of women employed in the U.S. radium dial painting industry prior to 1950. Notable increases in the incidence and mortality of myeloma were evident for those ever employed, and significant increases were found for workers employed prior to 1930, when exposures to radium were reportedly higher. The excesses of incidence and mortality were particularly elevated among those employed longest. A statistical association of four living incident cases with varying internal measurements, based on the expectation of myeloma deaths, was stronger when duration of employment was considered rather than internal radium intake. Stebbings et al. contend that external γ-radiation may be the biologically significant exposure. Associations with internal radium intake such as from tipping the brush in the mouth were weak because of lack of a good measure of internal exposure.

Multiple myeloma occurrence among persons exposed to radiation is well documented, with increased risks reported primarily among older persons. The strongest association between multiple myeloma risk and radiation exposure has been observed among atom bomb survivors who experienced high doses instantaneously and among radiologists and radium dial workers who experienced a lower dose over a long period of time. Risk associated with exposure to diagnostic and therapeutic x-rays is contradictory. With the advent of nuclear power, concern for cancer risk has increased among power plant workers and local residents. Among nuclear plant workers, the strongest associations of radiation exposure and multiple myeloma have been observed for low dose exposures occurring over a 10- to 15-year period. Associations of multiple myeloma in areas situated near nuclear facilities have generally proved negative. Evidence from geographic cancer clusters, hospital record reviews, and case control studies of environmental radiation exposure is weak, partly because of lack of reliable exposure data and adequate sample size.

## ENVIRONMENTAL AND OCCUPATIONAL EXPOSURES

Over the past decade, much information on potential environmental and occupational risk factors for multiple myeloma has been ascertained from epidemiologic investigations of various design. Table 23-1 presents positive associations between specific occupations/industries and multiple myeloma reported from case control, prospective, and proportionate incidence/mortality studies. Ecologic mortality studies and correlational studies are not included. These data must be interpreted with caution, since some of these statistical associations may have occurred by chance alone as a consequence of multiple occupations or exposures being compared in a single study. Results from studies using death certificates in particular should be viewed carefully to prevent possible misclassification of occupation codes or cause of death or lack of detailed occupational information.

### Agriculture

Of the studies listed in Table 23-1, an overwhelming majority have indicated a statistically significant positive association between multiple myeloma and agriculture (predominantly farming),[62,63,79–82,101–113] but a few have demonstrated no association (not shown).[114–116] The absence of statistically significant associations in some studies may be attributable to insufficient sample size, the low prevalence or absence of farming as an occupation among study subjects, varying farming practices, or misclassification of cause of death.

Perhaps the earliest association between multiple myeloma and agriculture was made by Milham[117] (not represented in Table 23-1), who noted a statistically significant association between farming occupations and death from multiple myeloma among white male decedents from Washington state. Statistically elevated risks among farmers have also been detected in an ecologic mortality study in Texas by Agu et al.[118] While information is lacking with regard to which specific type of farming may elevate risk of multiple myeloma, a correlational study by Priester and Mason[119] found an excess of multiple myeloma among residents of the southeastern United States, in counties with large poultry populations. At least two other studies[104,105] have reported positive associations between chicken farming and risk of death from multiple myeloma. The significance of exposure to chicken production is unclear but may support the role of a zoonotic oncogenic virus in the etiology of multiple myeloma. This hypothesis was suggested by previous experiments involving the agent of Marek's disease, a malignant lymphoma in chickens; the lymphoma was grown in mammalian cells[120] and was found to have cross-reacting antigens with human tumors.[121]

Other investigations have found associations of multiple myeloma with hog production,[104] dairy farming,[101] sheep farming,[111] exposure to beef cattle,[111] working with farm animals,[108] and orchard farming.[110] Because of the variety of associations reported, it is impossible to determine whether oncogenic zoonotic viruses, animal insecticides, agricultural chemicals, or some combination of these exposures are responsible for the increased risk of multiple myeloma.

Additional studies[80,82,112,122] have suggested that agriculturally related exposures, such as grain dust[122] and engine exhaust[82] from farm equipment, may influence the development of multiple myeloma. Gallagher et al.[80] reported increased risks of multiple myeloma among farm workers, for those workers exposed to processed

**Table 23-1.** Reported Positive Associations Between Occupational Exposures and Multiple Myeloma

| Investigators | Study Population and Size | Design | Risk Estimate | Adjustments[a] |
|---|---|---|---|---|
| | **Farming Occupation** | | | |
| Boffetta et al. (1989)[81] | American Cancer Society Prevention Study Volunteers ($n$ = 1,410) | Case control within prospective | | |
| | Exposure: Farmers | | OR = 3.4[b,d] | |
| | Farming and pesticides | | OR = 4.3[d] | cr |
| Brownson et al. (1989)[102] | Missouri Cancer Registry 1984–1988 ($n$ = 15,000) | Case control | | A |
| | White male farmers | | OR = 1.4 | |
| La Vecchia et al. (1989)[107] | Hospital patients from greater Milan, Italy 1983–1988 ($n$ = 506) | Case control | OR = 2.0[d] | E |
| Cuzick and De Stavola (1988)[79] | Referral center patients, England and Wales ($n$ = 798) | Case control | RR = 1.8[d] | cr |
| Levi et al. (1988)[63] | Vaud Cancer Registry, Switzerland, agriculture workers, 1977–1984 (No. cases = 53) | Proportional mortality | PMR = 210[d] | J |
| McLaughlin et al. (1988)[108] | Swedish Cancer Environment Registry; National Swedish Cancer Registry, males (No. cases = 808) | Nonconcurrent prospective | | |
| | Exposure: Farmers | | SIR = 1.2[d] (incidence) | B |
| | Animal workers | | SIR = 1.3[d] (incidence) | B |
| Flodin et al. (1987)[82] | Selected Swedish hospital registries and clinics ($n$ = 562) | Case control | RR = 1.9[d] | cr |
| Morris et al. (1986)[109] | SEER registrants (Washington, Utah, metropolitan Detroit, metropolitan Atlanta) ($n$ = 2,381) | Case control | OR = 2.6[b,d] | H |
| Nandakumar et al. (1986)[62] | Leukemia and Allied Disorders Registry; Cancer Registry of Western Australia, decendents 1975–1984 ($n$ = 1,245) | Case control (mortality) | OR = 1.44[c] | cr |
| Pearce et al. (1986)[111] | New Zealand Cancer Registry, male interviewees ($n$ = 391) | Case control | | |
| | Exposure: Farming | | OR = 1.7[d] | C |
| | Sheep farming | | OR = 1.9[d] | C |
| | Beef cattle | | OR = 1.7[d] | C |
| Steineck and Wiklund (1986)[112] | 1960 Swedish Population and Housing Census Respondents, Swedish Cancer Environment Register ($n$ = 2,739), males | Nonconcurrent prospective | RR = 1.2[d] | B |
| Vagero and Persson (1986)[113] | Self-employed Swedish male farmers, Swedish Cancer Environment Register 1961–1979 (No. cases = 347) | Nonconcurrent prospective | SMR = 115[d] (morbidity) | B |
| Delzell and Grufferman (1985)[106] | Decreased nonwhite North Carolina farmers, 1976–1978 <65 years old (No. cases = 10) | Proportional mortality | PMR = 250[c,d] | G |
| Pearce et al. (1985)[110] | New Zealand Cancer Registry, 1977–1981 males ($n$ = 410) | Case control | | |
| | Exposure: Farming (age 20–64) | | OR = 2.22[b,d] | A |
| Cantor and Blair (1984)[105] | Deceased male Wisconsin farmers ($n$ = 1,337) | Case control | | |
| | Exposure: Farming | | OR = 1.4[c,d] | K |
| | Fertilizer use | | OR = 1.7[c,d] | K |

(*continued*)

**Table 23-1.** (*continued*) Reported Positive Associations Between Occupational Exposures and Multiple Myeloma

| Investigators | Study Population and Size | Design | Risk Estimate | Adjustments[a] |
|---|---|---|---|---|
| | **Farming Occupation** (*continued*) | | | |
| Burmeister et al. (1983)[104] | Deceased white male Iowa farmers ($n$ = 1,650) 1964–1978 | Case control | | |
| | Exposure: Farming | | OR = 1.48[c,d] | cr |
| | Hog production | Year of birth | OR = 1.83[c,d] | cr |
| | Herbicide use | | OR = 2.65[c,d] | cr |
| | Insecticide use | 1890–1900 | OR = 1.96[c,d] | cr |
| Gallagher et al. (1983)[80] | A. Maxwell Evans Clinic patients, Vancouver, B.C. ($n$ = 252) | Case control | | |
| | Exposure: Farm workers | | OR = 2.2[d] | cr |
| | Processed grain | | OR = 2.4 | cr |
| | Industrial occupation | | OR = 2.1[d] | cr |
| Burmeister (1981)[103] | Deceased white male Iowa farmers, 1971–1978 (No. cases = 133) | Proportional mortality | PMR = 127[c,d] | A |
| Bross et al. (1978)[101] | Roswell Memorial Park cancer patients; Buffalo, New York ($n$ = 14,000; No. cases not available) 1956–1965 | Prospective | | |
| | Exposure: Dairy farming | | RR > 2.0 | A |
| | **Metal Exposure** | | | |
| Sorahan and Cooke (1989)[130] | Male U.K. steel foundry workers 1946–1985 (No. cases = 9) | Nonconcurrent prospective | SMR = 122 (mortality) | G |
| Cuzick and De Stavola (1988)[79] | Referral center patients, England and Wales, exposed ≥10 years to metals/dusts 1978–1984 ($n$ = 798) | Case control | RR = 1.1 | cr |
| McLaughlin et al. (1988)[108] | Swedish Cancer Environment Registry: National Swedish Cancer Registry, male smelter/metallurgy workers (No. cases = 18) | Nonconcurrent prospective | SIR = 1.7 (incidence) | B |
| Morris et al. (1986)[109] | SEER registrants (Washington, Utah, metropolitan Detroit, metropolitan Atlanta) ($n$ = 2,381) | Case control | OR = 1.5[d] | H |
| Giles et al. (1984)[128] | Residents of Tasmania, 1972–1980 ($n$ = 232) | Case control within prospective | | |
| | Male metal workers | | RR = 1.0 | cr |
| | Male foundry workers | | RR = 1.5 | cr |
| Gallagher and Threlfall (1983)[127] | Male metal workers in British Columbia (No. cases = 33) | Proportional mortality | PMR = 128[c] | A |
| Greene et al. (1979)[129] | Male employees of U.S. printing office, 1948–1977 | Proportional mortality | PMR = 219[c,d] | G |
| | Whites (No. cases = 8) | | PMR = 246[c,d] | G |
| | Nonwhites (No. cases = 2) | | PMR = 153[c] | G |
| | **Rubber Manufacturing** | | | |
| Cuzick and De Stavola (1988)[79] | Referral center patients, England and Wales 1978–1984 ($n$ = 798) | Case control | RR = 1.4 | cr |
| Gustavsson et al. (1986)[138] | Male Swedish rubber workers (No. cases = 5) | Nonconcurrent prospective | SMR = 128 (morbidity) | G |
| Delzell and Grufferman (1985)[106] | White male union rubber reclaim workers, 1940–1971 (No. cases = 6) | Nonconcurrent prospective | RR = 4.5[d] | G |
| Andjelkovich et al. (1978)[135] | U.S. white female rubber workers, 1964–1973 (No. cases = 2) | Nonconcurrent prospective | SMR = 234 | I |
| Monson and Nakano (1976)[136] | Female rubber workers in Akron, Ohio (No. cases = 9) | Nonconcurrent prospective | SMR = 214[c] | G |

(*continued*)

**Table 23-1.** (*continued*) Reported Positive Associations Between Occupational Exposures and Multiple Myeloma

| Investigators | Study Population and Size | Design | Risk Estimate | Adjustments[a] |
|---|---|---|---|---|
| | | **Benzene** | | |
| Rinsky et al. (1987)[141] | White male Ohio rubber plant workers 1940–1965 (No. cases = 4) | Nonconcurrent prospective | SMR = 409[d] (mortality) | A |
| | | **Wood, Leather, and Textile Industries, and Occupations** | | |
| Cuzick and De Stavola (1988)[79] | Referral center patients England and Wales exposed to leather tanning 1978–1984 ($n$ = 798) | Case control | RR = 1.9 | cr |
| McLaughlin et al. (1988)[108] | Female Swedish textile workers (No. cases = 11) | Nonconcurrent prospective | SIR = 2.7[d] (incidence) | B |
| Flodin et al. (1987)[82] | Swedish cases from selected medical clinics and population controls exposed to fresh wood ($n$ = 562) | Case control | RR = 3.2[d] | A |
| Walrath et al. (1987)[152] | Employees of leather shoe manufacturing company, 1960–1979 | Proportional mortality | | |
| | Males (No. cases = 10) | | PMR = 193[c,d] | G |
| | Females (No. cases = 8) | | PMR = 346[c,d] | G |
| Milham (1983)[145] | Deceased Washington state paper and pulp mill workers (No. cases = 19) | Proportional mortality | PMR = 182[c,d] | G |
| | | **Petroleum Refining, Petroleum Production, and Fuel Combustion Products** | | |
| Flodin et al. (1987)[82] | Selected Swedish hospital registries and clinics ($n$ = 562) | Case control | | |
| | Exposure: Engine exhausts | | RR = 2.6[d] | A |
| Linet et al. (1987)[164] | Hospital patients, Baltimore, MD ($n$ = 200) | Case control | | |
| | Exposure: Petroleum | | OR = 3.7[b,d] | F |
| Kaplan (1986)[158] | Male U.S. petroleum refinery workers (No. cases = 16) as of 1980 | Nonconcurrent prospective | SMR = 123 (mortality) | A |
| Morris et al. (1986)[109] | SEER registrants (Washington, Utah, metropolitan Detroit, metropolitan Atlanta) ($n$ = 2,381) | Case control | | |
| | Exposure: Carbon monoxide | | OR = 1.8[d] | H |
| Rushton and Alderson (1983)[157] | Male British oil distribution center employees, 1950–1975 (No. cases = 11) | Nonconcurrent prospective | SMR = 117 (mortality) | G |
| Thomas et al. (1982)[156] | Deceased white male members of Oil, Chemical and Atomic International Union (No. cases = 9) | Proportional mortality | PMR = 204 | G |
| | | **Miscellaneous Exposures** | | |
| Raffn et al. (1989)[174] | Male Danish asbestos cement industry workers, 1928–1984 (No. cases = 8) | Nonconcurrent prospective | SMR = 168 (mortality) | G |
| Cuzick and De Stavola (1988)[79] | Referral center patients England and Wales, 1978–1984 ($n$ = 798) | Case control | | |
| | Exposure: Asbestos | | RR = 3.5 | cr |
| | Paint | | RR = 1.9 | cr |
| | Chemicals | | RR = 2.0[d] | cr |
| | Photography | | RR = 6.0 | cr |
| | Electric cable | | RR = 3.0 | cr |

(*continued*)

**Table 23-1.** (*continued*) Reported Positive Associations Between Occupational Exposures and Multiple Myeloma

| Investigators | Study Population and Size | Design | Risk Estimate | Adjustments[a] |
|---|---|---|---|---|
| | **Miscellaneous Exposures** (*continued*) | | | |
| Gustavsson et al. (1988)[177] | Swedish trade union chimney sweeps (No. cases = 6) | Nonconcurrent prospective | SMR = 262 (morbidity) | G |
| Schwartz et al. (1988)[173] | SEER registrants (Washington, Utah, metropolitan Detroit, metropolitan Atlanta) ($n$ = 2,381) | Case control | | |
| | Exposure: High levels of asbestos | | OR = 1.1 | H |
| Edling et al. (1987)[168] | Abrasive manufacturing, males exposed to aluminum oxide, silicon carbide and formaldehyde dust, 1955–1983 (No. cases = 2) | Nonconcurrent prospective | SMR = 400 (morbidity) | G |
| Linet et al. (1987)[164] | Hospital Patients, Baltimore, MD ($n$ = 200) | Case control | | |
| | Exposure: Asbestos | | OR = 3.5[b,d] | F |
| Lundberg (1986)[166] | Swedish paint industry, male workers, 1955–1975 (No. cases = 3) | Nonconcurrent prospective | SMR = 549[d] (mortality) | G |
| Morris et al. (1986)[109] | SEER registrants (Washington, Utah, metropolitan Detroit, metropolitan Atlanta) ($n$ = 2,381) | Case control | | |
| | Exposure: Asbestos | | OR = 1.3 | H |
| | Paint | | OR = 1.6[d] | H |
| Spinelli et al. (1984)[179] | British Columbia, female hairdressers and cosmetologists, 1950–1978 (No. cases = 3) | Proportional mortality | PMR = 619[c,d] | A |
| Guidotti et al. (1982)[178] | Los Angeles County Tumor Registry Cosmetologists/hairdressers and manicurists (No. cases = 8) | Proportional incidence | PIR = 467 | A |

[a] Adjustments: A, for age; B, for age and area of residence or region; C, for age and familial relationship; D, for age and smoking; E, for age, gender, area of residence, and smoking; F, for self-respondent or surrogate respondent; G, for age and calendar period; H, for age, gender, race, and study site; I, for age and race; J, for age and gender; K, for age and marital status.

[b] Estimate of the odds ratio for matched pairs.

[c] Death certificate-based study.

[d] Statistically significant at the 0.05 level.

[e] Calculated by D.A. Riedel.

*Abbreviations:* cr, unadjusted (crude); No. cases, observed number of myeloma cases.

grain, and for those who worked in dusty occupations. A statistically significant increased risk of myeloma among farm workers remained after controlling for allergies. It was noted that hypersensitivity responses, such as allergic reactions involving the skin, may increase risk of multiple myeloma. Steineck and Wiklund,[112] in their study of Swedish agricultural workers, also suggested that agriculture workers may encounter exposures that evoke both allergic reactions and multiple myeloma. In a mortality study of grain workers,[122] 6 deaths from multiple myeloma among grain workers were observed versus 3.3 deaths expected. Owing to the small number of cases, it is unclear whether the culpable exposure(s) arose from work in various grain processing plants or exposure to pesticides as part of grain processing.

Case control studies using death certificates,[104,105] case control interview studies,[81,107,109,111] and prospective studies[123] have explored an association of agricultural pesticides (including herbicides and insecticides) and multiple myeloma. Specific pesticides that might account for the excess of multiple myeloma among farmers have not been identified. Exposure to phenoxy herbicides and chlorophenols,[124,125] chemicals commonly used in farming, have been associated with an increased risk of lymphomas. Similar links with multiple myeloma are lacking. Studies that have examined exposure to various pesticides have not been able to distinguish between the effects of different groups of chemicals on the risk of multiple myeloma.

Associations with pesticides and multiple myeloma have been shown to occur among farmers born in more recent years,[126] particularly among farmers from industrialized countries, including the United States, Canada, and Sweden. This phenomenon may reflect a change to modern chemical farming methods over the past 40 years.[105] Both herbicide and insecticide usage were associated with multiple myeloma among male Iowa farmers born in or after 1890, in a case control study using

death certificates.[104] Neither insecticide nor herbicide use was associated with myeloma among those born before 1890. Cantor and Blair[105] noted an association with fertilizer use and acres treated with insecticides in a case control study of Wisconsin farmers who died between 1968 and 1976. Of particular interest was a significant association of multiple myeloma with higher insecticide use among persons born after 1905. Cantor and Blair proposed that this increase in risk from multiple myeloma may be related to more intense use of insecticides after 1945.

A number of case control studies[81,107,109,111] have examined pesticide use and myeloma in general populations and hospital populations. Morris et al.[109] reported a 2.5-fold risk of multiple myeloma associated with pesticide use. Boffetta et al.[81] found that risk of myeloma did not increase appreciably among those who were exposed either to farming or to pesticide use but that risk rose dramatically for those exposed to both farming and pesticides (odds ratio = 4.3) over the risk for those exposed to neither. Pearce et al.[111] noted nonsignificant elevated risks for farmers and railway workers who reported potential exposure to phenoxy herbicides. The study also reported a nonsignificant increase in myeloma risk for exposures incurred by workers maintaining fences, by sawmill and timber workers, and by meat workers, as these activities involve potential exposure to chlorophenols. An Italian study[107] reported no association between pesticide use and multiple myeloma.

A recent study[123] reported no increased risk of multiple myeloma in a cohort of licenced pesticide applicators exposed to a plethora of insecticides, herbicides, and fungicides between 1965 and 1982. Results of this study should be regarded as preliminary, as most of the pesticide applicators were exposed infrequently (on a part-time basis), not enough information was gathered concerning individual chemical exposures, and a greater time interval should be considered to evaluate a possible latent effect.

## Metals

Statistical associations have been made between exposures to various metals and occupations believed to entail metal and metal dust exposure.[79,108,109,127-130] Small numbers of cases and lack of information on actual exposures have made it difficult to assess whether particular metal fumes or dusts or other occupational exposures are responsible for observed elevations in risk. Studies have not been consistent in indicating an excess risk of myeloma among any particular racial group of workers.

Blattner et al.[32] observed a significant increase of workers employed in printing and in the manufacture of fabricated metal and machinery within U.S. state economic areas (SEA) with high rates of multiple myeloma mortality. Correlations between occupation and SEAs with high myeloma mortality were restricted to non-whites. A later case control study by Cuzick et al.[79] failed to detect an excess of multiple myeloma risk among printers. No specific information was available concerning the kinds of metals involved in these occupations in either of the above studies.

Greene et al.[129] found a significant excess of myeloma deaths in male employees of the Government Printing Office. Unlike the findings in the correlational study above,[32] cases were mainly confined to white compositors, whose major exposure was to inorganic lead and lead vapor.[129]

Data from a case control study[109] revealed an elevated risk of multiple myeloma for employees who reported occupational exposures to metals (i.e., lead vapors and liquid, arsenic, cadmium, and copper powder and fumes). Analysis by race showed a significantly increased risk among whites who were exposed to metals but a non-significantly decreased risk among blacks who reported similar exposures. A nonsignificant elevated risk was observed for exposure to dyes. The presence of trace levels of lead and cadmium in U.S. water supplies has also been positively correlated with mortality from multiple myeloma.[131]

A mortality study of Canadian metal workers revealed a significant excess of multiple myeloma among machinists.[127] Machinists are typically responsible for the production of machine parts, usually from hard alloys, and may be exposed to cutting oils and mineral oil lubricants,[127] some of which may contain potential carcinogenic components, such as polycyclic aromatic hydrocarbons.[132] In the mouse plasmacytoma model, mineral oil induces myeloma-like tumors in the susceptible strains.[133]

McLaughlin et al.[108] noted an excess significant risk of multiple myeloma among smelter and metallurgy workers. Studies of foundry workers by Sorahan and Cooke[130] and by Giles et al.[128] revealed nonsignificant elevations in risk of multiple myeloma. Giles et al.[128] did note a significantly increased risk of myeloproliferative and lymphoproliferative disorders among foundry workers, suggesting that these diseases may share a common etiology with regard to metal exposure.

## Rubber Manufacturing

Mason[134] noted that white males who resided in U.S. counties in which the manufacture of synthetic rubber, synthetic fibers, and plastics occurred had a statistically significant elevation in multiple myeloma mortality rates as compared with total U.S. rates and control counties. Myeloma mortality rates for white females were unremarkable. The major employers in these counties were chemical companies that used vinyl chloride in primary manufacturing processes. Cuzick and De Stavola[79] reported a nonsignificant excess risk of multiple myeloma among persons reportedly working in rubber manufacturing.

Two other epidemiologic studies[135,136] reported excess

risks of multiple myeloma mortality among female rubber workers. In studies by Monson and Nakano,[136] the majority of females worked in the industrial products division, where rubber bands, hoses, belts, and molded rubber goods were made. White male employees were not at increased risk.[137] In the study of Swedish rubber workers, a slight excess of myeloma incidence was also seen.[138] Among workers who were assigned to weigh and mix chemicals used in processing, excess incidence was associated with those who had a longer exposure time to the mixing procedure, including employment during a period when dust control was minimal.

Delzell and Monson[139] subsequently reported a statistically significant risk of death from multiple myeloma for white male rubber reclaim workers and a notable excess of death from multiple myeloma among white reclaim workers versus white nonreclaim workers. Risk of death from multiple myeloma among black reclaim workers did not reach significant levels, as there were few blacks in this study. Reclaim workers were exposed to both natural and synthetic rubbers that were ground and devulcanized under heat and pressure as part of the reclaim process. A recent mortality study of male British rubber industry workers found no association with multiple myeloma mortality.[140]

## Benzene

Rinsky et al.[141] describe an occupational cohort of workers who were exposed to the manufacture of rubber hydrochloride. The manufacturing process included dissolution of natural rubber in benzene. A statistically significant excess of multiple myeloma mortality was observed among rubber workers who were exposed to benzene at low levels. Further analysis indicated a strong dose-response gradient for leukemia, as the number of deaths rose significantly with exposure to benzene. Based on the differences in benzene exposure among those who died of leukemia versus multiple myeloma, Rinsky et al. stated that perhaps low doses of benzene produce well-differentiated cancers such as multiple myeloma, while high doses may lead to leukemia. Decoufle et al.[142] noted that the benzene exposure in a petrochemical plant cohort may have played an etiologic role in the pathogenesis of several tumors of B-cell lineage, since two cases of myeloma and a case of chronic lymphocytic leukemia (CLL) were observed.

Benzene exposure has also been noted in several case reports of multiple myeloma. Aksoy et al.[143] reported seven cases of multiple myeloma, four of whom were occupationally exposed to benzene (a shoemaker, plastic factory worker, airplane factory worker, and furniture shop owner). A benzene link was also suggested by a case report from Japan by Nakayama et al.[144] of a conjugal cluster in which both husband and wife experienced 30 years of exposure to benzene hexachloride related to agricultural employment.

## Wood, Leather, and Textile Industries and Occupations

Most associations of multiple myeloma and the wood industry have been with pulp and paper making. Agu et al.[118] found a significant correlation of work in the paper industry and multiple myeloma mortality. However, this association disappeared after controlling for race. In another correlation study,[32] rates of multiple myeloma mortality were significantly elevated among white males who resided in state economic areas in which a large percentage of people were employed in paper production. Neither of these studies found an association for myeloma mortality and lumber and furniture manufacturing occupations. Milham[145] noted, in an evaluation of occupational mortality in Washington state, that proportional mortality for myeloma was significantly increased among paper and pulp mill workers. Nonsignificant increases were noted for carpenters and plywood workers, while no appreciable association was noted for those who worked in harvesting and milling timber or cabinet making. Subsequently, Milham and Demers[146] suggested that the risk among pulp and paper workers may vary depending on whether the sulfate or sulfite process is used in pulping, since the type of wood processed and chemicals differ in each method.[146–149] Schwartz[149] also noted a nonsignificant increased risk of mortality from lymphoma and multiple myeloma combined among paper and pulp workers in New Hampshire (not shown in Table 23-1). Another study found a significant association of myeloma with fresh wood exposure among persons employed by sawmills and paper factories in Sweden.[82] By contrast, several case control studies have failed to show any association between work in wood-related industries and multiple myeloma.[62,79–81,111,150,151]

Results from epidemiologic studies of manufacturing of leather have not been consistent. In a clinic-based study by Cuzick and De Stavola,[79] multiple myeloma cases who reported working in the leather tanning industry had a nearly twofold increase in risk over controls; however, this association was not significant. A mortality study of 4,876 former employees of a shoe manufacturing company in upstate New York indicated a significant excess in mortality from multiple myeloma of twofold among men and over threefold among women between 1960 and 1979.[152] The two correlation studies mentioned previously[32,118] found no association with leather manufacturing.

Results of studies evaluating an association of myeloma with textile processing appear contradictory. A linkage study of Swedish cancer incidence data and occupational census data[108] revealed a nearly threefold increased risk of multiple myeloma among women textile workers in the wool industry. The correlation study using U.S. data[32] reported a slight increase in the number of deaths from multiple myeloma in economic areas with textile manufacturing over the period 1950 to 1969. The correlation study using Texas data[118] found a negative

association of borderline significance. No excess myeloma mortality with employment in the textile industry was observed in a proportional mortality study of female workers in North Carolina.[153]

## Petroleum Refining, Petroleum Products, and Fuel Combustion Products

A number of occupational studies have investigated the relationship between employment in the petroleum industry and mortality from multiple myeloma. Blattner et al.[32] found a high correlation between multiple myeloma mortality and SEAs where a high percentage of white males were employed by the petroleum industry.

Thomas et al.[154–156] evaluated mortality patterns of workers from three Texas oil refineries in several reports. The first report[154] found an excess of multiple myeloma deaths (six cases) among active white male long-time union members, who were union members for 10 or more years and employed in petroleum refining and production of petrochemicals (not shown). In the second study,[156] which included retirees, an additional three multiple myeloma deaths were identified. Interestingly, there were no multiple myeloma deaths among nonwhite workers from all three refineries during the study period. When company work histories of cases and controls were included, no specific associations were found with specific work category/product exposure (not shown).[155]

Other occupational studies have reported associations of exposure to petroleum and combustion products with myeloma in British oil distribution centers[157] and U.S. petroleum refineries.[158] An excess of deaths due to cancers of lymphatic tissue has been seen in several petroleum refinery populations,[159–161] while similar studies have not found this association.[162,163] In a case control study by Linet et al.,[164] a significantly elevated risk of multiple myeloma was seen among subjects occupationally exposed to petroleum. An association between myeloma and exposure to engine exhausts was suggested in a case control study conducted by Flodin et al.[82] A statistically significant trend association for myeloma cases occupationally exposed to gases and fumes for at least 10 years has also been reported.[79] Morris et al.[109] noted a statistically significant elevation in risk of multiple myeloma from purported exposures to carbon monoxide (i.e., exposure to diesel, jet fuel, or automobile exhausts, coal fumes, smoke). Another case control study[81] did not find a significant excess of myeloma cases among subjects exposed to gasoline or diesel exhausts, coal products, or chemical solvents.

## Miscellaneous Environmental and Occupational Exposures

Occupational exposures such as paints, chemicals, and asbestos have been evaluated as potential risk factors of multiple myeloma. Paints and chemicals represent broad exposure categories, making it difficult to identify the specific component responsible for an excess risk.

Positive associations between multiple myeloma and exposure to paint have been reported in case control and prospective studies.[79,109,165,166] Painters are typically exposed to a mixture of aromatic, chlorinated, and aliphatic hydrocarbons, ketones, ethers, and esters.[109] However, the specific chemical exposures that heighten myeloma risk have not yet been identified. A study of Swedish paint manufacturing workers reported a statistically significant excess of multiple myeloma deaths among those employed for at least 5 years.[166]

A Swedish cancer morbidity study noted an excess of deaths from myeloma and malignant lymphomas combined among chemical factory workers exposed to established or suspected carcinogens, including piperazine, urethane, formaldehyde, benzyl chloride, ethylene oxide, and epichlorohydrin (not shown in Table 23-1).[167] A small number of myeloma cases were noted among a cohort of workers from an abrasive manufacturing company with work exposures to dust from processes using aluminum oxide and silicon carbide abrasives.[168]

Asbestos exposure has been linked to myeloma in several early case reports[169–172] of miners and others with occupational exposures. At least four case control studies[79,109,164,173] and one prospective study[174] have reported a positive association between multiple myeloma and exposure to asbestos. In the case control study by Cuzick and De Stavola[79] multiple myeloma cases who reported being exposed for at least 10 years had a significantly greater chance of the development of multiple myeloma than did hospital control patients. A nonsignificant excess risk of myeloma was reported for those employed in photography and for those exposed to electric cable. An association between occupational exposure to electromagnetic fields and multiple myeloma was not shown in two studies attempting to evaluate this relationship.[175,176]

A marginally significant increase in multiple myeloma incidence among Swedish chimney sweeps was reported in a recent cohort study.[177] Potential occupational exposures include polycyclic aromatic hydrocarbons (formed by combustion of coal, wood, coke, and oil) and metals such as arsenic, nickel, and chromium.[177]

Recent studies have reported excess multiple myeloma cases among beauticians and cosmetologists.[118,178,179] A myriad of organic and inorganic chemicals, including lead-based hair dyes, are handled in this occupation, making the agents responsible for excess risk difficult to assess. One study that evaluated cancer incidence among cosmetologists[180] did not find an association with multiple myeloma.

The role of drugs has been suggested by case reports of myeloma following use of phenytoin[181] and sulfinpyrazone.[182] Friedman[83] ascertained the use of phenytoin and other drugs among multiple myeloma cases and controls. Propoxyphene use was predictive for multiple myeloma (not shown), but no association was observed for phenytoin. In the case control study by Linet et al.,[164] nonsignificant elevated risks of multiple myeloma were found for prior use of phenytoin, phenobarbital, diaze-

pam, propranolol, ibuprofen, diet drugs, and stimulants (not shown). Use of laxatives was significantly associated with risk of multiple myeloma.

The role of occupational exposures on the risk of multiple myeloma remains unclear. To date, the most consistent association has been observed for farming occupations. The epidemiologic literature has found nonspecific associations for metal, rubber, benzene, wood, leather, textile, petroleum, and miscellaneous occupations and industries. However, given the wide variety of exposures incurred in all these areas, links and causal associations with specific chemical agents and type of work are lacking. None of these associations explains the continuing increase of multiple myeloma in the United States.

## FAMILIAL AND GENETIC FACTORS

Familial occurrence of myeloma is well established, and a previous review documents that the median age and sex ratio of the 75 reported familial cases resemble those of nonfamilial cases.[10] Although there continue to be reports of siblings affected with myeloma, no evidence has been presented that conclusively implicates multiple myeloma as an inherited disease. Additional research has been conducted to ascertain genetic markers and environmental variables that correlate with multiple myeloma.

### Case Reports Among Siblings and Spouses and Other Family Members

Several reports from the past decade document multiple myeloma occurring among siblings.[183,184] In a review of 37 families with at least two members with myeloma, Shoenfeld et al.[184] noted that the disease occurred among siblings in 25 of these families. Patients with familial myeloma did not differ significantly from those with nonfamilial myeloma with respect to sex, age, distribution of monoclonal proteins, and other clinical data. Isobe et al.[183] reported multiple myeloma in a brother and sister. The siblings produced different monoclonal immunoglobulins, IgA-κ and IgG-κ. Ig levels among three children of the sister indicated that all had decreased IgM levels.

Cases of multiple myeloma among spouses have been reported for many years[185–192] and suggest the role of environmental factors in myeloma etiology. In a report of a multiple myeloma cluster, Kyle et al.[190] noted that two of the six cases were husband and wife. None of the cases appeared to share any unusual exposures, and the cause of the cluster remains unknown.

In 1984, Linet[191] reported chronic lymphocytic leukemia in a husband and multiple myeloma in a wife. The diagnoses were made approximately 1 year apart. The couple encountered several shared environmental exposures, including interior wall paint, insecticide spray, embalming fumes or fluid from a work uniform, and smoke exhaust from a nearby diesel engine parts plant. Of these, weekly insecticide spray was the heaviest exposure and may be the most incriminating. A variety of sprays had been used, some of which contained pyrethrins and perhaps benzene.

In 1983, Kyle and Greipp[188] introduced the first report of multiple myeloma in successive spouses. In one instance, a husband had two wives in whom myeloma developed. In the second instance, a woman had two husbands who died from multiple myeloma. Exposure to chemicals, radiation, and other environmental and infectious agents was unremarkable in both situations; however, both husbands who died of myeloma had been exposed to benzene in their occupations as mechanics. McCrea and Morris[193] studied three families in Northern Ireland in which multiple myeloma occurred in two first-degree relatives concurrently. The monoclonal type of immunoglobulin varied in both cases within each family.

Recently, several case control studies have been published that examine the occurrence of multiple myeloma and other disorders in related family members.[194–196] Results from a case control study of multiple myeloma conducted in North Carolina revealed a nonsignificant elevated risk of multiple myeloma associated with a history of multiple myeloma among first-degree relatives.[194]

Linet et al.[196] interviewed myeloma cases and controls in Baltimore for family history of autoimmune disorders and cancer among first-degree relatives. Results indicated a statistically significant risk of multiple myeloma associated with family history of autoimmune disorder (mainly rheumatoid arthritis), systemic lupus erythematosus, pernicious anemia, and leukemia.

In a recently published case control study,[195] multiple myeloma cases had a higher proportion of first-degree relatives with degenerating or demyelinating central nervous system diseases than did control subjects. Bernard et al.[197] previously noted an association between multiple sclerosis and lymphomas and leukemias. Risk was elevated for cases who had a family history of Parkinson's disease and multiple sclerosis. In addition to shared genetic susceptibility for these diseases among family members, a second environmentally based etiologic step may be required for pathogenesis.

### Genetic Marker Studies

Over the past 10 years, several genetic studies of multiple myeloma have been conducted to determine the similarities and differences that myeloma cases and controls have with respect to immunogenetic markers.[198–201] Ludwig and Mayr[201] tested three groups of Caucasian patients who resided in the vicinity of Vienna, Austria, for ABO blood group, G1m and Km immunoglobulin complex allotypes, and human leukocyte antigens (HLA) in an effort to describe susceptibility to multiple myeloma. No differences for HLA-A, -B, and -C loci, G1m and Km immunoglobulin allotypes, and ABO blood groups were noted between multiple myeloma patients and con-

trols. The predominant immunoglobulin allotype among multiple myeloma patients was G1m(x).

Two reports indicate there may be a genetic basis of multiple myeloma etiology. Horwitz et al.[199] reported multiple myeloma in a sister and two brothers. Both brothers had monoclonal IgG-κ myeloma, and the sister had κ light chains in the urine, indicating a genetic basis of this disease among the three siblings. Grosbois et al.[198] reported multiple myeloma in nontwin brothers who were identical for $A_2B_{12}Bf_sDR_4GIo2/A_9B_{27}Bf_sDR_2GIo1$, the HLA genotype of monoclonal immunoglobulin of the IgG-κ isotype variety. Four of nine members were haploidentical for one of the above haplotypes and had hypogammaglobulinemia. It is possible that identical major histocompatibility markers is indicative of genetic factors playing a role in the development of myeloma.

Several reports published during the 1970s have indicated that the frequency of the HLA "4C" group was slightly increased in myeloma cases.[202–205] HLA "4C" has been specified as HLA-B5, -B15, -B18, and -Bw35.[206,207] Smith et al.[208] also suggested an association of w22 (Bw54-56) with κ-chain myeloma and A9 with immunoglobulin A (IgA) myeloma. A three- to fourfold excess of antigens A28 and B27 in myeloma was reported by Tananov.[209] In 1983, Leech et al.[210] reported an association between multiple myeloma with HLA-Cw5 antigen, based on a study of 22 black patients and 138 control patients. This finding has not yet been replicated by other studies.

Leech et al.[200] examined whether Ig allotypes of the Gm series, which code for IgG heavy chain, are associated with multiple myeloma among black patients. The G3m(g5) allotype was found to be significantly associated with myeloma. It was concluded that G3m(g5) indicates inherited susceptibility toward the development of multiple myeloma among members of this population.

One important cytogenetic abnormality of etiologic relevance to multiple myeloma is the 14q+ abnormality. Wurster-Hill et al.[211] reported the first examples of this abnormality in cases of plasma cell leukemia and multiple myeloma, a finding subsequently confirmed by several case reports.[212–214] Gould et al.[215] examined 115 myeloma patients for karyotypic abnormalities and found that the translocation t(8;14)(q24;q32) was statistically associated with IgA myeloma protein. This translocation was found in 80 percent of all Burkitt's lymphomas examined.[216] Although the 14q+ abnormality has not been found in every case of multiple myeloma, the pattern suggests that a common cytogenetic abnormality may play a role in the pathogenesis of various B-cell neoplasms; this may have a biologic basis, since human immunoglobulin genes have been assigned to this chromosome.[217] Other chromosomal aberrations in multiple myeloma patients include rearrangements of chromosomes 1 and 14, trisomy 3, 5, 7, 9, and 11, and monosomy 8 and 13.[218]

Recent studies have implicated malignant transformation by oncogenes and chromosomal abnormalities in malignant plasma cells of multiple myeloma patients in the pathogenesis of the disease.[215,219–221] Selvanayagam et al.[221] found an increased level of c-*myc* mRNA from myeloma plasma cells in 9 of 37 myeloma patients, two of whom had rearrangements of the c-*myc* locus. Gould et al.[215] found that identical cytogenetic abnormalities and *myc* alterations were mostly associated with IgA myeloma. Ernst et al.[219] isolated a myeloma cell line from a patient with a rearranged *myc* allele that was found to have an additional activated *ras*$^n$ gene. Co-transfection with *myc* and *ras* may have implications for degree of tumorigenicity, and a synergistic relationship between *myc* and *ras* may exist in human disease. Transfer of the human oncogene c-*myc* to positions juxtaposed to Ig genes on chromosomes 2, 14, and 22 has also been defined for Burkitt's lymphoma.[222] A chromosome study was conducted in Japan[220] on 61 patients with differentiated B-cell malignancies. Four of 26 myeloma patients had 14q+ marker chromosomes [two cases with t(14;18)(q32.3;q21.3) one case with t(3;14)(p11;q32), one case undetermined]. One Waldenström's macroglobulinemia (WM) case had a t(14;18)(q32;q21) rearrangement. One case each of WM and myeloma had 14q+ markers associated with the *bcl*-2 oncogene. Further research of chromosome rearrangements may help in diagnosing B-cell malignancies and in predicting prognosis.[220]

Additional consideration must be given to determine at what stage in the B-cell cycle abnormalities occur. Altered disease manifestation may occur if genetic abnormalities occur during pre-B cell development or later in differentiation of the Ig secreting plasma cell.[223] Epstein et al.[224] evaluated the expression of early and mature B-cell surface markers among 44 myeloma patients. One or both of the following cellular markers were expressed: an early B-cell marker known as common acute lymphoblastic leukemia antigen (CD10 formerly, CALLA) and/or a mature plasma cell antigen (R1-3), suggesting that pre-B cell involvement has an important role in the development of myeloma.

## Related Disorders

Benign monoclonal gammopathy (BMG) has occasionally been reported in the relatives of myeloma cases.[225,226] Nevertheless, some myeloma-susceptible families have had clinically normal relatives with benign M spikes, suggesting that a variant of familial myeloma is associated with paraproteinemia.[227–229] Axelsson and Hallen[230] uncovered three families with BMG in close relatives in a population-based survey in Sweden. Williams et al.[231] also reported that probands with BMG have an increased number of relatives with BMG, as compared with control families. Genetic determinants of BMG are also suggested by the relationship to certain HLA types[211,232,233] and by the predominance of the IgG1 subclass.[234]

Several studies have also suggested that polyclonal Ig levels are increased among the close relatives of myeloma cases.[235,236] In some myeloma-susceptible families, other lymphoproliferative neoplasms have been de-

scribed, including giant follicular lymphoma, with an IgM paraprotein, CLL, and *Mycosis fungoides*.[237–239]

In contrast to myeloma, the relatives of patients with Waldenström's macrogammaglobulinemia (WM) seem to have a plethora of immunologic abnormalities, including an excess of polyclonal IgM, benign IgM spikes in close relatives, excess κ light chains, various autoantibodies, and subclinical immune defects.[10,235,240–247] Seligmann et al.[247] reported a high frequency of rheumatoid factor (an IgM autoantibody) in patients with WM and in their relatives compared with healthy control subjects, especially for those under 60 years of age. HLA types A2, B8, and DRw3 were reported in a familial cluster of macroglobulinemia and immunologic abnormalities.[241] These individuals also had positive reactions for the B-cell allo-antigens Ia 172 and 350, previously reported in patients with the lymphoma-susceptible sicca syndrome.[248] A heritable abnormality in the immunoregulation of B lymphocytes may have occurred, suggesting that a defective immune response gene may predispose to lymphoproliferation or autoimmunity. In a recent report of WM in four brothers,[246] three of four shared a common HLA haplotype, A19.2 B7 DR2. All brothers produced an excess of IgM and either κ or λ light chains.

Numerous case reports of myeloma among siblings, spouses, and family members have been documented; however, no conclusive evidence of myeloma as an inherited disease has been presented. New studies have highlighted some similarities of HLA types and monoclonal Ig types among related myeloma patients; however, the results generally lack consistency, and common familial environmental exposures must be ruled out. Associations with oncogenes and chromosomal aberrations among myeloma patients have become more specific and are intriguing, particularly when genes coding for Igs are involved.

## ROLE OF CHRONIC ANTIGENIC STIMULATION

Myeloma research has become increasingly focused on the role of the immune system in the disease[249] and has attempted to define chronic antigenic stimulation (CAS) and explore CAS as an etiologic factor. Recent studies[79–81,111,164,250–252] examine CAS as past exposure to viral or bacterial infectious agents, to autoimmune disorders, or to inorganic material that may stimulate the immune system. While some of the above studies report statistically significant associations between multiple myeloma and allergies and related disorders,[111,164,252] chronic bacterial infections,[164] diabetes,[81] and medical implants[251] and view these exposures as immune system stimulants, others have found no relationship with diabetes,[80] viral and bacterial illnesses,[251] childhood illnesses and immunizations,[79,251] autoimmune disorders,[80,164,253] and allergies.[251] A Los Angeles-based study did not find a relationship between AIDS and multiple myeloma.[254]

Similarly, other studies have focused on pre-existing conditions in patients that similarly stimulate the immune system to produce the monoclonal antibodies frequently found in myeloma. An example is the association of rheumatoid arthritis, an autoimmune disorder, with multiple myeloma.[255–257] Pettersson et al.[258] observed four patients with sarcoidosis (a condition that can lead to B-cell stimulation and hypergammaglobulinemia) in whom myeloma subsequently developed.

Multiple myeloma patients have difficulty in combating bacterial infections, since they exhibit a decrease in their primary response against bacterial infections, have defective complement activation against bacterial pathogens that require complement activation for maximum resistance,[259] and have granulocytic defects.[260]

The inconsistency between the association of multiple myeloma and CAS may be attributable to differences in the definition criteria of CAS used by investigators. Cohen et al.[261] explored the hypothesis that chronic infections and allergic and autoimmune disorders are more frequent among cases of multiple myeloma. Patients were interviewed on past medical history and family medical history for immune stimulating conditions, including pyelonephritis, urinary tract infections, prostatitis, rheumatoid arthritis, allergies, bronchitis, tuberculosis, and other chronic illnesses, as outlined in a previous study.[262] No association was found for history of immune stimulating conditions. In fact, cases had significantly fewer of these exposures than did controls, which may be been an artifact of studying a hospital-based population.

Koepsell et al.[263] evaluated CAS in a more systematic and comprehensive manner. Case patients and control patients were interviewed for exposures that may have resulted in antigenic stimulation. In addition to examining each antigenic exposure as a separate risk factor, taxonomies for the exposures were created with respect to the biologic nature of the antigen, chronicity of exposure, and route of entry. Dose of antigen was calculated on the basis of a summary score of total number of viral and bacterial illnesses, number of immunizations, and number of allergy desensitization injections received. Only rheumatic fever and urinary tract infections were specifically associated with multiple myeloma. There was a marginal increase in risk of multiple myeloma with an increase in the number of bacterial illnesses and an inverse relationship for number of diseases for which immunizations were received. While Koepsell et al. controlled for education as a marker for socioeconomic status, the inverse relationship with number of immunizations may indicate that there is residual confounding on this basis.

The role of CAS in multiple myeloma is inconclusive, mainly because of inconsistencies of the definition of CAS. Studies of prior exposure to infectious agents and diseases have indicated contradictory results. Investigations of CAS and myeloma have become more focused on the particular biologic characteristics of the disease agent and are beginning to consider immunologic char-

acteristics and effector mechanisms of the immune system used in fighting various disease agents. Perhaps with further laboratory-based investigations that incorporate immunogenetic measures of immune function and more biologically relevant definitions of CAS, the role of CAS in myeloma will become more meaningful.

## CONCLUSIONS

The causes of multiple myeloma and related dyscrasias are largely unknown. Multiple myeloma is a disease of older age. In the United States, myeloma rates are increasing dramatically for both blacks and whites; however, black rates remain higher than white rates. Internationally, incidence rates in industrialized nations are higher than in developing nations, which may be a reflection of greater access to health care and more aggressive cancer registry coverage in the industrialized nations. Socioeconomic status measures have not shown a consistent relationship with myeloma incidence, mortality, and survival. It is likely that other factors, such as availability and level of medical care, not measured by socioeconomic status play a more direct role in myeloma risk.

Well-documented risk factors include radiation and certain occupational exposures, such as farming or pesticide use, or both. Radiation-induced multiple myeloma does not fit the age pattern seen for radiogenic leukemia[93] (i.e., increases at earlier ages). Instead, radiation appears to amplify the risk of multiple myeloma among exposed groups at the usual age of diagnosis for this cancer. While associations of myeloma with other exposures (e.g., metals, rubber, benzene, wood, petroleum, CAS) have been documented in this review, consistent definitions of the implicated exposures are lacking, making causal inferences with myeloma difficult. Plausible conclusions about myeloma risk on the basis of available epidemiologic studies may be hampered by failure to consider an adequate latent period of the exposure, in addition to the lack of precise and accurate exposure information.

New research on chromosomal aberrations and oncogenes in myeloma may shed light on the pathogenic mechanism of the disease as well as provide genetic information that may be useful in the prediction and prognosis of myeloma and other B-cell malignancies. While the role of CAS and multiple myeloma is not well understood, future studies should incorporate laboratory-based immunologic measures to explore possible mechanisms within the immune system.

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## REFERENCES

1. World Health Organization: Manual of the International Statistical Classification of Diseases, Inquiries, and Causes of Death. WHO, Geneva, 1949, 1959, 1969, 1979
2. Sondik EJ: Cancer Statistics Review 1973–1986. DHHS publication no. NIH 89-2789. US Government Printing Office, Washington DC, 1989
3. Fraumeni JF, Jr: Environmental and genetic determinants of cancer. J Environ Pathol Toxicol 1:19, 1977
4. Cutler SJ, Young JL: The Third National Cancer Survey: Incidence data. Natl Cancer Inst Monogr 41:22, 1975
5. Linos A, Kyle RA, O'Fallon MW et al: Incidence and secular trend of multiple myeloma in Olmsted County, Minnesota: 1965–1977. JNCI 66:17, 1981
6. Devesa SS, Silverman DT, Young JL, Jr et al: Cancer incidence and mortality trends among whites in the United States, 1947–84. JNCI 79:701, 1987
7. Pickle LW, Mason TJ, Howard N et al: Atlas of U.S. Cancer Mortality Rates and Trends Among Whites, 1950–1980. DHHS publication no. NIH 87-2900. US Government Printing Office, Washington DC, 1987
8. Pickle LW, Mason TJ, Howard N et al: Atlas of U.S. Cancer Mortality Rates and Trends Among Nonwhites, 1950–1980. DHHS publication no. NIH 90-1582. US Government Printing Office,Washington DC, 1990
9. Davis DL, Lilienfeld AD, Gittelsohn A, Scheckenbach ME: Increasing trends in some cancers in older Americans: fact or artifact? Toxicol Indust Health 2:127, 1986
10. Blattner WA: Epidemiology of multiple myeloma and related plasma cell disorders: an analytic review. p. 1. In Potter M (ed): Progress in Myeloma: Biology of Myeloma. Elsevier/North-Holland, New York, 1980
11. Carli PM, Bailly F, Tavernier C et al: Multiple myeloma: epidemiological features in a well-defined population in Burgandy, France. Int J Epidemiol 18:330, 1989
12. Carli PM, Milan C, Lorenzini JL et al: Incidence of hematopoietic malignancies in a well defined population in France. Oncology 43:354, 1986
13. Dawson AA, Ogston D: High incidence of myelomatosis in north-east Scotland. Scott Med J 18:75, 1973
14. Dimitrova E, Plesko I, Somogyi J, Kiss J: Trends and patterns in cancer incidence in Czechoslovakia, 1968–1985. Neoplasma 36:245, 1989
15. Greally JM, O'Toole G, McCann H et al: Monoclonal gammopathies in the west of Ireland: a preliminary study. Ir J Med Sci 154:94, 1985
16. Egan EL, Grimes H, O'Beirn DP: Multiple myeloma in the west of Ireland, presentation and frequency. Ir Med J 71:23, 1978
17. Kim SI, Lee CK: Leukemia among Koreans. A statistical and hematological study of 601 cases of leukemia and allied conditions. Gann Monogr Cancer Res 18:229, 1976
18. Lickiss JN, Giles GG, Baikie MJ et al: Myeloproliferative and lymphoproliferative disorders in Tasmania, 1972–80: patterns in space and time. JNCI 72:1223, 1984
19. Ludwig H, Fritz E, Friedl HP: Epidemiologic and age dependent data on multiple myeloma in Austria. JNCI 68:729, 1982
20. Miller RW: Cancer epidemics in The Peoples Republic of China. JNCI 60:1195, 1978
21. Quiroga Micheo E, Calcagno EJ, de Sijvarger SR et al: Epidemiology of hemopoietic system neoplasms in Argentina. Biol Trace Elem Res 1:183, 1979

22. Ramsey DM: A five year cumulative survey of cases of leukemia and myelomatosis in the south-east of Scotland. Health Bull (Edinb) 33:58, 1975
23. Shapira R, Carter A: Multiple myeloma in northern Israel, 1970–1979. Cancer 58:206, 1986
24. Stalsberg H: Lymphoreticular tumors in Norway and in other European countries. JNCI 50:1685, 1973
25. Storm HH, Prener A: Second cancer following lymphatic and hematopoietic cancers in Denmark, 1943–80. Natl Cancer Inst Monogr 68:389, 1985
26. Weiss NS: Geographic variation in the incidence of the leukemias and the lymphomas. Natl Cancer Inst Monogr 53:139, 1979
27. Waterhouse JA, Muir C, Correa P et al: Cancer Incidence in Five Continents. IARC Publication 15. Vol. 3. International Agency for Research on Cancer, Lyon, France, 1976
28. Waterhouse JA, Muir C, Shanmugaratnam K et al: Cancer Incidence in Five Continents. IARC Publication 42. Vol. 4. International Agency for Research on Cancer, Lyon, France, 1982
29. Muir C, Waterhouse J, Mack T et al: Cancer Incidence in Five Continents. IARC Publication 88. Vol. 5. International Agency for Research on Cancer, Lyon, France, 1987
30. Parkin DM: Cancer Occurrence in Developing Countries. IARC Publication 75. International Agency for Research on Cancer. Lyon, France, 1986
31. Kyle RA, Nobrega FT, Kurland LT: Multiple myeloma in Olmsted County, Minnesota, 1945–1964. Blood 33:739, 1969
32. Blattner WA, Blair A, Mason TJ: Multiple myeloma in the United States, 1950–75. Cancer 48:2547, 1981
33. MacMahon B, Clark DW: The incidence of multiple myeloma. J Chron Dis 4:508, 1965
34. McPhedran P, Heath CW, Jr, Garcia J: Multiple myeloma incidence in metropolitan Atlanta, Georgia: racial and seasonal variations. Blood 39:866, 1972
35. Blattner WA, Jacobson RJ, Shulman G: Multiple myeloma in South African blacks. Lancet 1:928, 1979
36. Payet M, Sakale M, Pene P et al: La Maladie de Kahle chez l'Africain, a propos de 38 cas. Bull Soc Med Afr Noire Lang Fr 8:838, 1963
37. Waldbaum B, Gelfand M: Myelomatosis in the Rhodesian African. Trop Geogr Med 26:26, 1974
38. Traub N: Multiple myeloma at the University Teaching Hospital, Lusaka: a retrospective study. Med J Zambia 11:148, 1977
39. Edington GM: Tumors of lymphoretricular tissue including the Burkitt lymphoma but excluding leukaemia in Nigeria with special reference to the northern savanna. Niger Med J 8:75, 1978
40. Edington GM, Hendrickse M: Incidence and frequency of lymphoreticular tumors in Ibadan and the western state of Nigeria. JNCI 50:1623, 1973
41. Iyun A, Issacs-Sodeye A: Multiple myelomatosis in Ibadan: a comparative study. East Afr Med J 53:581, 1976
42. Mukiibi JM, Kyobe J: Pattern of multiple myeloma in Kenyans. Trop Geogr Med 40:20, 1988
43. Otieno LS, Ogada T: Multiple myeloma at Kenyatta National Hospital 1973–1976. East Afr Med J 54:574, 1977
44. DeVilliers LS: Dysgammaglobulinemia in the Bantu. S Afr Tydskrifuir Geneeskunde 43:536, 1969
45. Levy LM: The pattern of haematological and lymphoreticular malignancy in Zimbabwe. Trop Geogr Med 40:109, 1988
46. Talerman A: Clinico-pathologic study of multiple myeloma in Jamaica. Br J Cancer 23:285, 1969
47. Takatsuki K, Uchiyama T, Veshima Y et al: Adult T-cell leukemia: proposals as a new disease and cytogenetic phenotypic, and functional studies of leukemic cells. Gann Monogr Cancer Res 28:15, 1982
48. Hinuma Y, Komoda H, Chosa T et al: Antibodies to adult T-cell leukemia associated antigen (ATLA) in sera from patients with ATL and controls in Japan: a nationwide seroepidemiologic study. Int J Cancer 29:631, 1982
49. Hinuma Y, Nagata K, Hanaoka M et al: Adult T-cell leukemia antigen in an ATL cell line and detection of antibodies to the antigen in human sera. Proc Natl Acad Sci USA 78:6476, 1981
50. Lin KT: Myeloma proteins in adult Chinese patients. Chin J Microbiol 10:28, 1977
51. Ohtani H: Myeloma and immunoglobulins. Jpn J Clin Pathol 24:287, 1976
52. Blattner WA: Multiple myeloma and macroglobulinemia. p. 795. In Schottenfeld D, Fraumeni JF, Jr (eds): Cancer Epidemiology and Prevention. WB Sanders, Philadelphia, 1982
53. Hansen NE, Karle H, Olsen JH: Trends in the incidence of multiple myeloma in Denmark 1943–1982: a study of 5500 patients. Eur J Haematol 42:72, 1989
54. Nandakumar A, Dougan LE, English DR, Armstrong BK: Incidence and outcome of multiple myeloma in Western Australia 1960 to 1984. Aust NZ J Med 18:774, 1988
55. Turesson I, Zettervall O, Cuzick J et al: Comparison of trends in the incidence of multiple myeloma in Malmo, Sweden and other countries, 1950–1979. N Engl J Med 310:421, 1984
56. Cuzick J, Velez R, Doll R: International variations and temporal trends in mortality from multiple myeloma. Int J Cancer 32:13, 1983
57. Velez R, Beral V, Cuzick J: Increasing trends of multiple myeloma mortality in England and Wales; 1950–1979: are the changes real? JNCI 69:387, 1982
58. Kato I, Tajima K, Hirose K et al: A descriptive epidemiological study of hematopoietic neoplasms in Japan. Jpn J Clin Oncol 15:347, 1985
59. Hoover RN, Mason TJ, McKay FW et al: Geographic patterns of cancer mortality in the United States. p. 343. In Fraumeni JF, Jr (ed): Persons at High Risk of Cancer, an Approach to Cancer Etiology and Control. Academic Press, San Diego, 1975
60. Devesa SS: A study of the association of cancer incidence with income and education among whites and blacks. Ph.D dissertation, The Johns Hopkins University, 1979
61. McWhorter WP, Schatzkin AG, Horm JW, Brown CC: Contribution of socioeconomic status to black/white differences in cancer incidence. Cancer 63:982, 1989
62. Nandakumar A, Armstrong BK, de Klerk NH: Multiple myeloma in Western Australia: a case-control study in relation to occupation, father's occupation, socioeconomic status and country of birth. Int J Cancer 37:223, 1986
63. Levi F, Negri E, La Vecchia C et al: Socioeconomic groups and cancer risk at death in the Swiss Canton of Vaud. Int J Epidemiol 17:711, 1988
64. Pearce NE, Howard JK: Occupation, social class and male cancer mortality in New Zealand, 1974–78. Int J Epidemiol 15:456, 1986
65. Johnston JM, Grufferman S, Bourguet CC et al: Socioeconomic status and risk of multiple myeloma. J Epidemiol Community Health 39:175, 1985

66. Lenhard RE, Enterline JP, Crowley J, Ho GYF: The effects of distance from primary treatment centers on survival among patients with multiple myeloma. J Clin Oncol 5:1640, 1987
67. Savage D, Lindenbaum J, Van Ryzin J et al: Race, poverty and survival in multiple myeloma. Cancer 54:3085, 1984
68. Weston B, Grufferman S, MacMillan JP, Cohen HJ: Effects of socioeconomic and clinical factors on survival in multiple myeloma. J Clin Oncol 5:1977, 1987
69. Cuzick J: Radiation induced myelomatosis. N Engl J Med 304:204, 1981
70. Ichimaru M, Ishimaru T, Mikami M et al: Multiple myeloma among atomic bomb survivors in Hiroshima and Nagasaki, 1950–1976: relationship to radiation dose absorbed by marrow. JNCI 69:323, 1982
71. Shimizu Y:, Kato H, Schull WJ et al: Life span study report II. Part 1. Comparison of risk coefficients for site-specific cancer mortality based on the D586 and T65DR shield kerma and organ dose. Radiation Effects Research Foundation Technical Report (RERF TR), 12-87, 1987
72. Wakabayashi T, Kato H, Ikeda T, Schull WJ: Studies of the mortality of A-bomb survivors. Report 7. Radiat Res 93:112, 1983
73. Hall CB, Hall WJ, Ashley FW et al: Serum immunoglobulin levels in atomic bomb survivors in Hiroshima, Japan. Am J Epidemiol 98:423, 1973
74. Kamada N, Kuramota A, Katsuki T et al: Chromosome aberrations in B lymphocytes of atomic bomb survivors. Blood 53:1140, 1979
75. Lewis EB: Leukemia, multiple myeloma and aplastic anemia in American radiologists. Science 142:1492, 1963
76. Ishimaru T, Finch SC: More on radiation exposure and multiple myeloma. N Engl J Med 301:439, 1979
77. Matanoski GM, Seltser R, Sartwell PE et al: The current mortality rates of radiologists and other physician specialists: specific causes of death. Am J Epidemiol 101:199, 1975
78. Matanoski GM: Risk of cancer associated with occupational exposure in radiologists and other radiation workers. p. 241. In Burchenal JH, Ottegen HF (eds): Cancer, Achievements, Challenges, and Prospects for the 1980's. Grune & Stratton, Orlando, FL, 1982
79. Cuzick J, De Stavola B: Multiple myeloma—a case-control study. Br J Cancer 57:516, 1988
80. Gallagher RP, Spinelli JJ, Elwood JM, Skippen DH: Allergies and agricultural exposure and risk factors for multiple myeloma. Br J Cancer 48:853, 1983
81. Boffetta P, Stellman SD, Garfinkel L: A case-control study of multiple myeloma nested in the American Cancer Society prospective study. Int J Cancer 43:554, 1989
82. Flodin U, Fredriksson M, Persson B: Multiple myeloma and engine exhausts, fresh wood, and creosote: a case-referent study. Am J Ind Med 12:519, 1987
83. Friedman GD: Multiple myeloma: relation to propoxyphene and other drugs, radiation and occupation. Int J Epidemiol 15:424, 1986
84. Blair A, Hayes HM: Mortality patterns among U.S. veterinarians, 1947–1977: an expanded study. Int J Epidemiol 11:391, 1982
85. Wang J-X, Boice JD, Jr, Li B-X et al: Cancer among medical diagnostic X-ray workers in China. JNCI 80:344, 1988
86. Dolphin GW: A comparison of the observed and the expected cancers of the haematopoietic and lymphatic systems among workers at Windscale: a first report. National Radiation Protection Board NRPB-R54, Harwell, England, 1976
87. Mancuso TE, Stewart A, Kneale G: Radiation exposure of Hanford workers dying from cancer and other causes. Health Phys 33:369, 1977
88. Darby SC, Reissland JA: Low levels of ionizing radiation and cancer: are we underestimating the risk? J R Stat Soc A 3:298, 1981
89. Gilbert ES, Petersen GR, Buchanan JA: Mortality of workers at the Hanford Site: 1945–1981. Health Phys 56:11, 1989
90. Smith PG, Douglas AJ: Mortality of workers at the Sellafield plant of British Nuclear Fuels. Br Med J 293:845, 1986
91. Beral V, Inskip H, Fraser P et al: Mortality of employees of the United Kingdom Atomic Energy Authority, 1946–1979. Br Med J 291:440, 1985
92. Forman D, Cook-Mozaffari P, Darby S et al: Cancer near nuclear installations. Commentary. Nature 329:499, 1987
93. Cook-Mozzaffari PJ, Darby SC, Doll R et al: Geographical variation of mortality from leukemia and other cancers in England and Wales in relation to proximity to nuclear installations, 1969–78. Br J Cancer 59:476, 1989
94. Dousset M: Cancer mortality around La Hague nuclear facilities. Health Phys 56:875, 1989
95. Johnson CJ: Cancer incidence in an area contaminated with radionuclides near a nuclear installation. Ambio 10:176, 1981
96. Berkheiser SW: Review of leukemia, lymphoma, and myeloma before and after the TMI accident. Penn Med 89:50, 1986
97. Jessop EG, Horsley SD: Multiple myeloma in South Cumbria 1974–80: problems of health analysis in small communities. J Epidemiol Community Health 39:231, 1985
98. Darby SC, Kendall GM, Fell TP et al: A summary of mortality and incidence of cancer in men from the United Kingdom who participated in the United Kingdom's atmospheric nuclear weapons tests and experimental programmes. Br Med J 296:332, 1988
99. Gardner M: Cancer among participants in tests of British nuclear weapons. Br Med J 296:309, 1988
100. Stebbings JH, Lucas HF, Stehney AF: Mortality from cancers of major sites in female radium dial workers. Am J Ind Med 5:435, 1984
101. Bross IDJ, Viadana E, Houten L: Occupational cancer in men exposed to dust and other environmental health hazards. Arch Environ Health 33:300, 1978
102. Brownson RC, Reif JS, Chang JC, Davis JR: Cancer risks among Missouri farmers. Cancer 64:2381, 1989
103. Burmeister LF: Cancer mortality in Iowa farmers, 1971–78. JNCI 66:461, 1981
104. Burmeister LF, Everett GD, Van Lier SF, Isacson P: Selected cancer mortality and farm practices in Iowa. Am J Epidemiol 118:72, 1983
105. Cantor KP, Blair A: Farming and mortality from multiple myeloma: a case-control study with the use of death certificates. JNCI 72:251, 1984
106. Delzell E, Grufferman S: Mortality among white and nonwhite farmers in North Carolina, 1976–1978. Am J Epidemiol 121:391, 1985
107. La Vecchia C, Negri E, D'Avanzo B, Franceschi S: Occupation and lymphoid neoplasms. Br J Cancer 60:385, 1989
108. McLaughlin JK, Malker HS, Linet MS et al: Multiple myeloma and occupation in Sweden. Arch Environ Health 43:7, 1988
109. Morris PD, Koepsell TD, Daling JR et al: Toxic substance

exposure and multiple myeloma: a case-control study. JNCI 76:987, 1986
110. Pearce NE, Smith AH, Fisher DO: Malignant lymphoma and multiple myeloma linked with agricultural occupations in a New Zealand cancer registry-based study. Am J Epidemiol 121:225, 1985
111. Pearce NE, Smith AH, Howard JK et al: Case-control study of multiple myeloma and farming. Br J Cancer 54:493, 1986
112. Steineck G, Wiklund K: Multiple myeloma in Swedish agricultural workers. Int J Epidemiol 15:321, 1986
113. Vagero D, Persson G: Occurrence of cancer in socioeconomic groups in Sweden. Scand J Soc Med 14:151, 1986
114. Brownson RC, Reif JS: A cancer registry-based study of occupational risk for lymphoma, multiple myeloma and leukaemia. Int J Epidemiol 17:27, 1988
115. Reif JS, Pearce NE, Fraser J: Cancer risks among New Zealand meat workers. Scand J Work Environ Health 15:24, 1989
116. Tollerud DJ, Brinton LA, Stone BJ et al: Mortality from multiple myeloma among North Carolina furniture workers. JNCI 74:799, 1985
117. Milham S, Jr: Leukemia and multiple myeloma in farmers. Am J Epidemiol 94:307, 1971
118. Agu VU, Christensen BL, Buffler PA: Geographic patterns of multiple myeloma: racial and industrial correlates, state of Texas. 1969–1971. JNCI 65:735, 1980
119. Priester WA, Mason TJ: Human cancer mortality in relation to poultry population, by county, in 10 southeastern states. JNCI 53:45, 1974
120. Bedigian HG, Sevoian M: Susceptibility of mammalian (hamster) cell culture to infection with cellular and cell-free type II leukosis (Marek's disease) virus. JNCI 50:129, 1973
121. Makari JG: Association between Marek's herpesvirus and human cancer. Oncology 28:164, 1973
122. Alavanja MCR, Rush GA, Stewart P, Blair A: Proportionate mortality study of workers in the grain industry. JNCI 78:247, 1987
123. Wiklund K, Dich J, Holm L-E, Eklund G: Risk of cancer in pesticide applicators in Swedish agriculture. Br J Ind Med 46:809, 1989
124. Hardell L, Eriksson M, Lenner P, Lundgren E: Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxyacids: a case-control study. Br J Cancer 43:169, 1981
125. Hoar SK, Blair A, Holmes FF et al: Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. JAMA 256:1141, 1986
126. Blair A, Malker H, Cantor KP et al: Cancer among farmers. Scand J Work Environ Health 11:397, 1985
127. Gallagher RP, Threlfall WJ: Cancer mortality in metal workers. Can Med Assoc J 129:1191, 1983
128. Giles GG, Lickiss JN, Baikie MJ et al: Myeloproliferative and lymphoproliferative disorders in Tasmania, 1972–1980: occupational and familial aspects. JNCI 72:1233, 1984
129. Greene MH, Hoover RN, Eck RL et al: Cancer mortality among printing plant workers. Environ Res 20:66, 1979
130. Sorahan T, Cooke MA: Cancer mortality in a cohort of United Kingdom steel foundry workers: 1946–85. Br J Ind Med 46:74, 1989
131. Berg JW, Burbank F: Correlations between carcinogenic trace metals in water supplies of cancer mortality. Ann NY Acad Sci 199:249, 1972
132. Williams GM, Weisburger JH: Chemical carcinogenesis. p. 107. In Klaassen CD, Amdur MO, Doull J (eds): Casarett and Doull's Toxicology. Macmillan, New York, 1986
133. Potter M: The plasma cell tumors and myeloma proteins of mice. p. 105. In Busch H (ed): Methods in Cancer Research. Academic Press, San Diego, 1967
134. Mason TJ: Cancer mortalities in U.S. counties with plastics and related industries. Environ Health Perspect 11:79, 1975
135. Andjelkovich D, Taulbee J, Blum S: Mortality of female workers in a rubber manufacturing plant. J Occup Med 20:409, 1978
136. Monson RR, Nakano KK: Mortality among rubber workers. II. Other employees. Am J Epidemiol 103:297, 1976
137. Monson RR, Nakano KK: Mortality among rubber workers. I. White male union employees in Akron, Ohio. Am J Epidemiol 103:284, 1976
138. Gustavsson P, Hogstedt C, Holmberg B: Mortality and incidence of cancer among Swedish rubber workers, 1952–1981. Scand J Work Environ Health 12:538, 1986
139. Delzell E, Monson RR: Mortality among rubber workers. X. Reclaim workers. Am J Ind Med 7:307, 1985
140. Sorahan T, Parkes HG, Veys CA et al: Mortality in the British rubber industry 1946–85. Br J Ind Med 46:1, 1989
141. Rinsky RA, Smith AB, Hornung R et al: Benzene and leukemia. An epidemiologic risk assessment. N Engl J Med 316:1044, 1987
142. Decoufle P, Blattner WA, Blair A: Mortality of workers exposed to benzene and other agents. Environ Res 30:16, 1983
143. Aksoy M, Erdem S, Dincol G et al: Clinical observations showing the role of some factors in the etiology of multiple myeloma. Acta Haematol (Basel) 71:116, 1984
144. Nakayama S, Kitajima K, Veno K et al: Multiple myeloma in spouses with special reference to BHC as a possible cause. Rinsho Ketsueki 21:73, 1980
145. Milham S, Jr: Occupational mortality in Washington State, 1950–1979. p. 72. DHHS publication no. (NIOSH) 83-116. US Government Printing Office, Washington DC, 1983
146. Milham S, Jr, Demers RY: Mortality among pulp and paper workers. J Occup Med 26:844, 1984
147. Henneberger PK, Ferris BG, Jr, Monson RR: Mortality among pulp and paper workers in Berlin, New Hampshire. Br J Ind Med 46:658, 1989
148. Robinson CF, Waxweiler RJ, Fowler DP: Mortality among production workers in pulp and paper mills. Scand J Work Environ Health 12:552, 1986
149. Schwartz E: A proportionate mortality ratio analysis of pulp and paper mill workers in New Hampshire. Br J Med 45:234, 1988
150. Miller B, Blair AE, Raynor HL et al: Cancer and other mortality patterns among United States furniture workers. Br J Ind Med 46:508, 1989
151. Reif J, Pearce N, Kawachi I, Fraser J: Soft-tissue sarcoma, non-Hodgkin's lymphoma and other cancers in New Zealand forestry workers. Int J Cancer 43:49, 1989
152. Walrath J, Decoufle P, Thomas TL: Mortality among workers in a shoe manufacturing company. Am J Ind Med 12:615, 1987
153. Delzell E, Grufferman S: Cancer and other causes of death among female textile workers, 1976–78. JNCI 71:735, 1983
154. Thomas TL, Decloufle P, Moure-Eraso R: Mortality among workers employed in petroleum refining and petrochemical plants. J Occup Med 22:97, 1980
155. Thomas TL, Waxweiler RJ, Crandall MS et al: Cancer mor-

tality patterns in three Texas oil refineries. Am J Ind Med 6:3, 1984
156. Thomas TL, Waxweiler RJ, Moure-Eraso R et al: Mortality patterns among workers in three Texas oil refineries. J Occup Med 24:135, 1982
157. Rushton L, Alderson MR: Epidemiological survey of oil distribution centres in Britain. Br J Ind Med 40:330, 1983
158. Kaplan SD: Update of a mortality study of workers in petroleum refineries. J Occup Med 28:514, 1986
159. Divine BJ, Barron V, Kaplan SD: Texaco mortality study. I. Mortality among refinery, petrochemical, and research workers. J Occup Med 27:445, 1985
160. Hanis NM, Holmes TM, Shallenberger LG, Jones KE: Epidemiologic study of refinery and chemical plant workers. J Occup Med 24:203, 1982
161. Wong O, Morgan RW, Bailey WJ et al: An epidemiological study of petroleum refinery employees. Br J Ind Med 43:6, 1986
162. Divine BJ, Barron V: Texaco mortality study. III. A cohort of producing and pipeline workers. Am J Ind Med 11:189, 1987
163. Hanis NM, Shallenberger LG, Donaleski DL, Sales EA: A retrospective mortality study of workers in three major U.S. refineries and chemical plants. Part 1. Comparisons with U.S. population. J Occup Med 27:283, 1985
164. Linet MS, Harlow SD, McLaughlin JK: A case-control study of multiple myeloma in whites: chronic antigenic stimulation, occupation, and drug use. Cancer Res 47:2978, 1987
165. Adelstein AM: Occupational mortality: cancer. Ann Occup Hyg 15:53, 1972
166. Lundberg I: Mortality and cancer incidence among Swedish paint industry workers with long-term exposure to organic solvents. Scand J Work Environ Health 12:108, 1986
167. Hagmar L, Bellander T, Englander V et al: Mortality and morbidity among workers in a chemical factory. Scand J Work Environ Health 12:545, 1986
168. Edling C, Jarrholm B, Andersson L, Axelson O: Mortality and cancer incidence among workers in an abrasive manufacturing industry. Br J Ind Med 44:57, 1987
169. Gerber MA: Asbestosis and neoplastic disorders of the hemopoietic system. Am J Clin Pathol 53:204, 1970
170. Kagan E, Jacobson RJ, Young K et al: Asbestos-associated neoplasms of B-cell lineage. Am J Med 67:325, 1979
171. Lieben J: Malignancies in asbestos workers. Arch Environ Health 13:619, 1966
172. Robertson MA, Harington JS, Bradshaw E: The cancer pattern in African gold miners. Br J Cancer 25:395, 1971
173. Schwartz DA, Vaughan TL, Heyer NJ et al: B cell neoplasms and occupational asbestos exposure. Am J Ind Med 14:661, 1988
174. Raffn E, Lynge E, Juel K, Korsgaard B: Incidence of cancer and mortality among employees in the asbestos cement industry in Denmark. Br J Ind Med 46:90, 1989
175. Milham S, Jr: Mortality in workers exposed to electromagnetic fields. Environ Health Perspect 62:297, 1985
176. Pearce N, Reif J, Fraser J: Case-control studies of cancer in New Zealand electrical workers. Int J Epidemiol 18:55, 1989
177. Gustavsson P, Gustavsson A, Hogstedt C: Excess of cancer in Swedish chimney sweeps. Br J Ind Med 45:777, 1988
178. Guidotti S, Wright WE, Peters JM: Multiple myeloma in cosmetologists. Am J Ind Med 3:169, 1982
179. Spinelli JJ, Gallagher RP, Band PR, Threlfall WJ: Multiple myeloma, leukemia, and cancer of the ovary in cosmetologists and hairdressers. Am J Ind Med 6:97, 1984
180. Teta MJ, Walrath J, Wister-Meigs J, Flannery JT: Cancer incidence among cosmetologists. JNCI 72:1051, 1984
181. Matzner Y, Polliack A: Lymproliferative disorders in four patients receiving diphenylhydantoin therapy: etiologic correlation or chance association? Is J Med Sci 14:865, 1978
182. Witwer MW, Schmid FR, Tesar JT: Acute myelomonocytic leukemia and multiple myeloma after sulphinpyrazone and colchicine treatment of gout. Br Med J 2:89, 1976
183. Isobe T, Shaura D, Itoh T, Fujita T: Myeloma in siblings. Acta Haematol Jpn 44:98, 1981
184. Shoenfeld Y, Berliner S, Shaklai M et al: Familial multiple myeloma. A review of thirty-seven families. Postgrad Med J 58:12, 1982
185. Brugiatelli M, Comis M, Iacopino P et al: Multiple myeloma in husband and wife. Acta Haematol (Basel) 64:227, 1980
186. Kanoh T: Multiple myeloma in spouses. (Letter.) Eur J Haematol 41:397, 1988
187. Kardinal CG: Multiple myeloma in a husband and wife. JAMA 239:22, 1978
188. Kyle RA, Greipp PR: Multiple myeloma. Houses and spouses. Cancer 51:735, 1983
189. Kyle RA, Heath CW, Jr, Carbone P: Multiple myeloma in spouses. Arch Intern Med 127:944, 1971
190. Kyle RA, Herber L, Evatt BL, Heath CW: Multiple myeloma. A community cluster. JAMA 213:1339, 1970
191. Linet MS: Chronic lymphocytic leukemia and multiple myeloma in husband and wife. Am J Med Sci 288:21, 1984
192. Pietruszka M, Rabin BS, Srodes C: Multiple myeloma in husband and wife. Lancet 1:314, 1976
193. McCrea AP, Morris TCM: Concurrent familial myeloma in northern Ireland. Cancer 58:394, 1986
194. Bourguet CC, Grufferman S, Delzell E et al: Multiple myeloma and family history of cancer. A case-control study. Cancer 56:2133, 1985
195. Grufferman S, Cohen HJ, Delzell ES et al: Familial aggregation of multiple myeloma and central nervous system diseases. J Am Geriatr Soc 37:303, 1989
196. Linet MS, McLaughlin JK, Harlow SD, Fraumeni JF, Jr: Family history of autoimmune disorders and cancer in multiple myeloma. Int J Epidemiol 17:512, 1988
197. Bernard SM, Cartwright RA, Darwin CM et al: A possible epidemiological association between multiple sclerosis and lymphoma/leukemia. (Letter.) Br J Haematol 65:122, 1987
198. Grosbois B, Gueguen M, Fauchet R et al: Multiple myeloma in two brothers. An immunochemical and immunogenetic familial study. Cancer 58:2417, 1986
199. Horwitz LJ, Levy RN, Rosher F: Multiple myeloma in three siblings. Arch Intern Med 145:1449, 1985
200. Leech SH, Brown R, Schanfield MS: Genetic studies in multiple myeloma. II. Immunoglobulin allotype associations. Cancer 55:1473, 1985
201. Ludwig H, Mayr WR: Genetic aspects of susceptibility to multiple myeloma. Blood 59:1286, 1982
202. Bertrams J, Kuwert E, Bohme U et al: HL-A antigens in Hodgkin's disease and multiple myeloma—increased frequency of W18 in both diseases. Tissue Antigens 2:41, 1972
203. Jeannet M, Magnin C: HL-A antigens in haematological malignant diseases. Eur J Clin Invest 2:39, 1971
204. Mason DY, Cullen P: HL-A antigens frequencies in myeloma. Tissue Antigens 5:238, 1975
205. McDevitt HO, Bodner WF: Histocompatibility antigens,

immune responsiveness and susceptibilility to diseases. Am J Med 52:1, 1972
206. Bodmer WF: Genetic factors in Hodgkin's disease. Natl Cancer Inst Monogr 36:127, 1973
207. Greene MH, McKeen EA, Li FP et al: HLA antigens in familial Hodgkin's disease. Int J Cancer 23:777, 1979
208. Smith G, Waldorf RL, Fishkin B et al: HL-A phenotypes, immunoglobulins and K and L chains in multiple myeloma. Tissue Antigens 4:374, 1974
209. Tananov AT: Histocompatibility (HLA) antigens and disease. Probl Gematol Pereliv Krovi 23:45, 1978
210. Leech SH, Bryan CF, Elston RC et al: Genetic studies in multiple myeloma. I. Association with HLA-Cw5. Cancer 51:1408, 1983
211. Wurster-Hill DH, McIntyre OR, Cornwell GG et al: Marker-chromosome 14 in multiple myeloma and plasma cell leukemia. Lancet 2:1031, 1973
212. Liang W, Nopper GE, Rowly JD: Karyotypic abnormalities and clinical aspects of patients with multiple myeloma and related paraproteinemic disorders. Cancer 44:630, 1979
213. Philip P: Marker chromosome 14q+ in multiple myeloma. Hereditas 80:155, 1975
214. Philip P, Drivsholm A: G-banding analysis of complex aneuploidy in multiple myeloma bone marrow cell. Blood 47:69, 1976
215. Gould J, Alexanian R, Goodacre A et al: Plasma cell karyotype in multiple myeloma. Blood 71:453, 1988
216. Secker-Walker LM, Goldman JM: Cytogenetics and leukaemogenesis. p. 372. In Hoffbrand AV, Lewis SM (eds): Postgraduate Haematology. Heinemann Professional Publishing, Oxford, 1989
217. Croce CM, Shander M, Martinis J et al: Chromosomal location of the genes for human immunoglobulin heavy chains. Proc Natl Acad Sci USA 76:3416, 1979
218. Lewis JP, MacKenzie MR: Non-random chromosomal aberrations associated with multiple myeloma. Hematol Oncol 2:307, 1984
219. Ernst TJ, Gazdar A, Ritz J, Shipp MA: Identification of a second transforming gene, ras$^a$, in a human multiple myeloma line with a rearranged c-myc allele. Blood 72:1163, 1988
220. Nishida K, Taniwaki M, Misawa W, Abe T: Nonrandom rearrangement of chromosome 14 at band q32.33 in human lymphoid malignancies with mature B-cell phenotype. Cancer Res 49:1275, 1989
221. Selvanayagam P, Blick M, Narni F et al: Alteration and abnormal expression of the c-myc oncogene in human multiple myeloma. Blood 71:30, 1988
222. Dalla-Favera R, Bregni M, Erikson J et al: Human C-myc onc gene is located on the region of chromosome 8 that is translocated in Burkitt lymphoma cells. Proc Natl Acad Sci USA 79:7824, 1982
223. Showe LC, Croce CM: The role of chromosomal translocations in B- and T-cell neoplasia. Annu Rev Immunol 5:253, 1987
224. Epstein J, Barlogie B, Katzmann J, Alexanian R: Phenotypic heterogeneity in aneuploid multiple myeloma indicates pre-B cell involvement. Blood 71:861, 1988
225. Kyle RA: Monoclonal gammopathy of undetermined significance: natural history in 241 cases. Am J Med 64:814, 1978
226. Youinou P: Genetic propensity to benignity in monoclonal-gammopathy. Acta Haematol (Basel) 62:173, 1979
227. Maldonado JE, Kyle RA: Familial myeloma. Report of eight families and a study of serum proteins in their relatives. Am J Med 57:875, 1974
228. Meijers KAE, Leeuw B, Voormolen-Kalova M: The multiple occurrence of myeloma and asymptomatic paraproteinaemia within one family. Clin Exp Immunol 12:185, 1972
229. Wiedermann D, Urban P, Wiedermann B et al: Multiple myeloma in twin brothers. Immunoglobulin levels among their relatives. Neoplasma 23:197, 1976
230. Axelsson U, Hallen J: Familial occurrence of pathological serum proteins of different gammaglobulin groups. Lancet 2:369, 1965
231. Williams RC, Erickson JL, Polesky HF et al: Studies of monoclonal immunoglobulins (M-components) in various kindreds. Ann Intern Med 67:309, 1967
232. Ritzman SE, Loukas D, Sakai H et al: Idiopathic (asymptomatic) monoclonal gammopathies. Arch Intern Med 135:95, 1975
233. Van Camp BG, Cole J, Peetermans ME: HLA antigens and homogeneous immunoglobulins. Clin Immunol Immunopathol 7:315, 1977
234. Pick AI, Soenfeld Y, Skvaril F et al: Asymptomatic (benign) monoclonal gammopathy-a study of 100 patients. Ann Clin Lab Sci 74:335, 1977
235. Festen JM, Marrink J, de Waard-Kuiper EH et al: Immunoglobulins in families of myeloma patients. Scan J Immunol 6:887, 1977
236. Odeberg H, Johansson GG, Berlin SO: Immunoglobulin analysis in families of myeloma patients. Acta Med Scand 96:361, 1974
237. Greene MH, Dalager NA, Lamberg SI et al: Mycosis fungoides: epidemiologic observations. Cancer Treatm Rep 63:597, 1979
238. Spengler GA, Butler R, Fischer C et al: On the question of the familial occurrence of paraproteinemia. Helv Med Acta 33:208, 1966
239. Wirtschafter SK, Rappaport SI: The familial occurrence of chronic lymphocytic leukemia and multiple myeloma. Calif Med 92:165, 1960
240. Bjornsson OG, Arnason A, Godmundsson S et al: Macroglobulinaemia in an Icelandic family. Acta Med Scan 203:283, 1978
241. Blattner WA, Garber J, Mann DL et al: Waldenström's macroglobulinemia and autoimmune disease in a family. Ann Intern Med 93:830, 1980
242. Fine JM, Lambin P, Massari M et al: Malignant evolution of asymptomatic monoclonal IgM after seven and fifteen years in two siblings of a patient with Waldenström's macroglobulinemia. Acta Med Scand 211:237, 1982
243. Fine JM, Lambin P, Valentine L et al: IgG monoclonal gammopathy in the sister of a patient with Waldenström's macroglobulinemia. Biomedicine 19:117, 1973
244. Fraumeni JF, Jr, Wertilecki W, Blattner WA et al: Varied manifestations of a familial lymphoproliferative disorder. Am J Med 59:145, 1975
245. Kalff MW, Hijmans W: Immunoglobulin analysis in families of macroglobulinemia patients. Clin Exp Immunol 5:479, 1969
246. Renier G, Ifrah N, Chevailler A et al: Four brothers with Waldenström's macroglobulinemia. Cancer 64:1554, 1989
247. Seligmann M, Dannon F, Mihaesco C et al: Immunoglobulin abnormalities in families of patients with Waldenström's macroglobulinemia. Am J Med 43:66, 1967
248. Moutsopoulos HM, Chused TM, Knudsen B et al: B Lymphocyte antigens in sicca syndrome. Science 199:1441, 1978

249. Anonymous: Anatigenic stimulation and myeloma. Lancet 1:252, 1978
250. Hakulinen T, Isomaki H, Knekt P: Rheumatoid arthritis and cancer studies based on linking nationwide registries in Finland. Am J Med 78:(suppl 1A)29, 1985
251. Williams AR, Weiss NS, Koepsell TD et al: Infectious and noninfectious exposures in the etiology of light chain myeloma: a case-control study. Cancer Res 49:4038, 1989
252. Penny R, Hughes S: Repeated stimulation of the reticuloendothelial system and the development of the plasma-cell dyscrasias. Lancet 1:77, 1970
253. Cuzick J, De Stavola BL: Autoimmune disorders and multiple myeloma. Int J Epidemiol 18:283, 1989
254. Bernstein L, Levin D, Menck H, Ross RK: AIDS-related secular trends in cancer in Los Angeles County men: a comparison by marital status. Cancer Res 49:466, 1989
255. Goldenberg GJ, Paraskevas F, Israels LG: The association of rheumatoid arthritis with plasma cell and lymphocytic neoplasms. Arthritis Rheum 12:569, 1969
256. Isomaki HA, Hakulinen T, Joustenlahti V: Excess risk of lymphoma, leukemia, and myeloma in patients with rheumatoid arthritis. J Chron Dis 31:691, 1978
257. Katusic S, Beard CM, Kurland LT et al: Occurrence of malignant neoplasms in the Rochester, Minnesota, rheumatoid arthritis cohort. Am J Med 78(suppl 1A):50, 1985
258. Pettersson T, Koivunen E, Ilvonen M et al: Sarcoidosis and multiple myeloma: an association. Br J Med 295:958, 1987
259. Cheson BD, Walker HS, Heath ME et al: Defective binding of the third component of complement (C3) to *Streptococcus pneumoniae* in multiple myeloma. Blood 63:949, 1984
260. Jacobson DR, Zolla-Pazner S: Immunosuppression and infection in multiple myeloma. Semin Oncol 13:282, 1986
261. Cohen HJ, Bernstein RJ, Grufferman S: Role of immune stimulation in the etiology of multiple myeloma: a case-control study. Am J Hematol 24:119, 1987
262. Isobe T, Osserman EF: Pathologic conditions associated with plasma cell dyscrasias: a study of 806 cases. Ann NY Acad Sci 190:507, 1971
263. Koepsell TD, Daling JR, Weiss NS et al: Antigenic stimulation and the occurrence of multiple myeloma. Am J Epidemiol 126:1051, 1987